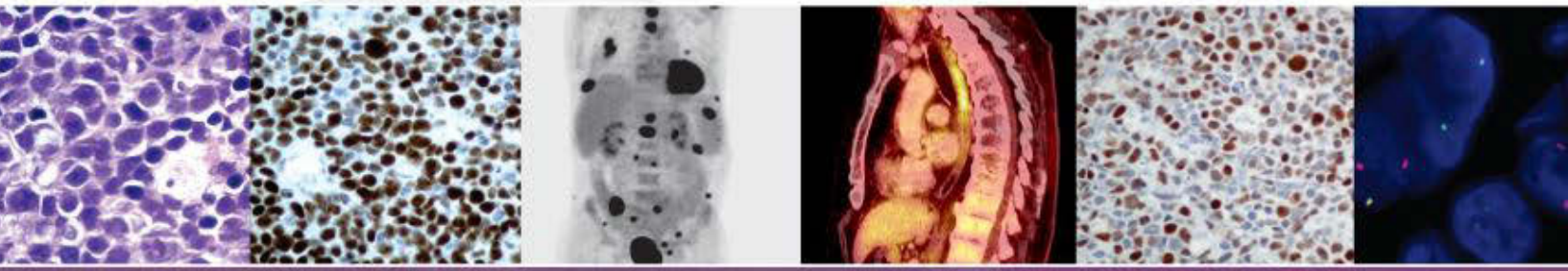
Edited by **Syed A. Abutalib** and **Maurie Markman**

CANCER CONSULT



Expertise for Clinical Practice

WILEY Blackwell

I wholeheartedly extend my gratitude towards our cancer experts who contributed to this fabulous project. They have elegantly combined their invaluable experience with clinical data and attempted to solve some of the most challenging and controversial issues in malignant hematology, hematopoietic stem cell transplantation, and oncology. I must add that this project would not have been a visible reality without constant support and love from the Supreme Lord and my family—which includes (and always will) my patients. I trust that readers will enjoy our work and would provide constructive feedback which should allow us to improve on subsequent editions.

Thank you kindly,
Syed Ali Abutalib
"I grow by that Hand which nurtures me"

I would like to thank my fabulous co-editor, Syed Abutalib, whose tireless efforts have made this book possible; the terrific contributors whose impressive chapters have created a publication of immense clinical value; the fantastic staff at Wiley Blackwell who have created this magnificent text; my wife (Tomes) and our wonderful children who have made it all worthwhile; and the patients I have had the genuine privilege and honor to meet and serve in my years of clinical practice.

Sincere regards,
Maurie Markman

Cancer Consult: Expertise for Clinical Practice

Edited by

Syed A. Abutalib, MD
Assistant Director
Hematology and Hematopoietic Cell Transplantation
Midwestern Regional Medical Center;
Cancer Treatment Centers of America
Zion, IL, USA

Maurie Markman, MD
Senior Vice President of Clinical Affairs
National Director of Medical Oncology
Cancer Treatment Centers of America;
Clinical Professor of Medicine
Drexel University College of Medicine
Philadelphia, PA, USA

WILEY Blackwell

Published by John Wiley and Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Cancer Consult: Expertise for Clinical Practice / edited by Syed A. Abutalib, Maurie Markman.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-118-58921-2 (pbk. : alk. paper) I. Abutalib, Syed A., editor. II. Markman, Maurie, editor.
[DNLM: 1. Neoplasms–Examination Questions. 2. Hematopoietic Stem Cell Transplantation–Examination Questions. 3. Leukemia–Examination Questions. 4. Medical Oncology–Examination Questions. QZ 18.2]
RC266.5
616.99′40076–dc23
2014008386

Cover image: Two center images courtesy of Shaunagh McDermott and Michael A. Blake (Chapter 131), all other images courtesy of Carmen Barcena and Laurence de Leval (Chapter 38).

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Contents

Part 4 | Gastrointestinal Oncology

Part 5 | Genitourinary Oncology

Part 6 | Skin Malignancies

PART 7 | Gynecological Malignancies

PART 8 | Sarcomas

PART 9 | Multidisciplinary Approach: Consultation with Surgical Oncology Team

PART 10 | Multidisciplinary Approach: Consultation with Radiation Oncology Team

PART 11 | Hereditary Cancer Syndromes and Genetic Testing in Oncology

PART 12 | Special Issues in Hematology and Oncology

List of Contributors

Jabeen Abutalib, MD
Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Syed A. Abutalib, MD
Hematology and Hematopoietic Cell Transplantation, Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

David Adelstein, MD, FACP
Department of Solid Tumor Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

D. Craig Allred, MD
Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA

Claudio Anasetti, MD
Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Kenneth Anderson, MD
Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics;
Dana-Farber Cancer Institute, Department of Medicine, Harvard Medical School, Boston, MA, USA

Magdalena Anitescu, MD, PhD
Department of Anesthesia & Critical Care, University of Chicago Medical Center, Chicago, IL, USA

James O. Armitage, MD
University of Nebraska Medical Center, Omaha, NE, USA

Hatem A. Azim Jr., MD, PhD
Breast Data Centre, Department of Medicine, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Joachim M. Baehring, MD, DSc
Departments of Neurology, Neurosurgery and Medicine, Yale University School of Medicine, New Haven, CT, USA

Brigitte Balme, MD
Pathology Unit, Lyon Sud Hospital, Claude Bernard Lyon 1 University, Pierre-Bénite, France

Carmen Barcena, MD
Institute of Pathology, University Hospital of Lausanne, Lausanne, Switzerland

Nancy L. Bartlett, MD
Division of Oncology, Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA

Gregory K. Behbehani, MD, PhD
Hematology and Oncology, Baxter Laboratory for Stem Cell Biology, Stanford University School of Medicine, Stanford, CA, USA

Frederick G. Behm, MD
Department of Pathology, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA

Charles L. Bennett, MD, PhD, MPP
Southern Network on Adverse Reactions (SONAR) of the South Carolina College of Pharmacy;
Arnold School of Public Health of the University of South Carolina;
William Jennings Bryan Dorn Veterans Administration Medical Center, Columbia, SC;
Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA

Al B. Benson III, MD, FACP
Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Gail Bentley, MD
Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

Andrea Bezjak, MDCM, MSc, FRCPC
Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Center, Toronto, ON, Canada

Shauna Birdsall, ND, FABNO
Western Regional Medical Center, Cancer Treatment Centers of America, Tulsa, OK, USA

Michael R. Bishop, MD
Hematopoietic Stem Cell Transplantation Program, Section of Hematology/Oncology, The University of Chicago, Chicago, IL, USA

Michael A. Blake, MD
Department of Abdominal Imaging, Massachusetts General Hospital, Boston, MA, USA

Nicholas A. Blondin, MD
Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

Agatha Bogard, MD
Department of Pathology, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA

Uma Borate, MD, MS
Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

Eduardo D. Bruera, MD, FAAHPM
Department of Palliative Care and Rehabilitation Medicine, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Albert S.Y. Chang, MD
Section of General Thoracic Surgery, Department of Surgery, Duke University Medical Center, Duke Raleigh Hospital, Raleigh, NC, USA

Christina H. Chapman, MD
Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI, USA

Robert Chen, MD
Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Saurabh Chhabra, MD
Division of Hematology/Oncology, Medical University of South Carolina, Charleston, SC, USA

Steven J. Chmura, MD, PhD
Department of Radiation and Cellular Oncology, The University of Chicago, Chicago, IL, USA

Jeffery Choh, MD
Interventional Radiology Department, Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Daniel Christiansen, MD
Dermatology Division, Vanderbilt Clinic, Vanderbilt University, Nashville, TN, USA

Daniel C. Chung, MD
Gastrointestinal Unit and GI Cancer Genetics Program, Cancer Center, Massachusetts General Hospital;
Department of Medicine, Harvard Medical School, Boston, MA, USA

Dennis L. Citrin, MB, ChB, PhD
Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Stefan O. Ciurea, MD
Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Ana M. Ciurea, MD
Department of Dermatology, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Anna Sancho Clayton, MD
Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA

Robert L. Coleman, MD
Clinical Research, Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Helen Collins, MD
Amgen Inc., Thousand Oaks, CA, USA

Jean Marie Connors, MD
Department of Medicine, Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Henry J. Conter, MD
Assistant Professor, Dentistry, University of Western Ontario, London, ON, Canada

Amanda B. Cooper, MD
Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Melanie Corbman, MS, LCGC
Genetics/Oncology Clinic, Eastern Regional Medical Center, Cancer Treatment Centers of America, Philadelphia, PA, USA

Steven M. Corsello, MD
Department of Medical Oncology, Dana-Farber Cancer Institute; Harvard Medical School, Boston, MA, USA

Daniel R. Couriel, MD
University of Michigan Blood and Marrow Transplant Program, Ann Arbor, MI, USA

Brian Czito, MD
Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA

Myron S. Czuczman, MD
Roswell Park Cancer Institute, Buffalo, NY, USA

Stephane Dalle, MD, PhD
Dermatology Unit, Lyon Sud Hospital, Claude Bernard Lyon 1 University, Pierre-Bénite, France

Emily Dalton, MS, CGC
Ambry Genetics, Aliso Viego, CA, USA

Thomas A. D'Amico, MD
Section of General Thoracic Surgery, Duke University Medical Center, Durham, NC, USA

Daniel J. DeAngelo, MD, PhD
Department of Medical Oncology, Dana-Farber Cancer Institute; Department of Medicine, Harvard Medical School, Boston, MA, USA

Claire Dearden, MD
Department of Haemato-Oncology, Royal Marsden NHS Foundation Trust, Sutton;
Institute of Cancer Research, London, UK

Laurence de Leval, MD, PhD
Institute of Pathology, University Hospital of Lausanne, Lausanne, Switzerland

Rony Dev, MD
Department of Symptom Control & Palliative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Curtiland Deville, MD
Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Courtney D. DiNardo, MD, MSCE
Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Antonio Di Stasi, MD
Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Stephane Doucet, MD
Department of Medicine, Centre Hospitalier de l'Université de Montréal (CHUM Hospital), Montreal, QC, Canada

Anita D'Souza, MD
Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Kieron Dunleavy, MD
National Cancer Institute, Bethesda, MD, USA

Vu H. Duong, MD
University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA

Dennis A. Eichenauer, MD
First Department of Internal Medicine, University Hospital Cologne;
German Hodgkin Study Group (GHSG), Cologne, Germany

Harry P. Erba, MD, PhD
Internal Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

Elihu H. Estey, MD
University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

William C. Eward, DVM, MD
Department of Orthopedic Surgery, Section of Orthopedic Oncology, Duke Sarcoma Program, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

Stefan H. Faderl, MD
Division of Leukemia, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA

Julia Fechtner, RD, CSO, CNSC
Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Stephen J. Forman, MD
Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Eric Fowler, MS, LCGC
Genetic Counseling, Outpatient Clinics, Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Patrik Gabikian, MD
Department of Neurosurgery, Kaiser Foundation Hospital, Los Angeles, CA, USA

Sujata S. Gaitonde, MD
Department of Pathology, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA

Sabha Ganai, MD, PhD
Department of Surgery, The University of Chicago Medicine, Chicago, IL, USA

Faithlore P. Gardner, MD
Division of Hematology/Oncology, Mayo Clinic, Jacksonville, FL, USA

Silvia Gentili, MD
Clinica di Ematologia, Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona, Ancona, Italy

Morie A. Gertz, MD
Department of Medicine, Mayo Clinic, Rochester, MN, USA

Hady Ghanem, MD
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Armin Ghobadi, MD
Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Mark R. Gilbert, MD
Department of Neuro-Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Timothy Gilligan, MD, MS
Departments of Solid Tumor Oncology, Urology, and Inpatient Solid Tumor Oncology, Center for Ethics, Humanities and Spiritual Care, Taussig Cancer Institute, and Center for Excellence in Healthcare Communication, Cleveland Clinic, Cleveland, OH, USA

Meredith E. Giuliani, MD, MEd, FRCPC
Department of Radiation Oncology, University of Toronto; Princess Margaret Cancer Center, Toronto, ON, Canada

Isabella C. Glitza, MD
Fellowship Program, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Rob Glynne Jones, MBBS
Gastrointestinal & Colorectal Cancer, Mount Vernon Cancer Centre, Northwood, UK

Lucy A. Godley, MD, PhD
Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, IL, USA

Jenna D. Goldberg, MD
Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center;
Weill Cornell Medical College, New York, NY, USA

Jason Gotlib, MD, MS
Stanford University School of Medicine / Stanford Cancer Institute, Stanford, CA, USA

William J. Gradishar, MD
Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ann W. Gramza, MD
NIH/NCI Endocrine Oncology Branch, Bethesda, MD, USA

Stephanie A. Gregory, MD, FACP
Rush University Medical Center/Rush University, Chicago, IL, USA

Alejandro A. Gru, MD
Department of Pathology, Ohio State University Wexner Medical Center, Columbus, OH, USA

Paola Guglielmelli, MD
Hematology Department, University of Florence, Florence, Italy

Charlotte Guldborg Nyvold, MS, PhD
Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

James L. Gulley, MD, PhD, FACP
Medical Oncology Service, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Thomas M. Habermann, MD
Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Parameswaran Hari, MD
Medical College of Wisconsin, Milwaukee, WI, USA

Jean-Luc Harousseau, MD
University of Nantes;
Cancer Center René Gauducheau;
Clinical Research Program, French National Cancer Institute, Nantes, France

Andrew C. Harris, MD
Blood and Marrow Transplant Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

Christopher R. Heery, MD
Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Fred H. Hochberg, MD
Department of Neurology, Harvard Medical School; Neurology, Massachusetts General Hospital, Boston, MA, USA

Dieter Hoelzer, MD, PhD
Department of Medicine II, University Hospital, Frankfurt am Main, Germany

Peter Hokland, MD, DMSc
Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

M. Naomi Horiba, MD
Marlene and Stewart Greenebaum Cancer Center, University of Maryland, Baltimore, MD, USA

Netanel A. Horowitz, MD
Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel

David H. Ilson, MD, PhD
Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Carol Ireton-Jones, PhD, RD, LD, CNSC, FASPEN, FAND
Department of Nutrition, Cancer Treatment Centers of America, Dallas, TX, USA

Elias Jabbour, MD
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Caron A. Jacobson, MD
Dana-Farber Cancer Institute, Boston, MA, USA

Nitin Jain, MD
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Jagoda K. Jasielec, MD
Department of Medicine, The University of Chicago, Chicago, IL, USA

Yixing Jiang, MD, PhD
Marlene and Stewart Greenebaum Cancer Center, University of Maryland, Baltimore, MD, USA

Antonio M. Jimenez, MD
Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Eric Jonasch, MD
Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Tapan Kadia, MD
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Virginia Kaklamani, MD
Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Nayana Kamath, MD
University of Rochester James P. Wilmot Cancer Center, Rochester, NY, USA

Hagop Kantarjian MD
Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Philip Kantoff, MD
Department of Medical Oncology, Solid Tumor Oncology, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute; Department of Medicine, Harvard Medical School, Boston, MA, USA

Reem Karmali, MD
Rush University Medical Center/Rush University, Chicago, IL, USA

Matthew H.G. Katz, MD
Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Partow Kebriaei, MD
Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Chris R. Kelsey, MD
Department of Radiation Oncology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

Irum Khan, MD
University of Illinois Hospital and Health Sciences System, Chicago, IL, USA

Carrie L. Kitko, MD
University of Michigan Blood and Marrow Transplant Program, Ann Arbor, MI, USA

Rami S. Komrokji, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Leonidas Koniaris, MD
Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

Grzegorz Korpanty, MD, PhD, MRCPI
Division of Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Geoffrey Y. Ku
Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Timothy M. Kuzel, MD
Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Robert A. Kyle, MD
Department of Laboratory Medicine and Pathology, Mayo Medical School, Rochester, MN, USA

Ann S. LaCasce, MD
Dana-Farber/Partners CancerCare Hematology-Medical Oncology; Harvard Medical School, Boston, MA, USA

Carolyn Lammersfeld, MS, RD, CSO, CNSC
Integrative Medicine, Cancer Treatment Centers of America, Zion, IL, USA

Ginna G. Laport, MD
Division of Blood and Marrow Transplantation, Stanford University Medical Center, Stanford, CA, USA

Nicole Larrier, MS, MD
Department of Radiation Oncology, Duke Sarcoma Program, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

Richard A. Larson, MD
Hematologic Malignancies Program, Section of Hematology/Oncology, The University of Chicago, Chicago, IL, USA

Natasha B. Leighl, MD, MMSc, FRCPC
Division of Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

John E. Levine, MD
Blood and Marrow Transplant Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

Alan Lipton, MD
Pennsylvania State University, Hershey, PA, USA

Alan F. List, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Anya Litvak, MD
Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Stephen V. Liu, MD
Norris Comprehensive Cancer Center, University of Southern California School of Medicine, Los Angeles, CA, USA

Megan G. Lockyer, MD
Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA

Sagar Lonial, MD
Department of Hematology & Medical Oncology, The Winship Cancer Institute of Emory University, Atlanta, GA, USA

Weidong Lu, MD
Department of Medicine, Harvard Medical School;
Osher Research Center, Harvard Medical School-Osher Institute;
Chinese Herbal Medicine, New England School of Acupuncture;
Zakim Center for Integrative Therapies, Dana-Farber Cancer Institute, Boston, MA, USA

Rimas V. Lukas, MD
Department of Neurology, The University of Chicago, Chicago, IL, USA

Matthew A. Lunning, DO
Hematology/Oncology Division, University of Nebraska Medical Center, Omaha, NE, USA

Gary R. MacVicar, MD
Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Jametta Magwood, MPH
Southern Network on Adverse Reactions (SONAR) of the South Carolina College of Pharmacy;
Arnold School of Public Health of the University of South Carolina;
William Jennings Bryan Dorn Veterans Administration Medical Center, Columbia, SC;
Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA

Kim Margolin, MD
University of Washington, Seattle, WA, USA

Maurie Markman, MD
Cancer Treatment Centers of America;
Drexel University College of Medicine, Philadelphia, PA, USA

Peter Martin, MD
Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY, USA

Michael J. Mauro, MD
Myeloproliferative Disorders Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Beryl McCormick, MD, FACR
External Beam Radiotherapy, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Shaunagh McDermott, MB, BCh, FFR RCSI
Department of Abdominal Imaging, Massachusetts General Hospital, Boston, MA, USA

Charles A. McDonald, MD
Western Regional Medical Center, Cancer Treatment Centers of America, Goodyear, AZ, USA

Bruno C. Medeiros, MD
Assistant Professor of Medicine, Stanford University School of Medicine, Stanford, CA, USA

Divyesh G. Mehta, MD
University of Arizona College of Medicine;
Division of Hematology Oncology, Maricopa Medical Center, Phoenix, AZ, USA

Tarek M. Mekhail, MD
Cancer Institute of Florida, Orlando, FL, USA

Subhasis Misra, MD, MS, FACCWS
Division of Surgical Oncology, Texas Tech University Health Sciences Center, Amarillo, TX, USA

Supriya Gupta Mohile, MD
University of Rochester James P. Wilmot Cancer Center, Rochester, NY, USA

Mohamad Mohty, MD
Hematology and Cellular Therapy Department, Saint-Antoine Hospital;
University Pierre & Marie Curie, Paris, France

Lori S. Muffly, MD
Department of Hematology/Oncology, The University of Chicago, Chicago, IL, USA

Line Nederby, MS, PhD
Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

Alpa M. Nick, MD
Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

LeAnn B. Norris, PharmD
Southern Network on Adverse Reactions (SONAR) of the South Carolina College of Pharmacy;
Arnold School of Public Health of the University of South Carolina;
William Jennings Bryan Dorn Veterans Administration Medical Center, Columbia, SC;
Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA

Tobenna Nwizu, MD
Department of Solid Tumor Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Barbara J. O'Brien
Department of Neuro-Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Susan O'Brien, MD
Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Jose Leonel Ochoa-Bayona, MD
Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Elizabeth K. O'Donnell, MD
Dana-Farber Cancer Institute;
Massachusetts General Hospital, Boston, MA, USA

Hans Beier Ommen, MD, PhD
Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

Claudia Paba Prada, MD
Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA

Manisha Palta, MD
Department of Radiation Oncology, Duke Regional Hospital, Durham, NC, USA

Harvey I. Pass, MD
Division of Thoracic Surgery and Department of Cardiothoracic Surgery, NYU Langone Medical Center, New York University, New York, NY, USA

Shreyaskumar Patel, MD
Department of Sarcoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Mrinal M. Patnaik, MBBS
Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Fedro A. Peccatori, MD, PhD
Fertility and Procreation in Oncology Unit, Division of Gynecological Oncology, European Institute of Oncology, Milan, Italy

Robert J. Pelley, MD
Director of GI Oncology Program, Cleveland Clinic, OH, USA

Miguel-Angel Perales, MD
Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center;
Weill Cornell Medical College, New York, NY, USA

Edith A. Perez, MD
Division of Hematology/Oncology, Mayo Clinic, Jacksonville, FL, USA

Marie Perier-Muzet
Unit of Dermatoloy, Lyon Sud Hospital, Claude Bernard Lyon University, Pierre-Bénite, France

Peter Pinto, MD
Prostate Cancer Section, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Evan Pisick, MD
Cancer Treatment Centers of America, Zion, IL, USA

Mitchell C. Posner, MD
Department of Surgery, The University of Chicago Medicine, Chicago, IL, USA

Leonard R. Prosnitz, MD
Department of Radiation Oncology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

Gordana Raca, MD
Laboratory of Cancer Cytogenetics and Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, IL, USA

Jerald P. Radich, MD
Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Abed Rahman, MD
Department of Pain Medicine, Cancer Treatment Centers of America, Zion, IL, USA

Raed Rahman, DO
Department of Pain Medicine, Cancer Treatment Centers of America, Zion, IL, USA

Jasleen Randhawa, MD
Medical College of Wisconsin, Milwaukee, WI, USA

Farhad Ravandi, MD
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Matthew C. Raynor, MD
Division of Urologic Surgery, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

Shahid Raza, MD
Clinical Research Specialist, Hollywood, FL, USA

Istvan Redei, MD
Hematology and Stem Cell Transplant, Cancer Treatment Centers of America, Zion, IL, USA

Paul Richardson, MD
Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA

Richard F. Riedel, MD
Department of Internal Medicine, Division of Medical Oncology, Duke Sarcoma Program, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

S. Mujtaba Rizvi, MD
Pennsylvania State University, Hershey, PA, USA

Damiano Rondelli, MD
Division of Hematology/Oncology, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA

Mark Roschewski, MD
Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

James E. Rosenberg, MD
Cancer Treatment Centers of America, Zion, IL, USA

David S. Rosenthal, MD
Department of Medicine, Harvard Medical School;
Department of Faculty of Arts and Sciences, Harvard University;
Zakim Center for Integrated Therapies, Dana-Farber Cancer Institute, Boston, MA, USA

Jacob M. Rowe, MD
Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center;
Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa;
Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel

Sarah Rutherford, MD
Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Vaibhav Sahai, MD, MS
Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ravi Salgia, MD, PhD
Departments of Medicine, Pathology, and Dermatology; Chest Oncology and Thoracic Oncology Research Program and Translational Research Program, The University of Chicago Medicine, Chicago, IL, USA

Leonard Saltz, MD
Gastrointestinal Oncology Service and Colorectal Oncology Section, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Kristen Sanfilippo, MD, MPHS
Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA

Charles A. Schiffer, MD
Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

Kathy Schneider, MPH
Cancer Genetics and Prevention Program, Dana-Farber Cancer Institute, Boston, MA, USA

David C. Seldin MD, PhD
Departments of Medicine and Microbiology, Section of Hematology-Oncology and Amyloidosis Center, Boston University, Boston, MA, USA

Anthony J. Senagore, MD, MS, MBA, FACS, FACRS
Central Michigan University School of Medicine, Mount Pleasant, MI, USA

Christina M. Shannon, ND, FABNO
Cancer Treatment Centers of America, Zion, IL, USA

Kristen M. Shannon, MS, CGC
Cancer Center Genetics Program, Massachusetts General Hospital Cancer Center, Boston, MA, USA

Tsiporah Shore, MD
Bone Marrow and Hematopoietic Stem Cell Transplant Program, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

Veerpal Singh
Fox Valley Hematology Oncology, Elgin, IL, USA

Sonali M. Smith, MD
Section of Hematology/Oncology and Lymphoma Program, The University of Chicago, Chicago, IL, USA

Stephen Smith, MD
Department of Internal Medicine, University of Washington, Seattle, WA, USA

Davendra Sohal, MD, MPH
Solid Tumor Oncology, Taussig Cancer Institute and Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA

Robert J. Soiffer, MD
Hematologic Malignancies Department and Stem Cell/Bone Marrow Transplantation Program, Dana-Farber Cancer Institute; Department of Medicine, Harvard Medical School, Boston, MA, USA

Neeta Somaiah, MD
Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Shiyu Song, MD, PhD
Department of Radiation Oncology, Virginia Commonwealth University Health System, Richmond, VA, USA

Eytan M. Stein, MD
Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Keith Stuart, MD
Tufts University School of Medicine, Boston, MA, USA

Madina Sukhanova, MD
Laboratory of Cancer Cytogenetics, Department of Medicine, The University of Chicago, Chicago, IL, USA

Laura Sunn, MD
Consultation-Liaison Psychiatry, Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

John Sweetenham, MD
Clinical Affairs, Huntsman Cancer Institute; Department of Medicine, University of Utah, Salt Lake City, UT, USA

Martin S. Tallman, MD
Leukemia Service, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical Center, New York, NY, USA

Constantine S. Tam, MBBS, MD
Department of Hematology, Peter MacCallum Cancer Center, Melbourne, VIC, Australia

Wayne Tam, MD
Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Ayalew Tefferi, MD
Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Margaret Tempero, MD, MPH
UCSF Pancreas Center, Pancreas Cancer Program, and Division of Hematology and Oncology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA

Constance E.H. Teo, MBBS, MRCS (Edin), MMed (Otorhinolaryngology)
Department of Otolaryngology, Singapore General Hospital, Singapore

Luc Thomas, MD, PhD
Dermatology Unit, Lyon Sud Hospital, Claude Bernard Lyon 1 University, Pierre-Bénite, France

Sandra Thomas, PhD
Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Tracey Thomas, ND
Cancer Treatment Centers of America, Zion, IL, USA

Ramon V. Tiu, MD
Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Marie Toft-Petersen, MD
Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

Christopher W. Towe, MD
Department of Cardiothoracic Surgery, NYU Langone Medical Center, New York University, New York, NY, USA

Ching-Wei D. Tzeng, MD
Department of Surgery, University of Kentucky, Lexington, KA, USA

Koen van Besien MD, PhD
Bone Marrow and Hematopoietic Stem Cell Transplant Program, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

Katherine Van Loon, MD, MPH
Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA

Alessandro M. Vannucchi, MD
Dipartimento di Medicina Sperimentale e Clinica, University of Florence, Florence, Italy

Gauri R. Varadhachary, MD
Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Cindy Varga, MD
Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA

Pankaj Vashi, MD
Gastroenterology/Nutrition & Metabolic Support, Cancer Treatment Centers of America, Zion, IL, USA

Thomas Velancia, MD
Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Srdan Verstovsek, MD, PhD
Leukemia Department, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Valeria Visconte, PhD
Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Justin M. Watts, MD
Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Randal S. Weber, MD
Department of Head and Neck Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Glen J. Weiss, MD
Cancer Treatment Centers of America, Goodyear, AZ;
Translational Genomics Research Institute (TGen);
University of Arizona College of Medicine, Phoenix, AZ, USA

Meir Wetzler, MD, FACP
Leukemia Section, Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA

Thomas M. Wheeler, MD
Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA

David C. White, MD
Section of General Thoracic Surgery, Department of Surgery, Duke University Medical Center, Duke Raleigh Hospital, Raleigh, NC, USA

Julia White, MD
Department of Radiation Oncology, The Ohio State University Comprehensive Cancer Center–Arthur
G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH, USA

Christopher Willett, MD
Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA

Michael B. Williams, MD, MS
Department of Urology, Eastern Virginia Medical School, Virginia Beach, VA, USA

Wyndham Wilson, MD, PhD
Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Jane N. Winter, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

Ignacio I. Wistuba, MD
Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Michael E. Woods, MD
Division of Urologic Surgery, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

Jay Yang, MD
Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

Andrew D. Zelenetz, MD, PhD
Department of Medicine and Lymphoma Service, Memorial Sloan Kettering Cancer Center;
Weill-Cornell Medical Center, New York, NY, USA

Pier Luigi Zinzani, MD, PhD
Institute of Hematology "Seràgnoli," University of Bologna, Bologna, Italy

Preface

It is commonplace in the oncology arena for patients to request a "second opinion."

But it is equally usual for oncologists to discuss with a colleague a complex or unusual case, or a patient with serious comorbidities, to insure that a particular individual is given the greatest opportunity to experience the benefits of therapy while minimizing the risks of possible treatment-related harm. Such discussions occur both within a particular specialty (e.g., surgery, radiation, or medical oncology) and between various specialties.

And as cancer management becomes more multimodal in nature, with an increasing focus on both maximizing the opportunity for extended survival and at the same time optimizing quality of life, the requirement for essential communication between individual specialists with their own unique knowledge and experience of critically relevant components of care becomes ever more important.

It is with these thoughts in mind that the editors conceived of an oncology text that would focus on the "expert perspectives" of oncology professionals. The intent was to have each individual book chapter be viewed as a "mini-consultation" provided by a specialist regarding a specific, highly clinically relevant issue in cancer management.

Considering the specific purpose and focus of the material presented, the book is written without detailed references (although a few selected readings are included at the end of each chapter). However, many of the authors have prepared a more extensive reference list, and the editors will be happy to email any reader the more detailed reference lists for individual book chapters, if so requested.

The chapters that follow have been written by clinicians selected for their recognized clinical expertise and experience. It is hoped that those reading this book will find the material of value in their own interactions with their patients.

Syed Abutalib and Maurie Markman
cancerconsult@gmail.com

SECTION 1

Malignant Hematology and Hematopoietic Cell Transplantation

PART 1

Acute Lymphoblastic Leukemia in Adults

CHAPTER 1

Diagnosis of acute lymphoblastic leukemia

Frederick G. Behm[1], Agatha Bogard[1], Syed A. Abutalib[2], and Sujata S. Gaitonde[1]

[1]University of Illinois Hospital and Health Sciences System, Chicago, IL, USA
[2]Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Hematopathologists are often called on to clarify how they arrived at a diagnosis of acute lymphoblastic leukemia (ALL). This is frequently due to confusion regarding how to interpret unusual flow cytometry (FC) immunophenotype or cytogenetic results. Occasionally, the diagnosis does not fit clinical findings, the clinical impression, or a referred diagnosis by another physician. The 2008 World Health Organization (WHO) classification provides good, general guidelines for the application of immunophenotype, cytogenetic, and molecular genetic studies in the classifications of these neoplasms. However, individual cases of acute leukemia may sit on the edge of these guidelines, resulting in questions if not confusion regarding the correct diagnosis. For example, the significance of aberrant expression of relatively lineage-specific markers by acute leukemia remains a confusing topic. On another front, the two most important factors that predict the favorable treatment response of a patient with ALL are cytogenetic and molecular genetic findings and early response to treatment. These are most conveniently followed by minimal residual disease (MRD) studies that also pose additional questions, such as when the bone marrow of a patient in clinical remission has morphologically observable lymphoid-like blasts in the bone marrow. This chapter addresses some of these issues by way of case presentations. We tried to avoid presenting diagnostic and classification information that is readily available in the 2008 WHO and other texts as well as readily available online from many sources.

Case study 1.1

The first case involves a patient with a provisional diagnosis of viral infection, but a review of a peripheral blood smear raises questions about the provided clinical diagnosis.

History

A 16-year-old male presents with fever and arthralgia. A complete blood count (CBC) shows anemia and elevated white blood cell (WBC) count with many atypical mononuclear cells. The physician's impression was a viral infection, and she refers the patient for hematology consult. Physical examination is significant for questionable splenomegaly and cervical lymphadenopathy. A repeat CBC shows a WBC of 56,000/μL normocytic anemia with hemoglobin (Hgb) of 8.5 g/dL and a platelet count of 128,000/μL. There is absolute neutropenia. Peripheral blood and bone marrow aspirate smears are reviewed. The marrow was very difficult to aspirate and on examination consisted of peripheral blood and no marrow particles.

1. Which of the following are possible diagnoses based on the clinical history, the CBC, and the cells shown in Figures 1.1 and 1.2? (Choose all that may apply)

A. Reactive lymphocytosis
B. Large granular lymphocytic leukemia (LGLL)
C. Granular acute lymphoblastic leukemia (granular ALL)
D. Acute myeloid leukemia (AML)

The cells shown have features of blasts with a high nuclear-to-cytoplasmic ratio with finely dispersed nuclear

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

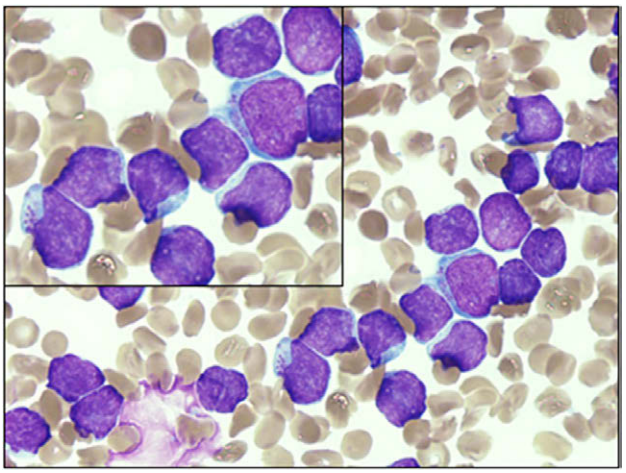


Figure 1.1 Peripheral blood smear. A monomorphous population of abnormal cells predominates in the peripheral blood. The insert shows azurophilic granules in the cytoplasm of several of these cells. Wright-Giemsa, 50×; insert, 63×. (Color plate 1.1)

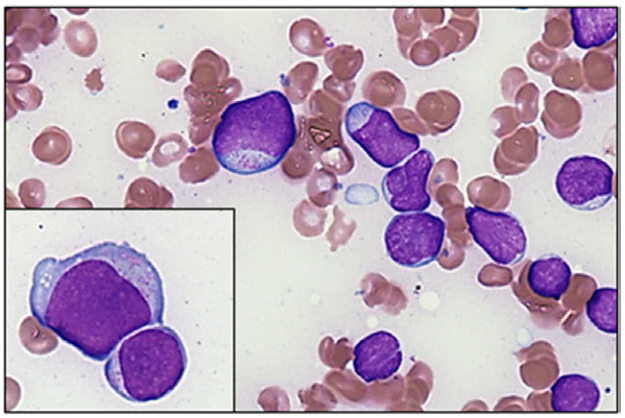


Figure 1.2 Bone marrow core biopsy touch preparation. Touch imprints of the bone marrow core biopsy substituted for a suboptimal bone marrow aspirate specimen. The marrow is involved with the same abnormal cells present in the peripheral blood. The insert shows two cells containing azurophilic cytoplasmic granules. Wright-Giemsa, 63×; insert, 100×. (Color plate 1.2)

chromatin. The presence of azurophilic cytoplasmic granules raised the possibility of LGLL, AML, and an uncommon subtype of acute lymphoblastic leukemia (ALL) called granular ALL. Large granular lymphocytes (LGLs) are a normal cell type in healthy individuals that may be of T- or NK-cell lineage. They have relatively large amounts of clear cytoplasm with a few, small azurophilic granules; acentric nuclei; and no nucleoli. LGLL, a relatively rare chronic leukemia of LGL cells, may be confused with acute leukemia. Although patients with LGLL may present with neutropenia and/or thrombocytopenia, the WBC count is usually normal with relatively few leukemic lymphocytes. The leukemic cells of LGLL rarely replace normal hematopoietic elements at initial diagnosis. Reactive lymphocytes are frequently mistaken for leukemic blasts in that they usually are large and frequently contain one or several nucleoli. However, they lack cytoplasmic granules and have intensely basophilic cytoplasm and dense, coarse nuclear chromatin. It would be unusual to see an abnormally high WBC count or normal marrow hematopoietic elements largely replaced by reactive lymphocytes. A rare exception may be a rare immune-compromised individual with a viral infection.

The more pressing question is whether the cells pictured are myeloblasts of AML or lymphoblasts of granular ALL. An experienced morphologist may be able to distinguish between these two acute leukemias by their cytologic features but will always confirm the initial impression by additional laboratory studies. Cytochemical stains for myeloperoxidase and Sudan black will differentiate between these leukemias, but they have been replaced by more informative FC immunophenotype studies. We recommend that routine cytochemical studies of acute leukemia be abandoned.

The histograms of a flow cytometry immunophenotype study of the peripheral blood are shown in Figure 1.3.

2. What is the lineage of the leukemia based on the studies shown in Figure 1.3?

A. B-cell
B. T-cell
C. Myeloid
D. Mixed-lineage leukemia

The studies shown in Figure 1.3 contain sufficient information to differentiate AML from ALL. In our experience, the minimum number of markers to identify the lineage of over 95% of acute leukemias is shown Figure 1.4. These are markers that are lineage restricted in normal hematopoiesis and lymphopoiesis. However, many acute leukemias do not follow the norm, and they frequently express markers of another lineage. For example, many AML express lymphoid antigens, as discussed later. Well-versed hematologists will be familiar with these 10 lineage markers and their application and limitations in assignment of a cell lineage.

The blasts of the patient express B-associated surface CD19 and CD22 plus cytoplasmic CD79a, but not T-associated CD7 or cytoplasmic CD3 and no myeloperoxidase (MPO). By the criteria of the WHO classification of acute leukemia,

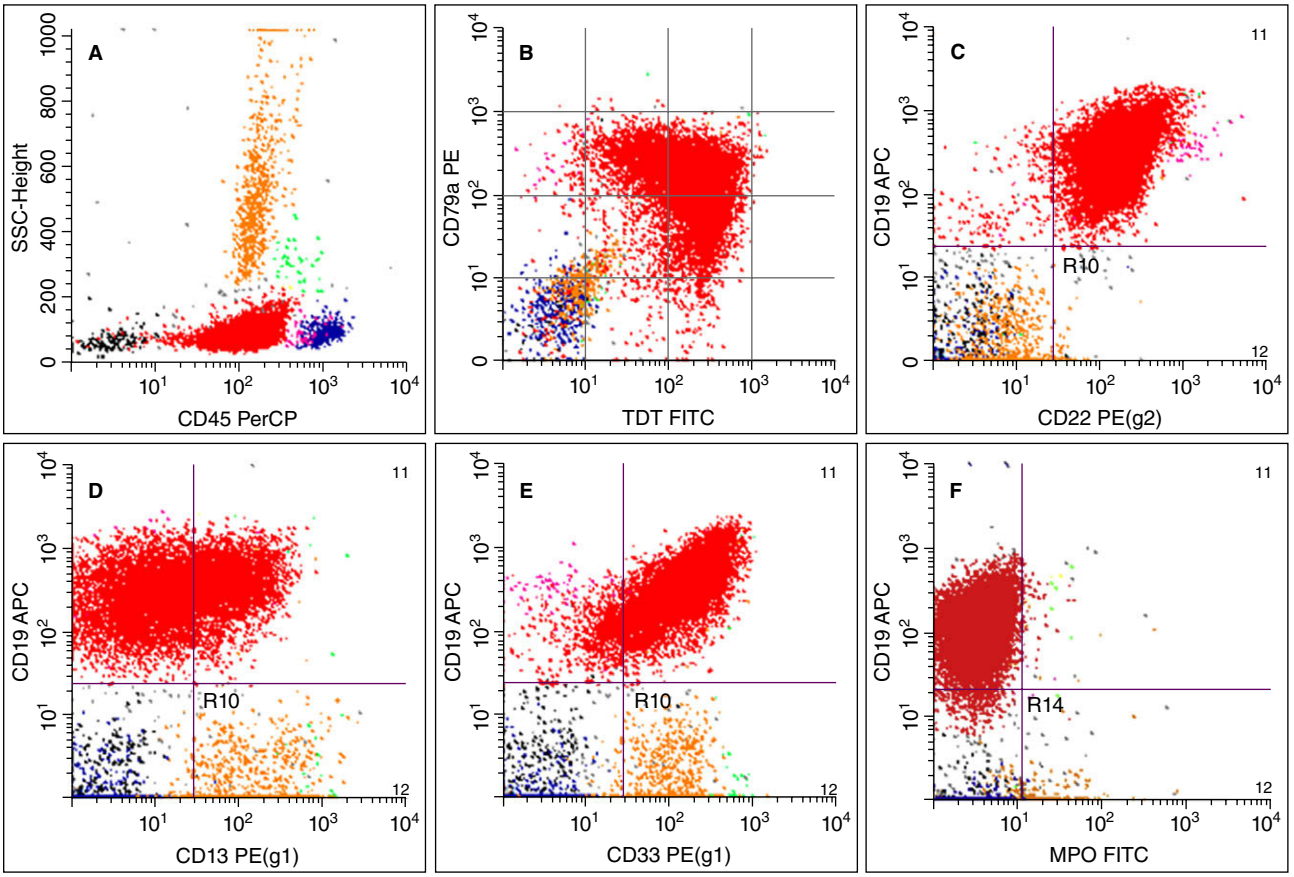


Figure 1.3 Flow cytometry immunophenotype study of the peripheral blood. The largest cluster of dots in frames A–F represents the abnormal cells shown in Figure 1.1. The smaller clusters and scattered dots represent mature lymphoid, monocytic, and granulocytic elements. Frame A shows the abnormal cells occupying the region of the histogram normally occupied by blasts and immature cells. Frame B shows these same cells co-expressing B-cell-associated cytoplasmic CD79a and blast-associated TDT (terminal deoxynucleotidyl transferase). The cells located in the lower left quadrant of frames C, D, E, and F are negative for the markers indicated on the x- and y-axes. SSC, side light scatter (a measure of internal cell complexity or granularity); MPO, myeloperoxidase. PerCP, FITC, PE, and APC are fluorochromes conjugated to antibodies used to identify cell antigens. (Color plate 1.3)

this patient has a precursor B-cell ALL. The immunophenotype excludes a T- or NK-cell LGLL. The patient's leukemic blasts also weakly express myeloid-associated CD13 and CD33; however, by WHO criteria, this patient does not have a mixed-phenotype acute leukemia (MPAL) since no myeloperoxidase is detectable and two largely but not totally B-cell restricted markers CD22 and CD79a are present. A descriptive immunophenotype diagnosis would be "precursor B-cell lymphoblastic leukemia with atypical expression of myeloid-associated CD13 and CD33." Up to 60% of precursor B-cell ALLs may express one or more myeloid-associated antigens, including CD13, CD15, CD33, and CD66c. The presence of one or more of these myeloid markers is not associated with a poor treatment response. However, if myeloperoxidase is detected in blasts that express CD19 or CD22 plus CD79a, the patient's leukemia would qualify as an MPAL. Most of these patients have a poor overall survival.

Precursor B-cell lymphoblastic leukemia can be further subclassified according to stages of normal B-cell maturation. These include Pro-B, Pre-B, Late Pre-B, and Transitional-B ALL. They are differentiated by their expression pattern of immunoglobulin heavy and light chains, as shown in Table 1.1.

(*Continued*)

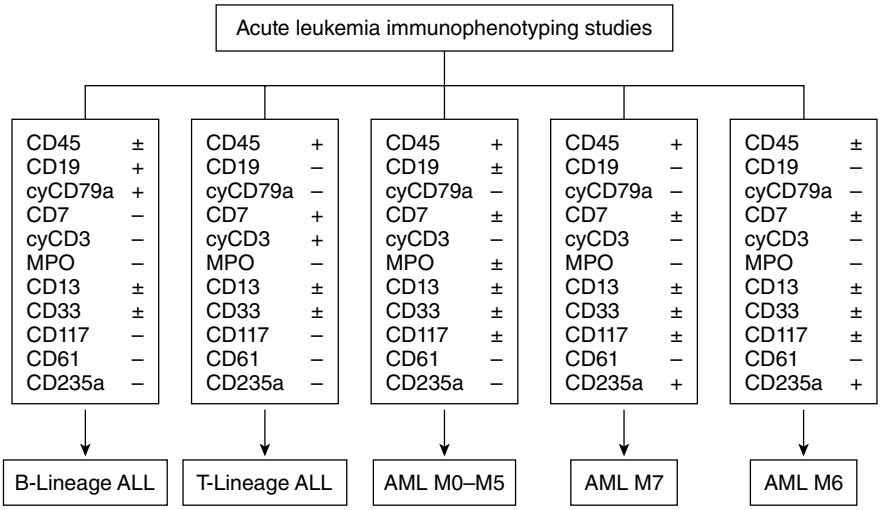


Figure 1.4 Algorithm for assigning the cell lineage to acute leukemias based on the expression of B-, T-, and myeloid-associated markers. A panel of 10 markers allows for the lineage assignment of over 95% of acute leukemias. Lineage associations of markers: (1) pan-leukocyte: CD45; (2) B-lineage: CD19 and CD79a (CD22 may be substituted for CD79a); (3) T-lineage: CD3 and CD7; (4) myeloid lineage: CD13, CD33, myeloperoxidase (MPO), and CD117 (CD117 is a common marker of myeloblasts, rarely expressed by T-cell acute lymphoblastic leukemia (ALL)); (5) erythroid: CD235a (glycophorin A); and (6) megakaryocytic: CD61. cyCD3, cytoplasmic CD3; cyCD79a, cytoplasmic CD79a, AML, acute myeloid leukemia; M0–M7, subtypes of the French-American-British (FAB) Classification of AML.

Table 1.1 Four subtypes of B-cell acute lymphoblastic leukemia (ALL) with their marker expressions.

ALL subtype	Marker						
	CD19	**CD79a**	**CD10**	**cyIgμ**	**sIμ**	**sIgκ**	**sIgλ**
Pro-B	+	+	+/−	−	−	−	−
Pre-B	+	+	+	+	−	−	−
Late pre-B[1]	+	+	+	+	+	−	−
Mature B[2]	+	+	−/+	+	+	*	*

cyIgμ, cytoplasmic mu heavy chain; sIgμ, surface mu heavy chain; sIgκ, surface kappa light chain; sIgλ, surface lambda light chain; +, positive; −, negative; +/−, usually positive; −/+, frequently negative.
*Either kappa or lambda expressed, but not both.
[1]Late pre-B-ALL blasts express surface Igμ bound to pseudo-lambda light chains (CD179a or CD179b).
[2]The mature-B-ALL subtype is uncommon and not the same as the leukemic phase of Burkitt lymphoma. Lymphoblasts express surface IgM (immunoglobulin mu heavy chains bound to either kappa or lambda light chains) plus CD34 and/or terminal deoxynucleotidyl transferase, and do not have a rearranged c-*MYC*.

3. Is the subclassification of precursor B-cell lymphoblastic leukemia, as shown in Table 1.1, useful in predicting a patient's response to treatment? Can you defend your answer?

A. Yes
B. No

Early studies of marker profiles of B-cell ALL showed a favorable patient treatment outcome for patients with common ALL (i.e., Pro-B ALLs that express CD10 or so-called common ALL antigen (CALLA)). By contrast, patients with pre-B fared less well. Subsequent investigations that included cytogenetic abnormalities or that placed patients on more intensive treatment regimens negated the importance of these subtypes. Furthermore, these studies showed that pediatric patients with leukemias that do not express CD10 usually have translocations involving *MLL* on chromosome 11q23 such as t(4;11)(q21;q23) or t(11;19)(q23;p13),

translocations associated with poor patient outcomes. Similarly, a quarter of patients with pre-B-ALL who lack CD34 have a t(1;19)(q23;p13), a translocation that requires more intensive treatment for a sustained remission.

If the peripheral blood and marrow aspirate specimens have a high blast count, the core biopsy offers little if any additional information. In fact, it is very difficult to distinguish blasts from other immature hematopoietic elements and, not infrequently, normal bone marrow lymphocytes. In our experience, the leukemia immunophenotype varies little between the blood and bone marrow. There may be minor losses or gains of CD10, CD20, CD34, and aberrant markers such as CD13 and CD33. However, the yield of cytogenetic abnormalities may be higher in marrow specimens. In our experience, up to 20% of pediatric patients with ALL may have bone marrows that cannot be aspirated or have "dry-taps." These same patients also tend to have no or very few peripheral blood blasts.

4. Are difficult aspirates or "dry-taps" of bone marrow involved with ALL due to reticulin fibrosis?

A. Rarely
B. Usually

The bone marrows of cases of ALL with "dry-taps" usually show total replacement of normal hematopoietic precursor elements but little if any significant increase of reticulin fibers. One plausible hypothesis for the dry-tap is that the leukemic blasts bind to each other due to high levels of cell surface adhesion molecules. However, studies to support this explanation are difficult to perform on formalin-fixed core biopsies. In our experience, patients with a dry-tap frequently have very few and sometimes no circulating lymphoblasts. In those patients, a core biopsy is essential for immunophenotype, cytogenetic, and molecular studies. Immunohistochemistry using formalin-fixed paraffin-embedded core biopsies can be used to study multiple lymphoid and myeloid markers. These include blast-associated antigens CD10, CD34, CD117, and terminal deoxynucleotidyl transferase (TDT). Lineage-restricted markers include B-cell-associated CD20, CD79a, and PAX5; T-cell markers CD2, CD3, CD5, and CD7; and myeloid-associated CD33, CD68, CD163, myeloperoxidase (MPO), and lysozyme. Cytogenetic, molecular genetic, and FC immunophenotype studies can be performed on cells teased out of a core biopsy.

Cytogenetic studies of this patient's marrow show a hyperdiploid karyotype, 55XY, with extra chromosomes 4, 10, 21, and others. The patient was begun on ALL chemotherapy with an excellent response. However, at approximately 18 months, the patient failed to show for a follow-up clinic visit. At 21 months post induction, the patient was seen and noted to have a low normal WBC count with a mild neutropenia and 2% blasts on morphologic exam of a peripheral blood smear. A bone marrow aspirate showed 20% blasts and 10% "atypical" lymphocytes. Myelopoiesis was slightly left-shifted, with a slight increase of erythropoiesis and megakaryopoiesis. Many of the late-stage erythroblasts demonstrated mild megaloblastoid changes and nuclear budding.

5. Which *one* of the following choices is most likely in this patient? Can you defend you impression based on the information above?

A. Early relapse of ALL
B. Early myelodysplastic syndrome, secondary to treatment
C. Relapse leukemia, suggestive of lineage switch to AML
D. Normal hematopoietic and lymphoid regeneration following chemotherapy

The marrow finding and the clinical history are most suggestive of normal hematopoietic and lymphoid regeneration following chemotherapy. Patients with hyperdiploid karyotypes with extra chromosomes 4 and 10 have an excellent therapy response of over 90% if they complete therapy. Given the patient's cytogenetic finding at diagnosis and excellent response to chemotherapy, an impression of early relapse of ALL would not be our first choice. The myeloid, erythroid, and megakaryocyte features are typical of a regenerating marrow at the end of therapy. If therapy is interrupted during maintenance, the preceding lymphoid and myeloid changes may also be observed. The development of myelodysplastic syndrome or AML in a patient with low-risk ALL before the completion of therapy would be highly unusual except for patients with chromosomal translocations involving *MLL*. However, with this all said, one must exclude early relapse by some other means. You have two options: a cytogenetic study to look for cells with a hyperdiploid karyotype and FC to detect abnormal lymphoblasts. Both studies were performed. Cytogenetics showed 46XY, and Figure 1.5 shows the histograms of the bone marrow FC study. The presence of three distinct B-lymphoid populations (Figure 1.5, populations 1, 2, and 3 in frame A) with different CD45 intensities is consistent with B-cell lymphoid regeneration. Frames B–F of Figure 1.5 show progressive B-cell maturation as indicated by the direction of the arrows. Cells in population 1 (light blue dots) are pro-Bs or lymphoblasts that express CD34, TDT, and CD10. Pre-Bs that have lost CD34 and TDT are present in population 2 (dark blue dots). Population 3 cells (red dots) are mature B-cells that express normal amounts of CD20 but not CD10. Further, none of the three populations express myeloid-associated CD13 or CD33, as noted at diagnosis. The final interpretation was "remission with hematopoietic and lymphoid regeneration."

(*Continued*)

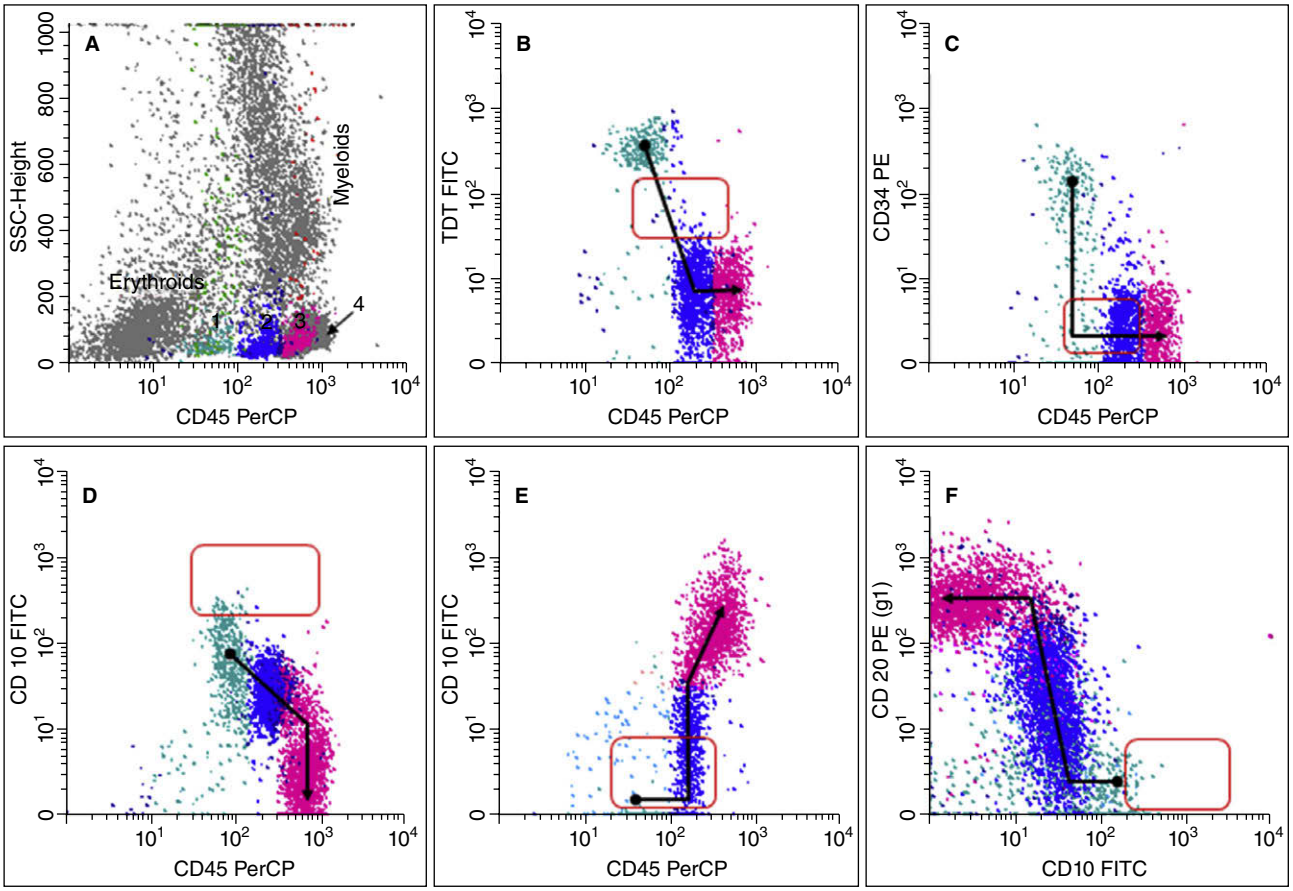


Figure 1.5 Flow cytometry immunophenotype study of the bone marrow aspirate at 18 months post induction chemotherapy. The dark gray dots represent CD19-positive B-cells. Frame A shows the relative positions of these three cell populations; they are labeled 1, 2, and 3, relative to their intensity of CD45 expression. Mature T-lymphocytes are located in the area labeled "4." Frames B, C, D, and E show the marker expression of TDT (terminal deoxynucleotidyl transferase), CD34, CD10, and CD20 based on their CD45 expression. Frame F is different in that it shows the intensities of CD10 versus CD20 for the three B-cell populations. The arrows indicate the direction of increasing B-cell maturation. A review of frame A of Figure 1.3 shows where the leukemic blast would be expected to be in a two-parameter histogram of CD45 versus side light scatter (SSC). The open rectangles are where the patient's leukemic blasts would be located based on studies prior to the start of therapy. (Color plate 1.4)

Bone marrows of patients who interrupt their maintenance therapy and marrows of patients one to several months post completion of therapy will have a vigorous regeneration of B-cell lymphopoiesis. Normal lymphoblasts and immature lymphocytes may constitute up to 30% to 40% of the marrow elements, and it is normal to find lymphoblasts and immature lymphocytes in the peripheral blood. The marrow frequently shows increased megakaryopoiesis and erythropoiesis with mild dyspoietic erythroid changes, as noted in this patient.

Case study 1.2

This case highlights the value of precision FC studies and an appreciation of their limitations.

A 20-year-old male seeking to donate blood was told that his hemoglobin level was too low to donate and was referred to a hematologist. Other than some mild fatigue on exertion, he had no other complaints. His physical exam was normal. Laboratory studies showed Hgb of 7.5 g/dL, WBC of 19,400/mL, and platelets of 137,000/mL.

1. Based on the blast features in Figure 1.6, what is the diagnosis? Choose the *one* best diagnosis from the following.

A. Acute lymphoblastic leukemia (ALL)
B. Atypical reactive lymphocytosis
C. Acute myeloid leukemia (AML)
D. Acute megakaryoblastic leukemia (AML M7)

Although we no longer advocate for the use of cytochemical studies, a myeloperoxidase (MPO) stain was performed in this case prior to FC analysis. The large blasts shown in Figure 1.6 stain positive for MPO, and without additional studies or information, a diagnosis of AML appears appropriate. However, additional immunophenotype studies by flow cytometry show that the small *and* large blasts express CD34, myeloperoxidase (MPO), B-lineage-associated CD22 and CD79a, plus myeloid-associated CD13 and CD33 (see Table 1.2).

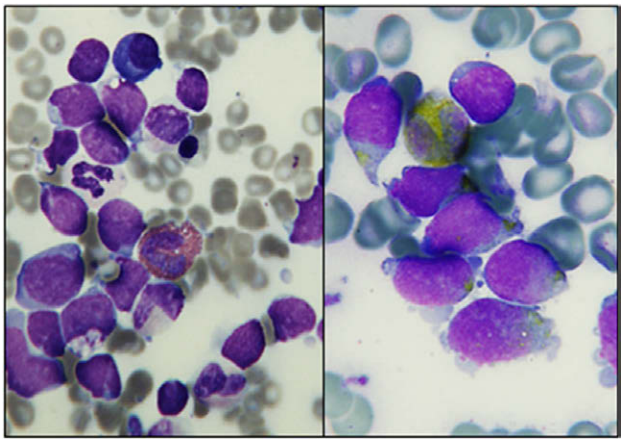


Figure 1.6 Images of stained bone marrow aspirate smears are shown in two frames. The left frame is a Wright-Giemsa-stained smear showing that the majority of marrow cells are a mix of small and large blasts. The right frame is a cytochemical stain for myeloperoxidase (MPO) using o'toluidine as the detecting agent. A color reaction product indicates the presence of MPO. Note the presence of MPO in a metamyelocyte and weak, focal MPO positivity in several of the blasts. By differential count, >20% of blasts are weakly positive for MPO. Left frame, 40×. Right frame, 100×. (Color plate 1.5)

2. Based on the flow cytometry immunophenotype study results presented in Table 1.2, which one of the following is the most appropriate diagnosis?

A. Mixed-phenotype acute leukemia (MPAL)
B. Acute myeloid leukemia (AML)
C. Acute undifferentiated leukemia (AUL)
D. Acute bilineal leukemia (ABL)

One of the most common requests of the hematopathologist is for clarification in distinguishing among the leukemias listed in this question. The 2008 WHO classification of acute leukemias lists the category of acute leukemias of ambiguous lineage (ALAL). This category includes MPAL, acute undifferentiated leukemia or acute leukemia of uncertain lineage (blasts lack lineage-specific antigens), and acute bilineal leukemia (two or more coexisting distinct blast populations of different lineages). The patient's leukemia fulfills the WHO criteria for MPAL in that his leukemia blasts co-express B-lineage and myeloid-lineage antigens. Less than 5% of all leukemias in children and adults are ALAL, and of these, the vast majority are MPALs.

The 2008 WHO monogram details fairly well the immunophenotype criteria for MPAL. However, in our experience no two cases of MPAL are alike in their marker profiles regarding the number of blasts co-expressing markers of two

Table 1.2 Expression myeloid- and lymphoid-associated markers by leukemic blasts in Case study 1.2.

Marker	Lineage association[1]	B-ALL	T-ALL	AML	Patient
CD45	Pan-leukocyte	+(−)[2]	+	+	+
CD19	Pan-B	+	−	− (+) +	
CD22	Pan-B	+	−	−	+
cyCD79a	Pan-B	+	− (+)	− (+) +	
CD7	Pan-T	−	+	− (+)	−
cyCD3	Pan-T	−	+	−	−
CD13	Myeloid, monocytic	− (+)	− (+)	+/−	+
CD33	Myeloid, monocytic	− (+)	− (+)	+/−	+
CD117	Myeloid, monocytic	−	−[3]	+/−	−
MPO	Myeloid, monocytic	−	−	+[4]	+

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; cyCD79a, cytoplasmic CD79a; cyCD3, cytoplasmic CD3; MPO, myeloperoxidase; +, positive; −, negative; −/+, positive in >70% of cases; −(+), usually negative but weakly expressed in up to 30% of cases.

[1]Expression by nonneoplastic leukocytes.

[2]Up to 10% of cases of B-cell ALL do not have detectable CD45.

[3]Expressed by some early pre-T ALL (less than 5% of all T-cell ALL).

[4]Not expressed in acute megakaryoblastic leukemia; negative in some acute monocytic leukemias.

(*Continued*)

different lineages and the intensities of expression of those markers. So you, as the oncologist, would want to be reassured of the criteria used by the hematopathologist for calling something positive. These finer criteria are not defined by the WHO monogram or by most texts. The oncologist should consult a hematopathologist with extensive FC experience and a thorough knowledge of its limitations when rendering an interpretation of MPAL. Furthermore, that hematopathologist should have studied more than just a few cases of ALAL. For purposes of this case discussion and in the simplest of terms, MPAL is diagnosed when it is clearly demonstrated that there is co-expression of lineage-specific lymphoid plus MPO by the leukemic blasts. This is true of the blasts of this patient. Though not intentional, the WHO classification further complicates matters by subgrouping MPAL based on cytogenetic abnormalities.

3. Which one of the following abnormal cytogenetic findings is not associated with ALAL?

A.	t(6;9)(p23;q34)	*DEK–NUP214 (CAN)*
B.	t(9;22)(q34;q11.2)	*BCR–ABL1*
C.	t(11;19)(q23;p13.3)	*MLL–ENL(MLLT1)*
D.	t(9;11)(p22;q23)	*MLLT3–MLL*
E.	t(4;11)(q21 ;q23)	*AF4(MLLT2)–MLL*

The WHO classification further subgroups MPAL based on the presence of chromosomal translocations of *MLL*, including t(4;11), t(9;11), and t(11;19); *BCR-ABL1*; or the absence of these translocations. If one of these translocations is absent, MPAL is further subclassified by immunophenotype results as follows: (i) T/myeloid, not otherwise specified (NOS); (ii) B/myeloid, NOS; and (iii) MPAL, NOS—rare types. One can consult the 2008 WHO monogram for more information on the diagnostic criteria for these subgroups.

Cytogenetic study of the patient's leukemia shows a *BCR–ABL1* translocation.

4. What other studies may be helpful in this case? Why?

Following the disappearance or persistence of *BCR–ABL1* transcripts by quantitative reverse transcription polymerase chain reaction (RT-PCR) or real-time quantitative PCR (RQ-PCR) is highly desirable for following the patient's response to treatment. Thus, an initial baseline quantitative *BCR–ABL1* transcript value followed by regularly monitored levels will be the single most important test for monitoring the patient's leukemia status. Studies for MRD by flow cytometry immunophenotyping may also be performed, but we do not recommend this duplication of effort if quantitative RQ-PCR is being performed. Likewise, karyotyping studies with a sensitivity of approximately 10^{-2} should not be performed if PCR studies are available. Recent reports indicate that adding imatinib mesylate or similar agents to the therapeutic regimen of patients with acute leukemias harboring *BCR–ABL1* is beneficial.

Case study 1.3

The diagnosis and management of a patient with a large leukemia burden at diagnosis are discussed from a clinical laboratory point of view. The following discussions highlight the value of FC for identifying an unfavorable subtype of T-cell ALL and detecting small numbers of leukemic cells in the marrow and other sites at diagnosis and following treatment.

History

A 35-year-old man is referred to Hematology service with a history of increasing shortness of breath and an anterior mediastinal mass. Physical examination is significant for supraclavicular lymphadenopathy. A CBC shows a marked leukocytosis with a WBC count of 96,000/μL and a manual differential of 85% blasts. The Hgb was 8.0 g/dL, and platelets were 100,000/μL. Normal bone marrow elements are replaced by blasts (Figure 1.7: frame A, Wright stain; frame B, myeloperoxidase stain). Peripheral blood was obtained for FC to establish the leukemia's lineage.

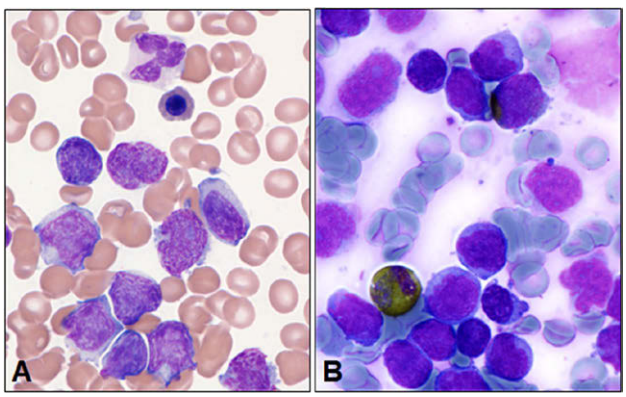


Figure 1.7 Cells of a bone marrow aspirate are shown in frames A and B. Frame A shows blasts, a neutrophil, and a late-stage erythroblast. Blasts resembling those in the peripheral blood comprise the majority of cells in the bone marrow. These blasts have monocytoid-like nuclear features but contain no cytoplasmic granules or Auer rods. Frame B is a cytochemical stain for myeloperoxidase (MPO) using o'toluidine. A single-band neutrophil is positive for MPO.
(Color plate 1.6)

1. Based on the flow cytometry studies in Figure 1.8A and 1.8B, which of the following leukemias is the patient's diagnosis?

A. Precursor B-cell ALL
B. Adult T-cell leukemia/lymphoma
C. Precursor T-cell ALL
D. Mixed-phenotype acute leukemia (MPAL), T/myeloid subtype

The absence of B-associated antigens excludes precursor B-cell ALL. Adult T-cell leukemia/lymphoma (ATLL) or HTLV-1 associated leukemia/lymphoma is composed of leukemic cells that correspond to mature T-cells. The presence of CD34 and CD117 on the leukemic blasts is indicative of an acute leukemia. The presence of CD7 plus cytoplasmic CD3 is diagnostic for T-cell lineage. The blasts also express myeloid-associated CD13 and CD33, but based on the criteria presented in Case study 1.2, this is not MPAL since there is no MPO. The co-expression of myeloid-associated markers by the blasts of T-ALL is less frequent than in B-cell ALL, but 25% of cases may express weak CD13 or CD33. Interestingly, up to 15% of cases may weakly express B-cell-associated CD79a but not B-cell-restricted PAX5 or CD22. A summary of the marker expression in Figure 1.8A and 1.8B plus several additional marker study results are shown in Table 1.3.

The additional information allows for subclassifying this patient's T-cell ALL. Classically, T-cell ALL was subclassified into three to five subtypes based on normal stages of T-cell maturation in the thymus. One such classification is listed in Table 1.4.

2. Based on the marker expression in Table 1.3 and the subclassification of T-ALL in Table 1.4, which one of the following choices best describes the patient's T-ALL?

A. Early pro-thymic T-ALL
B. Early thymic T-ALL
C. Common thymic T-ALL
D. Late thymic T-ALL

Early studies suggested that patients with common thymic T-cell ALL had a better overall survival rate than those with early or late thymic T-cell ALL. The expression of CD10 by T-ALL is associated with better overall survival in many studies but loses significance with improved treatment. More recently, a key investigation recognized a distinct entity of T-cell ALL that resembles early T-cell (ETC) precursors in the thymus. These ETC precursor cells retain stem cell–like features. These leukemias have a distinctive immunophenotype, $CD7^+$, $CD1a^-$, $CD8^-$, or CD5weak/$^-$, with one or more stem cell (CD34, CD117, or HLA-DR) or myeloid markers (CD11b, CD13, CD33, or CD65). These patients also have an ETP-related gene expression signature. Patients with this form of leukemia had a "high risk of remission failure or hematologic relapse."

3. Based on the immunophenotype profile of this patient, would you consider him a patient with ETP-ALL? If yes, what treatment options, if any, do you have?

Yes, the patient is an example of ETP-ALL. For this patient, the hematopathologist should be expected to provide up-to-date information on potential molecular studies that would allow for consideration of treatment options at time of relapse. For example, the above study identified a high recurring rate of mutations that affect three pathways associated with AML. Other studies show an association of *FLT3* mutations with ETP-ALL. It remains to be seen if therapies directed toward AML would be beneficial for patients with ETP-ALL.

4. What other two important studies have not yet been discussed for this patient?

Cytogenetics and cerebrospinal fluid (CSF). Abnormal karyotypes are identified by classical cytogenetics in 50% to 60% of T-ALL. The most common recurring abnormalities involve the alpha and delta TCR at 14q11.2, the gamma TCR at 7p14–15, and the beta TCR at 7q35. Cytogenetic study of the bone marrow of this patient showed 46XY, der(11)del(11)(p11.2p15) inv(11)(p11.2q22), which is not a recurrent cytogenetic abnormality in T-ALL.

Leukemic blasts can be identified in the CSF in up to 30% of patients at diagnosis. Those with central nervous system involvement are at higher risk of relapse, and thus every patient with T- or B-cell ALL must have their CSF examined for leukemic blasts. However, the detection of small numbers of blasts is very difficult by cytologic examination. In part, this is due to the apoptosis of leukemic blasts in CSF that is not examined shortly (within 1 hour) after the lumbar puncture procedure. Further, artifacts created by the cytospin preparation smear may result in non-neoplastic lymphocytes taking on the features of blasts or in blasts being lost by this methodology. FC immunophenotype study of CSF greatly improves the sensitivity and specificity of detection of small numbers of leukemic blasts. This patient's CSF fluid contained 5 WBC/μL with several questionable blasts as shown in Figure 1.9. A study of the CSF by FC detected a significant population of $CD3^+$ and TDT^+ leukemic blasts, as shown in Figure 1.10.

The detection of MRD in ALL following induction chemotherapy is a powerful prognostic indicator of treatment success. Levels of 10^{-2} to 10^{-3} at end of induction are highly correlated with risk of relapse and are independent of other clinical, cytogenetic, and molecular prognostic factors. Serial

(*Continued*)

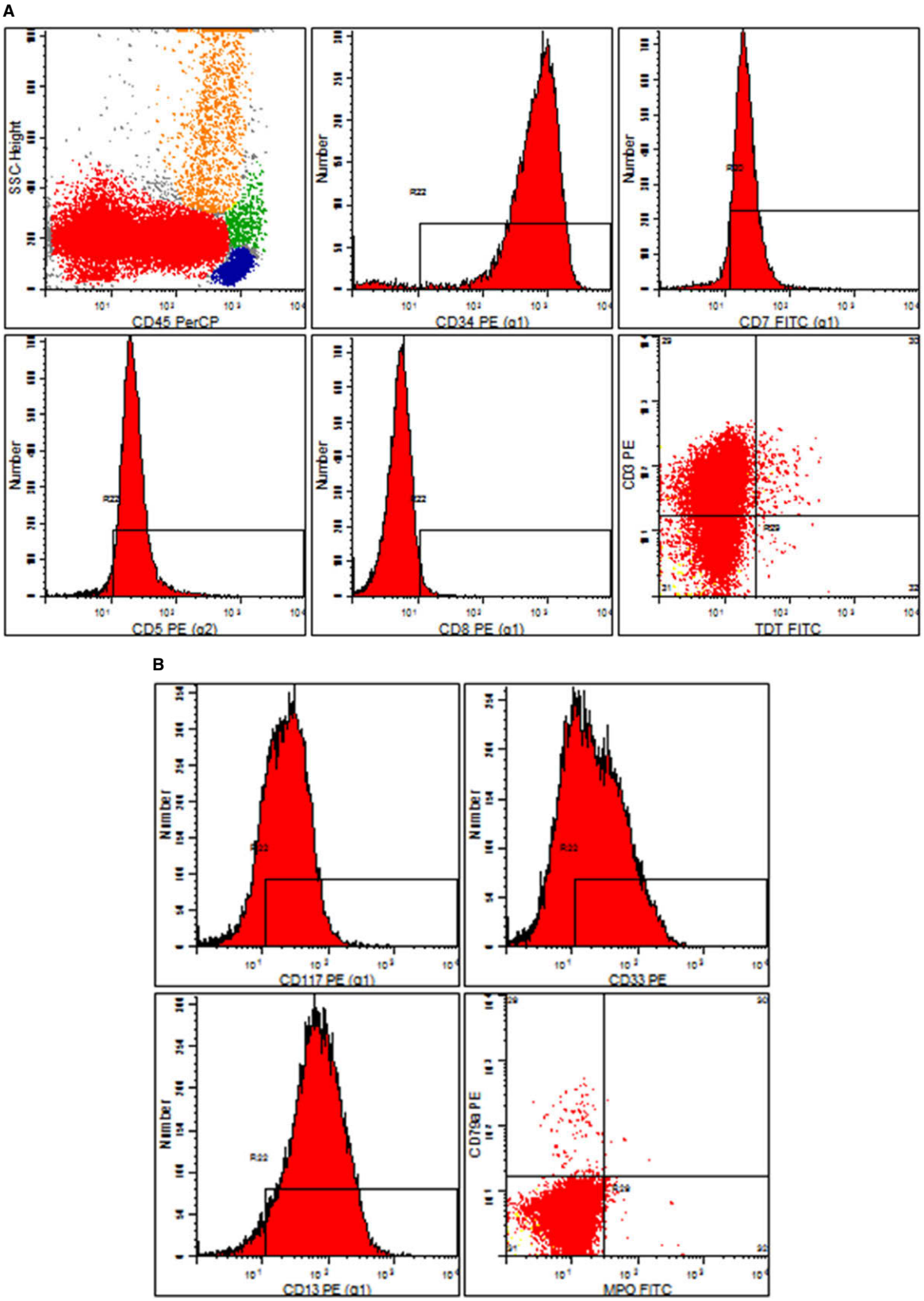


Figure 1.8 (A) Flow cytometry immunophenotype study of the peripheral blood. Marker expressions of the neoplastic blasts in the peripheral blood are shown in six representative histograms. The clusters of dots represent blasts, mature lymphocytes, monocytes, and granulocytes. The left upper frame of an SCC (side light scatter) versus CD45 histogram shows no to weak expression of CD45 by the blasts. The cells within the open black rectangles represent blasts that are positive for CD34, CD7, CD5, or CD8. For example, almost all blasts express CD34 but not CD8. As indicated by the lower right histogram, the blasts express weak cytoplasmic CD3 but not terminal deoxynucleotidyl transferase. (B) Flow cytometry immunophenotype study of the peripheral blood. The four frames show additional studies of CD117, CD33, CD13, myeloperoxidase (MPO), and CD79a expression by the leukemic blasts. Refer to Figure 1.8A for interpretation of positive or negative expression of these five markers. (Color plate 1.7)

Table 1.3 Marker expressions by the leukemia blasts in Case study 1.3.

Marker	Lineage Association	B-ALL	T-ALL	AML	Patient
CD45	Pan-leukocyte	+[1]	+	+	+
CD34	Blasts	+/−	−/+	+/−	+
TDT	Lymphoblasts	+	+(−)	−	−
CD117	Blasts	−	−[2]	+(−)	+
CD1a	Thymic T-cell	−	+/−	−	−
CD2	Pan-T; NK-cells	+	−	−	−
cyCD3	T-cells	−	+	−	+
CD3	T-cells	−	−/+	−	−
CD4	Helper T-cells	−	+/−	−	−
CD5	Pan-T cell	−	+[3]	−	−
CD7	Pan-T cell / NK-cells	−	+	− (+)	+
CD56	Cytotoxic T-cells and NK-cells	−	−/+	−/+	−
CD19	Pan-B cell	+	−	−[4]	−
cyCD79a	Pan-B cell	+	−[4]	−[4]	−
CD13	Myelo/monocytic	−/+	−/+	+ (−)	+
CD33	Myelo/monocytic	−/+	−/+	+ (−)	+
MPO	Myeloperoxidase	−	−	+ (−)	−

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; cyCD79, cytoplasmic CD79a; cyCD3, cytoplasmic CD3; TDT, terminal deoxynucleotidyl transferase; MPO, myeloperoxidase; +, positive; −, negative; +/−, positive in >70% of cases; − (+), usually negative, but weakly expressed in up to 30% of cases; + (−), usually positive, but negative in up to 30% of cases.
[1]Up to 10% of cases of B-cell ALL do not have detectable CD45.
[2]3% to 5% of T-ALLs express CD117.
[3]∼5% of T-ALLs do not express CD5.
[4]Weakly expressed in a minority of cases.

Table 1.4 Classification of T-ALL based on corresponding stages of normal thymic T-cell maturation.

Thymic stage	Marker expression								
	CD34	CD7	cyCD3	sCD3	CD5	CD1a	CD4	CD8	CD10
Early pro-T	+/−	+	+	−	+/−	−	−	+/−	−
Early-thymic	−	+	+	−	+	−	−	+/−	−
Mid-thymic	−	+	+	+/−	+	+/−	+/−[1]	+/−[1]	+
Late-thymic	−	+	+	+	+	−	+[2]	+[2]	−

[1]Co-expression of CD4 and CD8 is common.
[2]Either CD4 or CD8, but not both, is expressed.

measurements of MRD during treatment also provide prognostic information, but the timing of these measurements may be crucial, and further discussion is beyond what is possible here.

Studies for MRD by molecular methods target clone-specific B- and T-cell receptor rearrangements (e.g., IGH, IGK, TCRγ, and TCRβ) and chimeric fusion gene transcripts (e.g., *BCR–ABL1* and *AF4–MLL*). However, performance of these studies by RQ-PCR is laborious, difficult to standardize, and expensive. Thus, FC evaluation of MRD is often favored over molecular methodologies. Since almost all cases of ALL express atypical intensities and/or aberrant markers (i.e., markers of another lineage), MRD by FC is possible in over 95% of ALL during treatment. The sensitivity for MRD by FC approaches that of molecular means, with levels of 10^{-4} in most cases. However, this level of sensitivity requires the identification of atypical and/or aberrant antigen expression by the leukemic blasts at diagnosis. Performance of MRD by FC requires carefully designed methodologies and optimal specimens. Laboratories performing MRD should provide the validation and sensitivity of their methodology upon request.

(*Continued*)

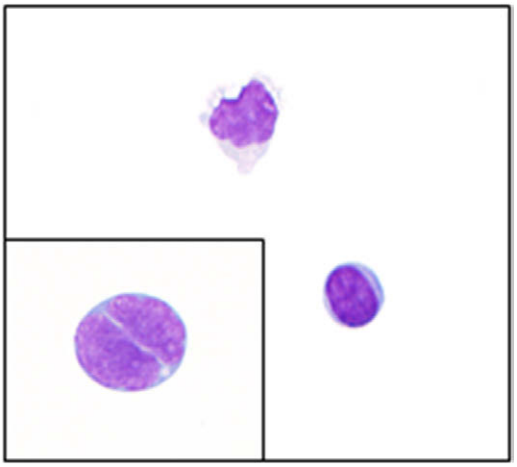


Figure 1.9 Images of a cerebrospinal fluid (CSF) cytospin preparation. No RBCs are present, indicating a clear "lumbar puncture" not contaminated with peripheral blood. The larger frame (40×) shows a small normal lymphocyte and monocyte. The inserted frame (100×) shows a blast form with a deeply indented nucleus and scant cytoplasm. Wright-Giemsa stain. (Color plate 1.8)

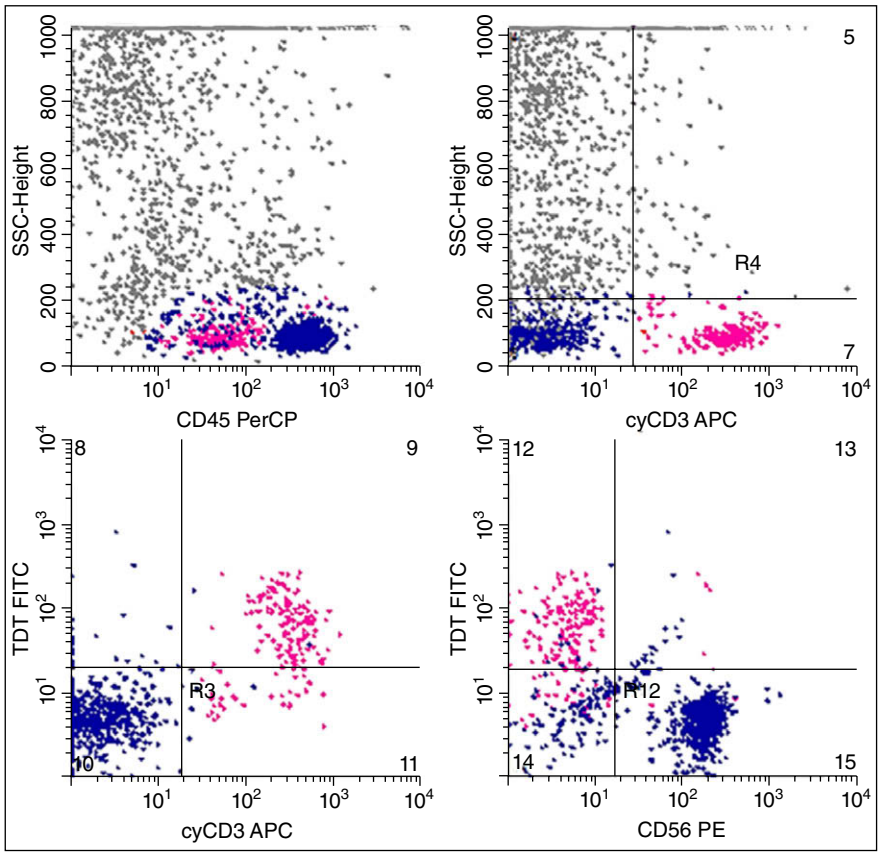


Figure 1.10 Flow cytometry immunophenotype study of cerebrospinal fluid (CSF). The upper left frame is a study of CD45 (common leukocyte antigen) intensity versus side light scatter (SSC). The blue dots are mature lymphoid elements. The pink dots are cells with weak or dim CD45 expression as is typical of blasts. The light-gray dots are dead cells and cellular debris. The other histograms represent studies of cytoplasmic CD3 (cyCD3 APC), terminal deoxynucleotidyl transferase (TDT FITC), and CD56 (CD56 PE), the latter being a marker of cytotoxic T-cells and NK-cells. The cells represented by the medium-gray dots co-express cytoplasmic CD3 and nuclear TDT (shown in the lower left histogram). Normal cerebrospinal fluid does not contain cells that co-express CD3 and TDT. (Color plate 1.9)

Case study answers

Case study 1.1

Question 1: Answer C and D
Question 2: Answer A
Question 3: Answer B
Question 4: Answer A
Question 5: Answer B

Case study 1.2

Question 1: Answer C
Question 2: Answer A
Question 3: Answer A

Case study 1.3

Question 1: Answer C
Question 2: Answer A

Selected readings

Coustan-Smith E, Mullighan CG, Onciu M, *et al*. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet. 2009;10:147–56.

Hoehn D, Medeiros LJ, Chen SS, *et al*. CD117 expression is a sensitive but nonspecific predictor of FLT3 mutation in T acute lymphoblastic leukemia and T/myeloid acute leukemia. Am J Clin Pathol. 2012;137:213–9.

Swerlow SH, Campo E, Harris HL, *et al*., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. IARC; Lyon; 2008.

Zhang J, Ding L, Holmfeldt L, *et al*. The genetic basis of early T-cell precursor acute lymphoblastic leukemia. Nature. 2012;481:157–63.

Zaremba CM, Oliver D, Cavalier M, *et al*. Distinct immunophenotype of early T-cell progenitors in T lymphoblastic leukemia/lymphoma may predict FMS-like tyrosine kinase 3 mutations. Ann Diagnostic Pathol. 2012;16:16–20.

CHAPTER 2

Prognostic markers and models in acute lymphoblastic leukemia

Dieter Hoelzer

University Hospital, Frankfurt am Main, Germany

Acute lymphoblastic leukemia (ALL) is not a uniform disease but is characterized by subgroups with different biological and clinical features and cure rates. They have prognostic impact for either the achievement of remission or the remission duration. There are two phases to evaluate prognostic factors: the first are the patient characteristics at diagnosis, and second is the response to treatment (Table 2.1). Pretherapeutic prognostic features are age, initial white blood cell count (WBC), immunophenotype, and abnormal cytogenetics or molecular genetics. Response parameters are achievement of complete remission (CR), now molecular remission (MolCR), and time to achieve a CR and MolCR. The aim of evaluating prognostic factors in ALL is to stratify patients into good and poor risk groups and to adapt different treatment strategies accordingly. The most important decision in adult ALL is, thereby, whether a patient should have a stem cell transplantation (SCT) in first remission or not.

Pretherapeutic prognostic markers

Age

- **What is the prognostic value of the age of an adult ALL patient, and what are the therapeutic implications?**
- **Is there a best age cut-off?**

Increasing age is undoubtedly associated with poorer outcome in all studies. The earlier defined age cut-off of 35 years was the best dichotomy in the survival curve, and was oriented on the age limit for allogeneic stem cell transplantation (allo-SCT) at that time. This age limit is still of relevance, but with a different therapeutic consequence; recently applied pediatric-inspired protocols for adolescents and young adults (AYAs) are applicable up to an age of 35 to 40 years, and beyond that are associated with an unacceptable toxicity. Patients older than this age limit have a substantially poorer outcome and an increasing incidence of adverse risk factors.

White blood cell count

- **Does WBC at diagnosis still have a prognostic impact?**
- **Is the WBC still of prognostic relevance with the cytogenetic and genetic markers now available?**

Elevated WBC at diagnosis (>30,000–50,000/ml) as a poor prognostic feature has been confirmed in various trials. It was even considered as the most deleterious prognostic factor in B-precursor ALL with overall survival of 19–29%. The biological reason for the highly resistant behavior of B-precursor ALL with high WBC is unclear. Probably in the future, additional molecular markers can help to clarify the underlying mechanisms. Due to the high relapse rate evaluation of minimal residual disease (MRD), the use of experimental drugs and SCT modalities seems particularly important.

Cytogenetic and genetic markers

- **Are cytogenetic and genetic markers relevant for treatment decisions?**

Yes, absolutely. Philadelphia chromosome–positive ALL with the t(9;22) translocation and the BCR–ABL fusion transcript is the most frequent cytogenetic abnormality in adults, which accounts for 25% of all adult B-lineage ALLs, with a strong age-related incidence, increasing from <3% in children up to 40–50% in adults aged >50–60 years. Ph+ ALL was so far the poorest ALL subtype, with a CR rate of ~70% and a survival rate at 5 years of <10% with chemo

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 2.1 Prognostic factors for risk stratification of adult acute lymphoblastic leukemia (ALL)[1].

	Good	Adverse	
Pretherapeutic		**B-lineage**	**T-lineage**
Clinical parameters			
• Age	**<35 years old**	**>35 years > 55 years > 70 years**	>100,000/μl (?)
• White blood cell count	**<30,000/μl**	**>30,000/μl**	
• Organ involvement[3]			
Immunophenotype	Thymic T	**Pro-B (CD10−)**	Early T (CD1a−, sCD3−)
		Pre-B (CD10−)	Mature T (CD1a−, sCD3+)
Cytogenetics, molecular genetics, and gene expression profiles	TEL–AML1 (?)	**t(9;22)/BCR–ABL**	HOX11L2[2] (?)
	HOX11[2] (?)	**t(4;11)/ALL1–AF4**	CALM–AF4[2] (?)
	NOTCH1[2] (?)	t(1;19)/E2A–PBX (?)	Complex aberrations (?)
	9p del (?)	Complex aberrations (?)	Low hypodiploid or near tetraploid (?)
	Hyperdiploid (?)	Low hypodiploid or near tetraploid (?)	
Treatment response			
Prednisone response	Good	Poor	
Time to complete remission	**Early**	**Late (>3–4 weeks)**	
MRD after induction	**Negative < 10^{-4}**	**Positive > 10^{-4}**	

[1]Generally accepted factors are printed in **bold**.
[2]Overexpression of genes.
[3]Organ involvement, particularly central nervous system involvement, and mediastinal tumors have lost their adverse impact with recent treatment strategies.
MRD, minimal residual disease.

and <30% with allo-SCT. Targeted therapy with tyrosine kinase inhibitors (TKIs) directed against the BCR–ABL fusion transcript has changed the perspective completely; CR rates are now >90% and survival >50%. This demonstrates convincingly that prognostic factors are changing with therapy, and thus risk group stratifications and treatment algorithms need constant refinement.

Immunophenotype

Immunologic subtypes are not only associated with different clinical presentations but also partly associated with distinct cytogenetic and/or molecular aberrations and with prognosis. The expression of surface antigens is of increasing importance for targeted therapy with monoclonal antibodies.

• Is there a difference in the prognostic impact of B-lineage ALL versus T-lineage ALL, and is it justified to have different treatment approaches?
The earlier observed adverse prognostic impact of T-lineage ALL compared to B-lineage ALL has disappeared.

• Within the B-lineage or T-lineage ALLs, are there subgroups with a different prognosis?

Pro-B-ALL/t(4;11)

Pro-B-ALL patients, where in most but not all cases the t(4;11) translocation can be detected, are considered high-risk patients in nearly all trials. They apparently benefit from high-dose cytarabine-based regimens and SCT as reported from the German Multicentre ALL (GMALL) studies. CD10-negative pre-B-ALL has been identified as a subgroup with similar adverse features as pro-B-ALL.

In B-lineage ALL patients, those with pro-B-ALL, defined as CD10-negative—mostly associated with the cytogenetic aberration t(4;11)—have an inferior outcome compared to those with pre-B and common ALL, but will benefit from an allo-SCT in CR1.

Common and pre-B-ALL

Within this B-lineage ALL, a variety of targeted monoclonal antibody therapies directed against surface antigens (e.g., CD20, CD19, and CD22) have developed and are under investigation.

• Is antigen expression by itself a prognostic marker?
The question arises of whether antigen expression itself within an immunologically defined subtype is a prognostic

marker. CD20 expression, observed in ~40% of adult pre-B-ALL and common B-ALL, seemed to have an adverse prognostic impact, being probably age related, but the data are controversial, and recently it has been shown not to have an adverse impact at least in childhood ALL. Also, the improved outcome of CD20-positive B-lineage ALL receiving anti-CD20 moAb (rituximab) has already overcome the potential adverse influence.

• Are cytogenetic and molecular markers overcoming the prognostic impact of an immunophenotype?

T-lineage ALL

T-ALL comprises the subtypes early T-ALL, thymic (cortical) T-ALL, and mature T-ALL, which was the most relevant prognostic factor for T-ALL in the GMALL studies.

There is a strong correlation of outcome to the immunophenotypic subtypes cortical-thymic T-ALL versus early T-ALL or mature T-ALL. Thymic T-ALL is CD1a-positive and constitutes about half of adult T-ALL patients; their survival at 5 years is >50–60%. The subtypes early T-ALL and mature T-ALL have a lower rate of CR and a poorer survival; both subtypes profit from an allo-SCT in CR1.

• Are genetic markers in T-lineage superseded by the prognostic impact of the immunophenotypic T-ALL subtypes?

It seems that the relevance of immunophenotype is even underlined by genetic markers; in fact, the overexpression of HOX11, HOX11L2, SILTAL1, and CALM–AF10 is associated with subtypes, that is, maturation states of thymocytes.

Some groups observed inferior outcomes for early T-ALL: coexpression of CD13, CD33, and/or CD34; a high expression of the transcription factors ERG and/or BAALC; and overexpression of HOX11L2 and SILTAL-positive ALL. Low expression of ERG and BAALC was associated with favorable outcome as well as overexpression of HOX11, which is associated with thymic T-ALL. Notch1-activating mutations with so far unclear prognostic relevance were identified in up to 50% of T-ALL cases. They may be targeted by γ-secretase inhibitors. Five percent of T-ALL shows the NUP214–ABL1 aberration, which may identify a target population for imatinib therapy.

Altogether, there have been more and more attempts to stratify T-ALLs by genetic markers, mostly based on retrospective analysis of study results, but the impact on prospective risk stratification and different treatment strategies is limited.

Response parameters

• Is achievement of CR a prognostic marker for overall outcome, or is time to CR more important?

Response parameters after induction therapy are highly predictive for the further outcome of a patient with an ALL, such as time to achieve a CR within 3–4 weeks or a MolCR after 14–16 weeks. The rate of CR is prognostically less relevant since >95% of children and >90% of adults achieve a CR. Although the CR rates are so high, 40–50% of adult patients eventually relapse. The reason is the limited sensitivity to measure the cell reduction by cytomorphology despite potentially 1–5% leukemic cells in the bone marrow, and the more sensitive method to detect leukemic cells on a molecular level is evaluation of MRD.

Stratification into risk groups

• What is the purpose of stratification into risk groups?

Pretherapeutic prognostic factors and response parameters, now preferably MRD, are used to define risk groups; standard-risk (SR) patients are generally defined as those without any adverse risk factors, whereas high-risk (HR) patients have one or more risk factors. Several large adult ALL study groups have similarly defined risk groups. The aim of these prognostic models is to identify an SR group with a good outcome (e.g., with an expected >50% survival probability at 5 years in adults) and the HR patient group with a less favorable outcome. HR patients are generally candidates for an immediate SCT in CR1, whereas SR patients in most studies continue with consolidation cycles ± reinduction and maintenance therapy.

In several study groups, there was also the definition of a very-high-risk (VHR) group in adults, preferentially patients with Ph- and bcr–abl-positive ALL. As discussed, however, the prognosis of this subtype has completely changed with combined treatment modalities using TKIs. Thus, to currently define Ph-positive ALL as a very poor risk group is a pitfall.

• Will MRD evaluation replace pretherapeutic risk factors?

Questions arise regarding whether the evaluation of MRD overcomes all pretherapeutic risk factors, and whether it should be combined with the pretherapeutic factors or remain as the only stratification criterion. The risk stratification used in the GMALL studies and shown in Figure 2.1 is a practical approach to bring the conventional prognostic factors and MRD into a decision algorithm. At diagnosis, patients are stratified into SR or HR patients. Because HR patients are candidates for a SCT in CR1 after induction and consolidation therapy, the optimal time point for the

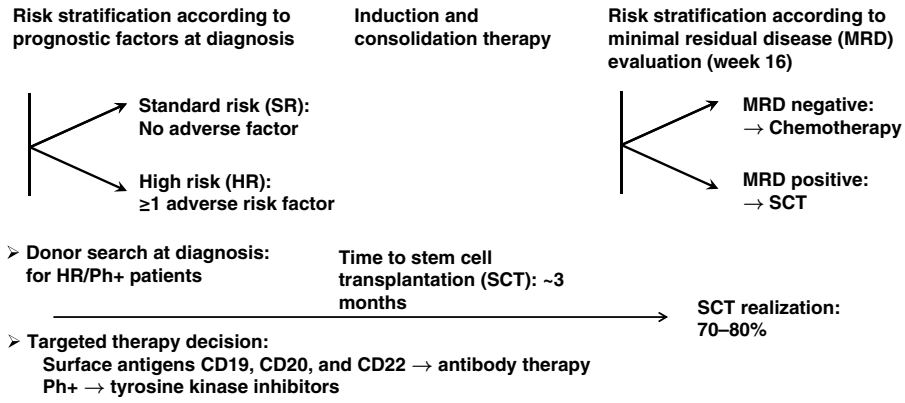


Figure 2.1 Practical approach for treatment stratification in adult acute lymphoblastic leukemia (ALL).

donor search is immediately after diagnosis. In this way, a suitable HLA-matched, mostly unrelated donor will be found within the period of ~3 months to guarantee a SCT rate of 79–80%. Initial diagnosis also identifies the patients who are candidates for a targeted therapy, for example, TKIs for Ph- and bcr–abl-positive patients, or monoclonal antibodies for those with specific surface antigens.

Selected reading

Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol. 2011;29(5):532–43.

Hoelzer D, Gökbuget N. Change in prognostic factors. Leuk Suppl. 2012;1:1–2.

Hoelzer D, Gökbuget N. Chemoimmunotherapy in acute lymphoblastic leukemia. Blood Rev. 2012;26(1):25–32.

Rowe JM. Prognostic factors in adult acute lymphoblastic leukaemia. Br J Haematol. 2010;150(4):389–405.

CHAPTER 3

Management of B-cell acute lymphoblastic leukemia

Hady Ghanem, Hagop Kantarjian, Nitin Jain, and Elias Jabbour

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

1. What is the standard of care for front-line management of Philadelphia chromosome–negative (Ph−) acute lymphoblastic leukemia (ALL)?

The front-line strategy for the management of adult ALL is similar to that in pediatrics, and it involves induction chemotherapy, multiple rounds of consolidation, a prolonged maintenance phase, as well as central nervous system (CNS) prophylaxis. Most protocols call for approximately 3 years of therapy in total. There are several accepted regimens employed in the United States, and most involve the same key agents, which include vincristine, anthracycline (e.g., doxorubicin or daunorubicin), and corticosteroids (e.g., prednisone or dexamethasone), with or without some form of L-aspariginase. One such regimen is hyper-CVAD, which employs the combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine. Cycles are repeated approximately monthly for eight cycles, at which point patients move to the maintenance portion of the regimen with daily mercaptopurine, monthly vincristine, weekly methotrexate, and monthly pulses of prednisone (POMP).

L-asparaginase, an enzyme used to deprive lymphoblasts of the non-essential amino acid asparagine, is considered an important component in pediatric ALL regimens. It is also included in several of the commonly used adult regimens, but the cumulative dose is generally less than that of the pediatric programs. A pegylated form of the drug allows for continuous exposure over a period of weeks, reducing the number of infusions or injections that a patient would be subjected to if receiving the conventional preparation. More recently, a study from the German Multicenter Study Group for Adult ALL (GMALL) was presented, indicating that intensifying the dose of pegylated asparaginase during induction and consolidation improved the survival of younger patients with standard risk disease at baseline. In this regimen, the drug was tolerated well, although there was a significant increase in the incidence of grades 3/4 hyperbilirubinemia. This led to treatment interruptions that were found to have a prognostic impact on the outcome. Other potential toxicities that pose a problem include pancreatitis, thrombosis, allergic reaction, hyperglycemia, and hypofibrinogenemia, among others. This makes it highly important to determine the optimal dose and timing of drug administration to prevent or avoid adverse effects that may compromise further antileukemic therapy. If the pegylated formulation is used, these problems can be delayed, arising typically 1 to 2 weeks after a dose is given. A detailed review of asparaginase toxicity and its management has recently been published by a group of experts.

2. What is the role of anti-CD20 immunotherapy in the treatment of B-lineage ALL (B-ALL)?

Approximately 50% of patients' leukemic blasts express the CD20 antigen. The prognostic role of CD20 expression in ALL is controversial, but it is a marker against which targeted therapies have been developed. Recently, data from the MD Anderson Cancer Center has indicated that the addition of rituximab, a monoclonal antibody against CD20, to the hyperCVAD regimen improves overall survival (OS) in younger patients. These results were confirmed by a European study that also evaluated the role of monoclonal antibody therapy added to conventional chemotherapy. Although rituximab was incorporated when CD20 expression was 20% or greater, anti-CD20 therapy may be beneficial regardless of CD20 expression at diagnosis. Ofatumumab is another CD20-targeted monoclonal antibody currently approved for the management of relapsed and refractory chronic lymphocytic leukemia

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

(CLL). Ofatumumab is being evaluated in combination with the hyperCVAD regimen in adults with newly diagnosed ALL.

3. What are the options for front-line management of Philadelphia chromosome–positive (Ph+) ALL?

Ph+ ALL continues to pose a major challenge for the adult population. Allogeneic stem cell transplantation (allo-SCT) is regarded as the only curative intervention for this subset of patients. Recently, the incorporation of small-molecule tyrosine kinase inhibitors (TKIs) has improved the outcome of these patients. The addition of a TKI to chemotherapy, including anthracyclines, vincristine, and cytarabine, may produce synergistic effects. Although the optimal schedule of TKIs has yet to be determined in ALL, early initiation and prolonged treatment courses have been implicated to provide the best outcomes.

Imatinib

Imatinib combined with conventional chemotherapy has been proven to be superior to chemotherapy alone in several trials that have been published or presented to date. A major mechanism of secondary resistance to imatinib appears to be related to the acquisition of point mutations within the BCR–ABL kinase domain, over 30 of which have been documented, including the gatekeeper mutation T315I, which causes resistance to imatinib as well as the second-generation TKIs. Other BCR–ABL-independent mechanisms of resistance include decreased drug influx and activation of other downstream or parallel cell-signaling pathways that promote cell proliferation and survival, such as the Src family of kinases (SFKs).

Dasatinib

Dasatinib is a second-generation TKI that is approximately 325-fold more potent against the BCR–ABL protein compared to imatinib, and it has the ability to block the SFKs (dual BCR–ABL and SRC kinase inhibitor). The SRC kinases have been implicated as being required for the development of Ph+ ALL. Dasatinib also retains activity against most known tyrosine kinase domain mutations that confer resistance to imatinib. Recently, dasatinib was found to be superior to imatinib for the initial treatment of chronic myeloid leukemia (CML) in the chronic phase. These favorable characteristics made it appropriate to test combination chemotherapy with the addition of dasatinib in the front-line setting for adult ALL. On a clinical trial recently published, 35 patients with newly diagnosed Ph+ ALL were treated with hyperCVAD and dasatinib. Dasatinib was administered at 100 mg once daily for the first 14 days during the induction and consolidation cycles. If patients completed the consolidation portion, they went on to receive monthly vincristine and prednisone while continuing on dasatinib 100 mg once daily. Ninety-four percent of patients achieved complete remission (CR), and the estimated 2-year survival was 64%. A very low percentage of patients proceeded with upfront allo-SCT (4 of 36); it will be important to assess whether dasatinib therapy modifies the conventional notion that a transplant is absolutely indicated for all patients who are fit for such a procedure and have an adequate stem cell source. Nevertheless, additional follow-up is required before that will be determined. In another recent report on older patients with Ph+ ALL (age >55 years), Rousselot and colleagues (2009) used induction treatment with steroids, vincristine, and dasatinib followed by consolidation cycles of dasatinib, and chemotherapy, which resulted in a CR rate of 97%. With a median follow-up of 12.4 months, median event-free survival and OS were not reached. Dasatinib is currently not US Food and Drug Administration (FDA) approved for front-line therapy of Ph+ ALL patients.

Nilotinib

Nilotinib is a second-generation TKI, derivative of imatinib, with an increased and more selective binding affinity to the adenosine triphosphate pocket of the BCR–ABL oncoprotein, resulting in activity that is 20–50 times higher than the inhibitory activity of imatinib. It has demonstrated activity against most kinase domain mutations, with the exception of T315I and P-loop mutations. It is currently approved for use in the treatment of newly diagnosed patients with CML and patients with chronic-phase CML who are resistant to or are intolerant of imatinib. Nilotinib is not approved for use in patients with Ph+ ALL. Kantarjian *et al*. (2006) first reported positive results in a phase I dose-escalation study of nilotinib in imatinib-resistant CML or Ph+ ALL, which included 33 patients in the blast phase. Based on the encouraging results of a phase II trial in the relapsed setting, Kim *et al*. (2011) reported on the use of nilotinib in combination with chemotherapy for front-line treatment of patients with newly diagnosed Ph+ ALL, with a 90% hematologic remission rate and a 54% complete molecular remission (CMR) rate. With a median follow-up of 17.4 months, the estimated recurrence-free survival and OS at 2 years were 71% and 66%, respectively.

Ponatinib

Although the results of second-generation TKIs combined with chemotherapy are quite encouraging, patients still relapse, and there are specific kinase domain mutations that are not sensitive to any first- or second-generation TKIs. The most notorious mutation for any Ph+ malignancy

is T315I, which confers resistance to imatinib, dasatinib, as well as nilotinib. Patients with Ph+ ALL receiving dasatinib in a European study appeared to develop this mutation at a relatively high frequency, making it important to develop and examine options to combat this problem. One strategy might be to utilize a TKI that has activity against T315I-mutated disease, such as ponatinib. Ponatinib is a rationally designed molecule that has activity against nearly all known BCR–ABL kinase domain mutations. Of note, ponatinib was approved in December 2012 for the treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase CML that is resistant or intolerant to previous TKI therapy or Ph+ ALL that is resistant or intolerant to previous TKI therapy. Approval was based on a trial of 449 patients with various phases of CML and Ph+ ALL. In this study, 41% of patients with Ph+ ALL achieved a major hematologic response (HR) for a median duration of 3.2 months. Importantly, ponatinib is active against all mutations, including T315I. It is currently being evaluated as a front-line strategy in combination with the hyperCVAD regimen. Preliminary results from the combination of ponatinib and hyperCVAD were presented at the 2013 American Society of Clinical Oncology (ASCO) meeting.

The National Comprehensive Cancer Network (NCCN) guidelines recommend similar approaches to those described here. Available data indicate that it is important to start a TKI as soon as the presence of the Philadelphia chromosome is confirmed. Moreover, the guidelines do not specify a preference for which TKI is initiated in the front-line setting (e.g., imatinib versus dasatinib). Despite the fact that outcomes appear to be improving with current therapies, the NCCN appropriately recommends first and foremost that patients be considered for ongoing clinical trials.

4. What are the potential strategies for salvage therapy in patients with relapsed B-ALL?

The prognosis of adults with relapsed or refractory ALL is generally poor, with median OS ranging between 4 and 7 months (Figure 3.1). As would be expected, patients who are resistant to initial induction therapy, or those who have a CR duration of less than 12 months, have a particularly unfavorable prognosis. The expected 5-year OS for adults with relapsed ALL is 5% to 10%, although some groups report improved outcomes for patients whose first CR duration was greater than 2 years. There are several salvage drugs and regimens endorsed by the current guidelines, but most of these strategies are suboptimal, and patients should always be considered for entry into a clinical trial first. There are several very promising new agents under investigation, and patients should be referred to centers that are accruing on these protocols.

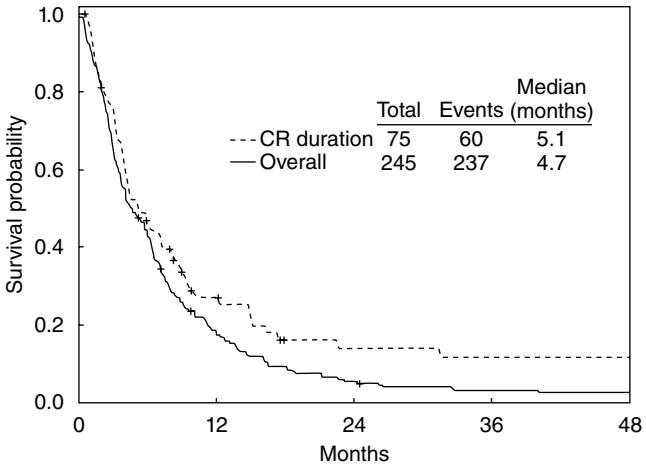


Figure 3.1 Remission duration and overall survival in relapsed acute lymphoblastic leukemia (ALL); CR, complete remission (Source: Kantarjian HM, *et al.* Cancer 2010;116:5568–74, 2010. Reproduced with permission of the American Cancer Society).

5. What are the available conventional strategies for treatment of relapsed B-ALL?

For patients who do not qualify for participation in a clinical trial, the decision to use a salvage strategy is largely based on the duration of first remission, performance status, and organ function. It is also very important to consider drug classes and agents that the patient has not yet been exposed to. Furthermore, one must revisit the cytogenetic and molecular characteristics of the particular patient's leukemia to appropriately design a treatment plan.

An augmented version of the hyperCVAD regimen was developed for use in adults with relapsed ALL. This program included intensified doses of dexamethasone and vincristine, and the addition of pegylated asparaginase to the traditional hyperCVAD backbone. Ninety patients were enrolled, most of them in first relapse, with 80% having received standard hyperCVAD prior to experiencing recurrent disease. The overall response rate (ORR) in the study was 64%, with 47% of the patients meeting the definition of CR. The 30-day mortality was less than 10%. This may be an ideal regimen for relapsed patients who have not received prior L-asparaginase.

Another approach could rely on using clofarabine in the relapsed setting. Clofarabine is a nucleoside analog approved for the treatment of pediatric ALL at time of second relapse. Several clofarabine combinations have also been explored in the pediatric and adult patient populations. Recently, a group from France tested two clofarabine-containing regimens in patients with relapsed ALL. The first regimen consisted of clofarabine, dexamethasone, mitoxantrone, etoposide, and pegylated asparaginase. The CR rate was 41%, with an early death rate of 14%. Five of

37 patients experienced grades 3/4 neurologic toxicity. The second regimen tested was a combination of clofarabine and cyclophosphamide. This program also led to a relatively high CR rate of 50%, with very little early mortality and minimal unexpected toxicities. A multicenter phase II trial was also conducted in a group of pediatric patients using clofarabine combined with etoposide and cyclophosphamide. These patients were heavily pretreated, with 84% receiving the regimen as salvage 2 or higher. The CR rate on this study was 28%, and several patients were able to move on to allo-SCT. Patients who had undergone allo-SCT prior to being enrolled in this study seemed to be predisposed to severe liver toxicity (e.g., veno-occlusive disease (VOD)), and the study was eventually amended to exclude this group. In adults, the Programa Espanol de Tratamiento en Hematologia (PETHEMA) published their experience with several clofarabine-based regimens. They reported a CR rate of 31% and manageable toxicity, with several patients being able to proceed to allo-SCT. Most of these patients had been treated with two or more chemotherapy regimens.

Vincristine is part of the conventional backbone of ALL therapy, but it causes peripheral neuropathy that can necessitate dose reductions and its use in salvage chemotherapy regimens may be problematic. The liposomal (sphingosomal) formulation of vincristine generally produces less toxicity (e.g., neurotoxicity) and increased efficacy compared with the conventional formulation. In 2012, liposomal vincristine was approved by the FDA for the treatment of the Ph− subset of patients with relapsed ALL. Approval was based in part on a phase II clinical trial of 65 heavily pretreated patients in which 20% achieved a CR (including CR with incomplete count recovery) with an ORR of 35%. The median duration of remission was 23 weeks. Of note, although capping doses of conventional vincristine at 2 mg have become common practice, liposomal vincristine may be administered without dose capping.

6. What are the available investigational and/or targeted strategies for treatment of relapsed B-ALL?

As discussed in this chapter regarding the use of rituximab and ofatumumab, target-directed therapy against antigens expressed on the surface of leukemic cells represents an attractive strategy for fighting this disease and improving patient outcomes. A description of currently available and investigational monoclonal antibodies can be found in Table 3.1. Aside from CD20, CD19, and CD22 are also antigens that are highly expressed on B-lymphoblasts. Monoclonal antibodies against CD19 and CD22 are moving into advanced stages of development, and they have demonstrated a high degree of activity, even in the most refractory settings.

Table 3.1 Monoclonal antibodies for acute lymphoblastic leukemia (ALL).

Drug	Target	Comment
Rituximab	CD20	Improves overall survival in younger adults with de novo ALL
Ofatumumab	CD20	Distinct binding site from rituximab may be beneficial
Inotuzumab	CD22	Antibody drug conjugate linked to the cytotoxin calicheamicin
Blinatumomab	CD19	Bispecific antibody that engages CD3-positive T-cells and directs them to CD19-positive B-cells
Alemtuzumab	CD52	Limited activity as a single agent in adults with refractory disease
Epratuzumab	CD22	Studied as part of combination chemotherapy in relapsed pediatric ALL; minimal activity as a single agent
SAR3419	CD19	Antibody drug conjugate linked to the tubulin toxin maytansine
Moxetumomab pasudotox (HA22)	CD22	Pediatric refractory ALL; moderate activity as a single agent

N, number of patients; S1, 1st salvage; S2, 2nd salvage; S3, 3rd salvage.

Anti-CD22 antibodies

The rapid internalization of CD22 upon receptor binding makes it an excellent target for monoclonal antibody–cytotoxic chemotherapy conjugates. Once internalized, the toxic component is released, causing cell destruction and death. In theory, this would allow for a minimal dose of chemotherapy to be delivered directly to the leukemic blasts, thus minimizing off-target toxicity.

CD22 expression occurs in more than 90% of patients with ALL. Inotuzumab ozogamicin is a monoclonal antibody against CD22 that is linked to calicheamicin, a potent cytotoxin that induces double-stranded DNA breaks. The initial trial was a dose-ranging study conducted in patients with B-cell non-Hodgkin's lymphoma. Objective responses were documented in 39% of patients who underwent treatment. The maximum tolerated dose (MTD) was determined to be 1.8 mg/m^2 administered every 3 to 4 weeks. Reversible thrombocytopenia was the most frequently encountered toxicity.

Based on the results of the phase I study, Kantarjian *et al*. (2012) conducted a phase II study in relapsed ALL patients. An initial dose of 1.3 mg/m^2 was given to the first three patients to ensure safety, but most patients went on to receive 1.8 mg/m^2 every 3 to 4 weeks. Patients with CD20-positive disease could have rituximab added to

Table 3.2 Response rates of inotuzumab compared to conventional chemotherapy.

Parameter	Overall response rate (%)				
	Inotuzumab			Chemotherapy ($N = 292$)	*P*-value
	Overall ($N = 89$)	Monthly ($N = 49$)	Weekly ($N = 40$)		
Overall	47	47	48	29	<0.001
S1	61	69	53	40	0.03
S2	44	38	60	16	<0.001
≥S3	37	42	33	16	0.02

N, number of patients;
S1, 1st salvage; S2, 2nd salvage; S3, 3rd salvage

inotuzumab starting on cycle 3 if they exhibited stable disease or no improvement. Forty-nine patients were enrolled, and 73% of the patients received inotuzumab as second salvage or greater. Fourteen percent of patients had previously undergone allo-SCT. After a median of two cycles of therapy, the ORR was 57%, with most patients achieving complete remission with incomplete platelet recovery (CRp) or complete remission with incomplete hematologic recovery (CRi). Fever within 48 h of drug administration was the most common nonhematologic toxicity, occurring in 59% of patients. Other important toxicities included elevations in bilirubin and hepatic transaminases. Twenty-two of 49 patients were treated and subsequently went to allo-SCT. Of concern was the development of clinical VOD in five patients (23%) in the post-transplant setting. Several of these patients had also received thiotepa or clofarabine as part of the preparative regimen, which are known to be potentially hepatotoxic. Two of the four patients undergoing a second allo-SCT had clinical evidence of VOD posttransplant. Importantly, allo-SCT did not appear to confer a survival benefit, potentially due to the refractoriness of the patients studied or transplant-associated complications.

A weekly schedule of inotuzumab was more recently explored as an attempt to optimize the benefit-to-risk ratio based on the pharmacodynamics and pharmacokinetics of the drug. Twenty patients were given inotuzumab according to the following schedule: 0.8 mg/m^2 intravenously (IV) on day 1, 0.5 mg/m^2 IV on day 8, and 0.5 mg/m^2 IV on day 15. Thus, the same cumulative dose per cycle was the same as given in the every 3- to 4-week schedule. Patients received a median of two cycles, with an ORR of 50%. The toxicity profile was similar to that of the previous study, with transient elevations of bilirubin and transaminases occurring in 35% of patients. Notably, however, there has been no occurrence of clinical VOD, including in the four patients who proceeded with allo-SCT after receiving inotuzumab. The safety and activity of the weekly regimen have been confirmed in a recent phase I multicenter study using weekly inotuzumab, which was administered in 28-day cycles with a maximum of six cycles. The final dose was determined based on both toxicity and evidence of efficacy. The single dose-limiting toxicity observed to date was a transient grade 4 elevation in lipase. The most frequent (≥10% of patients) treatment-related adverse events were thrombocytopenia (31%, all grade 3/4), neutropenia (15%), and elevated alanine aminotransferase (15%). Responses were observed across all doses explored (total dose: 1.2–2.0 mg/m^2/cycle). The preliminary ORR was 82%, including 36% of patients with a CR and 45% with a CRi. Median time to response was 43 days. Six of nine (67%) patients who achieved CR or CRi also achieved negative minimal residual disease (MRD).

Most recently, the MD Anderson experience has been updated. The response rates of inotuzumab compared to conventional chemotherapy in the salvage setting is presented in Table 3.2. A total of 83 patients were treated, 49 with single dose and 34 with weekly dose, with 71% of the patients in salvage 2 or beyond. Overall, 14 patients (17%) achieved CR, 23 (28%) had CRp, and nine (11%) had marrow CR (no recovery of counts), for an ORR of 55%. The response rate was 57% with a single dose and 53% with a weekly dose. Only four patients died in the first 4 weeks of therapy. Among 28 patients with cytogenetic abnormalities who achieved response, 25 (89%) achieved completed cytogenetic response. Among 44 patients who achieved response and had MRD studies by multiparameter flow cytometry, 28 (64%) became MRD negative. The median survival was 5.4 months, 5.0 months with the single dose and 6.3 months with the weekly dose. Reversible grade 1–2 and 3–4 bilirubin elevations were observed in 24% and 4%, respectively, on single dose and in 3% and 0% on weekly dose. Reversible grade 1–2 and 3–4 liver enzyme elevations were observed in 55% and 2%, respectively, on single dose and in 21% and 6% on weekly dose. Adverse factors for response included salvage 2 or later versus salvage 1 (49%

vs. 71%); Ph+ and t(4;11) abnormalities versus others (39% vs. 62%). Allo-SCT was performed on 22 of 49 patients (49%) on single dose and in 9 of 34 (26%) so far (shorter follow-up) on weekly schedule: VOD was observed in 5 of 22 with single dose (23%) and in 1 of 9 with weekly dose (11%). These data are encouraging given the refractory nature of the patients who were treated. The combination of inotuzumab with reduced-intensity hyperCVAD ("mini-hyperCVAD") chemotherapy is being tested as front-line therapy in patients >60 years old with Ph– CD22+ ALL. Preliminary results of this combination were presented at the 2013 ASCO meeting (unpublished data).

Anti-CD19 antibodies

CD19 is another surface receptor with nearly universal expression on B-ALL cells. The receptor also internalizes sufficiently upon binding, making it reasonable to target with immunoconjugated compounds. Harnessing one's immune system as a cancer-fighting modality has been studied extensively. Recruiting T-cells directly to leukemic blasts using monoclonal antibody technology may lead to synergistic effects and improved outcomes.

Blinatumomab is in a class known as the bispecific T-cell engaging (BiTE) molecules that actually contain components of two monoclonal antibodies. One arm of blinatumomab is designed to bind CD3+ cytotoxic T-cells, while the other recognizes CD19. Upon binding to CD19, the T-cell becomes activated, thereby leading to the death of the malignant cell. Because of its short half-life, blinatumomab is given as a continuous infusion for 4 weeks, followed by a 2-week treatment break. The agent was initially used in adult patients with ALL who had persistent or resurgent MRD after induction or consolidation therapy. This group would be expected to be at very high risk of clinical relapse with continuation of conventional chemotherapy alone. Of 20 patients enrolled, 16 converted to MRD− status, and eight patients subsequently received allo-SCT. One patient had to be taken off study after the development of a seizure, which was reversible after discontinuation of the blinatumomab. Other common toxicities included fever and lymphopenia.

The GMALL group subsequently initiated a phase II study to evaluate blinatumomab in patients with clinically relapsed disease. The results were updated this year at the American Society of Hematology (ASH) annual meeting. Three dosing regimens were explored (Table 3.1) to identify the optimal regimen with respect to efficacy and toxicity. All regimens were given as 28-day infusions followed by a 14-day rest period. Responding patients had the option to receive three additional cycles of treatment or to proceed to allo-SCT. Within two cycles of therapy, 68% of patients achieved the definition of CR or CRi; 24 out of 26 (92%) responders also achieved a molecular response (MRD below 10^{-4} as measured by polymerase chain reaction) within the first two cycles. Thirteen patients proceeded to allo-SCT after blinatumomab treatment, and one of them developed a medullary CD19− relapse after allo-SCT. The median survival for all 36 treated patients is 9.0 months with a median follow-up time for OS of 10.7 months. The final dose selected was $5\,mcg/m^2/day$ for 7 days, followed by $15\,mcg/m^2/day$ for 21 days. The most common adverse events included fever (70%), headache (39%), and tremor (30%). Reversible CNS side effects were observed in six patients, four of whom were able to resume and tolerate treatment at lower doses. Thus, this final dosing regimen of blinatumomab resulted in very high rates of hematologic and molecular response with acceptable toxicity. A global phase II study to confirm these data is underway.

7. What are the future directions and perspectives in the treatment of front-line and relapsed B-ALL?

It is clear that the incorporation of monoclonal antibodies is changing the treatment paradigm for adults with ALL. Thus far, the only antibody that has been evaluated as part of the front-line treatment strategy is rituximab, and its benefit was demonstrated when it was added to an accepted chemotherapy regimen. The use of monoclonal antibodies against CD20 is potentially hampered by the varying degrees of expression of this antigen on lymphoblasts. An interesting concept that has recently been studied is the potential for corticosteroid-induced upregulation of CD20 expression, which would broaden the applicability of these agents.

Some of the most promising agents are showing very exciting results in patients with relapsed and refractory disease. As data continue to accumulate, it will be important to move the most active agents to the front-line management strategy. Inotuzumab ozogamicin and blinatumomab are able to induce molecular remission in a high number of patients, which is critical to outcomes for patients undergoing induction and consolidation chemotherapy. Monoclonal antibodies also appear to be less toxic than conventional cytotoxic agents, making them particularly interesting for elderly patients with ALL. A strategy utilizing inotuzumab in combination with reduced doses of cyclophosphamide, vincristine, and corticosteroids (alternating with methotrexate and cytarabine) is underway. The anthracycline is omitted completely from this protocol, as it tends to cause significant problems for this age group.

Novel active single agents may be identified in the future, although they may be active only against limited specific molecular subsets of ALL. This progress is likely to accelerate with parallel efforts in search of genetic abnormalities that drive the growth of ALL cells and serve as

new targets for novel agents. An example of these molecules would be the use of targeted therapies against specific molecular markers. Recently, small molecules that inhibit DOT1L have been found to decrease the expression of MLL fusion target genes, inducing apoptosis selectively in leukemia cell lines derived from MLL-rearranged leukemia patients.

A far-reaching goal will be to one day incorporate multiple monoclonal antibodies into the frontline approach, thereby minimizing the use of cytotoxic chemotherapy. The challenge will be to determine the optimal way to sequence such combinations, and how much cumulative exposure is necessary to maintain durable responses (i.e., cure). Monoclonal antibodies are large molecules, so it will be important to monitor the impact that increased use has on isolated CNS disease. The prophylactic approach may also have to be modified. Ultimately, the use of these targeted antibodies to surface receptors would need to be tailored to the flow cytometric and molecular characteristics in an individualized approach.

Selected reading

Faderl S, O'Brien S, Pui CH, *et al*. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer. 2010;116:1165–76.

Kantarjian H, Thomas D, Jorgensen J, *et al*. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol. 2012;13:403–11.

Ravandi F, O'Brien S, Thomas D, *et al*. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood. 2010;116:2070–7.

Thomas DA, O'Brien S, Faderl S, *et al*. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010;28:3880–9.

Topp MS, Kufer P, Gokbuget N, *et al*. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011;29:2493–8.

CHAPTER 4

Management of T-cell acute lymphoblastic leukemia

Daniel J. DeAngelo

Dana-Farber Cancer Institute *and* Harvard Medical School, Boston, MA, USA

Case study 4.1

A 20-year-old male patient presents with a 2-week history of dyspnea on exertion and fatigue. A chest radiograph reveals a large mediastinal mass that is confirmed by computed tomography (CT) scan. The presenting leukocyte count is 20×10^9/L with 58% lymphoblasts. He also has a hemoglobin level of 12.3 g/dL and a platelet count of 110×10^9/L. A bone marrow aspirate reveals 70% lymphoblasts with an immunophenotype positive for CD34, TdT, cytoplasmic CD3, CD1a, CD5, and CD7. The blasts were negative for myeloperoxidase and other B-cell and myeloid markers. The cytogenetics revealed a normal 46XY karyotype. The findings are consistent with T-cell acute lymphoblastic leukemia (T-cell ALL, or T-ALL). The patient inquires as to what is the most appropriate therapy.

• What is the most appropriate therapy for adult patients with T-ALL?

The intensification of the induction regimen, such as those developed by the Cancer and Leukemia Group B (CALGB), has resulted in a significant improvement in complete remission (CR) rates, with greater than 80% of adult patients achieving a CR. Induction therapy is built on a backbone of vincristine and a glucocorticoid (prednisone or dexamethasone). Most regimens add asparaginase and an anthracycline (daunorubicin or doxorubicin), which has resulted in improved CR rates ranging from 72% to 92%. Pioneered in the treatment of pediatric ALL, the contributions of asparaginase to response rates and duration of response in adults are not clear as there are no randomized studies supporting its use in adult patients. The toxicities of asparaginase in adults include pancreatitis, hepatotoxicity, and coagulopathy. An analysis CALGB 8811 study showed a marginal benefit in disease-free survival (DFS) at 3 years for patients who received all prescribed doses of asparaginase (55% vs. 48%). Eighty-five percent of the 197 patients in that trial achieved CR after induction. Ongoing trials by the German Multicenter ALL (GMALL) group of the long-acting asparaginase, polyethylene glycol–asparaginase, suggest a potential survival benefit in older adults with ALL when the drug is administered at slightly lower doses than have been used by pediatricians.

An alternative treatment regimen known as hyper-CVAD was developed at the MD Anderson Cancer Center and uses hyperfractionated cyclophosphamide, dexamethasone, vincristine, and doxorubicin without asparaginase during induction and high-dose cytarabine and methotrexate during consolidation. The CR rate of hyper-CVAD is 91% with 3- and 5-year DFS rates of 50% and 38%, respectively.

The goal of using granulocyte colony-stimulating factor (G-CSF) is to shorten the period of neutropenia to prevent possibly fatal infections, and previous studies demonstrate the utility of this drug with induction regimens for ALL. In the Leucémie Aigüe Lymphoblastique de l'Adulte (LALA)-94 trial, patients were randomized to receive G-CSF, granulocyte-macrophage CSF (GM-CSF), or no CSF. When given on day 4 of induction until the return of an absolute

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

neutrophil count of 1000/μL, patients receiving G-CSF had significantly shorter hospital stays, less time to neutrophil recovery, and fewer severe infections compared with patients who did not receive G-CSF. The CALGB 9111 trial highlighted the benefit of using this drug in patients prone to difficulty with hematologic recovery, specifically older patients. The study observed a trend toward increased CR rates in patients 60 years of age or older in the G-CSF arm compared with the placebo arm.

• What is the most appropriate therapy for young adult patients with T-ALL?

Increasing age is one of the most important poor prognostic factors of outcome in newly diagnosed patients with ALL. The 5-year DFS is approximately 80% for children and 40% for adults with ALL. Recent retrospective data suggest that younger patients between the ages of 16 and 21 years fare better when treated according to intensive pediatric ALL treatment regimens rather than conventional adult regimens. Despite slight differences in treatment approaches across the different cooperative groups, many retrospective studies have demonstrated significantly better outcome for the patients when they are treated in pediatric studies, where survival has been reported to be in the range of 60% to 65%. In contrast, when the same age group is treated in adult cooperative-group ALL treatment trials, survival has been only 30% to 40%.

From these retrospective studies, it appears that the major differences in treatment between the adult and pediatric regimens are the more intensive use of the nonmyelosuppressive agents (glucocorticoids, asparaginase, and vincristine), earlier and more intensive central nervous system (CNS)-directed therapy, and more prolonged maintenance therapy used in the pediatric regimens. In addition to the obvious treatment differences between adult and pediatric trials, there has been much debate about the potential differences in adherence to therapy protocols among pediatric and adult medical hematologists and the patients who they treat.

Several prospective European and American studies that administered pediatric regimens to younger adults have confirmed improved outcomes for patients aged 16 to 30 years, with DFS rates of 60% to 65%. The Dana-Farber consortium has also presented preliminary results applying this pediatric approach to adults up to the age of 50 years, with an event-free survival rate of 63% with short follow-up. The US Intergroup recently completed a large phase II trial (CALGB 10403) for younger adults up to age 40 years that tested the successful approach used by the Children's Oncology Group for treatment of high-risk adolescents with ALL. Older adults (over the age of 45 years) may not benefit from this approach due, in part, to their inability to tolerate the intensive asparaginase, glucocorticoid, and vincristine dosing upon which these regimens are based.

• Is CNS-directed therapy critical for patients with T-ALL?

Although less than 10% of adults with ALL will present with CNS involvement, CNS relapse will occur in 35% to 75% of patients at 1 year if prophylactic CNS-directed therapy is not incorporated into treatment. A lumbar puncture at the time of ALL diagnosis is always performed in pediatric studies, but this is typically delayed in most adult ALL regimens. Unless a patient has CNS symptoms, the CALGB regimens perform an initial lumbar puncture at the start of consolidation (postremission) chemotherapy. Symptoms may include headache, meningismus, fever, or cranial nerve palsies. However, some patients are asymptomatic. If symptomatic CNS disease is present at diagnosis, such as focal cranial nerve palsies, concurrent radiation therapy and intrathecal chemotherapy are administered.

Initially, CNS-directed therapy included the use of intrathecal methotrexate and 24 Gy of cranial radiation in the pediatric population. Although in children it is known that combination treatment can result in toxicities that include seizures, early dementia, cognitive dysfunction, slow growth, and second cancer, the long-term effects on adults are less clear. Combined radiation and intrathecal chemotherapy in adults can cause substantial acute toxicities that may delay postremission consolidation treatment. Therefore, lower doses of cranial radiation are currently being explored. An alternative combination strategy that uses intrathecal chemotherapy without radiation has also been investigated. This treatment regimen includes a so-called *triple therapy* that uses intrathecal methotrexate, cytarabine, and corticosteroids without radiation.

CNS relapse rates as low as 5% have been achieved without radiation by using combination intrathecal treatment in conjunction with high-dose systemic treatment that can penetrate the cerebrospinal fluid. However, the German GMALL investigators have reported higher CNS relapse rates of 9% versus 5% when CNS-directed radiation was postponed. Therefore, although CNS-directed prophylactic therapy is required in ALL treatment, there is no single modality or combination that has been proven to be superior. Of note, the pediatric groups generally still recommend cranial irradiation as part of CNS prophylaxis for high-risk T-ALL, as do the German study groups.

Case study 4.2

A 28-year-old female patient presents with a 1-month history of bruising and fatigue. A complete blood count (CBC) reveals a leukocyte count of 32×10^9/L with 62% lymphoblasts. She also has a hemoglobin level of 9.7 g/dL and a platelet count of 42×10^9/L. A bone marrow aspirate reveals 58% lymphoblasts with an immunophenotype positive for CD34, TdT, cytoplasmic CD3, CD7, CD33, and myeloperoxidase. The blasts were negative for CD1a, CD4, CD8, and other B-cell and myeloid markers. The findings are consistent with those for T-ALL. CT scans that are performed on the chest, abdomen, and pelvis reveal no mediastinal mass, but scattered lymphadenopathy is present. The liver and spleen appear normal. The cytogenetics revealed a normal 46XX karyotype. The patient wants to know her overall prognosis.

- **Do all patients with T-ALL have the same prognosis?**

There are three distinct immunologic subtypes of T-ALL that correspond to different stages of T-cell development: *thymic* (also referred to as *cortical*) *T-ALL*, which expresses CD1a, with or without surface CD3 expression, and also expresses CD2 and CD4 or CD8; *mature* (*medullary*) *T-ALL*, which expresses surface CD3 but not CD1a; and *early T-cell precursor* (*ETP*) *ALL*, which expresses neither surface CD3 nor CD1a. ETP ALL is also characterized by lack of expression of CD4 and CD8, presence of the "double negative 1" (DN1) thymocyte, and frequent aberrant expression of myeloid lineage markers, including CD33. ETP ALL represents about 15% of T-ALL and is associated with a poorer prognosis in both children and adults, compared with thymic (cortical) T-ALL. Several leukemia groups are testing a strategy of referring these high-risk patients for stem cell transplantation (SCT).

Five different T-cell oncogenes (*HOX11*, *TAL1*, *LYL1*, *LMO1*, and *LMO2*) that are aberrantly expressed are found in the absence of chromosomal abnormalities in patients with T-ALL. These five oncogenes have different gene expression signatures that are indicative of a developmental arrest at specific stages of thymocyte development. Patients with a *HOX11* mutation have an extremely favorable outcome with an overall survival (OS) rate of greater than 90%, which may be a result of the overexpression of genes involved in proliferation and the lack of *BCL2* expression. In addition, other novel genetic mutations have been recently reported in T-ALL. The *NUP214–ABL1* fusion is a constitutively activated tyrosine kinase that transforms Ba/F3 cells to factor independent growth. The presence of the *NUP214–ABL1* fusion appears to be present in about 5–10% of patients with T-ALL. Importantly, the *NUP214–ABL1* fusion is inhibited by imatinib, thereby suggesting its use as a therapeutic strategy in T-ALL patients with *NUP214–ABL1* fusions.

- **What is the role of hematopoietic SCT for patients with T-ALL?**

The role of allogeneic SCT (allo-SCT) has been established in patients with well-known risk factors such as t(9;22) and t(4;11) cytogenetics, and it may represent the optimal approach for curing these patients. Determining whether other patients may also benefit from SCT in first CR (CR1) has been an area of intense study, and at this point there seems to be no clear advantage for allo-SCT in patients with T-ALL. In an early trial from the Netherlands, 54 patients (aged 15–51 years) with ALL and 15 patients with lymphoblastic lymphoma were treated with induction and consolidation chemotherapy. Thirty patients had a human leukocyte antigen (HLA)-matched sibling, and 22 of those patients were scheduled to undergo SCT. The DFS of these patients was 58% (±11%) at 5 years, a result not significantly different from the outcomes of the other patients in the study who did not receive transplantation as part of their regimens.

The French LALA-87 trial attempted to evaluate the best postremission strategy in ALL, comparing consolidation chemotherapy versus auto-SCT versus allo-SCT. The results of this trial, which analyzed 572 patients with 10 years of follow-up data, showed that survival was 46% for patients who received an allo-SCT versus 31% for patients who received chemotherapy ($P = 0.04$). When broken into high-risk and standard-risk groups [with high risk including Philadelphia chromosome–positive (Ph+) status, age >35 years, white blood cell (WBC) count $>30 \times 10^6$/mL, and time to CR >4 weeks], OS at 10 years was 44% in the allo-SCT group versus 11% for the chemotherapy group ($P = 0.009$). In the standard-risk group, survival rates in the allo-SCT group (49%) and the chemotherapy group (39%) were similar ($P = 0.6$). Thus, this study demonstrated a survival benefit for allo-SCT in CR1, but it was limited to only the high-risk patients.

Similarly, the LALA-94 trial reevaluated the benefit of allogeneic transplantation in high-risk patients. The results of this intent-to-treat analysis showed that patients with high-risk ALL and patients with CNS involvement had a better outcome if a donor was available for transplantation. Among high-risk patients, those allocated to the allo-SCT arm had a better median DFS of 20.8 months compared with a median DFS of 15.2 months in the auto-SCT arm and a median DFS of only 11 months in the chemotherapy arm ($P = 0.007$). These results confirm the findings of the

(*Continued*)

LALA-87 trial showing benefit of allo-SCT in high-risk patients if a sibling donor is available.

The Medical Research Council United Kingdom ALL (MRC UKALL) 12–Eastern Cooperative Oncology Group (ECOG) 2993 study is the largest prospective randomized trial comparing allo-SCT with chemotherapy as a postremission treatment strategy. In this study, 1913 patients aged 15 to 59 years were enrolled between 1993 and 2006, with the upper age limit extended to 64 years in 2003. The study schema allocated all patients younger than 50 years (later amended to 55 years) and having an HLA-matched sibling to receive a transplantation. All Ph+ patients were assigned to transplantation, using a matched unrelated donor if necessary. Younger patients without a family member donor and patients older than 50 years (or 55 years later in the study) were randomized to either auto-SCT or further chemotherapy for consolidation treatment. High-risk T-ALL patients in this study were defined by age >35 years and WBC count >100,000/mL. The patients with a donor had a 5-year OS rate of 53% versus 45% for patients without a donor ($P = 0.01$). In stark contrast to the two LALA trials discussed in this chapter, standard-risk patients were the only group to benefit from transplantation, with 5-year OS rates of 62% versus 52% ($P = 0.02$) in patients who had a donor versus those who did not, respectively. The benefit from transplantation in high-risk patients was not statistically significant ($P = 0.2$), with OS rates of 41% and 35% in the donor group and no-donor group, respectively. The trial also showed that in all groups, auto-SCT offered no more benefit than chemotherapy alone. As opposed to the LALA trials, the joint MRC UKALL–ECOG 2993 trial showed that transplantation was most beneficial to standard-risk patients, as defined, rather than high-risk patients.

Auto-SCT has been studied as a treatment option for patients who do not have an HLA-matched sibling donor. In a review of the French LALA-85, -87, and -94 trials, investigators studied 175 patients who received auto-SCT and 174 patients who were treated with chemotherapy. Their results showed that receiving auto-SCT was associated with a lower incidence of relapse compared with treatment with chemotherapy (66% vs. 78% at 10 years, respectively; $P = 0.05$). However, DFS and OS were not significantly different between the groups.

- **What is the role of *Notch* in patients with T-ALL?**

The *NOTCH1* signaling pathway has been shown to be a potential therapeutic target in T-ALL and was discovered due to its involvement in the t(7;9) chromosomal translocation, which is only rarely seen in T-ALL. Subsequently, *NOTCH1* was shown to be essential for normal development of T-cell progenitors, and mutated forms of *NOTCH1* can reliably produce T-ALL in animal models. Recent data suggest that 50–60% of patients with T-ALL have *NOTCH1* gain-of-function mutations, suggesting that *NOTCH1* plays a critical role in the pathogenesis of T-ALL. In order to generate critical downstream signals, activated forms of *NOTCH1* require the activity of the γ-secretase enzyme. In vitro γ-secretase inhibitors can completely abrogate the stimulatory effects of mutated *NOTCH1*, and strongly inhibit the proliferation of *NOTCH1*-mutated human T-ALL cell lines. These findings provide a strong rationale to test γ-secretase inhibitors in T-ALL, and several studies are ongoing.

- **Should patients who present with T-cell lymphoblastic lymphoma receive different chemotherapy as compared to those with T-ALL?**

T-cell lymphoblastic lymphoma represents approximately 2% and 30% of adult and pediatric non-Hodgkin lymphomas, respectively. The peak incidence is in the second decade of life, with a smaller peak in adults >40 years of age. Males are affected twice as often as females. The immunophenotype of T-cell lymphoblastic lymphoma overlaps with that of T-ALL. The clinical distinction between these two entities is arbitrarily determined by the degree of bone marrow involvement. Patients with ≥25% bone marrow replacement by lymphoblasts are considered to have T-ALL, whereas patients with a lesser degree of replacement or no detectable abnormal lymphoblasts in the marrow are classified as having T-cell lymphoma. In fact, lymphoblasts can be detected in the bone marrow in about 20% of patients with T-cell lymphoblastic lymphoma using conventional morphologic examination of bilateral bone marrow aspirates and biopsies. Using a flow cytometric method that allows the detection of 1 lymphoblast cell among 10,000 normal cells, marrow involvement is present in 72% of children with newly diagnosed T-cell lymphoblastic lymphoma, a proportion that is much higher than that previously established by morphologic examination. The levels of involvement ranged from 0.01% to 31.6%. Moreover, high levels of marrow disease (≥1%) were associated with a poorer event-free survival (EFS). The treatment strategy for lymphoblastic lymphoma is similar to that used for T-ALL. Intensive multi-agent systemic chemotherapy regimens incorporating CNS-directed therapy have resulted in EFS rates of 75% to 90% in children and 40% to 80% in adults.

Case study 4.3

A 28-year-old male patient presents with a history of T-ALL that was diagnosed 7 months ago; he is currently receiving maintenance chemotherapy and returns for a regular appointment feeling well. On routine laboratory assessment, the leukocyte count is 2.1×10^9/L with 28% lymphoblasts. He also has a hemoglobin level of 8.9 g/dL and a platelet count of 57×10^9/L. A bone marrow aspirate reveals 42% lymphoblasts with an immunophenotype positive for CD34, TdT, cytoplasmic CD3, CD1a, CD5, and CD7. The blasts were negative for myeloperoxidase and other B-cell and myeloid markers. The cytogenetics revealed a normal 46XY karyotype. The findings are similar to the initial presentation and consistent with recurrent T-ALL. The patient and his family wish to know what treatment options are available.

- **What is the most appropriate therapy for patients with relapsed T-ALL?**

Although the majority of adult ALL patients reach CR, many will eventually relapse and subsequently be much less responsive to salvage therapy. First relapse typically occurs within the first 2 years after induction, and remissions lasting longer than 18 months are associated with improved response to salvage regimens. CR rates for salvage regimens range from 31% to 78%, and survival for these patients remains poor.

Nelarabine, a deoxyguanosine analog prodrug, is approved as single-agent therapy for both pediatric and adult patients. The CALGB used nelarabine to treat relapsed and refractory patients and demonstrated a CR rate of 41% and OS rate of 28% at 1 year. These results were especially impressive given that many of the patients had failed two or more inductions or had not achieved CR with their last induction regimen. Similar data were seen in the Children's Oncology Group study in pediatric patients with relapsed or refractory T-ALL. The use of nelarabine also allowed patients to proceed to SCT. Based on the significant activity in relapsed disease, several studies are incorporating nelarabine into frontline therapies in hopes of improving the outcome of patients with newly diagnosed T-ALL.

Other salvage regimens include multidrug regimens that usually contain intermediate- to high-dose cytarabine. Clofarabine, a novel purine nucleoside analog, is approved for relapsed ALL in children, but its use in adults as a single agent or in combination is less well studied. Several drugs that target aberrant *NOTCH1* expression resulting from activating mutations in *NOTCH1* are currently being explored in clinical trials. Allo-SCT using reduced-intensity conditioning regimens is another novel approach to the treatment of older patients with relapsed ALL that might result in a potent antileukemia effect while minimizing the unacceptably high treatment-related mortality.

- **What is the overall prognosis for patients with relapsed T-ALL?**

To evaluate the role of SCT in relapsed disease, the large MRC UKALL–ECOG 2993 trial evaluated the outcome of 609 relapsed patients treated with chemotherapy, auto-SCT, or allo-SCT. The 5-year OS rates for the chemotherapy, auto-SCT, matched unrelated donor SCT, and sibling SCT arms were 4%, 15%, 16%, and 23%, respectively, with a significant survival difference between the chemotherapy and transplantation groups. The LALA-94 trial observed similar results in relapsed patients with active disease or in second CR (CR2), with SCT producing improved DFS and OS and with a 5-year OS rate of 25%. In these trials, initial postremission therapy and risk stratification group did not affect relapse rates; however, achieving CR2 prior to SCT did improve outcomes. These studies, as well as previous studies, show that allo-SCT is the only potentially curative therapy in relapsed or refractory ALL. Available data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show that patients receiving transplantation with an HLA-identical sibling donor for ALL in CR2 have approximately a 35% to 40% chance of long-term DFS, whereas patients receiving transplantation with disease not in remission have a DFS of only 10% to 20%.

Selected reading

DeAngelo DJ, Yu D, Johnson JL, *et al*. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood. 2007; 109:5136–42.

Kantarjian HM, O'Brien S, Smith TL, *et al*. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18:547–61.

Larson RA, Dodge RK, Linker CA, *et al*. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood. 1998;92:1556–64.

Stock W, La M, Sanford B, *et al*. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112:1646–54.

Zhang J, Ding L, Holmfeldt L, *et al*. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012; 481:157–63.

CHAPTER 5

Minimal residual disease in acute lymphoblastic leukemia

Meir Wetzler

Roswell Park Cancer Institute, Buffalo, NY, USA

Case study 5.1

A 54-year-old white male diagnosed with pre-B acute lymphoblastic leukemia (pre-B-ALL) with normal karyotype underwent induction treatment according to a Berlin–Frankfurt–Münster (BFM) regimen. The patient is currently at day 7 following initiation of treatment and has persistent circulating blasts.

1. What is your next step?

A. You are concerned that the patient has high-risk disease and contact the Transplant Team to initiate a donor search
B. You reassure the patient that B-cell acute lymphoblastic leukemia (B-ALL) is a "slow responder" and that the persistence of blasts at this point is of no concern
C. You recommend waiting for day 14 bone marrow results
D. You recommend waiting for day 28 bone marrow results

The role of in vivo blast sensitivity to chemotherapy can be used to predict outcome in adult ALL. Specifically, the persistence of circulating or bone marrow blasts after a multi-agent chemotherapy regimen was shown to confer adverse outcome in adult ALL. For example, the probability of continuous complete remission (CR) at 10 years with persistent circulating blasts on day 7 was only 15% compared with 44% for those who cleared their peripheral blasts by day 7 ($P = 0.009$). Similarly, persistent day 14 bone marrow blasts following vincristine, doxorubicin, and dexamethasone induction was 27% compared with 44% for those who cleared their blasts on day 14 ($P = 0.02$). Interestingly, these effects diminished after using a more intensive induction treatment [fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine (hyper-CVAD)]. However, the same group showed that circulating blasts at day 7 were still significant even following the more intensive regimen, finding a rate of continuous CR at 3 years of 55% for those clearing their blasts compared to 36% for those with persistent circulating blasts on day 7 ($P = 0.02$). Therefore, if no other methods for measuring minimal residual disease (MRD) are available, one can consider day 7 circulating blasts as a surrogate for MRD and outcome prediction.

Measurement of MRD by morphology in the bone marrow is hampered by the presence of lymphoid precursors, called hematogones. These are heterogeneous in size and are nonclonal. If the ALL blasts express myeloid markers, the hematogones, by definition, are devoid of these and therefore can be distinguished from leukemia blasts. In summary, assessment of MRD by morphology following recovery from chemotherapy is not an optimal approach. Furthermore, with the CR rate around 80% with current contemporary regimens, more sophisticated methods are needed to identify "responders" and to distinguish them from "super-responders," those who can be recommended less intensive approaches and no allogeneic stem cell transplantation (SCT).

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 5.2

A 37-year-old white female with normal karyotype CD1a^{-}, CD8^{-}, CD5^{weak}, early T-ALL has completed course I, module A, of the hyper-CVAD regimen. She is asking you about her prognosis.

1. What would you reply?

A. You would quote the known literature about intermediate-risk T-ALL that achieves CR after one course of induction

B. You would recommend measuring MRD by T-cell gene rearrangement at this point

C. You would explain that measurement of MRD, by either T-cell gene rearrangement or flow cytometry, is not sensitive enough at the end of induction

D. You would recommend measuring MRD by flow cytometry at this point

The first method to separate leukemic blasts from the normal constituents of the marrow was the measurement of nuclear terminal deoxynucleotidyl transferase and T-cell markers. This was followed by the development of monoclonal antibodies and clinical flow cytometers that led to the current use of multiparameter flow cytometry (MFC). Simultaneously, polymerase chain reaction (PCR) was developed initially to measure fusion transcripts such as *BCR–ABL* or *MLL* rearrangements and later to measure antigen receptor genes. These methods became the current mainstay of measuring MRD.

MFC can be used to detect three different leukemia-associated immunophenotypes. The first set relates to proteins that are tissue restricted, such as T-cell markers that are thymus restricted. Those are obviously limited to T-lineage ALL. The second set of leukemia-associated immunophenotypes is expressed by fusion proteins. One such example is the expression of high-molecular-weight melanoma-associated antigen, the human homolog of the rat NG2, on the surface of 11q23-positive ALL. The third set of leukemia-associated immunophenotypes is exemplified by an abnormal combination of markers usually present during lymphohematopoiesis.

PCR to measure fusion transcripts can distinguish leukemic blasts from normal cells in cases that harbor such transcripts; those are present in approximately 50% of adult ALL. Alternatively, PCR can measure clonal rearrangement of immunoglobulin and T-cell receptor genes. The first step in such an assay is to screen for clonal rearrangement by using PCR primers that match the opposite ends of various V and J regions of the immunoglobulin and T-cell receptor genes. The product is then sequenced, and the results can be used to design patient-specific oligonucleotides. Of note, T-cell receptor gene rearrangements are present in up to 95% of B-lineage ALL, and immunoglobulin gene rearrangements are present in approximately 20% of T-lineage ALL.

The benefit of MFC is that the leukemia-specific immunophenotype can be readily defined at diagnosis and used to detect MRD at a level of 0.01%. A limiting factor for the reliability of the assay is the number of cells to be assayed. For example, to detect one leukemic cell in 10,000, at least 100,000 cells have to be evaluated because 10 leukemic events are the minimum required for results interpretation. Finally, immunophenotype shifts at relapse have been described, decreasing the assay sensitivity.

The strength of the PCR technique to evaluate fusion transcripts is the association between the molecular aberration and the leukemic clone. However, the amount of transcript per leukemic cell may vary among patients with the same genetic aberration. Recently next generation sequencing emerged as a sensitive method for MRD detecting one cell in a million mononuclear cells.

The advantage of the PCR technique to evaluate antigen receptor genes is that the rearranged gene is present in one copy per cell, allowing quantitative PCR to accurately measure MRD. However, these genes may undergo secondary recombination events during the disease course, resulting in oligoclonality. This will complicate the ability to detect MRD because it cannot be predicted which subclone will cause relapse. Therefore, most will recommend measuring at least two markers.

The timing of measuring MRD is not yet standardized. In the largest study for de novo ALL, the Associazione Italiana di Ematologia Pediatrica (AIEOP)-BFM-ALL 2000 study, children were evaluated for MRD by PCR for antigen receptor gene expression at the end of induction (day 33) and at the end of induction consolidation (day 78). Interestingly, for the 3184 pre-B-ALL children, measuring MRD at the end of induction was highly predictive of relapse. However, for the 464 children with T-ALL, measuring MRD at the end of induction consolidation was the most important predictive factor of relapse. Specifically, the outcome of patients who were MRD-negative at day 78 was independent of their MRD status at day 33. No such studies exist in adult ALL.

Finally, a comparison of MFC and antigen receptor gene expression by PCR was recently conducted in 102 children and 136 adult ALL cases. Good concordance was detected between the two methods. Specifically, 13 samples, out of a total of 598 samples, were positive by the antigen receptor assay but negative by flow cytometry, and nine were vice versa. The conclusion was that if standardization and good quality control are maintained, both techniques are equal for MRD measurement.

Case study 5.3

A 45-year-old black male diagnosed with pre-B-ALL underwent induction, consolidation, and interim maintenance treatment with a BFM regimen, and he remained MRD-positive at 0.1% by immunoglobulin gene rearrangement. The patient is inquiring about his treatment options.

1. What should you recommend?

A. The patient should undergo workup for allogeneic SCT
B. The patient should receive re-induction treatment with hyper-CVAD
C. The patient should be enrolled on a clinical trial with blinatumumab
D. The patient should continue with the current treatment because this is too early to make any changes

Persistence of MRD after chemotherapy is associated with clinical relapse in a median of 4–5 months. For example, the 3-year relapse rate among those who had MRD less than 0.01% was zero, while the relapse rate among those who had MRD greater than 0.01% was 94%. This would suggest that patients who have MRD following chemotherapy should undergo allogeneic SCT.

The significance of MRD prior to allogeneic SCT is unclear. For example, in the Medical Research Council United Kingdom ALL (MRC UKALL) 12–Eastern Cooperative Oncology Group (ECOG) 2993 study, the persistence of MRD before allogeneic SCT did not adversely affect outcome for those transplanted in first CR. However, Spinelli *et al*. showed that the overall survival of patients who were MRD-negative prior to undergoing allogeneic SCT was 80% at 3 years compared to 49% for those who were MRD-positive prior to undergoing allogeneic SCT. Similarly, Bassan *et al*. assigned patients with MRD to undergo allogeneic SCT; even though some patients were rescued by this approach, the overall survival of the transplanted patients was only 25%, suggesting that allogeneic SCT may not always overcome the deleterious effect of MRD positivity. Furthermore, in a recent study of unrelated cord blood SCT for pediatric and adult ALL patients, those who had MRD pre-SCT had greater incidence of relapse (30%) and lower 3-year disease-free survival (30%) compared to those without MRD (relapse rate 16%, $P = 0.05$; disease-free survival 55%, $P = 0.02$). Therefore, this suggests that achieving MRD negativity prior to allogeneic SCT may improve SCT outcome.

Blinatumumab is a T-cell engaging bispecific single-chain antibody against CD3 and CD19. It was recently tested to induce an MRD-negative state in pre-B-ALL patients with a MRD-positive state after induction and consolidation therapy. After a median follow-up of 33 months, the relapse-free survival of the 20 patients was 61% and the relapse-free survival of the nine patients who underwent allogeneic SCT was 65%. Therefore, it seems appropriate to offer enrollment in a clinical trial with blinatumumab for patients with MRD positivity prior to allogeneic SCT.

Case study 5.4

A 60-year-old white female diagnosed with pre-B-ALL, carrying the *BCR–ABL* translocation, underwent induction and consolidation chemotherapy with imatinib. The quantitative PCR for *BCR–ABL* at the end of the second course of chemotherapy is still >1% by international standard (IS).

1. How would you proceed?

A. You inform the patient that her risk of relapse following SCT is high
B. You proceed to allogeneic SCT
C. You switch to another tyrosine kinase inhibitor and hold off the plan for SCT
D. You proceed to an autologous SCT after purging the stem cells

The addition of imatinib to conventional chemotherapy for *BCR–ABL*-positive disease has improved the outcome of this disease. However, a significant number still relapse. Recently, the impact of MRD kinetics during imatinib-based treatment was studied by Lee *et al*. Based on MRD at the end of two imatinib-based chemotherapy courses, those who showed persistent major molecular response (a ≥3-log reduction in the *BCR–ABL* message by IS) after two courses of chemotherapy had lower cumulative incidence of relapse at 5 years (5.3% vs. 54.1%, $P = 0.007$) and disease-free survival at 5 years (95% vs. 29.9%, $P = 0.001$) compared to those who had MRD levels >1% (a <2-log reduction). Interestingly, MRD at the end of induction (one course of imatinib-based chemotherapy) was not predictive of outcome, suggesting that MRD at the end of induction is compensated by the subsequent imatinib-based treatment.

The results from Lee *et al.* are somewhat different from those of a previous report by Yanada *et al.* studying the level of MRD at the same time points. In the latter report, negative MRD was not associated with longer relapse-free survival or a lower relapse rate. The difference may stem from different imatinib administration schedules (concomitant vs. sequential) and methods to quantify *BCR–ABL* message (IS vs. non-IS), among others. We would recommend following MRD after imatinib-based chemotherapy. Currently, a study evaluating the role of blinatumumab in *BCR–ABL*-positive disease is about to start. We would recommend enrolling a patient as described here on such a trial.

Case study 5.5

A 58-year-old white male is diagnosed with pre-B-ALL, carrying the BCR–ABL translocation. He achieved remission with imatinib-containing regimen and underwent allogeneic SCT from his brother. Count recovery has been achieved, and the patient is wondering whether he should continue imatinib.

1. How would you reply?

A. The patient does not need to start imatinib because he just completed a curative treatment for his disease
B. The patient should start imatinib prophylactically
C. The patient should start imatinib only if reverse-transcriptase PCR will become positive for BCR–ABL
D. The patient should start dasatinib if reverse-transcriptase PCR will become positive for BCR–ABL.

In a recent prospective randomized trial comparing initiation of imatinib either prophylactically or following detection of MRD, the prophylactic administration of imatinib significantly reduced the incidence of molecular relapse after SCT compared with MRD-triggered administration of imatinib (40% vs. 69%; $P = 0.045$). The median duration of PCR negativity was 26.5 months for those treated prophylactically versus 6.8 months for those treated upon molecular response ($P = 0.065$). Of note, the 5-year survival in both groups was similar (80% vs. 74.5%). Therefore, prophylactic use of imatinib is recommended after allogeneic SCT.

Case study 5.6

A 56-year-old black male with pre-B-ALL carrying the *BCR–ABL* translocation achieved remission on imatinib-based chemotherapy. The patient had no matched donors and therefore is planned to undergo autologous SCT. The stem cells were collected and are minimally positive for *BCR–ABL* (>3-log reduction).

1. What is your next step?

A. You would not proceed to autologous SCT and would type his son as a potential haplo-identical donor
B. You would proceed to transplantation because MRD of the stem cells does not affect outcome
C. You would start the patient on dasatinib and re-collect the stem cells at a later stage
D. You would start the patient on ponatinib and re-collect the stem cells at a later stage

Data from CALGB (now Alliance) 10001 on 19 ALL patients with the *BCR–ABL* translocation show that MRD of the stem cells did not affect outcome following autologous SCT. The reason for this finding is most probably the continuous use of imatinib after SCT. Therefore, we would recommend that the patient proceeds to autologous SCT as planned.

2. The same patient described in the previous question is now 2 years after autologous SCT and has MRD with a >3-log reduction by IS while on imatinib. What is your recommendation?

A. You suggest that the patient be considered for allogeneic SCT
B. You recommend switching imatinib to dasatinib
C. You recommend continuing imatinib
D. You recommend switching the patient to ponatinib

Data from CALGB (now Alliance) 10001 suggest that patients after autologous SCT with MRD of >3-log reduction are doing well with a median overall survival not reached at a follow-up exceeding 6 years. Therefore, we would recommend that the patient continues on imatinib treatment at this point.

Case study answers

Case study 5.1

Question 1: Answer A

Case study 5.2

Question 1: Answer C

Case study 5.3

Question 1: Answer C

Case study 5.4

Question 1: Answer A

Case study 5.5

Question 1: Answer B

Case study 5.6

Question 1: Answer B
Question 2: Answer C

Selected reading

Campana D. Minimal residual disease monitoring in childhood acute lymphoblastic leukemia. Curr Opin Hematol. 2012;19(4):313–8.

Kantarjian H, Thomas D, Wayne AS, *et al*. Monoclonal antibody-based therapies: a new dawn in the treatment of acute lymphoblastic leukemia. J Clin Oncol. 2012;30(31):3876–83.

Ribera JM. Optimal approach to treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: how to best use all the available tools. Leuk Lymphoma. 2013;54(1):21–7.

Rizzari C, Conter V, Stary J, *et al*. Optimizing asparaginase therapy for acute lymphoblastic leukemia. Curr Opin Oncol. 2013;25(Suppl 1):S1–9.

CHAPTER 6

Hematopoietic cell transplantation in adult acute lymphoblastic leukemia

Netanel A. Horowitz[1,2] and Jacob M. Rowe[1,2,3]

[1]Rambam Health Campus, Haifa, Israel
[2]Israel Institute of Technology, Haifa, Israel
[3]Shaare Zedek Medical Center, Jerusalem, Israel

Case study 6.1

A 29-year-old male presents with complaints of fever and increasing fatigue. The complete blood count shows a white blood cell (WBC) count of 45,000/μL, most of which are lymphoblasts; hemoglobin of 7 g/dL; and platelets of 7000/μL. Further work-up reveals retroperitoneal adenopathy, an elevated lactate dehydrogenase (LDH) of 516 U/L, and a markedly hypercellular bone marrow. He is diagnosed with CD20+ precursor B-cell acute lymphoblastic leukemia (ALL). Cytogenetics and molecular diagnostic tests disclosed Philadelphia chromosome (Ph) with *BCR–ABL1* fusion gene. The cerebrospinal fluid (CSF) evaluation is unremarkable. He achieves complete morphologic, cytogenetic, and molecular remission after the first round of chemoimmunotherapy. While you plan for a second session of therapy for this patient, he and his family request you to comment on the following questions.

• What is the optimal duration of chemotherapy prior to proceeding with allogeneic transplantation?

The case presented in the vignette concerns a young patient recently diagnosed with Philadelphia chromosome–positive (Ph+) ALL. The Ph chromosome is the most frequent genetic abnormality in adult ALL; its prevalence in the 18–35 age group is reported to be 12% to 30%, and it is associated with a highly unfavorable prognosis. That is why the recommended consolidation therapy after achieving complete remission (CR) is matched related or matched unrelated stem cell transplantation, depending on finding an appropriate histocompatible donor. The introduction of tyrosine kinase inhibitors (TKIs) into the therapy of Ph+ ALL has significantly improved patient survival. For instance, in the large international ALL study, UKALLXII/E2993, the combination of imatinib-based induction followed by allogeneic stem cell transplantation (SCT) resulted in a 3-year overall survival (OS) rate of 59%. In a recent study conducted by the GMALL group, the OS rate at 3 years was 72%. Both studies reported a poor outcome when transplantation was not performed despite the inclusion of imatinib in the protocol. The most important factor for performing a successful allogeneic SCT is achieving CR. There are several well-established protocols for the treatment of ALL, all of them with very high rates of postinduction CR. However, in all of these well-known studies, allogeneic SCT is never performed prior to completion of all induction and at least three intensification courses, even if CR is achieved early in the treatment course, although this has never been prospectively studied. *Therefore, based on current data, we recommend completing all phases of induction and intensification and confirming CR before proceeding to allogeneic SCT.*

• How many sessions of prophylactic intrathecal chemotherapy are considered optimal prior to and following allogeneic transplantation?

Reports from a variety of studies indicate that between 5% and 10% of adult ALL patients have central nervous system (CNS) involvement at presentation. Factors associated with CNS disease at presentation include a higher WBC count at diagnosis, a T-cell immunophenotype, and the presence of a mediastinal mass. In the largest clinical trial performed so far on adult ALL, the presence of Ph positivity was not found to be a risk factor for CNS involvement. Moreover, the rate of CNS involvement in Ph+ ALL was not significantly higher than in Ph− ALL. The administration of CNS-penetrating agents such as cytarabine and high-dose methotrexate (MTX) as prophylactic therapy to prevent CNS involvement is an inherent part of all established protocols

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

for ALL. In this regard, dasatinib has an advantage over imatinib treatment since it has the ability to cross the blood–brain barrier and therefore augment the existing armamentarium for prophylaxis against CNS relapse. Most protocols also include repeat intrathecal (IT) administration of MTX only, or triple therapy (i.e., MTX, cytarabine, and dexamethasone) as part of this prophylactic strategy. However, there are no comparative studies regarding the optimal number of prophylactic IT therapy prior to proceeding to allogeneic SCT. *In the absence of such data, we conclude that for a patient with no evidence of CNS involvement at presentation, we typically, based on the UKALLXII–E2993 study, administer up to eight courses of IT therapy as CNS prophylaxis with triple therapy. Clearly, any protocol specific variation is reasonable.*

• Should he continue TKIs until the time of myeloablative preparative regimen?

TKIs are an integral part of induction regimens for newly diagnosed Ph+ ALL. Previous studies demonstrated that treating patients with TKIs as monotherapy (combined only with steroids) resulted in a high rate of CR. However, the long-term outcome of such an induction strategy is not known. In fact, in a recent study of elderly patients, combining TKI with a low dose of standard ALL induction chemotherapy resulted in a 90% CR rate with a short median OS of 27 months. Therefore, for young patients, TKIs should be combined with chemotherapy-based induction regimens. The optimal intensity of chemotherapy that is required to achieve the best clinical results with minimal therapy-related morbidity and mortality is unknown. Most ALL protocols integrate TKIs with intensive protocol regimens. For example, in the hyper-CVAD protocol, dasatinib is given for the first 14 days of each course. The main issue with continuous administration of TKIs is prolonged myelotoxicity. The question of how long to administer TKIs before allogeneic SCT has never been studied in clinical trials; *however, we administer TKIs once this patient's blood count recovers, after completion of the induction phases, and continue thereafter until the initiation of conditioning therapy for transplant.*

• When should he resume treatment following allogeneic transplantation?

This is a very important, yet unanswered, question. Existing data regarding this complex issue date to the imatinib clinical trials. A few studies reported that resuming imatinib treatment after allogeneic SCT is associated with high rates of drug discontinuation or dose reduction due to severe side effects. In the PETHEMA trial, only 62% of patients were able to resume imatinib treatment at a median of 3.9 months after myeloablative allogeneic SCT. In the GMALL study, patients were randomized to upfront imatinib, resuming 3 months after allogeneic SCT, or starting imatinib upon any BCR–ABL transcript reappearance. The upfront approach resulted in poor tolerance, and no difference in clinical outcome has yet been observed between the two approaches. Other small single-center nonrandomized trials demonstrated a trend toward improved clinical outcome in patients who can tolerate imatinib pre- and postallogeneic SCT. Data regarding dasatinib in this scenario are lacking. For the time being, a firm and evidence-based recommendation cannot be made on this issue. That being said, in this relatively young, very high-risk patient, we would recommend resuming dasatinib administration early after allogeneic SCT and no later than 3 months posttransplant, depending on the rate of engraftment. A regular quantitative BCR-ABL monitoring policy is mandatory. *At this time, we would continue TKI therapy indefinitely, awaiting studies that indicate that TKIs can be safely discontinued at some point.*

This patient undergoes successful myeloablative fully human leukocyte antigen (HLA) matched sibling donor (MSD) transplantation. Approximately 2 years later, he remains in morphologic and cytogenetic complete remission (CR); however, the BCR–ABL fusion gene converts to detectable levels in the bone marrow aspirate. He is now 31 years of age with a Karnofsky performance score of 90% and a calculated hematopoietic cell transplantation comorbidity index (HCT-CI) of 0. He did not receive tyrosine kinase inhibitor (TKI) therapy following allogeneic transplantation. He does not have chronic GvHD but does have a brief history of steroid-sensitive grade II acute skin GvHD.

• Should this patient undergo a second allogeneic transplantation, assuming that he achieves second molecular remission with single-agent therapy? If you were to recommend second allogeneic transplantation, which source of graft would be the best option for the patient: MSD or matched unrelated donor (MUD)?

Relapsed ALL, especially after allogeneic SCT, is one of the most difficult clinical scenarios to manage. The rate of CR is less than 50%, and even for a patient who achieved CR the median remission duration is extremely short and estimated to be between 3 and 4 months. That is why a second allogeneic SCT is the treatment of choice. Since this patient was not treated with dasatinib before molecular relapse, dasatinib should be started immediately in order to achieve a second CR (CR2). Our patient does not have graft-versus-host-disease (GVHD), which suggests no alloreactivity of the transplant against the leukemia cells. *That is why we recommend an extensive search for another matched sibling or matched unrelated donor.* In a recent study describing the outcomes of Ph− ALL patients transplanted from an unrelated donor in first CR, 5-year treatment-related mortality (TRM), relapse, and OS were 42%, 20%, and 39%, respectively. In a multivariate analysis, TRM as well as OS were significantly higher with HLA *mismatched* but not matched donors. *Other potential sources for transplant such as cord blood or haploidentical donors might be considered.*

Multiple choice and discussion questions

1. Which of the following patient(s) should be considered for upfront allogeneic transplantation assuming the availability of MSD for all of the patients?

A. 16-year-old female with precursor B-cell ALL, positive BCR–ABL1 fusion gene, and in molecular remission
B. 56-year-old female with precursor B-cell ALL, positive BCR–ABL1 fusion gene, and in molecular remission
C. 35-year-old male with precursor B-cell ALL and normal cytogenetics who presented with a WBC count of 15,000/μL with predominant lymphocytes
D. 35-year-old male with precursor B-cell ALL and MLL–AF4 gene fusion, and in molecular remission following 4 weeks of therapy

Before discussing each case separately, a short discussion regarding standard and high-risk ALL is appropriate. The generally accepted prognostic factors defining high risk are age, WBC count, immunophenotyping, high-risk cytogenetics and mutations, and response to induction therapy. OS ranges from 34% to 57% for patients younger than 30 years compared with only 15% to 17% for patients older than 50 years. A WBC count greater than 30,000/μL or 50,000/μL for B-lineage ALL and greater than 100,000/μL for T-lineage ALL is associated with poor prognosis. T-lineage ALL also appears to have better outcomes than B-lineage ALL. The presence of the Ph chromosome or t(4;11)(q21; q23) has been associated with inferior survival in multiple large series. Additionally, the presence of t(8;14)(q24.1;q32), complex karyotype defined as ≥5 chromosomal abnormalities, or low hypodiploidy or near triploidy was noted to have poor survival in the UKALL XII–ECOG 2993 trial. However, even in the standard-risk group, the relapse rate approaches 40–55%. In order to better sort the standard-risk group, the GMALL trialists performed serial measurements of minimal residual disease (MRD) by flow cytometry after induction chemotherapy in 196 standard-risk patients. The 10% of patients who had a rapid MRD decline to lower than 10^{-4} or below detection limit at day 11 and day 24 had a 3-year relapse rate of 0%. Using MRD as a tool for making clinical therapeutic decisions regarding the best consolidation therapy may be highly beneficial in the future and currently is tested in clinical trials. MRD as a prognostic tool may indeed supersede other established prognostic markers. As discussed previously, the pivotal role of allogeneic SCT in the setting of Ph+ ALL patients in CR1 is very well established. *Thus, the 16-year-old female with Ph+ B-cell ALL in molecular remission should definitely be considered for upfront allogeneic SCT.*

The second case, of a 56-year-old female with the same clinical scenario, is more challenging. In the UKALL XII–ECOG 2993 trial, performing a myeloablative allogeneic SCT in the high-risk group (most of these were patients older than 35 years) did not translate into improved OS due to high rates of nonrelapse mortality, most of them due to GVHD or infections. However, the rate of relapse was significantly lower in the high-risk group patients who were transplanted in CR1. The availability of reduced-intensity conditioning (RIC) protocols has made allogeneic SCT an attractive therapeutic option for elderly patients with Ph+ ALL. In the relatively small single-center study conducted in high-risk ALL patients (median age: 56 years), the subgroup of Ph+ ALL patients receiving nonmyeloablative conditioning at CR1 had a 3-year OS of 62% with a relapse rate of 32%. Considering that beyond CR1, SCT is curative in only a minority of patients, *we conclude that this patient should be treated with an upfront RIC allogeneic SCT followed by TKI therapy.*

The third patient is defined as a "pre-therapy" standard-risk patient. There is no information regarding his MRD status at the end of induction therapy. Nevertheless, data exist supporting performing an upfront allogeneic SCT for standard-risk young ALL patients in CR1. This was the main finding of the UKALL XII–ECOG 2993 trial as well as the HOVON trial, and it was later validated by meta-analyses. *Thus, unless this patient has a negative MRD in a very reliable laboratory on days 11 and 24, we would recommend an upfront allogeneic SCT.*

The fourth patient has the cytogenetic translocation t(4:11), which is associated with an adverse prognosis. However, after 4 weeks of induction therapy, he is in complete molecular remission. Does MRD negativity after 4 weeks of induction therapy overcome the adverse prognosis of t(4:11)? This question is very hard to answer as patients with rare adverse prognostic factors are usually diluted within the whole ALL population. An early study demonstrated the prognostic power of MRD monitoring in this rare biologic entity; however, there are no data regarding MRD-based intervention in t(4:11) ALL patients. Furthermore, currently, there is no consensus regarding standardization of MRD measurement techniques or MRD monitoring intervals. *Therefore, we conclude that outside the setting of a clinical trial, this patient should be offered an upfront allogeneic SCT.*

- **In the absence of an MSD, should any of the patients presented in Question 1 be considered for autologous transplantation?**

The role of autologous SCT in ALL has been studied in several clinical trials. Using biological randomization to compare autologous SCT or chemotherapy to allogeneic SCT led to a general consensus that for high-risk patients, allogeneic SCT is associated with significantly higher rates of disease-free survival (DFS) and OS compared to autologous SCT or chemotherapy. No significant difference was noted between chemotherapy and autologous SCT. In the MRC–ECOG trial, 476 patients who were randomized to autologous SCT had significantly lower event-free survival

and a significantly higher relapse rate than patients who were randomized to chemotherapy. No significant difference was found between high-risk and low-risk patients, although this analysis was not statistically powered. A recent retrospective analysis suggested that high-risk patients who are MRD− before autologous SCT had a significantly better survival rate than patients who were MRD+. However, sorting high-risk patients for autologous SCT based on their pretransplant MRD status remains to be proven in well-conducted randomized control trials. *Three of our patients are defined as having a high-risk disease due to adverse genetic risk factors (i.e., Ph and t(4:11)); therefore, in the absence of a matched related donor, one should search for a histocompatible unrelated donor. If no donor is available, autologous transplant remains a valid option. For the relatively young patient with standard-risk disease, currently there are no data to support a beneficial role for autologous SCT over standard chemotherapy in ALL.*

Case study 6.2

You are seeing a 34-year-old female with Ph+ precursor B-cell ALL with your transplant fellow. The patient is in complete remission. You plan and discuss the role of myeloablative allogeneic transplantation with the patient.

• Your fellow requests you to help him understand the best myeloablative and immunosuppressive regimen in this disease and why you would not consider reduced-intensity conditioning (RIC) regimen for this patient.

Standard myeloablative conditioning regimens are based on total body irradiation (TBI) combined with cyclophosphamide or etoposide. According to the European Bone Marrow Transplantation (EBMT) Registry, the use of reduced-toxicity myeloablative regimens, for example using IV busulfan, to avoid TBI-related short- and long-term toxicity is gaining popularity.

Head-to-head comparisons between different myeloablative conditioning regimens in the setting of ALL have never been studied in clinical trials; therefore, a firm recommendation regarding specific myeloablative regimens cannot be made. We think that this decision should be made based on institutional preference, mainly extensive experience with a specific protocol. The traditional immunosuppressive therapy is based on methotrexate and cyclosporine treatment.

Data regarding RIC for ALL patients are scarce relative to myeloid or other low-grade lymphoid malignancies. In a recent study from the CIBMTR, data of Ph− ALL patients were analyzed. Ninety-three RIC patients were compared with 1428 myeloablative SCT counterparts. Interestingly, regimen intensity had no impact on transplant-related mortality or relapse risk on a multivariate analysis. In a similar analysis from the EBMT, RIC patients experienced a significantly decreased risk for nonrelapse mortality and an increased risk for relapse. The risk for relapse is significantly higher in RIC conditioning than in a full myeloablative regimen. Furthermore, data regarding RIC conditioning for young patients with ALL are scanty and premature. *Therefore, we conclude that for this young patient, existing data suggest that a full myeloablative regimen followed by a matched-sibling SCT is the therapy of choice.*

Case study 6.3

You are seeing two patients with Ph+ precursor B-cell ALL; both are 24-year-old males in morphologic and cytogenetic remission, and they are 4 months into chemotherapy. You plan to move forward with allogeneic transplantation in both patients knowing that one of the patients is still positive for the BCR–ABL fusion gene by polymerase chain reaction (PCR).

• In your opinion, how should these two patients with Ph+ precursor B-cell ALL be managed, assuming the availability of fully HLA-matched related and unrelated grafts for these two patients?

Ph+ ALL is a high-risk disease. As discussed in this chapter in detail, it is widely accepted that these patients should undergo myeloablative allogeneic SCT at CR1. *There is no doubt that for the patient who is in CR 4 months into chemotherapy, allogeneic SCT should be performed*. Given that the patient has Ph positivity, we assume that he is on imatinib treatment. In that case, *we would try switching from imatinib to a second-generation TKI (i.e., dasatinib) in order to achieve CR before proceeding to allogeneic SCT*, knowing that achieving CR prior to initiating a myeloablative regimen will result in a better outcome for this patient.

Case study 6.4

A 25-year-old male with "standard risk"—presenting WBC count of 12,000/μl, normal cytogenetics, and obtained morphologic CR within 4 weeks of therapy—precursor CD10+ B-ALL comes to you for a second opinion approximately 8 weeks after initiation of therapy. He was recommended MSD allogeneic transplantation at a university-based hospital. You decide to continue current therapy. At week 16 of therapy, he remains in morphologic remission and the level of minimal residual disease (MRD) is $<10^4$ with immunophenotypic criteria.

• In the absence of a clinical trial, should this patient proceed with allogeneic transplantation?

As discussed in earlier questions, the use of MRD monitoring during therapy as a tool for clinical decision making is currently evaluated in clinical trials. Although encouraging data are starting to emerge, multiple and very important questions are still open. For example, should the immunophenotypic approach be used, or PCR amplification of clone-specific T-cell receptor rearrangements? What is the best time point for MRD negativity: very early into induction therapy, at the end of this period, or maybe even later? In different studies, varying time points are being used. Not to mention that no international standard method for MRD monitoring has been established; therefore, different laboratories might receive different results. The patient presented in the vignette has a standard-risk ALL based on pretreatment risk factors, and it has been decided by his physician to continue with conventional therapy. However, considering all the caveats regarding MRD monitoring, *we would recommend allogeneic SCT for this patient with no delay, since it is very well known that the utility of allogeneic SCT from a matched sibling is significantly better if transplant is carried out while the patient is in CR rather than in early relapse.*

Case study 6.5

You are scheduled to see two patients with T-ALL/lymphoblastic lymphoma (LBL) (T-LBL). Both are 38-year-old males in CR1 following 4 weeks into frontline therapy. Patient 1 presented with symptomatic mediastinal mass and has T-cell LBL (without marrow involvement). Patient 2 has T-cell ALL (T-ALL) and has negative bone marrow biopsy 3.5 weeks into induction therapy. Both patients had a negative CSF evaluation and presented with a WBC of 45,000/μL with predominant lymphocytes.

1. Which of the following are acceptable treatment option(s) for Patient 1 (T-LBL) and Patient 2 (T-ALL)?

A. Maintenance POMP therapy
B. High-dose chemotherapy followed by autologous rescue
C. Allogeneic transplantation

T-LBL is a neoplasm of immature T-cells arising from precursor thymic T-cells at varying stages of differentiation. In the past, LBL and ALL were considered the same disease with different clinical presentations. The word "lymphoma" is used where there is a bulky mass in the mediastinum or elsewhere with minimal or no involvement of bone marrow or peripheral blood. New data, however, suggest different molecular profiles of T-ALL and T-LBL. From a clinical point of view, therapeutic aspects seem to differ among these two acute leukemia subtypes. For example, mediastinal irradiation is recommended in addition to chemotherapy for T-LBL, while mediastinal masses in T-ALL will respond to a chemotherapy-only regimen. Valid prognostic factors have not been identified for T-LBL. In the GMALL series of T-LBL, no single risk factor was associated with relapse risk and high LDH was the only risk factor for OS. In the MD Anderson series, only CNS involvement at diagnosis was associated with poor outcome. In addition, no molecular or chromosomal abnormalities have been shown to be linked with adverse clinical course. Several attempts have been made to create prognostic models for LBL; however, no significant predictive value was demonstrated. Recently, and as discussed before, the role of MRD monitoring as a validated tool for making therapeutic decisions has emerged in ALL; whether this approach is relevant in patients with LBL remains to be defined. LBL patients should be treated with an ALL-type regimen in order to achieve a high rate of CR and DFS. Since the rate of mediastinal relapse is high among T-LBL patients, most authors recommend consolidating patients with mediastinal irradiation given after a dose-intensive ALL treatment.

The management of posttherapy residual mediastinal mass is controversial and beyond the scope of this question. The role of autologous SCT as consolidation strategy for LBL has been studied in a few small series, all of them suggesting a DFS benefit. A single, relatively small (119 patients) study conducted by the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group prospectively randomized LBL patients (68% with T-LBL) to

autologous SCT or conventional chemotherapy. Performing autologous SCT in CR1 resulted in a trend for improved relapse-free survival (24% vs. 55%; $P = 0.065$), but did not translate into improved OS compared with conventional-dose therapy (45% vs. 56%). The role of allogeneic versus autologous SCT in this setting has been evaluated in a large retrospective series. In this study, allogeneic SCT was associated with fewer relapses than autologous SCT (at 5 years, 34% vs. 56%; $P = .004$) but higher TRM (at 6 months, 18% vs. 3%; $P = .002$), which masked any potential survival advantage. So far, no OS benefit has been demonstrated for autologous or allogeneic SCT over conventional chemotherapy regimens. Moreover, clear indications for performing SCT at first CR could not be defined since no valid risk model for LBL exists at present. *Therefore, we conclude that for the patient with T-LBL in CR1, maintenance POMP therapy is the recommended mode of treatment.* In T-ALL, autologous SCT has no advantage over conventional chemotherapy, as has been shown by the large international UKALL XII–ECOG 2993 trial. Traditional risk factors for high-risk T-ALL are WBC > 100,000/dl at presentation, adverse cytogenetics, and early T-precursor ALL. These risk factors are taken into consideration when considering allogeneic SCT for T-ALL patients. Myeloablative allogeneic SCT has been incorporated in several small studies; all of them use various risk factors to assign patients to allogeneic SCT. In the largest study reporting on T-ALL patients, a donor versus no donor randomization was implemented, and all T-ALL patients with a histocompatible sibling donor were assigned for allogeneic SCT regardless of the presence of traditional high-risk factors. OS at 5 years was 46% for the no donor group and 61% for the donor group, a difference maintained at 10 years. *Therefore, we conclude that for the young patient with T-ALL, allogeneic SCT is recommended if an appropriate suitable donor is available.*

Case study 6.6

• In your opinion, how crucial is (i) determination of intrathymic (pro-T, pre-T, cortical-T, or medullary-T) differentiation status and (ii) identification of specific cytogenetic or molecular abnormalities in appropriately selecting patients for frontline autologous or allogeneic transplantation for precursor T-cell leukemia or lymphoma?

The immunophenotypic definition of intrathymic differentiation status of leukemic cells is based on the commonly used European Group for the Immunological Characterization of Leukemias (EGIL) classification system. Several studies have shown an association between T-cell developmental subgroups and prognosis. In both pediatric and adult ALL clinical trials, lower remission rates, early relapses, and shortened OS were associated with immunophenotypically immature T-ALL. For instance, in the GIMEMA LAL 0496 trial, 91% of the cortical mature group achieved CR relative to only 56% in the pro-T/pre-T group. CD1a is a biomarker expressed in the cortical thymocyte stage and not in the pro-T/pre-T stage. In the UKALL XII–ECOG 2993 study, patients with CD1a+ expression at diagnosis had a better 5-year OS (64%) compare with CD1a− patients (39%). Four different genetic subgroups could be identified among T-ALL patients. The TAL–LMO group is characterized by variety of rearrangement in chromosomes 1, 7, 11, and 14. The TLX3–HOX11L2 group shares the t(5:14) translocation. The main cytogenetic findings in the third group are t(7:10) and t(10:14). Overexpression of the HOXA gene characterizes the last group. High expression of the TLX1–HOX11 is associated with higher rates of EFS and OS. The good prognosis conferred by high TLX1–HOX11 expression was independent of phenotyping expression. While many clinical trials evaluated the impact of immunophenotypically characterized T-ALL subtypes and cytogenetic aberrations on disease clinical outcomes, in most of them, these variables have not been used as clinical tools for making therapeutic decisions regarding the best consolidative or maintenance therapy. That being said, in the GMAAL trial, patients with immature T-ALL are defined as high-risk patients and assigned to postinduction upfront allogeneic SCT, while patients with mature "standard-risk" T-ALL are treated with conventional chemotherapy guided by MRD monitoring. Although this group reported good clinical outcomes for early T-ALL patients, the question of whether allogeneic SCT for mature T-ALL patients will result in a significantly better survival advantage cannot be answered by this trial. It is very plausible that these patients will have better clinical outcomes from an aggressive therapeutic strategy as suggested by the UKALL XII–ECOG 2993. Therefore, *we conclude that outside of well-conducted clinical trials, all young T-ALL patients with a matched histocompatible sibling should be offered full myeloablative conditioning followed by SCT, regardless of their intrathymic differentiation status or specific cytogenetic aberrations.*

Case study 6.7

A 35-year-old female is being prepared to undergo allogeneic transplantation for ALL in CR1.

• Outside of a clinical trial, how are the decisions made for or against T-cell-depleted allogeneic transplantation for adult ALL?

Only about one-third of patients who need transplant will have a matched sibling donor. For other patients, a search for an alternative donor should be performed. Matched unrelated donor (MUD), unrelated cord blood (UCB), and haploidentical donors are all reasonable options. In recent years, data regarding the efficacy and safety of MUD transplant are accumulating and showing promising results. A multicenter large retrospective study reported no significant difference in 5-year DFS in 221 high-risk ALL patients transplanted from a matched related versus matched unrelated donor. Data from the CIBMTR showed no difference in leukemia-free survival (LFS) or transplant-related mortality between sibling and MUD allogeneic SCT in 672 ALL patients. However, such data need to be cautiously interpreted as there is an inherent selection bias in deciding who should undergo MUD transplant.

UCB SCT is an acceptable alternative to a well-matched unrelated donor. A large registry data suggested that LFS in patients after UCB was comparable with that after 8/8 and 7/8 allele-matched peripheral blood or bone marrow transplantation. However, in that study, transplant-related mortality was significantly higher after UCB than 8/8 allele MUD transplantation. Another study looked at 623 ALL patients treated with myeloablative allogeneic SCT. Sixty-nine patients received UCB transplant. Relapse rate and 5-year LFS were not significantly different in UCB, well-matched unrelated donor transplant, or matched sibling donor transplant. An alternative option for ALL patients with no matched related or unrelated donor is haploidentical donor SCT. Several strategies to prevent extreme GVHD and graft failure are available, mainly modifications in preparative conditioning regimens and immunosuppression or using T-cell-depleted graft. However, a haploidentical SCT is associated with higher rates of graft failure and severe infections due to slow immune recovery relative to other forms of transplantation. Ciceri *et al.* (2011) conducted a large survey concerning haploidentical SCT in high-risk acute leukemia patients. Ninety-three patients had ALL, and all grafts were T-cell depleted. At transplantation, there were 24 ALL patients in CR1 and 37 in in CR2 or further complete remission, and 32 had active disease. The median follow-up was 29 months in all ALL groups. Engraftment was observed in 91% of all patients. LFS at 2 years was 13% for patients in CR1; and 30% for patients in CR2 or further complete remission; only 7% in those undergoing SCT were in nonremission. In another study for high-risk leukemia patients, a short course of high-dose posttransplant cyclophosphamide was used as GVHD prophylaxis after infusing a T-cell-depleted haploidentical bone marrow graft. The cumulative incidences of grades II–IV and grades III–IV acute GVHD by day 200 were 34% and 6%, respectively. The cumulative incidences of nonrelapse mortality and relapse at 1 year were 15% and 51%, respectively. Actuarial OS and EFS at 2 years after transplantation were 36% and 26%, respectively. These studies demonstrate that performing allogeneic SCT is feasible and may be efficacious even when lacking a well-matched related or unrelated donor. *However, outside the setting of a well-conducted clinical trial, a T-cell-depleted strategy should be reserved only for haploidentical SCT where data regarding the efficacy of this approach exist. For the patient described in the question, T-cell depletion is not recommended if a matched related or unrelated donor can be found.*

Mutiple choice answer

Question 1: Answer C

Case study answer

Case study 6.5

Question 1: Answer C

Selected reading

Goldstone AH, Richards SM, Lazarus HM, *et al.* In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111:1827–33.

Marks DI, Paietta EM, Moorman AV, *et al.* T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype,

cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). Blood. 2009;114: 5136–45.

National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology (NCCN Guidelines™). Acute lymphoblastic leukemia version 2.2012. 2012. Available from: http://www.nccn.org/professionals/physician_gls/pdf/all.pdf

Ram R, Storb R, Sandmaier BM, *et al*. Non-myeloablative conditioning with allogeneic hematopoietic cell transplantation for the treatment of high-risk acute lymphoblastic leukemia. Haematologica. 2011;96:1113–20.

Tomblyn MB, Arora M, Baker KS, *et al*. Myeloablative hematopoietic cell transplantation for acute lymphoblastic leukemia: analysis of graft sources and long-term outcome. J Clin Oncol. 2009;27:3634–41.

PART 2

Acute Myeloid Leukemia in Adults

CHAPTER 7

Prognosis in acute myeloid leukemia: cytogenetics and beyond

Gordana Raca, Madina Sukhanova, and Lucy A. Godley
The University of Chicago, Chicago, IL, USA

Case study 7.1

A 32-year-old woman presents to her primary doctor with fever and sore throat of 10 days' duration. On physical exam, she has gingival hyperplasia and petecchiae. A complete blood cell count (CBC) shows a total white blood cell (WBC) count of 80,000/μL with 40% blasts. The patient is referred to the hematology/oncology department with a suspected diagnosis of acute myeloid leukemia (AML).

1. When should I order cytogenetic analysis and when fluorescent in situ hybridization (FISH)?

A. I should always order only FISH
B. I should always order only cytogenetic analysis
C. I should always order both tests
D. I should order only molecular tests

Chromosomal abnormalities (e.g., deletions, duplications, gain and loss of chromosome material, translocations, and inversions) are common drivers of pathogenesis. Conventional chromosome analysis is a critical part of laboratory work-up for acute myeloid leukemia (AML), as it can provide (i) diagnostic information; (ii) information useful for classification, staging, and prognostication; (iii) information to guide an appropriate choice of therapy; and (iv) evidence of remission or relapse. Karyotyping is the only clinically available test to detect both balanced (translocations and inversions) and unbalanced (deletions and duplications) rearrangements at any chromosomal location, and it is irreplaceable at diagnosis, when no information is available about the abnormalities that might be present in the sample.

FISH is a highly sensitive, targeted test for known chromosome rearrangements. The method does not, however, provide the genome-wide screen obtainable by classical cytogenetics. At diagnosis, FISH can be a useful adjunct to karyotyping in specific situations, if a particular chromosomal abnormality is strongly suspected based on the morphology or clinical picture. For example, it is faster to confirm the presence of the t(15;17)-PML–RARA (promyelocytic leukemia and retinoic acid receptor alpha) in suspected acute promyelocytic leukemia (APL) by FISH than by karyotyping. In addition, the inv(16) should always be confirmed by FISH, since it causes a subtle change in the chromosome 16 banding pattern, and is therefore often difficult to recognize reliably by karyotyping, especially in samples with poor morphology. When a variant translocation is seen by karyotyping, FISH should be used to verify the presence of the expected gene rearrangement. However, the most important application of FISH is not at diagnosis, but rather to evaluate follow-up samples for residual disease, assuming that a FISH assay is available for the cytogenetic abnormality that was detected at diagnosis. FISH is useful particularly for cases in which it is not possible to monitor residual disease by another more sensitive method (e.g., flow cytometry or polymerase chain reaction (PCR)). Furthermore, in cases that will be monitored for residual disease by FISH, it is advisable to perform the analysis on the diagnostic sample to verify the signal pattern for future comparison.

2. What molecular tests should be ordered with cytogenetic analysis?

A. *FLT3* mutation test
B. *NPM1* mutation test
C. *CEBPA* mutation test
D. All of the above

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

In addition to cytogenetic abnormalities, several molecular abnormalities have been shown to have prognostic importance in patients with AML. Four molecular genetic markers are included in current National Comprehensive Cancer Network (NCCN) and European LeukemiaNet guidelines for diagnosis, prognostic assessment, and therapeutic decision making (*FLT3*, *NPM1*, *CEBPA*, and *KIT*).

3. Do you need to perform multiple tests that assess the same molecular rearrangement? For example, for a patient with APL, do you need to order FISH, cytogenetic analysis, and reverse transcription PCR (RT-PCR) for PML-RARA?

A. You need to order routine chromosome analysis only
B. You need to order FISH and RT-PCR
C. You need to order all of the above tests
D. It is important to use an appropriate combination of tests for each patient

No single genetic testing procedure fulfills all the needs of clinical care for patients with AML. It is important to use a combination of testing methods that are best suited for each clinical situation. At diagnosis of AML, conventional chromosome analysis is essential for initial identification of chromosome abnormalities. If abnormalities identified by karyotyping cannot be tracked by FISH or RT-PCR due to a lack of suitable probes or primers, conventional cytogenetics becomes the sole method for detecting the presence of genetically abnormal clones in follow-up samples. However, many common chromosome abnormalities associated with AML (t(9;22), t(15;17), inv(16), and t(8;21)) can be detected by all three clinically used methods: chromosome analysis, FISH, or RT-PCR. In these cases, the genetic test of choice should be selected according to the clinical situation, turnaround time, and cost. Conventional cytogenetic analysis should be repeated whenever there is a concern for disease progression or relapse, since it can detect additional abnormalities that were not present at diagnosis and are consistent with clonal evolution and disease progression. However, FISH or RT-PCR are superior to karyotyping for monitoring patients who are believed to be in remission, since these methods are more sensitive and quantitative. RT-PCR is the most sensitive of the three assays, and when available, it might be the method of choice; it has proven useful to test for very low levels of the *BCR–ABL1* and other fusion transcripts in patients after treatment or post bone marrow transplantation. Due to its quantitative nature, RT-PCR is the standard method to monitor responses to tyrosine kinase inhibitor therapy in chronic myeloid leukemia. For abnormalities for which RT-PCR assay is not available, FISH can be a viable alternative for confirming that a patient remains in remission.

Case study 7.2

A 52-year-old man is admitted to the Leukemia Service with AML, and cytogenetic analysis shows inv(16). The medical student tells him that he has "good prognosis" leukemia.

1. Which chromosome-based or molecular test results change your clinical management?

A. t(15;17)
B. t(6;9)
C. Bi-allelic *CEBPA* mutation
D. All of the above

The karyotype of the leukemic cells is the strongest predictor of response to induction therapy and for survival in AML. Risk classification schemes based on cytogenetic abnormalities have been developed over a period of almost two decades by large collaborative groups, the Southwest Oncology Group (SWOG), the Medical Research Council (MRC), and Alliance/CALGB (Cancer and Leukemia Group B). Importantly, all three classification schemes distinguish three major prognostic groups—favorable, intermediate, and unfavorable—with good concordance regarding the cytogenetic abnormalities that predict favorable (t(8;21), inv(16), and t(15;17)) as well as unfavorable outcomes (complex karyotype, t(6;9), abnormal 3q, myeloid-lymphoid leukemia (MLL) rearrangements, −5/del(5q), and −7/del(7q)). More recently, the characterization of a number of molecular markers has allowed further refinement of risk stratification in AML. Systematic evaluation for nonrandom mutations in AML has allowed better stratification of AMLs with normal cytogenetics (CN-AML), which represents a large proportion (almost 50%) of newly diagnosed cases. The recently proposed European Leukemia Network (ELN) classification uses the presence of the *FLT3*–ITD mutation, as well as *CEBPA* and *NPM1* mutation status, to stratify AML with intermediate-risk cytogenetics, including CN-AML. After induction, patients with favorable genetic findings are recommended to receive consolidation chemotherapy, whereas an allogeneic stem cell transplant from a suitable HLA-matched donor is currently considered the treatment of choice for patients with unfavorable cytogenetic abnormalities.

2. Is it important to check the mutation status of *KIT* at initial presentation for this patient?

A. Yes, *KIT* mutation status should be checked in all patients with inv(16) and t(8;21)

B. No, *KIT* mutation status should only be checked in patients with t(8;21)
C. Yes, *KIT* mutation status should be checked in all patients with inv(16)
D. No, *KIT* mutation status has no bearing on the prognosis of patients whose cytogenetic analysis puts them in a good risk category

Although patients with inv(16), t(16;16), and t(8;21) are considered to have an overall favorable prognosis, point mutations in the *KIT* gene identify a subset of patients who have a noticeably poorer prognosis. The most common *KIT* mutations encode changes at aspartic acid 816 of the KIT protein and confer a growth advantage to the leukemic cells. Gene expression profiling has confirmed that *KIT*-mutant AMLs have a distinct gene expression signature. NCCN guidelines place *KIT*-mutated core binding factor leukemias into an intermediate-risk group, opening up the consideration of allogeneic stem cell transplant in first remission.

3. Can chromosomal and molecular tests give false-negative results?

A. Karyotyping can give false-negative results, but molecular methods are always accurate
B. FISH can give false-negative results, but karyotyping and molecular methods are always accurate
C. Molecular methods can give false-negative results, but karyotyping and FISH are always accurate
D. Each method can sometimes give false-negative results

A possible reason for obtaining false-negative results by chromosome analysis is a failure of tumor cells to grow in tissue culture. When malignant cells do not proliferate *in vitro*, a normal karyotype is typically obtained from nonmalignant, actively dividing cells in the bone marrow sample, and without further studies it is impossible to decipher whether leukemic cells failed to be analyzed or were indeed cytogenetically normal. While rarely a problem in acute leukemias, this is a major limitation for cytogenetic testing of indolent diseases like plasma cell malignancies and chronic lymphocytic leukemia.

The presence of submicroscopic (cryptic) abnormalities, which are not detectable by karyotyping due to its limited resolution, is another potential cause for obtaining false-negative results by conventional cytogenetics.

FISH testing will occasionally give false-negative results in cases of atypical chromosomal rearrangements. Fusion genes can sometimes be generated by small interstitial insertions of chromosomal material, which may be undetectable by clinically used FISH probes. Additionally, although FISH has much higher resolution than karyotyping, some microdeletions (which remove only a part of the region targeted by a FISH probe) will be too small for detection by FISH.

PCR assays developed for detection of fusion genes may give false-negative results due to breakpoint heterogeneity. PCR assays are typically optimized to detect fusion transcripts generated through most frequent breakpoints; the cases with less common breakpoints within one or both partner genes will be missed by most clinically available PCR tests.

Chance mutations in primer binding sites, leading to allelic dropout, also serve as a source of false-negative results for any PCR-based molecular test. Finally, mutations present in a very small fraction of cells are usually undetected by traditional (Sanger) sequencing, due to its limited sensitivity.

4. Which result do you believe if there are discordant results from FISH versus karyotype analysis?

A. You should only believe karyotyping, since it is a "gold standard"
B. You should only believe FISH, since it is more sensitive
C. If the results are discordant, neither method should be believed
D. A discrepancy is not a reason to disregard either result

Karyotype analysis and FISH have different indications, strengths, and weaknesses, and they do not always provide the same answers. Discrepancies that occasionally occur between a karyotype and a FISH result do not imply that either assay failed or is not reliable. A normal karyotype in a case with a clearly abnormal FISH result may be observed for multiple reasons, including (i) low or no yield of metaphases from tumor cells, (ii) tumor cells with a very poor chromosome morphology, or (iii) deletions, duplications, translocations, and other structural abnormalities involving small chromosomal regions, so that the resolution of conventional analysis is insufficient for their identification.

Possible explanations for a negative FISH result when an abnormality is observed by karyotyping may include (i) an abnormality that looks by G-banding like a particular translocation or other specific structural rearrangement identifiable by FISH (t(15;17), t(9;22), inv(3), etc.), but actually involves different chromosomal regions and different breakpoints; and (ii) a chromosome or a chromosomal region appears to be missing by conventional analysis, but is actually present within marker chromosomes and other unidentifiable chromosomal segments in the karyotype.

When thinking about FISH, it is very important to remember its targeted nature. A negative FISH result does not mean an absence of chromosomal abnormalities in leukemic cells; it only indicates that specific abnormalities tested for by the selected FISH probes are not present.

Case study 7.3

A 28-year-old woman achieves a clinical and cytogenetic remission from an AML with t(8;21).

1. After the initial cytogenetic-molecular analysis, how often should you repeat these tests if the patient appears to be in a clinical remission?

A. Perform them on bone marrow annually for 5 years
B. Perform them on peripheral blood samples every 3 months for the first 2 years, and, after that, annually for at least another 3 years
C. There is no reason to perform these tests once a patient has completed consolidation therapy since relapse rates are so low
D. Perform them monthly with the peripheral blood draws for 2 years

Patients with good-risk AML who undergo consolidation therapy and achieve clinical and cytogenetic-molecular remission are still at risk for relapse—about 36% of these patients relapse by 3 years. Generally, it is considered prudent to identify relapse as soon as possible; therefore, waiting for overt relapse in the peripheral blood and with patient symptomatology is not advised (this topic is covered in detail in this volume).

2. For which acute leukemias does the reappearance of the molecular abnormality signal impending relapse?

A. t(15;17)
B. *NPM*
C. *FLT3-ITD*
D. All of the above

For most acute leukemias, the identification of the original molecular abnormality after achieving a molecular remission is indicative of impending relapse. This is true for t(15;17), *FLT3*–ITD, and *NPM* mutations.

Case study 7.4

An 82-year-old woman presents with AML and is found to have del(5q) as well as bi-allelic CEBPA mutations.

1. When do additional cytogenetic abnormalities have prognostic value?

A. Additional abnormalities always indicate worse prognosis
B. Additional abnormalities often indicate worse prognosis
C. Additional abnormalities always indicate better prognosis
D. Additional abnormalities have no prognostic significance

Cytogenetic abnormalities are present in association with the *CEBPA* mutation in approximately 25% of the cases, and although the data are limited, some studies suggest that the patients with *CEBPA* mutations and chromosomal rearrangements do more poorly than those with a normal karyotype.

However, additional cytogenetic abnormalities do not always signify adverse prognosis. Disease-initiating cytogenetic mutations associated with a favorable outcome (like t(8;21), t(15;17), and inv(16)) are commonly accompanied at diagnosis by additional chromosomal abnormalities. AML with the t(15;17) shows trisomy 8 as the secondary abnormality at diagnosis in up to one-third of the cases. The t(8;21) is seen as a sole anomaly in only 20% of the cases, while the remaining 80% have additional numerical (two-thirds) or structural (one-third) anomalies. A loss of Y or X chromosome is seen in half of the cases of AML with t(8;21). Less frequently observed secondary anomalies include del(7q) or −7, +8, and del (9q). The inv(16) is accompanied by additional rearrangements in one-third of the cases, with +8 and +22 being the most frequent changes (in 15% of the cases each). Based on the current data, additional chromosomal abnormalities do not appear to have negative impacts on prognosis for patients with t(15;17) or t(8;21). Some studies even predicted a better outcome in patients with inv(16) in the presence of trisomy 22.

In contrast to the secondary aberrations associated with the t(8;21), inv(16), and t(15;17), in most other situations a complex karyotype is considered a sign of genetic instability that correlates with an advanced-stage and aggressive disease. It is important not to confuse AML with a favorable cytogenetic marker and secondary aberrations and AML with a complex karyotype. In risk stratification of AML, a complex karyotype is defined as multiple unrelated cytogenetic abnormalities seen in a single karyotype; in SWOG and CALGB prognostic classifications, three or greater abnormalities are required for this definition, whereas the MRC defines a complex karyotype by the presence of four or more abnormalities. In all currently used risk stratification schemes, a complex karyotype is considered as a marker of very poor prognosis.

2. What is the clinical significance of bi-allelic *CEBPA* mutations?

A. There is no clinical significance to bi-allelic *CEBPA* mutations
B. They confer a poor prognosis

C. They are often found in acute promyelocytic leukemia
D. They may be seen in a familial predisposition syndrome in which patients inherit one mutated *CEBPA* allele

About 10% of patients who have bi-allelic *CEBPA* mutations have inherited one of the mutated alleles as a germline mutation. It is important to identify such individuals, because there may be other family members who carry the familial germline mutation and would benefit from genetic counseling, mutation testing, and potentially increased surveillance. In the case of familial bi-allelic *CEBPA* mutations, often the germline mutation is found within the 5′ end of the gene, and development of AML is accompanied by acquisition of a second somatic mutation, usually within the 3′ end of the gene, although germline 3′ *CEBPA* mutations have also been identified. Familial AML with mutated *CEBPA* is inherited in an autosomal dominant fashion, and it appears to confer nearly complete penetrance for the development of AML. Bi-allelic *CEBPA* mutations confer a relatively favorable prognosis and are treated as lower-risk AMLs.

Case study 7.5

A 75-year-old woman complains to her primary doctor that she feels tired. A CBC shows a hemoglobin of 7 g/dL, and a bone marrow biopsy shows 5q− syndrome.

1. 5q− syndrome is a "good prognosis" MDS; why is that a "bad" prognostic indicator for AML?

A. Deletions in MDS and AML affect different critical regions of 5q
B. Different genes and pathways play a role in pathogenesis
C. Different outcomes are related to the presence or absence of associated genetic abnormalities
D. All of the above

A deletion of the long arm of chromosome 5 is one of the most frequent cytogenetic abnormalities in MDS and AML, occurring in 10% to 15% of the cases. The 5q− syndrome is a distinct type of MDS defined by a medullary blast count of less than 5% and the deletion of 5q (del(5q)) as the sole karyotypic abnormality. It is characterized by macrocytosis, anemia, a normal or high platelet count, hypolobulated megakaryocytes in the bone marrow, a female preponderance, and a good prognosis with approximately 10% of patients transforming to AML. In contrast, cases of non-5q− syndrome myeloid disorders with losses of genetic material involving chromosome 5 have consistently been associated with poor prognoses.

The commonly deleted regions (CDRs) in 5q disorders have been extensively studied, with two distinct CDRs mapped to 5q33.1 (more telomeric) in 5q− syndrome, and 5q31.1 (more centromeric) in non-5q− syndrome MDS and AML.

Major advances have been made in understanding molecular pathogenesis of the 5q− syndrome by the demonstration that haploinsufficiency for the ribosomal gene *RPS14* results in ribosomal deficiency, further causing p53 activation and defective erythropoiesis.

Completely different molecular pathways seem to play a role in the pathogenesis of non-5q− syndrome MDS and AML. The 1–1.5-Mb CDR at 5q31 identified in these disorders includes two main candidate genes for the role in pathogenesis: *EGR1* and *CTNNA1*.

Critical differences between 5q− syndrome and non-5q− syndrome MDS and AML also lie with mutations and genomic aberrations on chromosomal regions outside 5q. Importantly, the del(5q) in non-5q− syndrome MDS and AML, particularly secondary AML, invariably occurs together with other karyotypic abnormalities and frequently as part of a complex karyotype. Additionally, mutations with loss of function of p53 are significantly associated with the del(5q) in therapy-related MDS and therapy-related AML after previous treatment with alkylating agents.

Case study 7.6

A 45-year-old man is diagnosed with a normal karyotype AML, and his doctor wonders if she should run any additional analysis to understand the drivers of the patient's leukemia.

1. Is there a role for performing array-Comparative Genomic Hybridization (array-CGH) based tests for AML patients?

A. Array-CGH-based tests can detect prognostically important abnormalities in AML
B. Array-CGH-based tests can detect microdeletions and microdeletions that are too small to be identified by karyotyping
C. Arrays with single-nucleotide polymorphism (SNP) probes can detect loss-of-heterozygosity events
D. All of the above

SNP array profiling allows for the detection of copy number changes and loss of heterozygosity (LOH) in cancer genomes. It is a powerful technique that has been applied productively to many hematologic cancers, including AML.

(*Continued*)

Application of SNP array–based analysis allows one to (i) detect gains and losses of genomic material (deletions and duplications) that are too small to be identified by conventional cytogenetics; (ii) precisely characterize chromosomal rearrangements (both the ones visible and invisible by karyotyping), including their exact size, genomic coordinates, affected genes, and so on; (iii) detect copy-neutral LOH, which is often associated with mutated genes; and (iv) reveal genomic complexity, which constitutes an independent predictor for short survival in AML. A potential application of SNP arrays in AML testing is at diagnosis to detect genomic markers that may have been missed by cytogenetics and molecular testing; array analysis may especially be indicated in AML cases with a normal karyotype and negative *FLT3*, *NPM1*, and *CEBPA* testing. However, it is important to understand the limitations of array technology: it cannot detect balanced rearrangements (translocations and inversions), low populations of tumor cells, and clonal heterogeneity. SNP array profiling and cytogenetics are therefore complementary techniques in AML genome analysis, each measuring genomic events not detectable through the other technology. SNP array profiling can be viewed as an emerging technology at the threshold of becoming a valuable additional tool for routine clinical testing in AML.

Table 7.1 Established and emerging prognostic markers in acute myeloid leukemia (AML).

	Genetic aberration	Chromosome	Prognostic impact
Routinely used markers	*NPM1*	5q35	Good prognosis with wild-type *FLT3*–ITD
	FLT3–ITD	13q12	Poor prognosis
	CEBPA	19q13.1	Good prognosis
Emerging markers	*IDH1*	2q33	Poor prognosis
	IDH2	15q26	
	WT1	11p13	Poor prognosis
	MLL–PTD	11q23	Poor prognosis
	EVI1	3q26.2	Poor prognosis with high expression
	RUNX1	21q22	Poor prognosis
	TET2	4q24	Poor prognosis
	miR-181a	1q32.1 9q33.3	Good prognosis with increased expression
	MN1	22q12.3	Poor prognosis with increased expression
	ASXL1	20q11	Poor prognosis
	BAALC	8q22.3	Poor prognosis with increased expression
	ERG	21q22	Poor prognosis with increased expression

2. What are the emerging molecular tests that might become clinically relevant within the next 5 years?

A. *DNMT3A* mutation test
B. *ASXL1* mutation test
C. *IDH1/IDH2* mutation test
D. The mutational analysis of a large set of genetic alterations

While *NPM1*, *FLT3*, *CEBPA*, and *KIT* mutation studies are now widely accepted as standard practice in AML diagnosis and prognostic assessment, studies over the last several years have identified numerous recurrently mutated genes that are also associated with prognostic differences in AML. Some of the more widely studied abnormalities include duplications in *MLL* and mutations in *DNMT3A*, *RUNX1*, *TET2*, *EZH2*, *ASXL1*, *IDH1*, *IDH2*, and *TP53* (Table 7.1). The challenge currently lies in trying to determine which mutations, or combinations of these mutations, represent clinically the most important abnormalities, and how to use the molecular information to guide the selection of therapeutic regimens. A recent landmark study by Patel *et al.* examined mutations in 17 genes and identified an 11-gene panel of abnormalities that greatly refines prognostic evaluation of AML. It is likely that the next few years will see numerous similar studies in an effort to define an optimal consensus panel. The major challenge for molecular diagnostic laboratories will be to identify techniques to evaluate such genetic panels in a timely, cost-effective manner.

3. Will next-generation sequencing (NGS) replace sending cytogenetic, FISH, and molecular tests?

A. It is likely that at least some of our testing in the future will involve NGS, but it is difficult to predict exactly which tests will be replaced
B. Yes, NGS will become standard within 1 year
C. No, NGS is too expensive to be adopted widely
D. The use of NGS will depend on institutional preferences and the availability of the specialized equipment

Although it is difficult to say for sure which tests will be performed by NGS, it is likely that at least some of our diagnostic or prognostic testing for acute leukemias will involve NGS within the near future. Currently, acute leukemias are distinguished based on morphologic, immunophenotypic, cytogenetic, and molecular bases. However, NGS has the capacity to assess several of these abnormalities simultaneously. The rapidly decreasing costs and the availability of panel-based testing in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories will facilitate the rapid incorporation of sequencing technologies into clinical practice.

Case study answers

Case study 7.1

Question 1: Answer C
Question 2: Answer D
Question 3: Answer D

Case study 7.2

Question 1: Answer D
Question 2: Answer A
Question 3: Answer D
Question 4: Answer D

Case study 7.3

Question 1: Answer B
Question 2: Answer D

Case study 7.4

Question 1: Answer B
Question 2: Answer D

Case study 7.5

Question 1: Answer D

Case study 7.6

Question 1: Answer D
Question 2: Answer D
Question 3: Answer A

Selected reading

Dohner H, Estey EH, Amadori S, *et al.* Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115:453–74.

Jourdan E, Boissel N, Chevret S, *et al.* Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. Blood. 2013; 121(12):2213–23.

Marcucci G, Haferlach T, Dohner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. J Clin Oncol. 2011;29:475–86.

O'Donnell MR, Abboud CN, Altman J, *et al.* Acute myeloid leukemia. J Natl Compr Canc Netw. 2012;10:984–1021.

Patel JP, Gonen M, Figueroa ME. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366:1079–89.

CHAPTER 8

Induction therapy in acute myeloid leukemia

Tapan Kadia and Farhad Ravandi

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 8.1

A 45-year-old man with no past medical history presents with easy bruising and pancytopenia, and he is diagnosed with acute myeloid leukemia (AML). Further work-up, including cytogenetic analysis, reveals inv(16) karyotype in all metaphases. He would like to know first about his prognosis and then about goals of therapy.

1. What should you tell him?

A. He has an adverse prognosis. His disease is characterized by low response to front-line chemotherapy and frequent relapses; treatment will be composed of two cycles of palliative chemotherapy, followed by observation and comfort care

B. He has a relatively good prognosis. His treatment will consist of eight cycles of intense multiagent chemotherapy with a good response rate, followed by 2 years of maintenance therapy with oral chemotherapy

C. He has a relatively adverse prognosis with a low response to front-line therapy. His treatment will consist of a round of high-intensity chemotherapy followed immediately by allogeneic stem cell transplantation (SCT)

D. He has a relatively good prognosis with good response to front-line chemotherapy and very good potential for long-term benefit. His treatment will consist of a round of intense chemotherapy followed by three or four more cycles of high-dose chemotherapy

Several studies investigating variations of induction and consolidation approaches in core binding factor (CBF) AML have demonstrated complete remission (CR) rates of >90% and overall survival (OS) rates of about 70% at 5 years or longer. Three to four cycles of high-dose ara-C-based consolidation are an important part of treatment for CBF leukemias. The goal of therapy is to achieve a CR, followed by postremission consolidation to maintain remission and contribute to long-term OS. CR in AML is defined by a bone marrow blast count of <5%, and recovery of peripheral absolute neutrophil count to >1000 and platelets to >100,000. Given the excellent long-term prognosis associated with CBF leukemias, allogeneic bone marrow transplant is typically not considered for patients in first remission. Recent data suggest that it may be possible to identify patients with CBF leukemia who are destined not to do well perhaps by identification of those patients with an associated *c-KIT* mutation or those with persistent minimal residual disease after induction and consolidation. Identification of *c-KIT* mutants may also be important therapeutically as these leukemias may be susceptible to the effects of KIT kinase inhibitors.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 8.2

A 62-year-old man is referred to you with pancytopenia and a new diagnosis of AML. His karyotype includes multiple chromosomal abnormalities, including −5, −7, +8, and 17p−. He has been told by his local oncologist that these portend an overall adverse prognosis with a lower rate of remission, high rate of relapse, and shortened OS using traditional regimens.

1. Is this true?

A. Yes
B. No

This patient's AML is characterized by multiple (≥3) abnormalities, including the presence of multiple monosomies. Complex karyotype, defined variably as ≥3, ≥4, and ≥5 abnormalities, has long been regarded as conferring the most adverse prognosis in AML—characterized by low response rates, high relapse rates, and poor long-term outcome. Recently, this definition of adverse, complex karyotype has been further refined by the introduction of the "monosomal karyotype" (MK). MK is defined as a karyotype with ≥2 distinct autosomal chromosome monosomies OR a single autosomal monosomy in the presence of an additional chromosomal structural abnormality. By this definition, this patient has an MK. Multiple studies comparing MK to the previously defined "complex karyotype" demonstrate improved prognostication and the identification of a subgroup of AML with an extremely adverse outcome. For example, Haferlach *et al*. (2012) compared the significance of MK to complex karyotypes (defined as ≥3 or 4 abnormalities (abnl)). The found that the MK predicted for an even more adverse prognosis than a complex karyotype (≥3 abnl) without MK and added further negative prognosis to those with complex and ≥4 abnl. The incidence of an MK karyotype in newly diagnosed AML appears to increase with increasing age: it is present in 6–10% of patients under age 60, but in up to 20% of patients >60. The MK confers a very adverse prognosis at any age, however. CR rates range from 24% to 50% in patients <60 years and only 13–34% in those >60. Overall survival rates are equally poor: 17–40% at 4 years in patients ≤30 years, 3–4% at 4 years in patients <60 years, and 1% at 4 years in patients >60 years. Such poor outcomes with standard approaches to treatment argue for newer, innovative approaches and clinical trials for this population. Due to the poor outcomes with standard therapies, these patients should be considered for investigational clinical trials and for early allogeneic SCT in first remission in appropriate candidates.

Case study 8.3

A newly diagnosed 37-year-old man with AML is found to have a *FLT3*–ITD mutation and is clearly concerned about his prognosis with standard therapy.

1. Are there any ways to target *FLT3* abnormalities in AML?

A. Yes
B. No

As mentioned in Case studies 8.1 and 8.2, mutated *FLT3* leads to constitutive activation of this receptor tyrosine kinase, and several small-molecule tyrosine kinase inhibitors are currently in investigational development for the treatment of *FLT3*-mutated AML. In a phase I–II study of sorafenib in combination with idarubicin and cytarabine in patients with AML, Ravandi *et al*. (2010) demonstrated an overall CR rate of 75%. In patients with *FLT3* mutations, the CR rate was 93%, with a 1-year OS rate of 74%. Correlative studies showed an on-target effect of sorafenib on *FLT3*, and the combination was well tolerated. Stone *et al*. (2012) studied the combination of midostaurin with daunorubicin and cytarabine in patients with AML. The CR rate was 80% in all patients overall, but 92% in those patients with *FLT3*-mutated AML. Importantly, the OS rates for *FLT3*-mutated patients at 1 and 2 years were 85% and 62%, respectively. These rates were similar to those with *FLT3* wild type, suggesting that the addition of midostaurin may have negated the negative impact of the *FLT3* mutation. Further studies to confirm these observations are ongoing. AC220 (quizartinib) is a new, potent FLT3 inhibitor that is currently in development. After positive results in a phase I trial, Cortes *et al*. (2012) recently presented the final results of a phase II trial of single-agent quizartinib in patients with relapsed and refractory AML regardless of their *FLT3* mutation status. The composite CR, CR with incomplete platelet recovery (CRp), and CR with incomplete hematologic recovery (CRi) rate was 32% in patients without *FLT3*–ITD mutations and 54% in those with a *FLT3*–ITD mutation. The OS in those with *FLT3*–ITD(+) AML treated with quizartinib was 25 weeks. These high response rates with single-agent quizartinib in a relapsed population are encouraging and have led to several ongoing studies of this agent in frontline AML in combination with chemotherapy. Our approach to patients with *FLT3*-mutated AML involves risk stratification based on *FLT3* mutation, allelic burden, and enrolling in an investigational trial implementing an *FLT3* inhibitor when available. Newer studies involving inhibitors of *FLT3–TKD* mutations are also ongoing and may be an important breakthrough for that subset of patients.

Case study 8.4

A 34-year-old female with no past medical history and no siblings presents with a new diagnosis of AML. Her bone marrow reveals 78% blasts with a myeloid immunophenotype and no evidence of dysplasia. Cytogenetics are diploid. Mutational screening is negative for *FLT3*, *NPM1*, or *CEBPA* mutations. She comes to see you for treatment options. She would like to know about the "standard" treatment, the overall plan, and goals of treatment.

• What should you tell her?

The case presented is of a young woman with newly diagnosed AML with a normal karyotype and no known molecular aberrations. Overall, she has intermediate-risk disease with none of the known favorable (CBF cytogenetics, *NPM1* mutation, and bi-allelic *CEPBA* mutation) or unfavorable (adverse karyotype, dysplasia, and *FLT3* mutation) characteristics. Her question regarding standard therapy in AML is a challenging one. Despite advances in understanding the biology of AML, there have been few changes in the treatment strategies used for the majority of patients. Outside of academic centers, the "standard" induction therapy for AML has been described as a combination of 7 days of cytarabine (ara-C) at a dose of 100–200 mg/m^2/d with an anthracycline (daunorubicin or idarubicin) during days 1–3; this is typically referred to as the 7+3 regimen. Following documentation of remission, the response is consolidated with four cycles of high-dose ara-C. Achieving a CR after induction chemotherapy is the most important factor predicting a favorable outcome and prolonged overall survival. Based on this approach, Mayer *et al*. (1994) reported a CR rate of 64%, and 4-year disease-free survival (DFS) and OS rates of 39% and 46%, respectively. The rates of CR, DFS, and OS were lower with increasing age. Multiple randomized trials have attempted to improve response rates and survival using newer agents and variations in doses. Important areas of investigation have included (i) dose of anthracycline, (ii) choice of anthracycline, (iii) dose of ara-C, and (iv) additional nucleoside analogs to implement three drug combinations.

• Is the dose of the anthracycline important? What is the optimal dose?

Intensifying the dose of daunorubicin above the "standard" 45 mg/m^2 has been suggested as means to achieve higher CR rates and prolong overall survival. Several single-arm studies have investigated higher doses ranging from 60 mg/m^2 to 90 mg/m^2, suggesting improved response rates. Investigators from ECOG conducted a study in newly diagnosed AML patients $\leq$60 years of age, randomizing them to therapy with daunorubicin 45 mg/m^2/d $\times$ 3 days versus 90 mg/m^2/d $\times$ 3 days, each in combination with ara-C 100 mg/m^2/d $\times$ 7 days. 582 patients were evaluable with a median age of 48 years. The CR rate (57% vs. 71%; $P < 0.001$) and median OS (15.7 vs. 23.7 months; $P = 0.003$) were significantly better in the higher-dose daunorubicin arm. There were no differences in the rate of serious adverse events in the two arms, and the death rates were similar (4.5% (low-dose) vs. 5.5%; $P = 0.6$). The greatest benefit was seen in patients with intermediate-risk disease, while those with adverse cytogenetics or *FLT3* mutation did not benefit. In a separate study based on these patient samples, Patel *et al*. (2012) performed an 18-gene mutational analysis to identify pretreatment genetic abnormalities that would predict for benefit from high-dose daunorubicin. They demonstrated that high-dose daunorubicin significantly improved outcomes in those patients whose AML had mutations in *DNMT3A*, *NPM1*, or translocations involving *MLL*.

In a study similar to the ECOG trial, the European Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research (HOVON/SAKK) cooperative group investigated the same question of 45 mg/m^2 versus 90 mg/m^2 of daunorubicin, but in patients above the age of 60. The treatment plan randomized patients to daunorubicin 45 mg/m^2/d $\times$ 3 days versus 90 mg/m^2/d $\times$ 3 days, each in combination with ara-C 200 mg/m^2/d $\times$ 7 days. A total of 813 patients were evaluable, with a median age of 67. The CR rate was higher (65% vs. 54%; $P = 0.002$) in the higher-dose arm. However, there was no difference seen between the two groups with regard to event-free survival (EFS) ($P = 0.12$), DFS ($P = 0.77$), or OS ($P = 0.16$). The 30-day mortality rate was similar in the two groups (12% vs. 11% in the high-dose group). The 2-year cumulative incidence of relapse was 61% versus 54% (in the high-dose group). However, this was offset by the increased rate of death in CR in the higher-dose group (10% vs.16%). In a post-hoc subgroup analysis, patients between the ages of 60 and 65 may have had some significant benefit with the higher-dose daunorubicin, including a better rate of CR (51% vs. 73%), 2-year EFS (14% vs. 29%; $P = 0.002$), and 2-year OS (23% vs. 38%; $P = 0.001$). Based on these data, higher-dose daunorubicin appears to be superior to the 45 mg/m^2 dose in younger patients with intermediate- or low-risk disease. The question remains whether an intermediate dose of 60 mg/m^2 is sufficient to improve outcomes and avoid excess toxicity—especially in the older AML population. This remains the subject of future clinical trials.

• Is the choice of anthracycline for induction in AML important?

Following from the question of dose intensity of anthracycline during induction of AML comes the question of choice between daunorubicin and idarubicin. Several comparisons

between idarubicin and daunorubicin have been conducted to resolve this debate, including a collaborative meta-analysis of five trials suggesting that treatment with idarubicin had higher rates of CR and overall survival. However, many of these studies have been fraught with dose inequalities when comparing 12 mg/m^2 of idarubicin to now "substandard" doses of daunorubicin. The Acute Leukemia French Association (ALFA) has conducted a number of studies to investigate this issue. In a randomized trial of 468 evaluable patients with AML and a median age of 60, Pautas *et al*. (2010) compared daunorubicin 80 mg/m^2/d × 3 (DNR) versus idarubicin 12 mg/m^2/d × 3 (IDA3) versus idarubicin 12 mg/m^2/d × 4 (IDA4), each in combination with ara-C 200 mg/m^2/d × 7. In this study, IDA3 was found to have a significantly superior CR rate compared to DNR (83% vs. 70%; $P = 0.007$). This superior response was also seen in patients with unfavorable karyotype. There were no significant differences in induction deaths or serious adverse events, except for slightly more mucositis with IDA. There was a trend for better 4-year EFS (12% vs. 21% for IDA3) and OS (23% vs. 32% for IDA3), but these did not reach statistical significance. In a more recent follow-up analysis of two large trials comparing idarubicin to daunorubicin, the ALFA group evaluated 727 patients who had received either DNR or IDA3. IDA3 was associated with a significantly higher CR rate (69% vs. 61%; $P = 0.029$). Although the OS was similar between the two groups, the investigators found a significantly higher cure rate associated with IDA3 compared to DNR (16.6% vs. 9.8%; $P = 0.018$). Based on the available data, treatment with idarubicin 12 mg/m^2/d 3× may be at least as good as, if not better than, high-dose daunorubicin (90 mg/m^2/d 3×). At the University of Texas MD Anderson Cancer Center, we favor the use of idarubicin over daunorubicin for induction therapy of younger patients with AML.

• Is the dose of cytarabine (ara-C) during induction of AML important? Is there an optimal dose?

Ara-C is the most active agent in the treatment of AML and forms the foundation for many of the standard and investigational combination regimens for this disease. Although "standard" doses of ara-C range from 100 to 200 mg/m^2, a steep dose–response curve for cytarabine in AML has prompted investigators to study dose escalation of ara-C in induction and consolidation. High-dose ara-C (HiDAC) typically refers to doses of >1000 mg/m^2. As mentioned previously, multiple studies of HiDAC in postremission consolidation have shown the benefit of this approach, particularly in patients with CBF AML. The utility of HiDAC in induction regimens of AML is less clear. Several randomized trials have attempted to answer this question. SWOG investigators conducted a randomized study in AML patients <65 years, investigating standard-dose ara-C (SDAC) of 200 mg/m^2/d × 7 to high-dose ara-C (HiDAC): 2000 mg/m^2 Q12 hours × 12 doses. Both groups received daunorubicin (DNR) at a dose of 45 mg/m^2/d × 3 days. Rates of CR and 4-year OS between the two groups were similar in all age groups. However, the 4-year relapse-free survival was better following HiDAC induction ($P = 0.049$): 33% (HiDAC) versus 21% (SDAC) in patients <50 years, and 21% (HiDAC) versus 9% (SDAC) in patients between 50 and 64 years. HiDAC was associated with significantly increased fatal and neurologic toxicity. In another study, Bishop *et al*. (1996) randomized patients ≤60 years to either HiDAC (3000 mg/m^2 Q12 × 8 doses) or SDAC (100 mg/m^2/d × 7 days). Both groups also received daunorubicin 50 mg/m^2/d × 3 and etoposide 75 mg/m^2/d × 7 days. Of 301 patients treated, there was no significant difference in the CR rate—71% (HiDAC) versus 74% (SDAC)—but significantly better median CR duration for the HiDAC group: 45 months versus 12 months (SDAC; $P = 0.0004$). The recurrence-free survival (RFS) at 5 years was 49% (HiDAC) versus 24%(SDAC). However, there was no significant difference in OS between the two arms. The HiDAC arm was associated with comparatively increased rates of toxicity, including leukopenia, thrombocytopenia, nausea, vomiting, and eye toxicity, but similar rates of neurotoxicity. Kern and Estey (2006) performed a meta-analysis of three randomized trials of standard versus HiDAC in AML induction. They concluded that induction therapy for AML with HiDAC improved long-term relapse-free survival and OS in patients <60 years of age. To summarize, data from these older studies suggest that the use of HiDAC does not affect rates of CR, but may lead to more durable remissions and a better rate of RFS. The higher burden of toxicities, however, may attenuate some of the overall survival benefit.

Recently, investigators from the HOVON/SAKK collaborative group conducted a large randomized study of 858 patients comparing induction with HiDAC versus "intermediate-dose" ara-C (IDAC). During cycle 1, patients received either HiDAC (ara-C 1000 mg/m^2 Q12 hours × 10 doses) or IDAC (ara-C 200 mg/m^2/d × 7 days). All patients also received idarubicin 12 mg/m^2/d × 3 doses. Importantly, all patients, regardless of their response to cycle 1, received cycle 2 as follows: HiDAC group: amasacrine 120 mg/m^2/d × 3 days + ara-C 2000 mg/m^2 Q12 hours × 8 doses (total dose: 16,000 mg/m^2); and IDAC group: amasacrine 120 mg/m^2/d × 3 days + ara-C 1000 mg/m^2 Q12 hours × 12 doses (total dose = 12,000 mg/m^2). Patients in CR after two cycles received either one dose of consolidation or stem cell transplant. The CR rates between the two arms were similar: 80% (IDAC) versus 82% (HiDAC). At 5 years, there was no difference in the rates of EFS, OS, risk of relapse, or death in CR in the two groups. There was no difference

(*Continued*)

in rates of 30-day mortality, but patients in the HiDAC arm had more skin, gastrointestinal, and ocular toxicity, as well as increased hospital days and platelet transfusions. In a post-hoc subgroup analysis, the only significant finding was an improved OS and EFS in patients with a monosomal karyotype receiving HiDAC treatment ($P = 0.02$). The authors conclude that there is no benefit to HiDAC over IDAC in induction therapy for AML, and that perhaps an intermediate dose of ara-C between 100 mg/m^2 and 3000 mg/m^2 would maximize antileukemia benefit while minimizing toxicity. While this may be a reasonable conclusion, it is important to note that the all patients in this study were, in fact, exposed to a high-dose ara-C-based regimen prior to their consolidation. While the IDAC arm received a standard dose of 200 mg/m^2 of ara-C during cycle 1, all eligible patients went on to cycle 2 and received a high-dose ara-C-based regimen with a total dose of 12,000 mg/m^2. The lack of a difference in CR, OS, and RFS could be accounted for by exposure to a high-dose ara-C-based approach, instead of a direct comparison between standard and HiDAC.

Studies performed by Plunkett *et al*. (1987) have established that higher doses up to 3 g/m^2 may be beyond the dose necessary to saturate ara-C uptake and maximal cellular ara-C-triphosphate (ara-CTP) levels (the active product of ara-C that is incorporated into DNA and is responsible for its cytotoxic effects). Therefore, escalation of the dose of ara-C can be beneficial but only up to the point before these maximal levels are surpassed. Therefore, one can consider an optimal ara-C dose able to achieve maximal cellular ara-CTP levels and not result in unwanted toxicity. Clinically, this dose may be between 1000 and 2000 mg/m^2/d. At the University of Texas MD Anderson Cancer Center, we believe that ara-C doses in the range of 1000 to 1500 mg/m^2/d in induction are optimal, achieve higher rates of CR, and are associated with a better RFS and OS.

• Is there a role for adding a second nucleoside analog for a three-drug combination in AML induction?

The cytotoxicity of ara-C is directly related to the intracellular concentration of its metabolite ara-CTP. Several purine nucleoside analogs have been shown to be synergistic in combination with ara-C by increasing intracellular ara-CTP. They act as potent inhibitors of ribnucleotide reductase—rapidly depleting intracellular deoxynucleotides, augmenting intracellular ara-CTP generation, and eventually leading to increased incorporation of lethal artificial analogs into a growing DNA strand. This preclinical rationale has translated into clinical trials of fludarabine, cladribine, and clofarabine showing significant activity in AML induction. In an older study examining the role of the combination of fludarbine, idarubicin, and ara-C (FIA) in patients with poor-prognosis, newly diagnosed AML and MDS, the CR rate was 51%. A phase II trial of clofarabine, idarubicin, and ara-C (CIA) in newly diagnosed patients younger than 60 showed significant activity of the three-drug combination. In 57 evaluable patients, the overall response rate was 79% with 74% CR and 5% CRp. With a median follow-up of 10.9 months, the EFS was 13.5 months, while the median RFS and OS were not reached. The regimen was well tolerated with a 4-week mortality of only 2%. Preliminary data from a phase II trial comparing FIA versus CIA in newly diagnosed AML demonstrated a CR rate of 76% (FIA) versus 82% (CIA) and 0% early mortality among 28 patients. Based on several positive studies combining cladribine with standard chemotherapy, the Polish Acute Leukemia Group (PALG) conducted a randomized phase III clinical trial in 400 patients with AML comparing the combination of daunorubicin and ara-C with or without cladribine. The median age of patients was 45. The CR rate was significantly higher in the three-drug arm versus the two-drug arm (64% vs. 47%; $P = 0.0009$) and the leukemia-free survival (LFS) in patients older than 45 years was 44% (three-drug) versus 28% (two-drug) ($P = 0.05$). In a follow-up study of 652 untreated AML patients, the PALG compared outcomes of either fludarabine (DAF) or cladribine (DAC) added to daunorubicin and ara-C (DA). Compared to DA, DAC was associated with a significantly higher CR rate (67.5% vs. 56%; $P = 0.01$) and better 3-year OS (45% vs 33%; $P = 0.02$). The survival benefit was maintained in patients older than 50, those with an initial white blood cell count >50, and in those with an unfavorable karyotype. DAF was not associated with significant improvement in outcome over DA alone. These studies suggest an advantage for the three-drug combinations over the standard doublet of ara-C + anthracycline. Further experience to confirm these results and measure long-term outcome is needed as we begin to incorporate these strategies into standard clinical practice. Front-line clinical trials in younger patients at MD Anderson Cancer Center are currently investigating three drug combinations as described here.

• Have any newer, novel therapies been approved for the treatment of AML?

Despite several decades of research into AML treatment, only one new drug has been approved by the US Food and Drug Administration (FDA) for the treatment of AML. In May 2000, the FDA granted accelerated approval to gemtuzumab ozogamicin (GO) for the treatment of older patients (older than age 60) with AML in first relapse who were not candidates for standard therapy. GO is an anti-CD33 monoclonal antibody conjugated to the potent cytotoxin, calicheamicin. The high surface expression of CD33 on AML blasts (particularly on acute promyelocytic leukemia) implied that this could be an ideal targeted therapy for this disease. Approval was based on a series of single-arm phase II trials of GO (9 mg/m^2) demonstrating a CR/CRp rate of 26% and an acceptable safety profile. However, the accelerated approval was conditional upon postmarketing studies confirming the benefit and safety of the drug. A postap-

proval study by SWOG (SWOG106) randomized 506 newly diagnosed patients to 7+3 with or without GO (6 mg/m^2) followed by a second randomization with or without GO during consolidation. The investigators found no difference in CR, EFS, DFS, or OS between the two groups, but they noticed a significant increase in 30-day mortality in the GO cohort. Important to note in the trial, however, is that the dose of daunorubicin in the GO arm was reduced (45 mg/m^2) relative to the control arm (60 mg/m^2). Nonetheless, based on these results, GO has been withdrawn from the market at the request of the FDA. Since the SWOG trial, several large studies investigating the use of GO in combination with chemotherapy have been published and may provide justification to reverse this decision. In the MRC AML15 trial, Burnett *et al*. (2011) randomized 1113 patients (under age 60) to three induction chemotherapy programs, each with or without GO (3 mg/m^2). Overall, there was no difference in the rate of response or OS. However, in a predetermined subgroup of favorable cytogenetics and in up to 70% of patients with intermediate-risk disease, there was a significant OS benefit ($P = 0.001$) for patient receiving GO. There was no increase in toxicity with the addition of GO. In a second trial, this time in older patients, Burnett *et al*. (2011) randomized 1115 patients to either daunorubicin–cytarabine or daunorubicin–clofarabine, each with or without GO (3 mg/m^2). Patients receiving GO had a significantly lower 3-year cumulative incidence of relapse ($P = 0.007$) and better 3-year survival ($P = 0.05$). Once again, there was no increased incidence of toxicity or early mortality with the addition of GO. Most recently, the ALFA group published the results of a randomized phase III trial of standard chemotherapy with or without GO (3 mg/m^2) in 280 patients between the ages of 50 and 70. Although there was no difference in CR rates between the two arms, GO was associated with a significant improvement in 2-year EFS ($P = 0.0003$), OS ($P = 0.04$), and RFS ($P = 0.0003$). As with the two MRC trials, there was no increase in risk of early death from toxicity. Results of these studies and the potentially important role of GO in the treatment of acute promyelocytic leukemia are driving the debate for reinstating the approval of this drug.

Case study 8.5

A 77-year-old man with a past history of hypertension, coronary artery disease, compensated congestive heart failure, and mild and moderate renal insufficiency has been diagnosed with AML. His bone marrow examination shows 39% blasts in a hypercellular bone marrow with a background of trilineage dysplasia. Chromosome analysis shows −5, −7, 17p−, +12, and +8, but mutational analysis is negative for mutations in the *FLT3*, *NPM1*, and *CEBPA* genes. He comes with his family and is considering palliative care. They are wondering if there are other low-intensity options that he would be able to tolerate and that would provide benefit. What are the treatment options for this patient? Is intensive chemotherapy appropriate for this patient?

The case presented here represents one of the most important challenges and perhaps controversies in the treatment of AML. Almost 55% of patients with AML are older than 65 at diagnosis, and about one-third are older than 75. Although age in itself may not be the sole factor in determining therapy and prognosis, older age is generally associated with increased comorbidities, poorer performance status, and the presence of other adverse features (e.g., dysplasia, antecedent hematologic disease, and poor-risk cytogenetics) at the time of diagnosis. Therefore, a significant proportion of the older patients may not be considered good candidates for and may not benefit from intensive chemotherapy. In some cases, the decision is often made to offer palliative or supportive care, rather than to risk high rates of early mortality from induction chemotherapy. However, observational studies have shown that patients receiving any therapy do better than those not receiving treatment. Kantarjian *et al*. (2006, 2010) examined the outcomes of older patients (≥65 years (2006) and ≥70 years (2010)) with AML who received intensive chemotherapy at the MD Anderson Cancer Center. Among the patients studied, the CR rate with intensive chemotherapy was about 45%, with a median OS of 4.6 months and a 1-year survival of only 28%. The rates of 4-week and 8-week mortality were 26% and 36%, respectively. Among factors that strongly influenced outcome by multivariate analysis were older age, complex karyotype, poor performance status, a history of antecedent hematologic disorder, and abnormal organ function (especially renal). The conclusion of the authors was that intensive chemotherapy did not benefit most, older patients with AML. Exceptions could be seen in those who were fit and had a favorable karyotype. The UK Medical Research Council (MRC) attempted to improve outcomes in older patients (>55 years), comparing three different intensive chemotherapy regimens. The overall CR rate was 55%, with an induction death rate (30 days) of 19% and a 26% rate of resistant disease. The 5-year OS was only 8–12%.

Low-dose ara-C (LDAC) has been studied as an alternative to supportive care in older patients who were deemed unfit for intensive chemotherapy. In a UK MRC study (AML14), 217 patients were randomized to receive LDAC

(*Continued*)

(20 mg SQ BID × 10 days) versus supportive care and hydroxyurea. LDAC had a significantly higher remission rate (18% vs. 1%, $P = 0.00006$) and improved overall survival (odd ratio: 0.60; $P = 0.0009$) compared to the supportive treatment arm. Patients who achieved a CR had a median survival duration of 80 weeks versus 10 weeks in patients with no CR. Tilly et al. (1990) compared LDAC with intensive therapy with 7+3 in patients older than 65 (with no previous history of AHD or MDS). In 87 patients, they reported a CR rate of 32% for LDAC versus 52% for 7+3. Patients receiving LDAC had a higher rate of PR (22% vs. 2%). However, patients on the 7+3 arm had a higher early death rate (31%), had more severe infectious complications, required more blood and platelet transfusions, and spent more days in the hospital. Additionally, there was no significant difference in CR duration or OS between the two groups.

More recently, hypomethylating agents such as 5-azacytidine (5-AZA) and decitabine (DAC) have been approved for the treatment of MDS and have been shown to have significant activity in older patients with AML with overall survival benefit compared to standard supportive care. Studies of 5-AZA in AML have shown CR rates in the range of 15–20%, translating into prolonged overall survival (median: 19–24.5 months). Studies with standard-dose decitabine in AML have shown similar response rates (18–24%) and survival benefit in responding patients (7.7 to 14.4 months). A recent retrospective study analyzed the outcomes of 671 older patients treated with intensive chemotherapy versus hypomethylating agents. Although the CR rate was higher (42% vs. 28% for intense vs. hypomethylating, respectively), there was no significant difference in 2-year RFS (28% vs. 39%) or OS (6.7 vs. 6.5 months). On multivariate analysis, outcome was dependent on age, cytogenetics, performance status, and creatinine, but not on type of treatment. Experience from these large studies with hypomethylating drugs suggests that they can affect the natural history of the disease and prolong survival independent of achieving a CR. The previous dogma of achieving a CR with one or two cycles of intense chemotherapy to convey a favorable outcome may not apply to these agents and approaches. More prolonged schedules of decitabine (20 mg/m^2/d × 10) have been shown to have superior response rates. A randomized study evaluating 5 or 10 days of decitabine is currently underway at our institution. Novel combinations of hypomethylating drugs with other agents such as clofarabine, lenalidomide, sorafenib, or histone deacetylase inhibitors are also showing promising activity and may be incorporated into the treatment of AML in older patients.

A recent large Swedish registry study offers an important alternative perspective in the treatment of older patients with AML. They reviewed 2767 patients with AML diagnosed in Sweden between 1997 and 2005 and reviewed the outcomes in patients receiving intensive versus "palliative" therapy. They noted that although outcomes were dependent on age and performance status (PS), PS was a more important determinant in each age group, including those >70 years. They reported that early death rates were higher in those offered palliative treatment versus intensive chemo and higher in those with poor PS. CR was achieved with intensive chemo in at least half of patients up to age 75 and, among patients with good PS, up to age 80. Long-term survivors aged 70–79 were more commonly seen in regions of the country where patients were more likely to be treated with intensive therapy. They concluded that most patients up to age 80 should be offered standard intensive therapy and that new treatments in older patients with AML should be compared to intensive therapy. Clearly, there is a subset of older patients with AML with better PS, better organ function, and more favorable disease biology that may benefit from intensive chemotherapy regimens. We agree that newer agents and regimens for fitter older patients should be compared to standard chemotherapy.

In our practice, each patient undergoes a risk stratification based on not only their age but also other risk factors—including comorbidities, organ function, pretreatment cytogenetics, history of AHD, predicted response to chemotherapy and patient preference and tolerance. An older, "fit" patient, for example, with favorable cytogenetics or normal karyotype and no other adverse features may be offered a more intensive induction with close monitoring in laminar air flow isolation. On the other hand, a patient in their 60s with adverse karyotype, organ dysfunction, poor performance status not related to the leukemia may be offered a clinical trial with a lower-intensity approach. The importance in gauging these pretreatment characteristics in every patient mandates an individualized approach that also involves waiting for appropriate cytogenetic and molecular studies and informed patient input before starting therapy.

Case study 8.6

A 48-year-old man with AML and pretreatment karyotype showing 46 XY, +8, and t(12;14) in 20 metaphases undergoes induction chemotherapy with idarubicin and cytarabine. A day 21 bone marrow shows 5% blasts, and cytogenetic analysis shows a diploid karyotype in five metaphases and 46XY, +8, and t(12;14) in five metaphases. Does this have any significance on the outcome? Does it have any effect on the treatment plan?

Yes, the presence of persistent cytogenetic abnormalities at day 21 in patients receiving intensive induction chemo-

therapy for AML has prognostic significance. Konopleva et al. (2003) examined 197 patients with AML and an abnormal pretreatment karyotype who underwent induction chemotherapy and had a day 21 cytogenetic analysis. They found that the CR rates in patients with a normal karyotype (complete cytogenetic response, or CCyR), a persistent abnormal karyotype in all metaphases (no CyR, or NCyR), and a mixture of normal and abnormal karyotypes (partial CyR, PCyR) were 79%, 27%, and 60% respectively. Interestingly, those patients whose cytogenetic analysis had no available metaphases (NAM) to count had a CR rate of 32%. The OS was longest in the group with CCyR at day 21, shortest in those with NCyR and NAM, and intermediate in those with PCyR. Patients with no normal metaphases at day 21 (NCyR or NAM) had a 2.7-fold increased risk of death compared to those with at least one normal metaphase. In their cohort, these patients had as poor of an outcome as patients who had pretreatment cytogenetics with -5 or -7 abnormalities. Similarly, Chen *et al*. (2011) reported on the significance of persistent cytogenetic abnormalities at time of CR. Those with persistent cytogenetic abnormalities at CR had a significantly shorter 3-year RFS (15% vs. 45%; $P = 0.001$) and 3-year OS (15% vs. 56%; $P < 0.001$) compared to those with CCyR at CR. By multivariate analysis, among patients with persistent cytogenetic abnormalities at CR, no significant differences in OS ($P = .25$) were observed between those who did or did not receive SCT, with a trend favoring SCT for RFS ($P = .08$).

• Is there a role for a "double induction" or early induction in patients with persistent disease during a midtreatment bone marrow evaluation?

Although this strategy is sometimes used, there is no convincing evidence that this is beneficial, and it may actually introduce increased toxicity. The ALFA group conducted a randomized study investigating a double induction or timed-sequential induction versus 7+3. Overall, there was no difference in relapse-free interval between the three arms except in a subgroup of younger patients (<50). There was no effect on EFS or OS. In a second randomized study, Buchner *et al*. (1999) studied the addition of HiDAC and mitoxantrone to standard induction at day 21 in patients, regardless of their bone marrow blasts. Overall, they found no difference in the CR rate, RFS, or early death rate between the two arms. However, in an exploratory subgroup analysis of higher-risk patients (residual blasts >40%, poor karyotype, and high LDH), they did find improved CR rate, EFS, and OS. Further studies evaluating double induction strategies in appropriate populations and newer agents are needed to define the utility of this approach.

With the current case, the persistence of cytogenetic abnormalities at day 21 should be regarded as a surrogate for resistant disease, translating into a shortened RFS and OS. Although the prognosis is not quite as adverse as one for a patient who has no normal metaphases, this patient should be considered for a potential allogeneic SCT in first CR.

• Is there a role for infection prophylaxis and other forms of infection control to improve outcomes in the treatment of AML?

Yes. Both antibacterial and antifungal prophylaxis has been studied and shown to reduce infections and improve outcomes in neutropenic patients treated for leukemia. A large meta-analysis evaluated 109 trials with 13,579 patients to address the question of antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients after chemotherapy. They found that prophylaxis significantly reduced the risk of infection-related deaths, death from all causes, the occurrence of fever, and clinically documented infection. The most significant reduction in mortality was observed in trials assessing prophylaxis with quinolones. The introduction of oral fluconazole as prophylaxis in patients with leukemia has significantly reduced the incidence of candidemia and systemic candidiasis, but increased the incidence of invasive fungal infections involving molds. Second-generation, mold-active azoles such as posaconazole and voriconazole have now become an important component of antimicrobial prophylaxis in severely immunocompromised hosts—leading to improved outcomes. Laminar air flow rooms with high-efficiency particulate air (HEPA) filters in protective, isolated environments have also been recommended for neutropenic patients with hematologic malignancies, and they have been associated with improved CR, early mortality, and overall survival in older patients with AML. Finally, the use of myeloid growth factors has been extensively studied as supportive care to reduce infectious complications, and as means to "prime" leukemic cells and sensitize them to chemotherapy. Multiple prospective studies have examined the role of growth factors before, during, and after therapy for AML. They have consistently demonstrated a reduction in the duration of neutropenia, but no definitive conclusion about their benefit in improving OS or in stimulating malignant leukemia blasts.

We routinely initiate triple oral prophylaxis in our AML patients with a flouroquinolone, an azole antifungal (preferably voroconazole or posaconazole, unless they are lower risk or have contraindications), and aciclovir (or valaciclovir). New AML patients older than 50 years of age receiving intensive induction would be offered placement in an isolation protective environment during their induction therapy.

Case study answers

Case study 8.1

Question 1: Answer D

Case study 8.2

Question 1: Answer A ("True")

Case study 8.3

Question 1: Answer A ("Yes")

Selected reading

Byrd JC, Mrozek K, Dodge RK, *et al*. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002;100: 4325–36.

Dohner H, Estey EH, Amadori S, *et al*. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115:453–74.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, *et al*. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2020;28: 562–9.

Lowenberg B, Ossenkoppele GJ, van Putten W, *et al*. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361:1235–48.

Schlenk RF, Dohner K, Krauter J, *et al*. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008;358:1909–18.

CHAPTER 9

Consolidation therapy in acute myeloid leukemia

Gregory K. Behbehani and Bruno C. Medeiros
Stanford University School of Medicine, Stanford, CA, USA

Case study 9.1

A 49-year-old male with a new diagnosis of acute myeloid leukemia (AML) with t(8;21) as a single cytogenetic abnormality and no molecular mutations comes in for a second opinion. He presents to your clinic after undergoing standard chemotherapy with continuous infusion cytarabine at 100 mg/m^2 daily and 90 mg/m^2 daunorubicin. His induction course was complicated by *Escherichia coli* sepsis and intensive care unit admission, which resolved without long-term sequelae. After achieving complete remission, he is reluctant to receive further chemotherapy and asks, "Is further treatment worth it if I'm likely to die anyway?"

• **Why is postremission therapy important in AML?**
Although up to 80% of patients younger than 60 years of age will enter complete remission (CR) following a standard induction regimen, essentially all patients will relapse without further therapy. The Eastern Cooperative Oncology Group (ECOG) showed that 100% of patients in CR randomized to receive no further therapy relapsed at a median time of 4.1 months, with all patients relapsing by 17 months. These patients experienced significantly inferior remission durations compared to those randomized to maintenance, and these findings led to early termination of this trial. A subsequent ECOG trial demonstrated that two cycles of postremission chemotherapy followed by maintenance led to longer duration of remission and improved 2-year survival. Similarly, the German AML Cooperative Group (AMLCG) demonstrated no long-term survivors in patients not receiving consolidation therapy.

• **How can risk-adapted strategies be used to select postremission therapy for younger adults with AML?**
Although there is wide variation in consolidation regimens across different cooperative groups, current evidence supports the use of a risk-adapted strategy emphasizing the use of consolidation chemotherapy for patients with good-risk disease and allogeneic hematopoietic stem cell transplantation (allo-HSCT) for patients with adverse-risk disease. (The treatment of acute promyelocytic leukemia has been revolutionized by the use of all-trans retinoic acid and arsenic trioxide; as it is now completely distinct, it will not be discussed further here.) Most of these data were generated from "genetic randomization" studies in which patients with matched allogeneic bone marrow donors undergo allo-HSCT, whereas those without a donor receive consolidation chemotherapy. These studies have consistently demonstrated that patients with favorable risk cytogenetics do not benefit from allo-HSCT in first CR (CR1) and should receive consecutive cycles of postremission chemotherapy. Conversely, a significant improvement in survival is noted in patients with adverse-risk disease following allo-HSCT. Patients with intermediate-risk features also appear to have a small, but significant, benefit with transplantation. The introduction of testing for molecular abnormalities in AML has further refined this classification by subdividing the normal-karyotype (intermediate-risk) patients into good-risk genotypes (NPM1-mutated and FLT3-wild-type, and bi-allelic CEBPA mutation) and poor-risk genotypes (the FLT3 ITD mutation and ASXL1 mutation). The impact

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

of risk-adapted strategies on the outcome of molecularly characterized patients needs to be fully characterized, although some data suggest that NPM1-mutated, FLT3-wild-type patients should not undergo allo-HSCT in CR1, whereas all other molecular genotypes may benefit.

• Is there a standard postremission regimen for younger patients with AML in CR1 who are not candidates for allo-HSCT?

For favorable-risk patients with CBF–AML, postremission therapy with multiple cycles of high-dose cytarabine (HDAC) has been shown to significantly improve relapse-free and overall survival (OS) compared to either standard doses of cytarabine or multi-agent chemotherapy. Autologous transplant (auto-HSCT) after at least one cycle of HDAC appears to lead to equivalent outcomes in this patient population, although a direct comparison has not been performed. Patients with normal-karyotype AML that is positive for the NPM1 mutation and negative for the FLT3 ITD mutation also appear to benefit from intensive therapy with either multiple HDAC cycles or autologous transplant. The optimal postremission therapy for intermediate-risk patients not undergoing allo-HSCT remains controversial, with some studies showing little benefit of high-dose cytarabine therapy compared to a variety of intensive standard-dose regimens, and others demonstrating a small but significant benefit of multiple cycles of HDAC for intermediate-risk patients. For poor-risk patients, different chemotherapy regimens have consistently failed to improve disease-free survival (DFS) or OS rates; thus, allo-HSCT remains the gold standard for these patients. Adverse-risk patients who are unable or ineligible for allo-HSCT in CR1 may derive a small benefit from HDAC-based regimens (particularly patients with monosomal karyotype), although the benefit is minimal and may not be of clinical significance.

The most commonly used postremission regimen is HDAC, which consists of 3000 mg/m^2 Q12h of cytarabine given on days 1, 3, and 5 for three to four total cycles. There is, however, significant evidence that regimens utilizing lower cytarabine doses of 2000 mg/m^2 every 12 hours on days 1–5, or even 1000 mg/m^2 every 12 hours on days 1–6 may produce similar outcomes. Standard-dose postremission regimens use infusional cytarabine at doses between 100 mg/m^2 and 400 mg/m^2 for 5 days combined with two doses of anthracycline. Such regimens may be a reasonable option for patients with intermediate- or poor-risk disease who are ineligible for transplant and are deemed unable to tolerate HDAC therapy. Last, the addition of gemtuzumab ozogamicin (GO) to conventional regimens results in improved survival in patients with favorable- and intermediate-risk AML. GO does not appear to be effective in the setting of auto-HSCT.

There also remains significant debate regarding the optimal number of cycles of postremission therapy. The majority of trials to date have utilized a total of three cycles of therapy (either as a single induction followed by two consolidation cycles, or as a double induction followed by a single consolidation cycle). However, controversy still remains. Data from Cancer and Leukemia Group B (CALGB) studies suggest that three to four cycles of HDAC consolidation (after a single induction) are superior to one HDAC consolidation for favorable cytogenetic risk. The CALGB also retrospectively compared four total cycles to five total cycles (single induction plus three or four courses of HDAC) for patients with normal-karyotype AML and demonstrated a significant recurrence-free survival (RFS) benefit of the fourth HDAC cycle in this group. An alternative approach was taken by the Australasian Leukemia and Lymphoma Group, which utilized a highly dose-intense, HDAC-based induction (idarubicin, cytarabine, and etoposide) followed by randomization to either a second identical cycle or two cycles of standard-dose cytarabine consolidation therapy. Outcomes between the two groups were equivalent and similar to previously described results. The Finnish Leukemia Group compared four total cycles of therapy (double induction plus two HDAC consolidations) to eight total cycles (double induction plus six consolidations) and demonstrated no benefit to the additional consolidation cycles. However, this study included only a small number of patients with favorable-risk cytogenetics (6%). In summary, >4 cycles of therapy may be ideal for younger patients; however, fewer cycles may yield comparable outcomes if a sufficiently dose-intense HDAC regimen is used for induction.

Case study 9.2

A 57-year-old male is referred to you for consideration of auto-HSCT. He was recently diagnosed with normal-karyotype AML that is negative for mutations of NPM1 and FLT3-ITD, and he successfully achieved a complete remission following one cycle of a standard 7+3 regimen of cytarabine and daunorubicin. He is currently in CR1 and has not received any further therapy since induction.

- **What is the role of auto-HSCT in CR1?**

Auto-HSCT has been considered an alternate postremission strategy for many years. The question of postremission chemotherapy versus auto-HSCT has been reported previously. In general, these studies demonstrate that auto-HSCT provides significantly lower relapse rates, but at the expense of slightly greater toxicity and reduced success of salvage therapies. No significant differences in OS between postremission chemotherapy and auto-HSCT have been reported. Recent retrospective data suggest that auto-HSCT may be a superior therapy for intermediate-risk patients or those with normal karyotype and FLT3 mutation. Thus, for this patient with intermediate-risk disease, auto-HSCT may be a reasonable postremission treatment.

- **Is there a role for maintenance in younger patients with AML in CR1?**

At this time, there is no role for maintenance cytotoxic chemotherapy in younger patients with AML who are able to tolerate standard treatments. Several studies over the past 25 years have consistently demonstrated that prolonged maintenance therapy delays time to relapse but does not improve survival. In an initial comparison between 8 months versus 3 years of maintenance (in patients in CR1), no change in survival or relapse rate was demonstrated. Subsequently, older individuals randomized to low-dose cytarabine or no further treatment following two cycles of therapy demonstrated that maintenance therapy delayed relapse but had no effect on OS. More recently, a study from the Japanese AML study group compared four cycles of standard dose consolidation to three cycles of similar therapy plus six courses of maintenance therapy and demonstrated no difference in DFS or OS across the two groups. The German AMLCG utilized a slightly different approach in which patients were randomized after double induction and a single consolidation treatment to receive either auto-HSCT or prolonged cytarabine-based maintenance therapy for 3 years. This study again demonstrated no difference in DFS or OS between the prolonged-maintenance and auto-HSCT groups. Thus, in younger patients who are able to tolerate intensive induction and consolidation therapies, there is no added benefit from maintenance therapy.

Case study 9.3

An otherwise healthy 70-year-old female presents to your clinic after your colleague successfully treated her with 7+3 induction chemotherapy for AML. Her initial cytogenetic studies failed, but she is now in remission. She wishes to discuss further therapy.

- **Is there a standard postremission regimen for older AML patients in CR1 who are not candidates for HSCT?**

There is currently no standard postremission therapy for patients over the age of 60 who achieve CR. In general, a clinical trial should be the first choice for treatment of elderly patients with AML. If a suitable clinical trial is not available, we would again encourage a strategy that is both risk adapted and adapted to the specific patient's treatment goals and therapy tolerance.

For such patients who are able to achieve CR after standard induction therapy, some form of postremission therapy should still be given, if tolerable. The available data suggest that an attenuated course of a cytarabine with or without an anthracycline at standard doses (e.g., DAT 2+5) would be the best consolidation treatment for this patient population, as more intensive regimens appear to confer no additional benefit. These studies demonstrated DFS and OS rates of 11–25% at 5 years. Data from the MRC 11 and MRC 14 trials suggest that a total of three courses of therapy (inclusive of induction) confers the optimal benefit, with further courses or intensification providing only modest improvements in DFS with no effect on 5-year OS. More recently, this group has shown that two cycles (double induction only) of therapy had similar survival to three cycles in older patients, with the possible exception of those who achieve minimal residual disease (MRD)-negative CR. A promising recent report from the French ALFA group has suggested that GO added to conventional postremission therapy may also

(*Continued*)

confer a significant benefit for this population, with improvements in estimated RFS (22.7% vs. 50.3%) and estimated OS (41.9% vs. 53.2%). This trial used one dose during each of two consolidation cycles (1000 mg/m^2 cytarabine Q12h on days 1–4 plus a single dose of 60 mg/m^2 of daunorubicin).

• What is the role of auto-HSCT in elderly patients with AML in CR1?

Autologous transplant for patients over the age of 60 has been shown to be feasible in a number of trials. A retrospective review of the European Group for Blood and Marrow Transplantation registry demonstrated that auto-HSCT yielded similar outcomes as reduced-intensity conditioning (RIC) allo-HSCT (although majority of the patients in this trial were between the ages of 50 and 60), with RFS of approximately 40% and OS of 50% at 2 years. Another retrospective review of autologous transplant outcomes for patients over the age of 60 demonstrated LFS and OS rates in the range of 20–30%, which compares well to the reported results of consolidation chemotherapy in this age group. It is important to remember that most trials of auto-HSCT in this age group have been performed on highly selected patient populations, and even these patient groups experienced significant transplant-related mortality on the order of 5–10%.

• Is there a role for maintenance in elderly patients with AML in CR1?

As many elderly patients cannot tolerate adequately intensive consolidation, they may benefit from prolonged maintenance chemotherapy. In the ALFA trial, patients receiving maintenance therapy had improved DFS and OS and fewer days of hospitalization. The German AMLCG performed a similar trial that also demonstrated that for patients over the age of 60 or with poor-risk cytogenetics, maintenance therapy after a HDAC-containing double induction resulted in superior DFS compared to intensive consolidation. A nonrandomized trial from this group demonstrated an acceptable DFS in the range of 20% for patients over 60, with prolonged maintenance (also following a double induction) that compares quite favorably to the outcomes from other reported trials for this age group. It is worth noting that in this setting maintenance chemotherapy is no more effective than in younger patients, but rather represents a more tolerable alternative treatment for a group of patients who are unlikely to tolerate dose-intense therapy and for whom a prolongation of DFS is a reasonable treatment goal.

• What is the appropriate follow-up upon completion of postremission therapy?

No data are available to make evidence-based recommendations regarding appropriate follow-up for patients following the completion of chemotherapy for AML. There is, however, good expert consensus from groups such as the US National Comprehensive Cancer Network (NCCN.org) and European LeukemiaNet that patients should be followed with history, physical examination, and blood counts every 1–3 months for the first 2 years (when relapse is most likely) and every 3 to 6 months until 5 years from diagnosis. Bone marrow biopsy need only be performed to evaluate blood count abnormalities. The goal of this monitoring is to detect relapse early before patients develop symptomatic cytopenias, leukocytosis, or other leukemia-associated complications that might compromise re-induction therapy. As patients with relapsed AML are potentially candidates for allo-HSCT, it is recommended that a donor search should be started for all patients following AML diagnosis so that a donor can be quickly identified in the setting of relapse. Follow-up is particularly important for young patients and those with good-risk disease, as transplant is a very viable salvage option in this population.

A variety of trials have evaluated the utility of MRD monitoring in AML utilizing either quantitative polymerase chain reaction or multiparameter flow cytometry. This testing can be performed either following induction or at the completion of postinduction therapy, and it can yield significant prognostic information. Early studies in both APL and AML suggest that treatment based on MRD measurement can improve the ultimate outcomes of patients with AML; however, at this time these approaches are still best employed in the setting of a clinical trial.

Selected reading

Burnett AK, Hills RK, Mulligan D, *et al*. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol. 2011;29(4):369–77.

Mayer RJ, Davis RB, Schiffer CA, *et al*. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. New Engl J Med. 1994;331(14):896–903.

Medeiros BC, Othus M, Appelbaum FR. Cytarabine dose for acute myeloid leukemia. New Engl J Med. 2011;364(22):2166–69.

Patel JP, Gönen M, Figueroa ME, *et al*. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. New Engl J Med. 2012;366(12):1079–89.

Wang J, Ouyang J, Zhou R, *et al*. Autologous hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission: a meta-analysis of randomized trials. Acta Haematologica, 2010;124(2):61–71.

CHAPTER 10

Management of acute promyelocytic leukemia

Eytan M. Stein[1] and Martin S. Tallman[1,2]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA
[2]Weill Cornell Medical Center, New York, NY, USA

Case study 10.1

A 32-year-old Hispanic woman presents to the emergency room with severe menorrhagia, bruising, and shortness of breath for 6 days. The complete blood count shows a white blood cell (WBC) count of 8000/μL, hemoglobin of 6.5 g/dL, and platelets of 6000/μL. Further laboratory evaluation shows hypofibrinogenemia, with elevated prothrombin and partial thromboplastin times. You suspect acute promyelocytic leukemia (APL). All-trans retinoic acid (ATRA) is started, and bone marrow examination is done. Several days into therapy, a noticeable improvement in the patient's condition is noted. The bone marrow findings are suggestive of APL, but the cytogenetics are reported as normal.

• What should be the best management strategy at this time: to continue APL-focused therapy until molecular tests are available, discontinue ATRA and initiate acute myeloid leukemia (AML) induction therapy with "7+3," or repeat bone marrow aspirate?

The correct answer is to continue APL-focused therapy until molecular tests are available. Acute promyelocytic leukemia is a unique subtype of AML characterized by a block at the promyelocyte stage of hematopoiesis. The original description and recognition of APL as a unique subtype of AML are credited to Leif Hillestad, a Scandinavian physician who reported three patients with rapidly progressive leukemia and a profound coagulopathy. This coagulopathy, similar to disseminated intravascular coagulation, produces a prolonged prothrombin time and partial thromboplastin time and hypofibrinogenemia. The patient described in this vignette has clearly developed a bleeding diathesis, with severe menorrhagia and shortness of breath that are attributable to anemia or perhaps pulmonary hemorrhage.

The sine qua non of APL is a recurrent reciprocal translocation between chromosomes 15 and 17. This translocation, first described by Janet Rowley and colleagues, fuses the promyelocytic leukemia gene (PML) with the retinoic acid receptor alpha gene (RARα) and leads to the promyelocytic leukemia phenotype. In routine practice, this translocation is easily visualized with standard chromosomal analysis. However, cases have been described in the literature of cryptic translocations that fuse PML and RARα, but are nevertheless not detectable on standard chromosomal analysis.

Because of the high clinical suspicion of APL, the first test done was a bone marrow aspiration and biopsy. Although we are not told the results of the bone marrow examination, APL patients typically have an abundance of promyelocytes with multiple granules that often coalesce and take the appearance of a bundle of sticks (so-called faggot cells). Based on the clinical history and bone marrow examination, the physician chose to initiate ATRA at the first suspicion of APL. Although the cure rates for APL are remarkable, early death (often defined as death within 30 days of diagnosis) remains the major cause of treatment failure. In clinical trials, the induction death rate ranges between 5% and 9%. In population-based studies, the early death rate ranges between 17% and 30%, and it is considerably higher in older patients. Indeed, the early death rate has not changed significantly since the introduction of ATRA. Emerging data suggest that early death may be related to

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

delays in receiving ATRA once patients present to the hospital. In a retrospective analysis of 194 patients, most patients (69%) had ATRA administered 2 days or more after presentation. Although the early death rate was not increased, the percentage of patients who died from hemorrhage was markedly increased when ATRA was delayed for more than 2 days. In addition, the results of this retrospective analysis confirmed that high-risk patients with APL who received their first dose of ATRA 3 or 4 days after they were suspected of having APL had an early death rate of 80%, compared with a rate of only 18% in high-risk patients who received ATRA on days 0, 1, or 2.

Because the patient is improving on ATRA-based therapy and the clinical picture is consistent with APL, the treating physician should wait for the results of sensitive molecular genetics tests for the PML–RARα fusion product.

Case study 10.2

A 45-year-old male presents with severe fatigue, shortness of breath, and epistaxis. Examination demonstrates diffuse petecchiae. The complete blood count shows a WBC count of 14,000/μL with 50% promyelocytes, hemoglobin of 5.3 g/dL, and platelets of 4000/μL. Further laboratory evaluation shows a fibrinogen level of 38, with prothrombin and partial thromboplastin times of 48 and 67, respectively. You plan to start APL induction therapy.

• Is there a preferred anthracycline for induction or consolidation therapy?

Before the introduction of ATRA, the paradigm for APL treatment was to use standard induction regimens with daunorubicin and cytarabine. The initial phase III trials of ATRA-based therapy sought to add ATRA to the standard induction regimen. The first trial to substitute idarubicin for daunorubicin was performed by the GIMEMA group and gave idarubicin on days 2, 4, 6, and 8 during induction chemotherapy. There are no randomized trials with a head-to-head comparison of idarubicin and daunorubicin. When using an anthracycline as a single agent with ATRA, some in the field prefer the use of idarubicin, as this is the regimen used successfully as monotherapy with ATRA in a number of clinical trials in Europe. When using an anthracycline in combination with cytarabine for induction and consolidation, experts generally prefer the use of daunorubicin (DNR) as was done in the North American Intergroup APL trials.

• What is the role of cytarabine in the management of APL?

The European APL group was the first to investigate the need for cytarabine during consolidation. The European APL 91 and APL 93 trials incorporated the use of DNR and cytarabine in consolidation, while the PETHEMA LPA 99 trial sought to eliminate cytarabine from induction and consolidation regimens. In order to test whether cytarabine could be eliminated from the treatment of APL, the European APL group designed a trial to determine the need for cytarabine in patients with low-risk disease. Patients younger than 60 years and with low-risk disease were randomized to the "standard" arm of ATRA, DNR, and cytarabine for induction followed by two cycles of consolidation with DNR and cytarabine, versus the investigational arm that eliminated cytarabine from consolidation. Patients with high-risk disease were not randomized.

Of the 356 patients enrolled on the trial, 196 patients were low risk and younger than age 60, and they were randomized to cytarabine versus no cytarabine. While the hematologic CR rates after induction and the molecular CR rates after consolidation were statistically equivalent in both treatment arms, the cumulative incidence of relapse (CIR) was significantly higher in the group not given cytarabine; the 2-year CIR was 15.9% in the no-cytarabine arm versus 4.7% in the group given cytarabine. In addition, the inclusion of cytarabine in this low-risk group of patients did not lead to a greater number of deaths as the overall survival (OS) of patients in the cytarabine arm at 2 years was 97.9% versus 89.6% in the no-cytarabine arm. While the results of this trial suggested that cytarabine is a necessary part of anti-APL therapy even for patients with low-risk disease, the absence of ATRA use in consolidation, as in the LPA 99 trial, made it difficult to interpret the results. Was cytarabine needed if ATRA was used in consolidation? Is it possible that cytarabine and ATRA in combination were only needed for high-risk disease?

To help determine the optimal role of cytarabine in APL, the PETHEMA group in conjunction with the Dutch HOVON group designed the LPA 05 trial. The design of this trial was similar to that of LPA 99, but patients with high-risk disease were given cytarabine in consolidation, with results compared to those of the historical control group of high-risk patients in the LPA 99 trial. While the CIR was higher in the historical control group with high-risk disease (14% in LPA 05 versus 27% in LPA 99 at 4 years), the disease-free survival (DFS) and OS were statistically equivalent, suggesting that patients who did relapse could be salvaged with subsequent therapy.

The GIMEMA group in the AIDA 2000 trial sought to answer similar questions as the PETHEMA group, specifi-

cally whether cytarabine could be eliminated from consolidation in low- and intermediate-risk patients and whether introducing ATRA during consolidation was an effective treatment strategy. In this study, patients received standard induction chemotherapy as given in the AIDA 0493 regimen (ATRA and idarubicin). Consolidation in the low- and intermediate-risk groups contained three cycles of monochemotherapy combined with ATRA, while in the high-risk group patients received three cycles of polychemotherapy (with cytarabine in cycles 1 and 3) with ATRA. Results were compared to the historical controls of the AIDA 0493 trial.

As would be expected from the results of prior trials, the outcomes in the AIDA 2000 among both low-risk and intermediate- or high-risk patients were improved over the AIDA 0493 trials. The 6-year DFS in the overall study cohort was 85.6% in AIDA 2000 versus 69.5% in AIDA 0493. The OS was 87.4% in AIDA 2000 versus 78.1% in AIDA 0493. Much of this was driven by improved outcomes in the high-risk group, with DFS of 84.5% in AIDA 2000 and 49.6% in AIDA 0493 and OS of 83.4% in AIDA 2000 and 61.3% in AIDA 0493.

• Bone marrow examination establishes the diagnosis of APL. Should a bone marrow biopsy be performed following induction therapy?

Following induction chemotherapy, the leukemia promyelocytes differentiate into mature neutrophils. This differentiation process can take weeks, and therefore performing a bone marrow biopsy after induction often leads to confusion rather than clarity, with immature forms seen in the marrow. In addition, primary resistance to induction therapy in APL has only very rarely been reported. For both of these reasons, we do not perform a bone marrow biopsy until 4–6 weeks after induction chemotherapy has been completed. Patients who are in a hematologic remission after induction may not become molecularly negative for the PML–RAR fusion product until one or two cycles of consolidation are completed.

On day 16 of therapy for APL, the patient develops fever, cough, pulmonary infiltrates, and right-sided pleural effusion. The oxygen saturation decreases to 88%. He is transferred to the intensive care unit with a presumptive diagnosis of pneumonia.

• How is a diagnosis of APL differentiation syndrome established?

• Would prophylactic steroids have prevented this complication?

• What is the treatment of APL differentiation syndrome?

After administering ATRA, the astute physician must be vigilant for APL differentiation syndrome. The differentiation syndrome, first described with the use of ATRA but also seen with the use of arsenic triooxide (ATO), is manifested clinically as noncardiogenic pulmonary edema that can cause respiratory failure requiring intubation and mechanical ventilation. Its etiology is poorly understood. It is thought to be caused by a capillary leak syndrome induced by the rapid differentiation of leukemic promyelocytes. The treatment, dexamethasone at 10 mg twice daily, should be prescribed immediately to patients who are thought to be developing the differentiation syndrome. In our practice, we administer dexamethasone prophylactically for 10 to 14 days to patients with high-risk disease.

• Your patient achieves complete remission (CR1) following induction therapy. Should consolidation therapy be tailored according to different risk groups in APL?

Although previous studies had explored chemotherapy in induction and maintenance, the possibility of using ATRA during consolidation had not been examined in a large clinical trial. Because of this, the PETHEMA group designed a successor study to LPA 96, designated LPA 99, that introduced the use of ATRA during consolidation to those patients with intermediate- or high-risk disease (low-risk patients were designated as having a WBC count less than 10,000/μl and a platelet count greater than 40,000/μl, and others were designated as intermediate or high risk). In addition to using ATRA in patients with intermediate- or high-risk disease, consolidation chemotherapy was intensified in the intermediate- and high-risk groups; cycle 1 of consolidation used idarubicin 7mg/m^2 (as opposed to 5 mg/m^2) for 4 days, and cycle 3 of chemotherapy used idarubicin 12mg/m^2 for 2 days (rather than 1 day). Results were compared to the historical group of patients who had been enrolled on the LPA 96 trial.

The CR rate for patients in LPA 99 was 90%, which was the same as that seen in the LPA 96 trial. Intriguingly, the DFS rate for intermediate- and high-risk patients in LPA 99 was 90% compared to 77% in LPA 96. Three-year OS was 78% in the LPA 96 trial and 85% in the LPA 99 trial, which was not statistically significant. However, when restricting the analysis to the intermediate- and high-risk groups, OS was 86% in the LPA 99 trial compared to 73% in the LPA 96 trial. In an updated analysis published in 2008, the 5-year OS in the LPA 99 trial was 82%. When only the intermediate- and high-risk groups were analyzed, the 5-year OS was 81%. This trial was among the first to demonstrate that risk-adapted therapy was feasible and effective in patients with high-risk disease.

The role of ATO in consolidation was investigated by the North American Intergroup in Protocol C9710, a trial that randomized patients to two cycles of consolidation with

(*Continued*)

ATO, versus ATRA- and chemotherapy-based consolidation. In this trial, 481 patients were randomized. Both event-free survival (EFS) and DFS were improved in the arm that received ATO (EFS of 90% versus 63%, and DFS of 90% versus 70%). OS trended toward improvement, with 86% of patients alive in the ATO consolidation group versus 81% in the standard treatment arm at 3 years follow-up ($P = .059$).

Following consolidation therapy, the patient returns to your clinic to discuss the role of maintenance therapy.

- **What is the optimal maintenance regimen?**

- **Should maintenance therapy be tailored according to the risk groups?**

- **Should a bone marrow biopsy be performed after maintenance therapy?**

The need for prolonged maintenance therapy after induction and consolidation for APL is controversial. This controversy stems from conflicting results from randomized clinical trials. In addition, all of the maintenance trials enrolled patients in CR, but some trials, before the widespread adoption of sensitive polymerase chain reaction (PCR) tests, used hematologic CR to define remission, whereas others used the more sensitive molecular CR. Finally, the induction and consolidation regimens in trials that evaluated maintenance therapy were varied, making it difficult to draw any conclusions between trials about the overall benefit of maintenance.

In 2007, the JALSG reported the results of a clinical trial that randomized patients with APL who were PCR negative for the PML–RARα fusion transcript after induction and consolidation to "intensified" maintenance with combination chemotherapy or observation (Asou *et al*. 2007). The induction regimen in this trial used a risk-adapted approach: patients with a low WBC count (less than 3×10^9) received ATRA monotherapy, while those with a higher WBC count received idarubicin and cytarabine in combination with ATRA during induction. Consolidation consisted of three cycles of multidrug chemotherapy (without ATRA). Patients randomized to the intensified maintenance arm received six cycles of multidrug chemotherapy without ATRA. At a median follow-up of 49 months, 28% of patients in the intensified maintenance group had relapsed and 15% had died as compared to only 20% of patients relapsing in the observation group and only 3% dying. The results of this study suggested that intensified maintenance after induction with ATRA and consolidation with combination chemotherapy may be harmful.

As discussed earlier, one question addressed by the North American Intergroup was the role of maintenance ATRA after achieving CR. In the long-term outcome data published in 2002, there was a distinct DFS advantage for patients assigned to ATRA maintenance; DFS in the ATRA maintenance group (regardless of induction regimen) was 61% and was only 36% in the observation arm. Those patients who received both ATRA in induction and ATRA maintenance had a DFS of 74% compared to a DFS of only 16% for those who received chemotherapy and observation.

In the European APL trial, patients who were in hematologic CR after consolidation were randomized to one of four maintenance arms: observation, ATRA ($45\,mg/m^2$/day for 15 days once every 3 months), chemotherapy (methotrexate $15\,mg/m^2$/week and 6-MP $90\,mg/m^2$/day), or ATRA with chemotherapy for a total of 2 years, with chemotherapy dose modifications based on blood counts. In the final analysis, the 10-year EFS and OS in the concurrent chemotherapy–ATRA and chemotherapy-alone maintenance groups were significantly better than the results in the ATRA and observation arms. The cumulative incidence of relapse was lowest in the ATRA–chemotherapy group (13.4%), followed by the chemotherapy group (23.4%), ATRA group (33.0%), and observation group (43.2%).

The AIDA 0493 trial used a similar maintenance scheme as the European APL trial, but it only enrolled patients who were in a molecular CR at the end of consolidation (Avvisati *et al*. 2011). Interestingly, this trial saw no benefit to the use of ATRA maintenance for those patients in molecular CR at the end of consolidation, contradicting the results of the previous European and first North American Intergroup trials. Despite the negative results, subsequent, modern trials have adopted the widespread use of maintenance with ATRA, 6-MP, and methotrexate after consolidation. In addition, the utility of maintenance therapy in the era when ATRA is given during consolidation has never been prospectively evaluated.

Approximately a year following completion of maintenance therapy, the patient is diagnosed with molecular relapse.

- **Does molecular relapse portend hematologic relapse?**

- **What is the best treatment for relapsed APL?**

- **Should screening lumber puncture be done at relapse?**

Patients with molecular relapse of APL will likely develop overt hematologic relapse. Because of this, intervention when the PML–RAR transcript level is rising is the accepted approach for patients with evidence of relapse. In general, ATO is used for the treatment of relapsed disease, followed by high-dose chemotherapy with autologous stem cell rescue. De Botton and colleagues retrospectively analyzed the outcomes of 122 patients in two successive multicenter APL trials conducted by the European Acute Promyelocytic Leukemia Group with first relapse APL who received an autologous or allogeneic stem cell transplant after achieving a second hematologic CR with chemotherapy. Of those receiving an autologous transplant, the 7-year overall

survival was 59.8% with 6% transplant-related mortality. In the patients who received an allogeneic transplant, 7-year overall survival was 51.8% with a substantial transplant-related mortality of 39%. Based on these and other data, we generally recommend an autologous transplant for patients with first relapse of APL.

At the annual meeting of the American Society of Hematology in 2012, Lo Coco and colleagues presented the results from APL 0406, a prospective randomized phase III clinical trial for patients with low-risk disease, demonstrating that ATRA and arsenic without any chemotherapy led to a non-inferior EFS compared with standard treatment (idarubicin and ATRA-based induction and consolidation). After 31 months, the primary endpoint of EFS was achieved in 97% of patients in the experimental arm and 86.7% in the standard arm. Overall survival was 98.7% in the experimental arm and 91.1% in the standard arm. This clinical trial may well change the standard of care in patients with newly diagnosed, low-risk APL. While it is anticipated, based on the early data, that few patients will relapse after induction with ATRA and ATO, the optimal salvage regimen for those patients who do relapse is unclear.

A number of patients with relapsed APL will have central nervous system (CNS) involvement at the time of relapse. Because of this, we perform a screening lumbar puncture and strongly consider empirical administration of intrathecal chemotherapy for CNS prophylaxis for six courses of intrathecal therapy.

Selected reading

de Botton S, Fawaz A, Chevret S, *et al*. Autologous and allogeneic stem-cell transplantation as salvage treatment of acute promyelocytic leukemia initially treated with all-trans-retinoic acid: a retrospective analysis of the European acute promyelocytic leukemia group. J Clin Oncol. 2005;23(1):120–6.

Lo-Coco F, Avvisati G, Vignetti M, *et al*. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: Powell BL, Moser B, Stock W, *et al*. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood. 2010;116(19):3751–7.

Sanz MA, Montesinos P, Vellenga E, *et al*. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood. 2008;112(8):3130–4.

Tallman MS, Andersen JW, Schiffer CA, *et al*. All-trans-retinoic acid in acute promyelocytic leukemia. New Engl J Med. 1997;337(15):1021–8.

CHAPTER 11

Minimal residual disease in acute myeloid leukemia

Hans Beier Ommen, Line Nederby, Marie Toft-Petersen, Charlotte Guldborg Nyvold, and Peter Hokland

Aarhus University Hospital, Aarhus, Denmark

Case study 11.1

A 49-year-old male with no prior medical history was admitted to a department of internal medicine at a district hospital with a sore throat subsequent to several weeks of general fatigue and night sweats. Clinical biochemistry at admission revealed leukocytosis, anemia, and thrombocytopenia. He was referred to a university department, where a bone marrow (BM) aspirate and biopsy showed acute myeloid leukemia (AML) characterized by a large number of monocytoid cells, FAB-type M5. Cytogenetic examination showed a normal karyotype, and molecular testing revealed no AML-related fusion transcripts. However, overexpression of the Wilms tumor (*WT1*) gene could be demonstrated by quantitative PCR (qPCR) analysis. The patient received four courses of standard chemotherapy and achieved a complete morphological remission (CR) after the first course.

- **Which techniques are available to detect residual leukemia in patients in CR?**

In theory, any technique with sensitivity higher than that of classical immunohistochemistry will yield information regarding the depth of the achieved remission. The most commonly used techniques are qPCR and multicolor flow cytometry (MFC). While qPCR techniques have been extensively validated in multicenter efforts, less formalized testing has been performed with MFC. Minimal residual disease (MRD) detection using qPCR targets RNA or DNA sequences, which are derived from fusion genes, mutated genes, or genes overexpressed in AML cells. Fusion transcripts, arising from balanced translocations, have for some time been well known to be present in a minority of AML patients. Point mutations (e.g., in the *NPM1* gene) are also an established qPCR target, whereas overexpression (e.g., of the *WT1* gene) is considered a useful but less specific qPCR target. MFC–based MRD detection usually relies upon the aberrant immunophenotypic profiles of AML cells. Here, advantage is taken of the surface expression on the leukemic cells of leukocyte differentiation antigens present in either abnormal combinations or densities. This extent of aberrancy of the leukemic blasts is used to construct leukemia-associated immunophenotypes (LAIPs), namely, immunophenotypes that are rarely seen in healthy hematopoiesis but often characterize AML cells.

- **Are MRD measurements of value in the evaluation of response to cytoreduction?**

For all major MRD markers, prognosis has been shown to be affected by the MRD level after the first course of chemotherapy. There is therefore no doubt that MRD levels reflect a more accurate and biologically relevant way of judging the extent of disease disappearance. However, only a few trials studying AML have applied the consequence of these findings, adjusting treatment according to MRD measurements. Importantly, in one study of childhood AML, intensification upon demonstrating high levels of MRD at first-response evaluation resulted in superior overall survival, providing proof of principle for this approach. Of note, this decision making based on MRD was performed in patients in CR by standard techniques. More trials are underway to formally validate the concept of adjusting treatment intensity based on MRD status.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

• **Can MRD markers be identified for all AML patients?**
The applicability of MRD markers varies considerably. *WT1* is one of the most widely applicable MRD markers, because more specific targets are not seen in more than two-thirds of patient cohorts. Specific markers such as fusion transcripts are each rarely applicable in more than 5% of AML cases, whereas *NPM1* mutation–based MRD measurement can be used in 35% of AML cases. The usefulness of the *WT1* gene can be seen from reports stating that it is overexpressed in up to 70% of AML patients.

For MFC, MRD markers include the common aberrant immunophenotypes (e.g., CD7 expression on myeloblasts). Such markers can usually be found for more than 80% of AML cases; however, the search for LAIPs in each patient entails extensive testing.

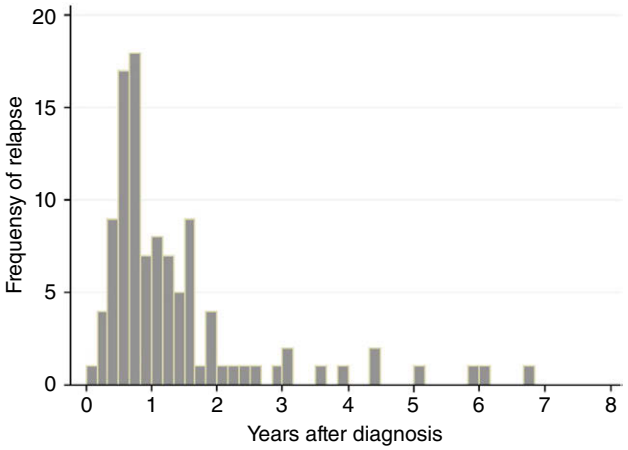


Figure 11.1 Time from end of chemotherapy to relapse in 84 Danish acute myeloid leukemia (AML) patients treated between 2000 and 2008.

• **The patient is followed with standard hematological techniques and qPCR targeting *WT1* every third month. The level of *WT1* transcripts in peripheral blood (PB) has been normal for 3 years. For how long is continuous measurement of an MRD marker pertinent?**
As can be seen from Figure 11.1, the majority of AML relapses occur within the first 2 years from diagnosis. That is not to say that relapse cannot occur later. However, on closer molecular characterization, late relapses will often turn out to be cases of secondary AML. The leukemic blasts of such patients are less likely to be recognized by measurements of the initial MRD marker. Many clinicians will thus opt to follow patients with MRD measurements for as long as clinical control is maintained, usually for 5 years. However, it might also be argued that cessation of MRD measurements (e.g., after 2 years) will be a welcome signal to the patient that the period of strict follow-up is over. Regardless, in terms of health economics, ending MRD follow-up after 2 to 3 years seems prudent.

Case study 11.2

A 37-year-old woman with mild arterial hypertension presented with easy bruising and repeated infections at her general practitioner. Blood cell counts revealed thrombocytopenia, anemia, and leukocytosis. After referral to a university department of hematology, she was diagnosed with AML. Cytogenetic examination showed a normal karyotype, but array comparative genomic hybridization revealed a microdeletion on the long arm of chromosome 4. Molecular testing showed no AML-related fusion transcripts, but overexpression of the *WT1* gene. The patient was also found to be *NPM1* mutation positive. She was treated with three courses of chemotherapy and achieved a CR after the first course. The *WT1* transcripts in both BM and PB normalized, but 7 months later overexpression was again detected in PB. Morphological examination of BM could not confirm a hematological relapse, although MFC showed up to 20% cells of the original LAIP (an aberrant CD7 density in immature myeloid cells). At this point, a search for a matched unrelated donor was initiated because a brother was not immunogenetically matched. Repeated BM examination 2 months later showed overt hematological relapse, and she received two courses of salvage chemotherapy. This resulted in a second morphological CR with slightly increased *WT1* levels, and she was referred to myeloablative allogeneic transplantation with an unrelated donor. She has remained in CR, with levels of *WT1* transcripts returning to normal in repeated PB samples.

• **Which is generally the most specific MRD marker: *WT1*, *NPM1*, or LAIPs?**
WT1 expression is not specific to AML cells, as *WT1* expression is seen in healthy hematopoiesis as well, albeit at a much lower level. Thus, it is necessary to define normalcy in the given laboratory. To this end, a patient-specific

(*Continued*)

threshold separating *WT1* expression of the residual leukemia from healthy hematopoiesis is commonly used. This approach solves the problem of specificity, but with respect to sensitivity *WT1* then becomes inferior to other MRD markers. In contrast to *WT1*, *NPM1* is a highly specific marker rivaling the specificity of fusion transcript MRD markers. With respect to LAIPs, this is more difficult to address because hematopoietic stem cells are known to be very heterogeneous, with LAIPs often reproducing the phenotype of rare subsets. Great care is therefore needed to choose a LAIP in which the frequency of the normal counterpart is very low. In addition, it is an advantage to choose LAIPs that have an aberrant density of at least one antigen included in the MFC assay.

• Which is the most sensitive MRD marker, *WT1* or *NPM1*?

Sensitivity can be defined as the degree of dilution of the leukemic blast in healthy BM that still allows for AML detection. Due to problems with background expression, *WT1*- and MFC-based markers rarely achieve the level of sensitivity seen in MRD detection targeting fusion transcripts or mutations (for a comprehensive list of MRD marker sensitivities, see Hokland *et al.*).

With a sensitivity that is never less than 1:5000, follow-up based on the *NPM1* mutation is vastly superior to *WT1* quantification, where sensitivity in this case was approximately 1:50. Indeed, after examining the patient's MRD curve (Figure 11.2), one could argue that if the patient had been followed with an *NPM1*-based assay, molecular relapse could probably have been detected one month earlier. However, the consequence of molecular relapse was the initiation of a donor search. As the patient had to undergo two series of salvage chemotherapy prior to transplantation, earlier detection of molecular relapse using *NPM1* rather than the executed *WT1* measurement would have made no difference in the treatment.

While the highest sensitivity assay should in general be the one employed, it should also be added that in many patients, low-sensitivity assays would be quite adequate for most treatment decisions. Thus, outside clinical protocols, *WT1* will usually provide sufficient information to decide whether initial and subsequent cytoreduction have been successful. In addition, the early detection of relapse by *WT1* qPCR will display kinetics, which allow for timely intervention like the one instituted in the present patient.

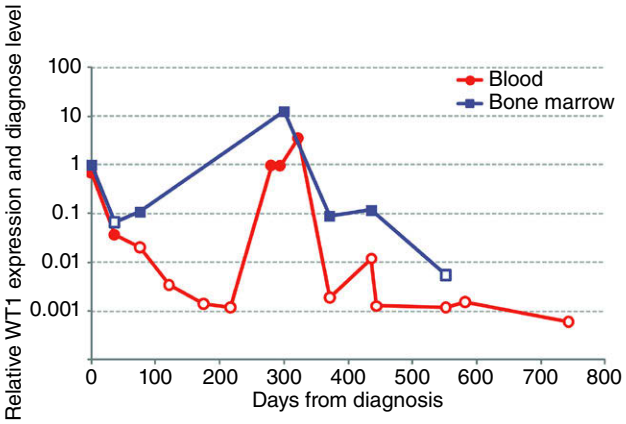


Figure 11.2 Minimal residual disease (MRD) follow-up using *WT1* expression as the molecular target. Open symbols denote undetectable levels of *WT1* expression or levels below the patient-specific threshold separating *WT1* expression of the residual leukemia from the background expression of *WT1* in healthy hematopoiesis.

• In this case, search for a matched unrelated donor was initiated based upon molecular relapse. At the time of molecular relapse, MFC showed 20% blasts in BM, but histological examination could not confirm the above findings. When then is the best time to initiate further chemotherapy?

There is only very sparse documentation for the effect of preemptive therapy in AML relapse; this is the initiation of chemotherapeutic treatment in patients who have had a molecular relapse (rising MRD levels of one log in 2–3 measurements at least 2 weeks apart) but not yet a clinical relapse (deterioration of BM function and more than 5% blasts morphologically in BM). In a Czech study, gemtuzumab ozogamicin or "2 + 5" (5 days of cytarabine 200 mg/m^2 and 2 days of idarubicine 12 mg/m^2) had no effect on progression to clinical relapse in a small patient cohort. Donor lymphocyte infusions (DLIs) in transplanted patients were seen to have some effect. In a more recent study of azacytidine-treated molecular relapse in *NPM1*-mutated AML, this was shown to prolong time to relapse even if relapse was not always averted. In another preliminary report, the effectiveness of DLIs upon molecular relapse was supported, as it increased overall survival from 14% to 44%. Thus, the course of action depends on the treating physician weighing the treatment options with the sparse documentation for the effect of such.

Case study 11.3

An 18-year-old male with no prior medical history was diagnosed with AML after 5 weeks of continued fever, which was initially interpreted as mononucleosis. Cytogenetics showed translocation t(8;21), and the patient was followed by qPCR targeting the fusion transcript *RUNX1–RUNX1T1* as an MRD marker. He achieved a morphological CR after the first course of chemotherapy. The *RUNX1–RUNX1T1* fusion transcript became undetectable in PB, while in BM it decreased by a factor of 10^4 (Figure 11.3). One year after diagnosis, the MRD levels were seen to increase. A bone marrow aspiration and biopsy could not confirm morphological relapse. Despite this, a donor search was initiated, and the patient was followed more closely by qPCR. Seven months later, the patient developed swelling behind his right ear, and a biopsy from the mastoid now showed myeloid sarcoma. The BM was continuously morphologically free from malignancy. The patient received two courses of salvage chemotherapy and achieved a second CR, now assessed by MRD and imaging. He was subsequently offered an allogeneic BM transplantation.

- **Does a positive MRD determination always result in a subsequent relapse?**

This is an important and recurring question at the center of the ongoing evaluation of MRD in AML. Even for highly disease-specific markers such as fusion transcript– or mutated gene–based qPCR, several groups have reported scant positive MRD samplings not followed by a subsequent relapse. The MRD reversals not followed by a clinical relapse are most often seen immediately after cessation of

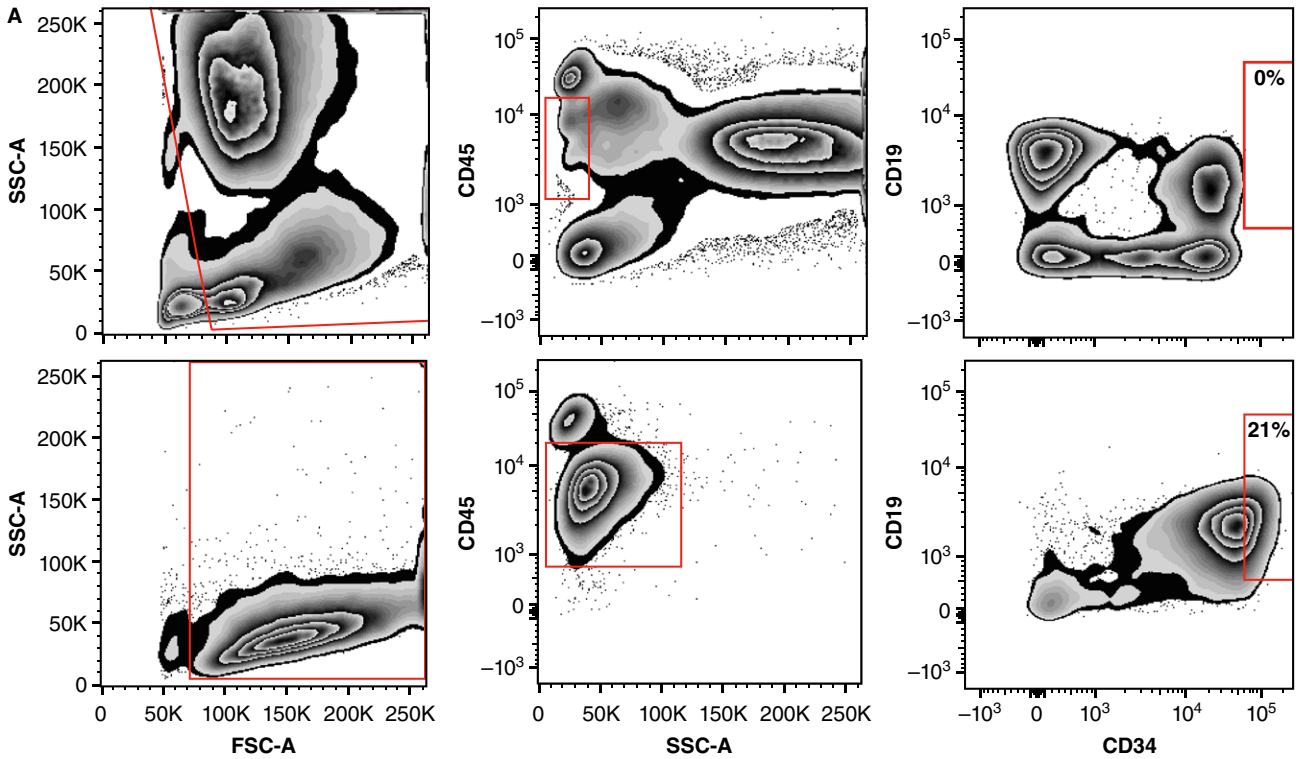


Figure 11.3 Flow cytometric and quantitative PCR (qPCR) results obtained during follow-up of case study 11.3. (A) The top panels illustrate the gating strategy in a normal donor, while the bottom panels depict the patient. In an FSC-A/SSC-A diagram, gates holding the leukocytes are made. In the second column, $CD45^{low}$/$SSC\text{-}A^{low}$ subsets of the leukocytes are defined. When analyzing the expression of CD34 and CD19 of the $CD45^{low}$/$SSC\text{-}A^{low}$ cells, a distinct immunophenotypic subset having a high density of CD34 and aberrant CD19 expression is recognized in the patient. Hence, CD34 and CD19 in combination can be used as minimal residual disease (MRD) markers in multicolor flow cytometry. (B) The MRD curve using *RUNX1–RUNX1T1* fusion transcripts as the molecular target. Open symbols denote undetectable levels of MRD. The flow cytometry plot illustrates the presence or absence of the malignant clone at four time points during follow-up.

(*Continued*)

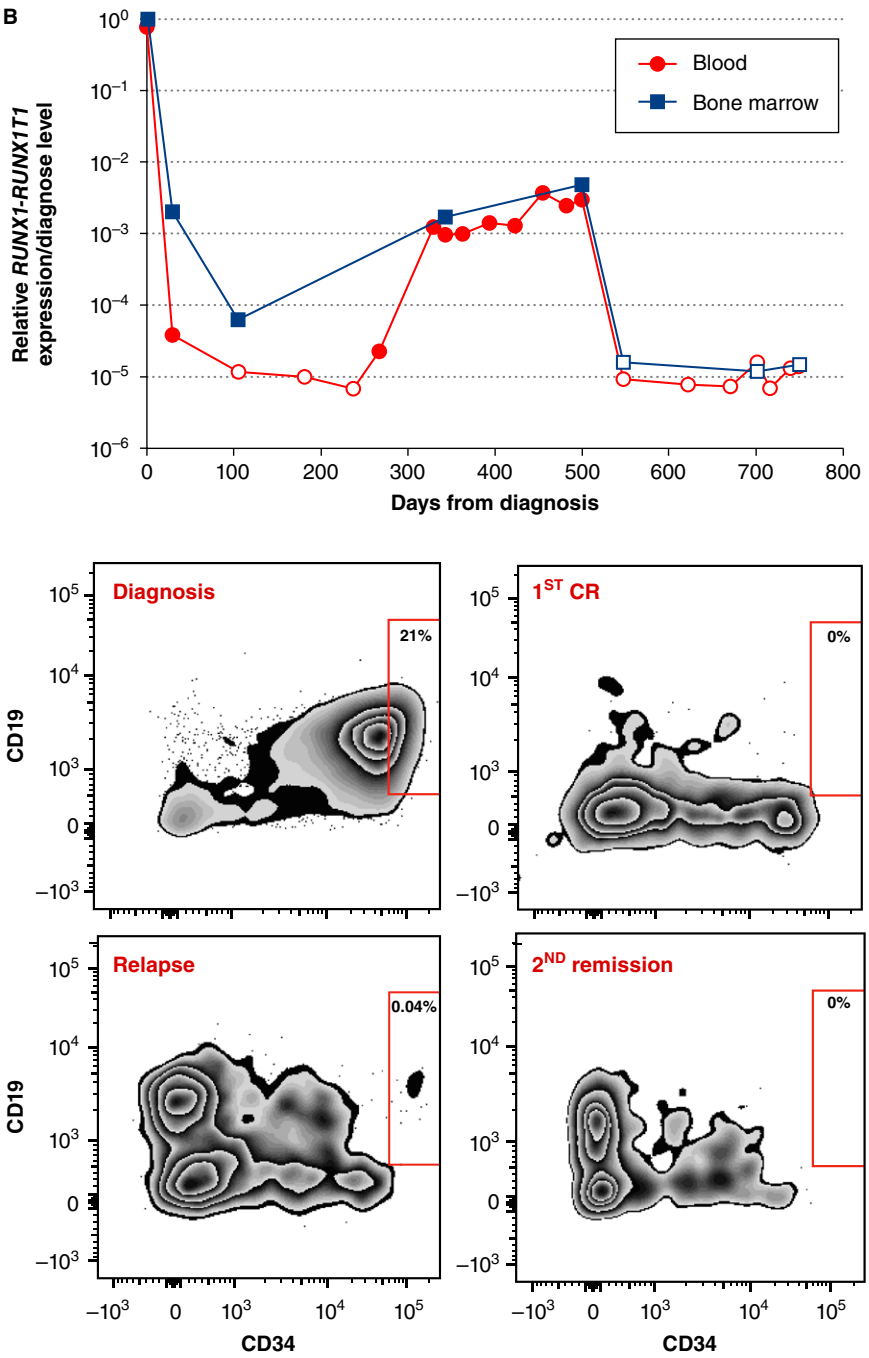


Figure 11.3 *Continued*

chemotherapy, but they can be seen in the postallogeneic setting as well. These are generally positive at very low, and stable, levels. This is most probably a reflection of temporary changes in disease levels at the time when both normal and malignant hematopoiesis are in the rebound phase. A strict follow-up with repeated measurements 2–3 weeks apart can be employed to delineate further changes.

- **In this case, two MRD markers were available, *RUNX1–RUNX1T1* and *WT1*. Is there evidence for the benefit of running the two markers in parallel?**

Some MRD markers, although positive in the diagnostic sample, turn negative upon relapse. Flow cytometry–based markers and *FLT3*–ITD-based MRD follow-ups are notoriously unstable. In the present case, the *RUNX1–RUNX1T1* marker is very stable and is superior to the *WT1* marker,

in which rare losses have in fact been reported. In cases in which only markers known to be unstable at relapse are available, this can be overcome by using two or more MRD markers in parallel, if the increased costs of the analyses are acceptable.

• **The patient had molecular relapse 7 months before clinical relapse was diagnosed. Does this give rise to any ethical considerations?**
In many patients, especially those less fit for further cytoreduction, relapse will spell ultimate treatment failure. Thus, in some cases the knowing of a molecular relapse may cause months of anxiety regarding the possibility of an ongoing relapse. This forces hematologists to prepare the patient for possible situations that may arise during the period of MRD follow-up. However, the predictive value of a negative MRD measurement is of great value in reducing patient anxiety. Finally, the diagnosis of molecular relapse provides additional months for donor searches and thus eases the logistics of preparing a transplantation, which compensates for the potential negative impact on the patients' quality of life.

Selected reading

Cilloni D, Renneville A, Hermitte F, *et al*. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. J Clin Oncol. 2009;27:5195–201.

Hokland P, Ommen HB, Nyvold CG, *et al*. Sensitivity of minimal residual disease in acute myeloid leukaemia in first remission—methodologies in relation to their clinical situation. Br J Haemotol. 2012;158:569–80.

Ommen HB, Schnittger S, Jovanovic JV, *et al*. Strikingly different molecular relapse kinetics in NPM1c, PML-RARA, RUNX1-RUNX1T1, and CBFB-MYH11 acute myeloid leukemias. Blood. 2010;115:198–205.

Schnittger S, Kern W, Tschulik C, *et al*. Minimal residual disease levels assessed by NPM1 mutation-specific RQ-PCR provide important prognostic information in AML. Blood. 2009;114:2220–31.

Voskova D, Schoch C, Schnittger S, *et al*. Stability of leukemia-associated aberrant immunophenotypes in patients with acute myeloid leukemia between diagnosis and relapse: comparison with cytomorphologic, cytogenetic, and molecular genetic findings. Cytometry B. 2004;62:25–38.

CHAPTER 12

Relapsed and refractory acute myeloid leukemia

Stefan H. Faderl

Hackensack University Medical Center, Hackensack, NJ, USA

Case study 12.1

A 54-year-old woman is diagnosed with acute myeloid leukemia (AML). The cytogenetics are reported to be normal. Molecular studies reveal mutations for the *NPM1* gene and for *FLT3*–ITD. The patient is undergoing induction chemotherapy with the combination of cytarabine and daunorubicin according to a standard "7 + 3" dose and schedule. She achieves a complete remission (CR) following the first cycle of induction and completes four cycles of high-dose cytarabine (HiDAC) consolidation. She has no siblings.

1. What is the likelihood of relapse in this patient?

A. The relapse likelihood is low (<10%) as the patient is younger than 60 years

B. The patient will not maintain the remission in the absence of allogeneic progenitor cell hematopoietic cell transplant (HPCT)

C. The likelihood of relapse is approximately 50% to 60%

Following current standard therapy, 20–30% of younger and up to 50% of older patients (usually defined as >60 years of age) with AML will have refractory disease and will not respond to induction therapy. Among patients who achieve CR, maintaining remission represents the biggest challenge as is reflected in long-term disease-free survival (DFS) rates of only around 30%. The risk of relapse is highest early after achievement of CR and declines with time. In a study of 1069 patients from the MD Anderson Cancer Center, the yearly risk of treatment failure was 69.1%, 37.7%, 17%, 7.6%, and 6.6% in the first to fifth years of remission, respectively. The likelihood of relapse-free survival (RFS) for patients who were alive and in remission at 3 years was 84%, at 6 years suggesting that patients who are in remission at 3 years and beyond could potentially be considered as cured. On the contrary, the risk of recurrence remained substantially higher for those patients over age 60 at diagnosis, for whom the 6-year rate of RFS was only 56.6% even after being in 3 years of remission.

2. Which of the following pretreatment prognostic factors is the most important predictor for relapse?

A. Cytogenetic and molecular studies

B. Age

C. White blood cell (WBC) count

Both patient- and disease-specific factors determine outcome. The patient-specific factors (i.e., age, performance status, organ function, and comorbidities) determine survival probability following induction therapy and become obvious early (<4 weeks) during the course of treatment. The disease-specific factors (i.e., diagnostic cytogenetics and molecular studies) determine resistance of blasts to therapy and are operative later during the course of therapy. Pretreatment karyotype remains the most important prognostic factor with regard to achievement of remission, risk of relapse, and overall survival (OS). Patients in unfavorable cytogenetics risk groups are virtually incurable with standard chemotherapy alone and will relapse without HPCT. The most favorable outcomes are observed in patients with core binding factor (CBF) AML (translocation t(8;21), inv(16), or t(16;16)) and acute promyelocytic leukemia (APL) with expected DFS rates of 60% and up to 90%, respectively. Patients with normal (diploid) karyotype belong to the intermediate prognostic risk group, which is the largest and most prognostically heterogeneous group. It is for patients with normal cytogenetics in whom information from molecular

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 12.1 Established molecular markers and impact on prognosis.

Mutation or deregulation	Frequency	Impact
FLT3–ITD	25% to 35% (NK)	Shorter OS and DFS
NPM1 without *FLT3*–ITD	45% to 60% (NK); 25% to 35% of AML	Favorable OS and RFS
Bi-allelic *CEBPA* without *FLT3*–ITD	10% to 20% (NK)	Favorable OS and RFS; higher rate of remission
KIT	25% to 30% (CBF)	Higher relapse likelihood

CBF, core-binding factor leukemia; DFS, disease-free survival; NK, normal karyotype; OS, overall survival; RFS, relapse-free survival.

studies has helped most to determine outcomes more precisely (Table 12.1). The combined information from cytogenetic and molecular analyses led to a revision by the European LeukemiaNet of the tripartite risk model that divided patients into four risk groups. Most significantly, the prognosis of patients with normal cytogenetics and mutations of *NPM1* or *CEBPA* with wild-type *FLT3*–ITD have the favorable outcomes reminiscent to that observed in patients with CBF AML. The patient in our example maintains an intermediate prognosis and intermediate-I according to the European LeukemiaNet model as both *NPM1* and *FLT3*–ITD are mutated (discussed in detail in Chapter 7).

Your patient, presented in Question 1, did not undergo HPCT and relapsed 14 months following consolidation therapy.

3. What is the expected response to salvage therapy and the likelihood of survival?

A. Expected response rate is 60%
B. Expected response rate is about 20% to 30%
C. This patient will not respond to further chemotherapy

In a study of 243 patients with AML, the remission rate of salvage therapy was 33% with a median survival of 18 weeks. The 5-year survival rates were 5% for the entire cohort of patients and 16% for those who achieved remission. The factor most strongly associated with response and survival was the duration of the initial remission; remission rates upon salvage therapy were as high as 60% with a first remission (CR1) of at least 2 years but decreased to as low as <20% for those patients with initial remission durations of less than 1 year. Despite this being an older study, the framework within which the data are presented remains similar to today's situation, and it remains a fairly accurate tool to predict outcomes.

Multiple choice questions

1. Which of the following factor(s) influence outcome at relapse?

A. Age at relapse
B. Duration of CR1
C. Cytogenetics at diagnosis
D. All of the above

As has become clear, a substantial number of patients may not benefit from intensive re-induction chemotherapy and a search for investigational therapies (i.e., a clinical trial is more appropriate). Yet, on the other hand, a small group of patients may indeed benefit from attempts at intensive re-induction therapy and carry an altogether more favorable prognosis. Several prognostic indices have been devised to more accurately predict outcome for patients in first relapse. In a study by Breems *et al*. (2005) of 667 patients with AML in first relapse, four clinical parameters determined outcome: duration of CR1, cytogenetics at diagnosis, age at relapse, and whether or not previous HPCT was performed. Using a stratification system, three risk groups were identified with OS rates ranging from 46% at 5 years in the best prognosis group to 4% in the worst prognosis group (Table 12.2), which included the majority (almost 70%) of the patients. The GOELAMS group presented a simplified prognostic score based on a multivariate analysis of 138 patients with relapsed or refractory AML, which was then validated in an independent cohort of 111 patients. The three strongest independent adverse prognostic factors for OS included disease status (relapse within the first 12 months or later), *FLT3*–ITD-positive status, and high-risk cytogenetics. Accordingly, patients with no adverse factors had an OS of 58%, whereas patients in the highest risk group (two or more adverse factors) had an OS of 12% at 2 years. Applying these scores to the described patient, the 5-year OS is 4% and the 2-year OS is 12% in the study by Breems *et al*. (2005) and the GOELAMS group, respectively.

Table 12.2 Prognostic scoring systems in patients with AML in first relapse (Source: Adapted from Breems D, *et al.* J Clin Oncol. 2005;23:1969–78; and Chevallier P, *et al.* Leukemia. 2011;25:939–44).

Author	Prognostic group	CR (%)	OS (%)
Breems *et al.*[a]	Favorable (score 0–6)	85	46 (5 year)
	Intermediate (score 7–9)	60	18
	Unfavorable (score 10–14)	34	4
Chevallier *et al.*[b]	Favorable (no adverse factor)		58 (2 year)
	Intermediate (one adverse factor)		38
	Unfavorable (≥1 adverse factors)		12

[a]Prognostic factors include (i) relapse-free interval (>18 months, 0 points; 7–18 months, 3 points; ≤6 months, 5 points); (ii) cytogenetics at diagnosis (t(16;16) or inv(16) ± other cytogenetic abnormalities, 0 points; t(8;21) ± other cytogenetic abnormalities, 3 points; other karyotype, 5 points); (iii) age at first relapse in years (≤35, 0 points; 36–45, 1 point; >45, 2 points); and (iv) stem cell transplant before first relapse (no, 0 points; yes, 2 points).
[b]Adverse factors include (i) relapse ≤12 months; (ii) expression of *FLT3*–ITD mutation; and (iii) high-risk cytogenetics.

2. True or false? Patients who relapse following high-dose cytarabine-based induction therapy are more likely to respond to salvage therapy than those who had received a standard dose cytarabine induction (e.g., "7 + 3") therapy.

A. True
B. False

Although the 7 + 3 combination consisting of standard doses of cytarabine (100 to 200 mg/m^2/dose) is the most widely used induction therapy, there is some evidence that higher doses of cytarabine during induction benefit younger adults (patients <60 years) and especially those patients <45 years of age. The question arises whether patients who fail to respond to higher-intensity induction regimens fare differently from those who relapse after a more standard and less intensive induction regimen. In a study of 1597 patients with AML between the ages of 18 and 85 years, 285 patients were refractory to HiDAC-based induction therapy. These patients on average tended to be older and were more likely to have a history of an antecedent hematologic disorder, blasts with unfavorable cytogenetics, and a higher WBC count at presentation. Only 43 patients (22%) responded to salvage therapy, and with a median follow-up of 72 months, only 11 patients stayed alive, mostly those who underwent an HPCT. The median survival of these patients was only 3.8 months, and among the patients who achieved remission, the median remission duration was only 9.1 months.

3. True or false? In adult AML, 1-year survival rates of up to 20% can still be achieved in some patients with multiple relapses.

A. True
B. False

Not surprisingly, the situation in second salvage looks worse, although differences between patient outcomes exist in this group as well. In a study of 594 patients with AML who underwent second salvage therapy by various modalities, including HPCT, standard- and higher-dosed cytarabine combinations, and non-cytarabine-based therapy, including phase I and II clinical trials, the remission rate was 13%, and median remission duration was 7 months with a median survival of 1.5 months and a 1-year survival rate of not higher than 8%. A multivariate analysis for survival identified seven independent adverse factors: CR1 duration <12 months, second remission (CR2) duration <6 months, bilirubin levels ≥1 mg/dL, albumin level <3 g/dL, age >60 years, marrow blasts ≥50%, and year of therapy prior to 1991. Patients could accordingly be divided (almost equally) into three prognostic groups with remission rates of 26%, 8%, and 2% and estimated 1-year survival rates of 22%, 6%, and 0%, respectively, ranging from the most favorable to the poorest group in terms of prognosis, respectively.

Case study 12.2

A 45-year-old woman with relapsed AML is admitted for salvage chemotherapy.

1. What is the principal goal of therapy for this patient?

A. Cure
B. Bridge to potentially curable strategy of allogeneic transplant
C. Palliation

The principal goal remains procurement of a second remission followed by HPCT. Without it, prognosis is indeed very poor. Achievement of this goal typically requires re-induction chemotherapy; however, a minority of patients are appropriate candidates for this strategy. The likelihood of benefit for the majority of patients, such as those with short remissions or refractory disease, those with complex karyotype, older adults, or those with multiple comorbidities or poor performance status, is so low that alternative strategies are considered (e.g., lower-intensity therapy, investigational therapies, and hospice). Even under the best of circumstances, chemotherapy alone will not cure relapsed patients, hence their main function is to serve as a "bridge to transplant" as the more effective long-term strategy. It is important to note that salvage therapy should be tailored to minimize toxicities and preserve the patient's immune status as much as possible.

2. What is the most appropriate statement with regard to conventional salvage chemotherapy regimens in AML?

A. Substantial differences in outcome exist between different salvage regimens
B. Outcomes between different salvage regimens are comparable
C. The addition of clofarabine to cytarabine leads to improved survival over the use of cytarabine alone

There is no standard salvage regimen for adults with relapsed or refractory AML. A number of salvage regimens have been published over the years, and some of these are summarized in Table 12.3. Although the studies differ widely among each other with respect to patient numbers and characteristics, the stage of salvage, and the reporting of the results, the outcome is fairly comparable. One of the largest studies conducted in patients with AML relapse has been

Table 12.3 Representative chemotherapy salvage regimens.

Study	*N*	RR (%)	30-day mortality (%)	Median OS (months)	DFS	EFS
AraC vs. Clo + AraC[a]	320					
AraC		22.9	5	6.3		16.6% (4 months)[h]
Clo + AraC		46.9	16	6.6		37.7% (4 months)
CLAG-M[b]	118	58		14% (4 years)[i]	30% (4 years)[j]	
FLAG[c]	38	55.3	10	9	13 months[k]	
FLAG-IDA[d]	19	63				
MEC[e]	32	66	6	8.6		
FA + G + amsacrine[f]	58	59	3.4	10.6		6.9 months[l]
GCLAC[g]	46	61		9		

AraC, cytarabine; CLAG-M, cladribine, high-dose cytarabine, mitoxantrone, and G-CSF; clo, clofarabine; FA + G + amsacrine, fludarabine, cytarabine, G-CSF, and amsacrine; FLAG, fludarabine, cytarabine, and G-CSF; FLAG-IDA, fludarabine, cytarabine, G-CSF, and idarubicin; GCLAC, clofarabine, high-dose cytarabine, and G-CSF cytarabine; MEC, mitoxantrone, etoposide, snd intermediate-dose.

[a]Faderl S, *et al.* J Clin Oncol 2012;30:2492–9.
[b]Wierzbowska A, *et al.* Eur J Haematol. 2008;80:115–26.
[c]Montillo M, *et al.* Am J Hematol. 1998;58:105–9.
[d]Parker JE, *et al.* Br J Haematol. 1997;99:939–44.
[e]Amadori S, *et al.* J Clin Oncol. 1991;9:1210–14.
[f]Fong CY, *et al.* Leuk Lymphoma. 2012 [Epub ahead of print].
[g]Becker PS, *et al.* Br J Haematol. 2011;155:182–89.
[h]% at 4 months; statistically significant difference.
[i]% at 4 years.
[j]% at 4 years; refers only to patients in complete remission.
[k]Median DFS in months.
[l]Median EFS in months.

(*Continued*)

a recently published, multinational, placebo-controlled, randomized study comparing intermediate-dose cytarabine with the combination of cytarabine and clofarabine (CLASSIC I). Clofarabine is a newer-generation nucleoside analog with activity in AML but no US Food and Drug Administration approval for myeloid leukemias. The study included 320 patients in first salvage with a median age of 67 years. The choice for the comparator was intermediate-dose cytarabine ($1\,g/m^2$ IV daily $\times$ 5 days). The primary endpoint was OS, which did not differ significantly between the two treatment groups. On the other hand, overall response and CR rate were in favor of the combination arm, although at the cost of a higher induction mortality (16% versus 5%). Furthermore, a higher number of patients on the combination arm could proceed with an HPCT. Very few other comparison studies between treatment regimens are available. In a retrospective analysis, investigators compared CLAG (cladribine, cytarabine, and granulocyte colony-stimulating factor (G-CSF)) with MEC (mitoxantrone, etoposide, and cytarabine). Comparing complete response rates of 36.8% versus 25.9% ($P = .35$) and a median OS of 6.7 months in both arms for patients in first relapse, no regimen emerged superior, although for patients with primary refractory disease, the benefits were tilted more in favor of CLAG.

Your patient with relapsed AML received salvage chemotherapy with fludarabine, cytarabine, G-CSF, and idarubicin (FLAG–Ida). She achieves CR2 following one cycle of treatment.

3. What should be the next step in her management?

A. Continue FLAG–Ida as it is obviously working
B. The patient should undergo a stem cell transplant as soon as possible
C. No further treatment should be given

Only a few patients can be rescued with chemotherapy alone, and transplant provides the best option for cure under these circumstances. However, similar to what has been described previously, there are also large outcome differences with regard to patients who undergo allogeneic transplantation. Achievement of a CR2 prior to transplant is crucial, with 5-year survival rates varying between 26% and 88% depending on the patient's pretransplant characteristics. The outcome of patients not in remission at the time of transplant was described in a large multicenter study including 1673 patients who underwent transplantation for relapse or refractory AML. The OS at 3 years was 19% with a 100-day mortality rate of 39%. Multivariate analysis revealed five adverse pretransplantation variables influencing survival: short first CR duration (<6 months), circulating blasts, donor other than an HLA-identical sibling, KPS <90, and poor-risk cytogenetics. Patients who had none of these variables had a 3-year survival likelihood of 42% compared to only 6% if three or more of these variables were present. Given the guarded prognosis of these patients with chemotherapy alone, alternative donor sources (umbilical cord units and haploidentical donors) should be approached at the time of relapse. The role of reduced-intensity conditioning (RIC) in this setting is under discussion, with some favoring this approach whereas others have expressed a more critical position regarding its efficacy (discussed in Chapter 13).

4. What are some of the strategies under investigation to prevent relapse following a hematopoietic progenitor cell transplant?

Disease relapse is one of the most important causes of treatment failure after transplant. Most relapses occur within one year of transplant. Common risk factors for recurrence have been established, including older age, unfavorable cytogenetics, mutations of *FLT3*–ITD, presence of an antecedent hematological disorder such as myelodysplastic syndrome (MDS), transplant in any other state than first remission, use of less intensive conditioning regimens, gender donor–recipient combinations other than female to male, single umbilical cord blood transplantation versus double transplants, specific killer cell immunoglobulin-like receptor haplotypes, and use of T-cell depletion procedures. Posttransplant strategies to reduce the risk of relapse are being evaluated. These include preemptive measures such as rigorous follow-up of minimal residual disease as well as active therapeutic interventions: treatment with hypomethylating agents, prophylactic donor lymphocyte infusions (DLIs), adoptive transfer of natural killer cells, leukemia-specific T-cells, and leukemia vaccines. This topic is further discussed in Chapter 67.

5. Your patient with AML who has undergone an allogeneic sibling transplant in the past has only recently relapsed. Which of the following factors would most increase the chances of a favorable outcome following a second allogeneic transplant?

A. A long (at least one year) duration of the remission following the first allogeneic transplant
B. Residual disease following re-induction chemotherapy and prior to a second allogeneic transplant
C. Older age

Prognosis remains poor following relapse from an HPCT, with a median survival of only 3 to 4 months. Not surprisingly, the number of patients who undergo a second transplant is low (<20%). Yet for a few patients, a second allogeneic transplant may provide more substantial benefit and hence play a significant role in the treatment of relapse. The best case scenario is patients who are younger, maintain a good performance status, are in remission at the time of the second transplant, and have been in remission for >6 to 12 months following the first transplant. Under those circumstances, the 3-year survival probability following the second transplant can be as high as 50%. In most situations,

the same donor is used, although there is no reason not to pursue an alternate donor (e.g., a different matched sibling or matched unrelated donor) if one is available. It remains to be emphasized, though, that these conditions are rare to encounter in daily practice as a substantial number of patients relapse early with a high tumor burden and often have chemotherapy-resistant disease.

6. Should relapsed or refractory AML patients be offered access to clinical trials?

A. Yes
B. No

Should transplant not be an option, or in cases where the leukemia remains refractory to re-induction attempts, investigational therapies should be seriously considered. In principle, almost every patient with relapsed AML should be offered participation in clinical trials as no defined or effective standard of care has been established and the prognosis of patients with AML relapse is almost uniformly poor. The breadth of approaches has expanded significantly over the last few years and includes not only novel small-molecule, targeted inhibitors of specific pathways, but also epigenetic therapy (DNA methyltransferase inhibitors and histone deacetylase inhibitors), immunomodulators, and novel chemotherapeutics, including novel nucleoside analogs such as clofarabine or sapacitabine (Table 12.4). In general, response rates are low and the duration of responses is short, but in some patients responses are sufficient enough to serve as a "bridge to transplant." This topic is discussed in detail in Chapter 13.

Table 12.4 Experimental therapies in AML relapse.

Class	Agent	Comment
Nucleoside analogs	Clofarabine	Response rates of up to 45% in AML salvage, but randomized study did not support survival benefit (despite higher CR and better event-free survival).[a]
	Sapacitabine	Clinical activity in early AML and MDS trials at different doses and schedule. Clinical development continues.[b]
Quinolone derivatives	Vosaroxin	Mechanistically similar to anthracyclines or anthracenediones. In a phase III trial vosaroxine plus cytarabine is being compared to cytarabine alone.[c]
DNA methyltransferase inhibitors (hypomethylators)	Azacitidine and decitabine	Both drugs have shown activity in AML although response rates are low.[d] The slow onset of action makes them unsuitable for patients with aggressively proliferative disease. Combinations with histone deacetylase inhibitors and other agents are being explored.
	SGI-110	A dinucleotide of decitabine and guanosine linked by a phosphodiester bridge. It is resistant to cytidine deaminase. It demonstrates improved pharmacokinetics over decitabine and is in clinical studies in patients with relapsed or refractory AML.
Histone deacetylase inhibitors	Vorinostat	Limited single agent activity. The potential in combinations with conventional chemotherapy is being investigated.[e]
Inhibitors of FLT3	Sorafenib Midostaurin Lestaurtinib Quizartinib Crenolanib	Quizartinib has demonstrated response rates of 50% as single agent salvage therapy in FLT3-ITD positive AML.[f] Development of point mutations at relapse has been observed. Other FLT3 inhibitors have more modest single agent activity and combinations with chemotherapy or other agents (e.g. hypomethylating agents) are being investigated. A recent randomized study in AML salvage did not show any benefit from adding lestaurtinib.[g] Crenolanib is a new FLT3 inhibitor with selective activity against the D835 point mutation.
Inhibitors of Aurora kinases	AMG-900	An oral, small molecule inhibitor of aurora kinases A, B, and C. The compound is in clinical trials in various types of leukemias.
Restoring p53	RO5045337 RG7112	These compounds block the interaction of p53–MDM2 and may thus overcome the negative consequences of MDM2 overexpression in leukemic blasts with the intent to restore function of p53.[h]
Inhibitors of MEK–ERK	Trametinib	An allosteric inhibitor of MEK1/2 that inhibits proliferation of myeloid cell lines. A phase I/II study is ongoing. Responses appear more likely in patients with RAS-mutated blasts.[i]

(*Continued*)

Table 12.4 *Continued*

Class	Agent	Comment
Aminopeptidase inhibitors	Tosedostat	Orally available with clinical activity in a phase I/II study in patients with AML and MDS.[j]
Inhibitors of the mTOR pathway	Everolimus Sirolimus	Limited clinical data suggest activity in the therapy of patients with relapsed AML.[k] Combination studies are being pursued.
Inhibitors of Wnt1	CWP232291	This agent inhibits proliferation of cancer cells by blocking the Wnt signaling pathway through promotion of degradation of beta-catenin. Beta-catenin is upregulated in most samples of AML blasts and more so in leukemia stem cells. A phase I study is ongoing.
Antibody conjugates	Gemtuzumab ozogamicin	Activity in multiple settings of patients with AML including in relapse. The role of gemtuzumab and similar agents is reevaluated in the wake of its withdrawal from the market more recently.[l]
Immunomodulation	Lenalidomide	Moderate single-agent activity.[m]

[a]Faderl S, *et al*. J Clin Oncol 2012;30:2492–9.
[b]Baer MR, Gojo I. J Natl Compr Canc Netw. 2011;9:331–5.
[c]Lancet JE, *et al*. Leukemia. 2011;25:1808–14.
[d]Czibere A, *et al*. Bone Marrow Transplant. 2010:45:872–6; and De Lima M, *et al*. Cancer. 2010;28:4919–5431.
[e]Garcia-Manero G, *et al*. J Clin Oncol. 2012;30:2204–10.
[f]Cortes J, *et al*. Blood 2012;120:abs. 48.
[g]Levis M, *et al*. Blood 2011;117:3294–301.
[h]Andreeff M, *et al*. Blood 2012;120:abs. 675.
[i]Borthakur G, *et al*. Blood. 2012;120:abs. 677.
[j]Lowenberg B, *et al*. J Clin Oncol. 2010;28:4333–8.
[k]Boehm A, *et al*. Eur J Intern Med. 2009;20:775–8.
[l]Hospital M-A, *et al*. Blood. 2011;118:abs. 2603; and Malfuson JV, *et al*. Ann Hematol. 2012 [epub ahead of print].
[m]Blum W, *et al*. J Clin Oncol. 2010;28:4919–25.

Case study answers

Case study 12.1

Question 1: Answer B and C
Question 2: Answer A
Question 3: Answer B

Case study 12.2

Question 1: Answer B
Question 2: Answer B
Question 3: Answer B
Question 5: Answer A
Question 6: Answer A

Mutiple choise answers

Question 1: Answer D
Question 2: Answer B ("False")
Question 3: Answer A ("True")

Selected reading

Faderl S, Wetzler M, Rizzieri D, *et al*. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I trial. J Clin Oncol. 2012;30:2492–9.

Ofran Y, Rowe JM. Treatment for relapsed acute myeloid leukemia: what is new? Curr Opin Hematol. 2012;19:89–94.

Oran B, de Lima M. Prevention and treatment of acute myeloid leukemia relapse after allogeneic stem cell transplantation. Curr Opin Hematol. 2011;18:388–94.

Parker JE, Pagliuca A, Mijovica A, *et al*. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukemia. Br J Haematol. 1997;99:939–44.

Price SL, Lancet JE, George TJ, *et al*. Salvage chemotherapy regimens for acute myeloid leukemia: is one better? Efficacy comparison between CLAG and MEC regimens. Leuk Res. 2011;35:301–4.

CHAPTER 13

Hematopoietic cell transplantation in acute myeloid leukemia

Antonio M. Jimenez and Stefan O. Ciurea

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 13.1

A 24-year-old Chinese female was diagnosed with FAB-M2 acute myelogenous leukemia (AML). Her initial diagnostic work-up was remarkable for the presence of a diploid karyotype, with molecular studies notable for *FLT3* internal tandem duplication mutation (*FLT3*–ITD) and wild-type *NPM1*. She achieved complete morphologic and molecular remission following standard induction with the "7 + 3" regimen. She has an identical twin and a second sibling who is a half (5/10) HLA match. An unrelated donor search yielded multiple 8/10 HLA matches. She recently completed her first consolidation with high-dose cytarabine and remains in complete morphologic remission with persistent polymerase chain reaction (PCR) positivity for *FLT3*–ITD.

1. What would be the best approach at this time?

A. Maintenance with sorafenib 300 mg twice daily
B. Four cycles of high-dose cytarabine ($3\,g/m^2$)
C. Syngeneic hematopoietic stem cell transplantation (HSCT)
D. 8/10 matched unrelated donor HSCT
E. Haploidentical HSCT

Available data suggest that clinical outcomes for *FLT3*–ITD-positive patients are significantly improved when allogeneic transplantation consolidation is used compared to nontransplant alternatives.

Cytogenetics at diagnosis is the most important prognostic factor in AML, and the benefit of aggressive consolidation strategies such as allogeneic stem cell transplantation in first remission (CR1) in high-risk cytogenetic patients is well established. In approximately 50% of AML patients with normal karyotype, the presence of *FLT3*–ITD mutation is associated with increased rates of relapse and inferior survival. This finding remains the most powerful molecular indicator of adverse outcomes. Available data suggest that allogeneic transplant in early CR1 may improve the long-term outcomes for patients with *FLT3*–ITD mutation AML.

Although there have been no prospective trials demonstrating that allogeneic stem cell transplantation improves overall survival in *FLT3*–ITD mutated patients, multiple retrospective series have shown that survival was significantly improved when allogeneic transplantation was compared to nontransplant alternatives such as high-dose cytarabine and targeted therapy. This series included patients who underwent allogeneic transplantation from various donors, including haploidentical matches. DeZern and colleagues (2011) reported the outcomes of 133 patients with AML, 31 of them with the *FLT3*–ITD mutation. Overall survival for this group was similar compared with that of 102 patients with wild-type *FLT3*–ITD (WT-*FLT3*–ITD) treated during the same 4-year time period. The authors suggested that the similar outcomes between the two groups was related to an aggressive transplant strategy, including the use of haploidentical donors for *FLT3*–ITD mutated patients in CR1, and they advocated for the use of allogeneic HSCT over chemotherapy or targeted therapy as a consolidative strategy in this group of patients.

Schlenk *et al*. (2008) correlated the *NPM1*, *FLT3*, *CEBPA*, *MLL*, and *NRAS* mutational status with the clinical outcomes of 872 patients with cytogenetically normal AML treated in four different clinical trials. Thirty-one percent of screened patients (164/531) had *FLT3*–ITD mutations. These patients were then "genetically randomized" to undergo allogeneic HSCT if a matched related donor was available, versus consolidation with high-dose cytarabine (HiDAC) or autologous transplantation for those patients without a donor. Of the 663 patients who received postinduction

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

therapy, 150 underwent HSCT from an HLA-matched related donor. Among complete responders, there was a significantly longer relapse-free survival ($P = 0.009$) in those who underwent transplantation. This finding was especially true for patients with *FLT3*–ITD mutation or "triple negative" (wild-type (WT) *NPM1*, CEBPA without *FLT3*–ITD), but not for patients with mutated *NMP1* without *FLT3*–ITD mutation.

Most recently, Huang and colleagues (2012) reported the results of a prospective, patient self-selected trial comparing haploidentical related donor stem cell transplantation ($n = 58$) with chemotherapy ($n = 74$) as postremission consolidation for patients with intermediate- or high-risk AML in CR1. The incidence of relapse was significantly lower in the haploidentical transplant group compared to the chemotherapy group (12.0% vs. 57.8%; $P < .0001$). This translated into a significantly superior survival benefit for patients who underwent transplantation compared to those who received chemotherapy alone (4-year disease free survival (DFS): 73.1% vs. 44.2%; $P < .0001$; 4-year overall survival (OS): 77.5% vs. 54.7%; $P = .001$). Postremission treatment (matched-related donor-HSCT vs. chemotherapy) and high white blood cell (WBC) count at diagnosis were identified as independent risk factors affecting relapse, DFS, and OS on multivariate analysis.

Data to support haploidentical stem cell transplantation for *FLT3*-ITD mutated patients are insufficient at this time. However, in this case the high risk of disease relapse, the likely benefit from graft-versus-leukemia (GVL) effect, and the prompt availability of a suitable donor improved outcomes with haploidentical transplantation the preferred option, especially when compared to an 8/10 mismatched donor or syngeneic HSCT. An 8/10 mismatched unrelated donor transplant is associated with a high incidence of both graft-versus-host disease (GVHD) and transplant-related mortality (TRM) and is no longer performed at most centers.

Case study 13.2

A 27-year-old man with relapsed AML following a matched-related donor stem cell transplant was referred to your clinic for further treatment recommendations. Three years ago, he was diagnosed with AML-M4 with diploid cytogenetics, *FLT3*-ITD mutation negative, and *NPM1* mutation positive. He achieved complete remission (CR) after standard induction therapy with the "7 + 3" regimen. After relapsing 9 months later, the patient underwent re-induction therapy, again achieved CR, and received a matched sibling donor transplant. The posttransplant course was uncomplicated, and his immunosuppressive therapy was tapered without evidence of GVHD. Unfortunately, he relapsed on day +380 with findings of 90% blasts in the bone marrow. He achieved a complete morphologic remission following salvage with a clofarabine-based regimen. On his most recent evaluation, a mutation in exon 12 of the *NPM1* gene was still detectable by PCR.

1. What is the best treatment strategy at this time?

A. Supportive care and close clinical observation
B. Donor lymphocyte infusion from his prior sibling donor
C. A second matched related donor HSCT using a different conditioning regimen
D. A cord blood transplant
E. Azacitidine maintenance indefinitely

Younger, fit AML patients with posttransplant relapse should be considered for second allogeneic HSCT if relapse occurred more than 6 months after the first HSCT and the patient achieved CR after salvage chemotherapy.

There is no consensus on the optimal management of AML relapse following transplant, and outcomes for patients who relapse following allogeneic stem cell transplantation are dismal. In general, patients with remissions lasting more than 6 (and especially more than 12) months and those achieving CR are more likely to benefit from a second allogeneic transplant. A retrospective, multicenter study from International Bone Marrow Transplant Registry (IBMTR) analyzed the outcomes of 125 patients with relapsed AML following stem cell transplantation who went on to receive a second HLA-identical sibling transplant. Risk of subsequent relapse was lower in patients who relapsed more than 6 months following first transplant (relative risk (RR): 3.02; $P = 0.0001$) and in patients who achieved CR prior to second transplantation (RR for relapse for patients with persistent disease: 2.47; $P = 0.0001$). Overall survival was superior for patients with prolonged posttransplant remission and for those younger than 20 years of age. For patients who met these criteria, 5-year OS was 51% compared to 3% in those who did not.

Outcomes for donor lymphocyte infusion (DLI) recipients in the posttransplant relapse setting are poor, with brief remissions seen in about 15% of patients. The European Bone Marrow Transplantation Registry (EBMT) reported on the outcomes of 171 patients with relapsed AML following HSCT who went on to receive DLI as salvage therapy. The benefit of DLI was limited to patients with normal cytogenetics, those with low tumor burden at time of relapse, and those who achieved CR prior to DLI. In a young patient with chemosensitive relapse and goal to treat with curative intent, observation alone would not be an appropriate choice. Maintenance therapy with azacitidine might be a reasonable option in older patients, those without a donor, or in younger patients as a bridge to a second HSCT. Sorafenib therapy would not be curative, and in a patient with persistence molecular residual disease, a second transplant with a readily available donor would be a more suitable choice.

Case study 13.3

An active and otherwise healthy 70-year-old man was recently diagnosed with AML and referred to you following completion of induction chemotherapy. The patient originally presented after atypical cells were incidentally found on a preoperative work-up prior to an elective surgical procedure 2 months ago. A bone marrow biopsy demonstrated the presence of leukemic blasts occupying 70% of the marrow space; karyotype revealed deletion of chromosome 7 in 8/20 metaphases. Patient received induction therapy with cytarabine 200 mg/m^2 and daunorubicin 45 mg/m^2. He achieved a complete morphologic and cytogenetic remission 6 weeks after induction therapy. He is an only child and has three healthy adult sons; a full HLA-matched unrelated donor was identified within the donor registry. The patient and his family are inquiring about the best curative approach at this time.

1. What do you recommend?

A. Standard-dose cytarabine (200 mg/m^2) +/− daunorubicin
B. Cytarabine 1 g/m^2 for 2–3 cycles
C. Haploidentical HSCT from his youngest son
D. Unrelated donor HSCT
E. Close observation

Age should not be an absolute contraindication to proceed with allogeneic transplant when pursuing a curative approach. It is important to consider performance status and comorbid conditions, rather than age alone, when evaluating transplant candidates.

Historically, high rates of transplant-related mortality have been a major obstacle in the management of elderly patients with AML for whom curative treatment is pursued. With the advent of reduced-intensity conditioning (RIC) regimens, HSCT has emerged as a therapeutic option for this patient population with acceptable toxicity and mortality rates. A recent Center for International Blood and Marrow Transplant Research (CIBMTR) study failed to demonstrate significant differences in relapse rates, nonrelapse mortality, or overall survival in 545 adult patients with AML receiving RIC- or nonmyeloablative conditioning–based related and unrelated donor HCST when outcomes were compared among different age groups (age groups: 40–54, 55–59, 60–64, or >64). Similarly, EBMT evaluated the outcomes of 1333 patients with myelodysplastic syndrome (41% with refractory anemia with excess blasts in transformation) undergoing related or unrelated donor HCST. No significant difference in survival was noted when outcomes between patients 50–60 years old and patients older than 60 years were compared. The 4-year OS was 31% for the whole cohort, and 34% and 27% for patients aged 50 to 60 years and >60 years, respectively ($P = .23$). Multivariate analysis failed to show a significant association between age and overall survival, NRM, or relapse. Despite the retrospective nature of these studies, heterogeneity in conditioning regimens, and the intrinsic selection bias when such studies are conducted, results from these trials seem to indicate that age should not be a contraindication to proceed with allogeneic transplant when pursuing a curative approach. It is important to consider performance status and comorbid conditions, rather than age alone, when evaluating transplant candidates. The case described in this vignette is not an uncommon scenario since adverse cytogenetic findings are often in older patients. The best treatment approach in this patient looking to pursue a cure is consolidation with allogeneic stem cell transplantation following a RIC regimen. Both consolidative chemotherapy and close observation are more likely to result in disease relapse. There are no data on the role of haploidentical transplantation in this age group, and at present it should not be considered if a more suitable donor (matched unrelated) is available.

Case study 13.4

Your new patient, a 47-year-old pediatrician, was diagnosed with FAB-M4 AML after initially presenting with fatigue, productive cough, and easy bruising. In addition to a WBC count of 120,000 with 30% circulating blasts, her diagnostic work-up was remarkable for the presence of inv(16) and the D816V mutation on exon 17 (mKIT 17). She achieved CR following induction with idarubicin and cytarabine chemotherapy. She has no living siblings; however, an unrelated donor search within the registry yields a full HLA match. The patient is very educated about her disease and asks your opinion regarding the best strategy to prevent relapse at this time.

1. What do you recommend?

A. Matched unrelated donor HSCT
B. Consolidation with standard-dose cytarabine (200 mg/m^2) +/− idarubicin
C. Consolidation with four cycles of high-dose cytarabine (2 g/m^2)
D. Low-dose decitabine

(*Continued*)

Relapse rates are higher in patients with inv(16) with mKIT mutations, especially those with mKIT17. Potentially inferior survival rates in this patient population may justify the use of allogeneic HSCT in fit patients with an available matched donor.

Inversion of chromosome 16 is detected in approximately 8% of adult patients with AML. This finding, along with translocation t(8;21)(q22;q22), defines the subgroup of core binding factor (CBF) AML. Patients with CBF-AML enjoy higher relapse-free survival rates following induction chemotherapy and are routinely treated with high-dose cytarabine (HiDAC) consolidation following CR1. Many groups have assessed the prognostic impact of additional genetic abnormalities in patients with CBF AML, including inv(16). The presence of particular mutations (KIT, particularly exon 17 and *FLT3*) correlates with inferior outcomes in this group of patients. The German-Austrian Study Group (AMLSG) recently evaluated the impact of secondary genetic abnormalities in 176 AML patients with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) CBFB-MYH11. The majority of patients (84%) were noted to have at least one additional mutation, with RAS being affected in the majority (53%) of patients, followed by KIT in 65 cases (37%), mKIT17 in 24 patients (14%), and *FLT3* in 17%. The presence of KIT mutations predicted for shorter relapse-free survival rates, but had no impact on overall survival. This finding of similar survival rates despite higher relapse rates has been attributed to a high response to salvage therapy in the KIT-mutant cohort (CR2 rates: 76%). Pashka *et al.* (2006) reported the outcomes of 110 CBF patients (61 with inv(16)) receiving post-induction consolidation with HiDAC in a study from the Cancer and Leukemia Group B (CALGB). This again demonstrated a higher rate of relapse in patients with mutant KIT, particularly mKIT17 (5-year relapse rate of 80% for mKIT17 vs. 29% for wtKIT; $P = 0.002$). More recently, Kim and colleagues (2013) analyzed the prognostic role of KIT mutations in 121 Korean patients with CBF AML (82 with RUNX1/RUNX1T1 (67.8 %) and 39 with CBFB/MYH11 (32.2 %)) treated with different consolidation strategies following a $7 + 3$ induction regimen. KIT mutations were detected in 32 patients (26.4%). Of these, 18 had mKIT17 and 16 had the D816 mutation. The presence of the KIT D816 mutation was associated with inferior event-free survival ($P = 0.03$) and overall survival ($P = 0.02$).

Survival disparities among studies might be partially explained by differences in patient selection, underpowered studies, and choice of salvage regimens. However, it is clear that relapse rates are higher in patients with inv(16) with mKIT, especially those with mKIT17. Although there are no prospective data demonstrating a survival advantage for mKIT patients undergoing allogeneic HSCT or significant improvement when outcomes are compared with standard HiDAC consolidation treatment, the high rates of relapse and potentially inferior survival in patients with mKIT17 may justify allogeneic HSCT in fit patients with an available donor. Therapies with tyrosine kinase inhibitors (TKIs) targeting KIT are currently undergoing evaluation and may play a critical role in the management of these patients.

Multiple choice question

1. Which of the following patients is most likely to benefit from allogeneic HSCT?

A. A 36-year-old female with high-risk acute promyelocytic leukemia in first molecular remission after standard induction; brother is a full HLA match

B. A 55-year-old male with AML with t (8;21) (q22;q22) in second morphologic remission; a 10/10 matched sibling donor is available

C. A 78-year-old female with evidence of myelodysplasia and 22% blasts in her bone marrow. Cytogenetics remarkable for monosomy 7; no unrelated donors available; daughter is a haploidentical match

D. A 29-year-old male with AML with normal cytogenetics and NPM1-IDH1 mutation in CR1 after $7 + 3$ induction. Multiple 10/10 matched unrelated donors available

Relapsed disease is an indication for allogeneic HSCT consolidation, even in patients with core-binding factor (CBF) leukemia, despite this traditionally been treated with high-dose chemotherapy following CR1. Prospective trials randomizing relapsed patients to chemotherapy versus HSCT consolidation are not available and would not be practical or logistically feasible to conduct at this time. High-risk acute promyelocytic leukemia (WBC count $>10 \times 10^9$/L) are not an indication for allogeneic transplantation in CR1. As described in case study 13.4, no data for allogeneic transplant from mismatched related donors are available for patients older than 70 years. In a recent phase III clinical study, Patel *et al.* (2012) conducted an 18-gene mutational analysis in 398 young AML patients randomly assigned to receive induction therapy with either high-dose or standard-dose daunorubicin; survival outcomes based on mutational status were analyzed. As described in previous studies, survival was inferior in patients with mutalated *FLT3*-ITD and MLL-PTD. CEBPA and IDH2 mutations were associated with improved overall survival. The favorable effect of NPM1 mutations was restricted to patients with co-occurring NPM1 and IDH1 or IDH2 mutations (3-year rate survival: 89% in patients with m*NPM1* vs. 31% in patients with wild-type *IDH1*/*IDH2*; $P < 0.001$). Considering the favorable outcomes in this group of patients, consolidation with allogeneic HSCT cannot be recommended at this time.

Case study 13.5

A 19-year-old college student was diagnosed with AML with normal cytogenetics. She achieved CR after standard 7 + 3 induction chemotherapy and subsequently underwent a matched-sibling donor HSCT consolidation. Unfortunately, she experienced disease relapse with findings of 70% blasts in the bone marrow 3 months after transplant. The marrow blast percentage decreased to 4% following re-induction with an etoposide-based regimen. She was referred to you for treatment recommendations.

1. Which one of the following characteristics portends for worse outcomes if a second transplant is pursued?

A. Duration of her first response
B. Blast percentage at time of relapse
C. Age
D. Bone marrow cytogenetics

Leukemia-free survival following first allogeneic transplant is the strongest predictor for clinical outcomes following a second HSCT. Eapen and colleagues (2004) reported the outcomes of 125 patients undergoing second allogeneic HSCT for relapsed AML. TRM, relapse risk, and overall mortality were higher in patients who relapsed $\leq$6 months after first HSCT (RR: 2.82, $P < 0.0001$; RR: 3.02, $P = 0.0001$; and RR: 1.94, $P < 0.0001$, respectively). Additional risk factors for inferior outcomes included persistent disease prior to transplant, age >20 years, and the use of RIC regimens.

Devillier *et al*. (2012) recently evaluated the effectiveness of salvage therapy in 54 AML patients who had relapsed disease following allogeneic HSCT. One-year overall survival was 19% for the whole cohort (median survival: 3.4 months). Patients who received intensive salvage therapy achieved higher remission rates (CR: 71%) and experienced superior survival rates (1-year OS: 33% with intensive salvage therapy vs. 7% without intensive salvage therapy; $P = 0.004$). Time to relapse and performance status predicted overall survival on multivariate analysis.

Case study 13.6

A 39-year-old man was diagnosed with M2 AML, with an initial work-up that was remarkable for a hypercellular bone marrow with 88% myeloblasts, normal cytogenetics (CN), and *FLT3*-ITD mutation negative. He underwent induction chemotherapy with the CIA regimen with findings of persistent disease (20% blasts) on repeat bone marrow biopsy at day 28. Re-induction with the FLAG regimen resulted in a hypocellular marrow at day 21 with evidence of persistent AML; cytogenetics were normal. Patient remains pancytopenic without evidence of circulating blasts. He has a good performance status and has a brother who is a full HLA match.

1. What is the next best step in managing this patient?

A. Proceed with matched related donor allogeneic HSCT as soon as possible
B. Decitabine for maintenance
C. Consolidation with standard-dose cytarabine +/− idarubicin
D. Re-induction chemotherapy with an etoposide-based regimen

Early HSCT should be considered in patients unresponsive to initial induction chemotherapy. HSCT can induce long-term survival rates in patients with acute leukemia who are not in CR at the time of transplant

Patients with refractory AML have a very poor prognosis and are usually resistant to any salvage strategy, with CR rates approaching 10%. The benefit of allogeneic HSCT in patients with persistent AML remains unclear although several studies demonstrated that long term survival can be achieved in these patients with early transplantation.

Duval and colleagues hypothesized that pretransplant variables may affect the outcomes of patients with relapsed or refractory AML undergoing salvage therapy with allogeneic HSCT. In this CIBMTR study, 1673 patients underwent allogeneic transplantation for AML following relapse or primary induction failure ($n = 636$). The median follow-up for survivors was 61 months with a 3-year overall survival of 19% for all AML patients. A predictive score was derived from multivariate analysis of pre-transplant patient variables for inferior survival, with each variable assigned one point for a total score of 5 if all variables are present. Survival was inferior in patients with circulating blasts, with a mismatched unrelated donor, with a related donor other than an HLA-matched sibling, with poor performance status, or with poor-risk cytogenetics. The patient in this scenario has a score of 0 on the basis of an available matched sibling donor, the absence of circulating blasts, normal cytogenetics, and good performance status. This score correlates to a 3-year survival of 46% compared to 10% for patients with scores $\geq$3. Therefore, this patient should proceed with transplant as soon as possible. While results from this study should be interpreted with caution given its retrospective nature, it demonstrated that HSCT can induce long-term survival in patients with acute leukemia who are not in CR at the time of transplant (3-year OS of 20% and higher for patients with low scores). Patients who underwent transplantation following primary

(*Continued*)

induction failure had better outcomes when compared to those who underwent transplantation following early relapse (<6 months). These findings suggest that early HSCT should be considered in patients unresponsive to initial induction chemotherapy. In fact, additional courses of induction chemotherapy could result in toxicity that might limit the success of future transplantation.

Despite encouraging results for patients with low scores, this predictive model needs to be interpreted with caution since it has not been studied prospectively or confirmed with an independent validation cohort. Decitabine has been evaluated in this setting with CR rates up to 16% and median OS approaching 6 months. This treatment modality could be considered in elderly patients and in patients who are not candidates for allogeneic HSCT.

Case study 13.7

A 55-year-old man was diagnosed with acute myeloid leukemia after initially presenting with fevers and gingival bleeding. Diagnostic work-up revealed pancytopenia and a fibrotic bone marrow with 38% megakaryoblasts with normal cytogenetics. He received induction chemotherapy with a 7 + 3 regimen, achieving a morphologic remission (CRp) at day 28. The patient is feeling well and is ready to be discharged from the hospital. His sister is a haploidentical match; two full HLA matches were identified through the registry along with several eligible cord blood units.

1. Which consolidation strategy would you recommend at this time?

A. Consolidation with high-dose cytarabine
B. Azacitidine maintenance
C. High-dose chemotherapy followed by autologous stem cell transplantation
D. Matched unrelated allogeneic stem cell transplantation
E. Haploidentical transplantation with sister as donor as soon as possible
F. Double umbilical cord blood transplantation

Given the aggressive behavior and high incidence of relapse in (M7) AML, allogeneic HSCT should be the consolidation strategy of choice for adult patients in CR1.

Acute megakaryoblastic leukemia (M7 AML) is a rare form of leukemia accounting for 1% of adult AML cases and characterized by a highly aggressive clinical course. M7 AML has a bimodal age distribution and occurs with a higher incidence in children with Down syndrome. Median survival for adult patients with M7 AML is 40 weeks despite satisfactory responses to induction therapy. Poor outcomes are related to high relapse rates, with only a minority of patients surviving beyond 3 years. In an effort to improve postremission outcomes, stem cell transplantation has been evaluated by multiple groups.

Garderet and colleagues (2005) evaluated the outcomes of 69 adults and 57 children with M7 AML who underwent autologous or allogeneic transplantation following achievement of CR1. Autologous transplantation was associated with unacceptably high rates of relapse (64%) in the adult cohort, resulting in very low LFS and OS rates (27% and 30% at 3 years, respectively). Despite higher TRM rates (26%), patients who received allogeneic HSCT enjoyed lower (28%) relapse rates, resulting in improved 3-year LFS and OS (46% and 43%, respectively) when compared to historical controls and to patients treated with autologous HSCT. Given the aggressive behavior and high incidence of relapse, the authors concluded that allogeneic HSCT should be the consolidation strategy of choice for adult patients with M7 AML achieving CR1.

Case study answers

Case study 13.1

Question 1: Answer E

Case study 13.2

Question 1: Answer C

Case study 13.3

Question 1: Answer D

Case study 13.4

Question 1: Answer A

Case study 13.5

Question 1: Answer A

Case study 13.6

Question 1: Answer A

Case study 13.7

Question 1: Answer D

Mutiple choice answer

Question 1: Answer B

Selected reading

Devillier R, Crocchiolo R, Etienne A, *et al*. Outcome of relapse after allogeneic stem cell transplant in patients with acute myeloid leukemia. Leuk Lymphoma. 2013;54(6):1228–34.

Duval M, Klein JP, He W, *et al*. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. J Clin Oncol. 2010;28(23):3730–8.

Lim Z, Brand R, Martino R, *et al*. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010;28(3):405–11.

Patel JP, Gönen M, Figueroa ME, *et al*. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366(12):1079–89.

Ramadan SM, Di Veroli A, Camboni A, *et al*. Allogeneic stem cell transplantation for advanced acute promyelocytic leukemia in the ATRA and ATO era. Haematologica. 2012;97(11):1731–5.

Yanada M., Matsuo K, Emi N, *et al*. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. Cancer. 2005;103(8):1652–8.

PART 3

Myelodysplastic Syndromes and Related Disorders

CHAPTER 14

Pitfalls in the diagnosis of myelodysplastic syndromes

Jay Yang, Gail Bentley, and Charles A. Schiffer
Wayne State University School of Medicine, Detroit, MI, USA

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell diseases characterized by peripheral cytopenias, ineffective hematopoiesis, and dysplasia in one or more major myeloid cell lines. While the diagnosis is often straightforward, it can also be difficult in cases in which some of the cardinal features are lacking. Here we present six cases that illustrate some of the complexities we have encountered in the clinic and our diagnostic approach.

Case study 14.1

A 50-year-old male was found to have a bicytopenia with hemoglobin of 10 g/dL and a platelet count of 75,000/μl; the mean corpuscular volume (MCV) was 105. All secondary causes of macrocytic anemia were excluded. The bone marrow biopsy was mildly hypercellular without lymphoid infiltrates. The aspirate smear showed "megaloblastoid" changes in the erythroid cell line in <10% of the erythroid precursors. Myeloid precursors and megakaryocytes showed no evidence of dysplasia. Conventional metaphase cytogenetics revealed a −Y clone.

1. What is the diagnosis?

A. Refractory anemia
B. Idiopathic cytopenias of undetermined significance (ICUS)
C. Megaloblastic anemia

According to the World Health Organization (WHO) Classification–2008, the morphologic diagnosis of a myelodysplastic syndrome requires evidence of dysplasia in at least 10% of cells in a cell line for the dysplasia to be significant. High-quality preparations are needed for accurate assessment of dysplasia, and the assessment of the degree of dysplasia is hampered by poor preparations, poor staining, or hemodilute samples. Samples that have been exposed to anticoagulants for more than 2 h are often unsatisfactory, and this can be an issue with marrow aspirates that are mailed overnight to centralized laboratories.

Persistent cytopenias without dysplasia can be diagnosed as a myelodysplastic syndrome if there is a specific cytogenetic abnormality considered typical of MDS. This excludes del(20),+8, and −Y, which, although common in MDS, are not defining cytogenetic abnormalities because they have also been present in patients with aplastic anemia and other cytopenic syndromes that have not progressed to MDS with extended follow-up. In addition, loss of the Y chromosome has been described in bone marrow cells with aging.

Persistent cytopenias without dysplasia and without a defining cytogenetic abnormality can be described as ICUS.

While not a recognized as a distinct entity in the WHO classification, ICUS serves as a descriptive "placeholder" for patients who do not meet the diagnostic WHO criteria for MDS.

2. What is the next diagnostic and/or therapeutic step? (Choose all that apply.)

A. MDS-directed therapies
B. Allogeneic hematopoietic stem cell transplantation

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

C. Continue to monitor the patient's clinical condition, blood counts, and peripheral smear morphology
D. Continue to evaluate for secondary causes of cytopenias
E. Consider a repeat bone marrow study in 6 months

It is premature to recommend treatment, and he is certainly not a candidate for transplantation at this time. Although the clinical course is not predictable and many patients can have stable counts for months and sometimes years, there is appreciable concern that his cytopenias can worsen and that his disease can progress to MDS. Therefore, he should be followed up initially with blood counts every few months. A repeat marrow should be done if the cytopenias worsen. Although a large number of molecular abnormalities have recently been identified in patients with MDS, there have not been systematic evaluations in patients classified as ICUS, and their diagnostic and prognostic utility have not been determined.

Case study 14.2

A 67-year-old man is admitted with fever and found to be pancytopenic. He had been told that he was moderately anemic a few months ago. A complete blood count (CBC) showed a white blood cell (WBC) count of 2400/μl, an absolute neutrophil count of 800/μl, hemoglobin of 8.0 gm/dl, and platelets of 72,000/μl. A bone marrow aspirate was hypercellular with evidence of trilineage dysplasia and 18% blasts by morphologic assessment. The blasts appeared to be myeloid and had modest amounts of cytoplasmic granules. Flow cytometry was done, and it was reported that 24% of the mononuclear cells were blasts positive for CD117 and CD34. Cytogenetics were normal. He is in good health otherwise and is eligible for treatment on a clinical trial evaluating a new intensive regimen for older patients with acute myeloid leukemia (AML).

1. You would tell him:

A. That he is eligible for the AML protocol because he has >20% blasts
B. That he is eligible for a protocol enrolling patients with high-risk MDS because he has <20% blasts
C. That you would recommend an allogeneic transplant at this time without beginning chemotherapy

This case highlights the not-uncommon difficulty that derives from the arguably arbitrary blast cutoff separating the diagnoses of myelodysplasia (MDS) and AML. It is quite common for older patients such as this to report poorly documented "anemia" of unknown duration prior to their initial definitive evaluation. Similarly, although the presence of dysplasia might be suggestive of AML evolving from prior MDS, it can also be present in apparently "de novo" AML. The normal karyotype is not informative in making this distinction, although actually the presence of a more typical "MDS karyotype," involving loss of part or all of chromosomes 5 and/or 7, would also not be diagnostic of either MDS or AML.

In the not-so-distant past, the diagnosis of AML required the identification of ≥30% blasts, usually based on a count of 500 nucleated marrow cells. The definition was modified by the WHO in 2002 to a cutoff of ≥20% blasts based on rather soft evidence after the review of a few trials that peripherally addressed this issue. Both definitions were based on morphologic assessments by experienced hematopathologists of blast percentage in good-quality bone marrow smears. Obviously, there is no difference in the biology and expected response to treatment of MDS and AML if a marrow has 19% versus 21% blasts (or, in the past, 29% vs. 31% blasts). Indeed, it is not easy to reproducibly do blast counts to this degree of accuracy. It is often difficult to distinguish undifferentiated myeloid blasts from dysplastic immature pronormoblasts, dysplastic myelocytes, or sometimes reactive lymphoid cells. Nonetheless, such categorization is important in defining populations of patients for protocol research studies to permit comparisons across studies.

More recently, many laboratories have begun to report marrow blast percentage based on flow cytometric analysis with the inference that this provides a more accurate quantification. Frequently, this information is provided even if the test had not been ordered by the clinician, and the results, because they are often discrepant from the morphologic assessment, can be confusing. Although the flow "differential" is the result of characterization of thousands of cells, there is no standardization of the definition of blast "gate" or the quantification of the population of other nucleated cells. In addition, although CD34 and/or CD117 expression is used to identify myeloid blasts, there can be considerable heterogeneity in the expression of these antigens in an individual patient's leukemia. Thus, although flow characterization of the number of blasts is intuitively more objective, further standardization is needed using this technique.

Thus, does our patient have MDS or AML, and is he eligible for the research protocol? And, if he is entered into an AML protocol, does it make sense to consider his disease the same as that of a patient with a more proliferative AML with an elevated WBC count and a cellular marrow with 80% blasts? In fact, current (and past) AML studies grouped patients with "MDSy" AML with the more proliferative disease, and it is very difficult to assess the relative number of patients in these two general categories in published studies, hence making comparisons of outcomes more complicated.

If a protocol is not a consideration, the clinical decision in this man is quite complex ranging from immediate allogeneic stem cell transplantation to continued observation, because many such individuals can "grumble" along for months with low but safe blood counts. Transplant physicians would express concern about a high posttransplant relapse rate because of the large number of marrow blasts and usually request an attempt to achieve remission before transplantation in the hope (largely unproven) that this will improve long-term outcome. The choice will then be between intensive AML induction therapy with cytarabine–anthracycline or less intensive approaches with hypomethylating agents. The intensive approach will be expected to produce higher complete response rates but is associated with hospitalization and greater morbidity and mortality, and it could also result in infectious complications that could preclude transplantation. In contrast, it often requires 3 to 4 months or courses of treatment with hypomethylating agents to achieve even partial responses, and the CR rate is very low. There are no randomized trials evaluating these strategies, and the decisions are often made according to institutional "tradition" with the added influence of the time it may take to identify a suitable allogeneic donor. Perhaps the reader will find the answer in the MDS section of this book!

Case study 14.3

The patient was a 42-year-old female who was referred for evaluation of pancytopenia. Although she continued to work full-time, she has noticed increased fatigue during the past 6 months as well as diffuse bruising and what she felt was "fragile" skin. She has had a weight decrease of 9 kg over the past 2 years. Physical examination was normal except for occasional ecchymoses on the arms. She appeared very thin with minimal subcutaneous tissue; she weighed 45 kg, and her BMI was 15.2.

CBC showed a WBC of 1600/μl, an absolute neutrophil count of 900/μl, hemoglobin of 13.6 gm/dL, MCV of 102, and platelets of 162,000/μl. The peripheral blood smear was morphologically unremarkable. Blood chemistries were unremarkable, with normal bilirubin and transaminases; the albumin was 4.1 g/dl. Vitamin B_{12} and red blood cell folate levels, serum copper and zinc levels, thyroid-stimulating hormone, ferritin, hepatitis serology, HIV antibody, and antinuclear antibody testing were normal.

A bone marrow aspirate and biopsy were done and showed a hypocellular (20%) marrow with decreased but maturing hematopoiesis. There was no increase in myeloblasts, and the karyotype was normal. There were multiple areas consistent with serous atrophy.

1. What is the diagnosis?

A. Malnutrition
B. Amyloidosis
C. Mucopolysaccharidosis

After the results became available, a more detailed nutrition history was obtained. She acknowledged that she ate inconsistently, eating very small portions "on the run," and rarely cooked meals for herself at home. She was referred to a nutritionist. Her CBC improved over the next 2 years with normalization of the MCV and neutrophil counts.

Serous atrophy of the bone marrow (gelatinous transformation) is a disorder characterized by weight loss and cytopenias. Bone marrow specimens exhibit fat cell atrophy, marrow hypoplasia, and the deposition of an extracellular amorphous substance that has been identified as mucopolysaccharides, which is rich in hyaluronic acid (see Figure 14.1). This has been confused with marrow necrosis or amyloid. The presence of mucopolysaccharides can be confirmed by strong Alcian blue staining at a pH of 2.5. The pathogenesis of serous atrophy is unknown, but it has been associated with conditions resulting in cachexia, such as anorexia nervosa, acute febrile states, alcoholism, AIDS, carcinomas, and lymphomas. The bone marrow changes and cytopenias can be reversed by treating the underlying condition.

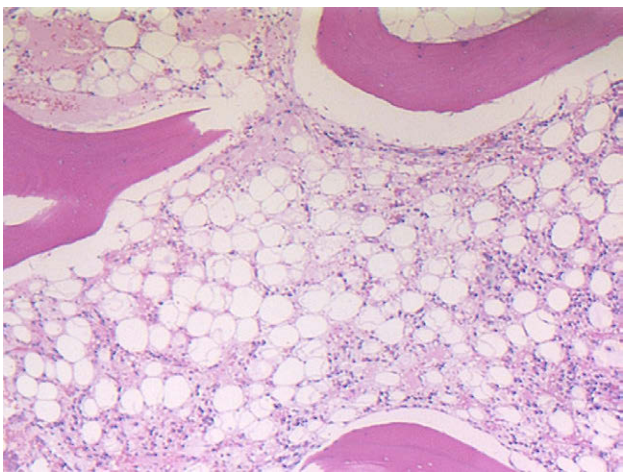


Figure 14.1 Serous atrophy. This bone marrow biopsy shows serous atrophy characterized by marrow hypoplasia, fat atrophy, and deposition of extracellular gelatinous material. The findings are similar to what is seen in acquired immunodeficiency syndrome. (Color plate 14.1)

Case study 14.4

A 36-year-old male with a history of gastric bypass surgery is referred to you because of transfusion-dependent anemia and neutropenia. Iron deficiency has been excluded. Bone marrow biopsy and aspiration reveal dysplasia and vacuolization in the myeloid precursors and an increase in ring sideroblasts. Conventional cytogenetic analysis reveals a normal karyotype. Examination reveals a distal sensory peripheral neuropathy.

1. Before making the diagnosis of MDS, what else should be ordered? (Choose all that apply.)

A. Copper level
B. Zinc level
C. Lead level
D. Ceruloplasmin level

Copper deficiency is probably an underrecognized cause of cytopenias. It may mimic MDS and can be easily misdiagnosed as such due to shared clinical and hematopathological findings. Patients have even been diagnosed with copper deficiency while undergoing evaluation for allogeneic hematopoietic stem cell transplantation for presumed MDS.

Anemia is almost universal at presentation, and coexisting leukopenia and neutropenia can also be seen. Significant thrombocytopenia is less common, and isolated thrombocytopenia has not been reported to our knowledge. The red cell indices can be microcytic, normocytic, or macrocytic. Histologic descriptions of bone marrows have included variable cellularity, an increase in ring sideroblasts, and dysplasia in the myeloid and erythroid series. Two of the most common features of copper deficiency are cytoplasmic vacuolization in granulocyte and erythroid precursors and the presence of stainable iron within macrophages and plasma cells.

Many patients with copper deficiency have a myeloneuropathy that can be seen with or without the hematological changes but often precede them. Neurological findings may include an abnormal gait, sensory ataxia, dorsal column dysfunction, lower extremity spastic paraparesis, and a polyneuropathy. This can be confused with subacute combined degeneration from vitamin B_{12} deficiency. The exact pathophysiology of these symptoms is unclear, but oxidative damage leading to demyelination and axonal degeneration has been hypothesized.

The most common cause of copper deficiency is decreased gastrointestinal absorption in patients with a history of bariatric surgery or gastric resection. Copper deficiency can also be a result of excess zinc ingestion, which inhibits the intestinal absorption of copper. Cases of copper deficiency have been described due to the use of zinc-containing denture creams or the overzealous use of zinc supplements. We have also witnessed a patient with a psychiatric condition who became copper deficient due to the surreptitious ingestion of pennies, which are ironically primarily composed of zinc.

The diagnosis of copper deficiency can be confirmed by the measurement of serum copper levels. In our laboratory, serum copper levels lower than 70 mcg/dL are considered diagnostic. Most patients also have decreased serum ceruloplasmin levels, but Wilson's disease, another cause of hypocupremia, must also be excluded. Twenty-four-hour urine copper excretion does not appear to correlate well with serum copper levels, and the use of this test is not encouraged. Zinc levels are often elevated, many times without an obvious explanation.

In summary, clinicians and hematopathologists should consider copper deficiency in the appropriate clinical scenario, including patients who have been given the diagnosis of low-risk MDS (without increased blasts) and a normal karyotype.

2. What is the treatment of choice?

A. Oral copper
B. Intravenous copper
C. Ethylenediaminetetraacetic acid (EDTA)

Dosing of copper is empiric, but we typically treat with copper gluconate using 2 mg tablets, starting at three times daily with tapering over the next several weeks. Many patients will need a maintenance dose of 2 mg daily. Despite poor absorption, most patients are responsive to oral formulations of copper and intravenous copper is reserved for cases in which copper repletion cannot be achieved by the oral route. Rarely, we have resorted to zinc chelation with EDTA in cases of zinc overingestion.

3. What are the chances of a therapeutic response (hematological and neurological)?

Hematological responses tend to be rapid with improvements seen within a few weeks and normalization of cytopenias within a few months of treatment. Marrow responses have also been reported. Neurological symptoms often do not reverse, but stabilization can be expected.

Case study 14.5

A 75-year-old female is found to have pancytopenia. Bone marrow biopsy shows a cellularity of 15%. Evaluation of morphology is limited due to the aparticulate nature of the aspirate, but dysplastic changes in the myeloid lineage are seen in less than 10% of cells. Cytogenetics and an "MDS" fluorescent in situ hybridization (FISH) panel are normal.

1. How should this be classified?

A. Aplastic anemia
B. Hypoplastic MDS
C. Uncertain

2. What other diagnostic testing should be considered?

A. Flow cytometry for lymphoproliferative disorders
B. Flow cytometry for MDS
C. Multiparameter flow cytometry with fluorescent aerolysin (FLAER) assay for paroxysmal nocturnal hemoglobinuria (PNH)

Although the large majority of patients with MDS have normo- to hypercellular bone marrows, MDS with hypocellular bone marrows is a well-recognized entity. It may be exceedingly difficult and even impossible at times to confidently distinguish between aplastic anemia and MDS with marrow hypoplasia. Indeed, a biologic and clinicopathologic overlap may exist, as suggested by the effectiveness of immunosuppressive therapy (IST) in some patients with MDS.

The presence of dysplastic changes favors MDS, but the low cellularity in the aspirates may make morphologic analysis difficult. Structural and perhaps evolving cytogenetic abnormalities also favor MDS but are present in only less than one-half of MDS cases. In addition, conventional karyotyping in hypocellular marrows may be limited by the low number of viable cells that can be induced into metaphase.

The quality of the bone marrow biopsy and aspirate is critical. Trephine bone marrow specimens may exhibit variable cellularity that may also confound the diagnosis, particularly when the sample is subcortical (see Figure 14.2). Continued clinical correlation and repeat high-quality bone marrow evaluations may be necessary. In this patient, we were not able to give a firm diagnosis based on the initial bone marrow examination. However, persistent and progressive cytopenias over the next 4 months prompted another bone marrow biopsy and aspirate, which was again hypocellular with only mild dysplasia. However, the cytogenetic analysis revealed a new abnormality—a deletion of chromosome 5 in 15 of 20 cells—that ultimately favored the diagnosis of MDS.

We do not often use flow cytometry in the evaluation and diagnosis of MDS unless otherwise indicated (e.g., because of lymphadenopathy; abnormal or increased numbers of lymphocytes on the peripheral smear; or lymphoid aggregates seen in bone marrow). Flow cytometry should not replace a careful manual differential of high-quality bone marrow aspirates for the quantification of blasts (see the discussion following question 2 of Case 14.1). Multiparameter flow cytometry has also been studied as an adjunctive diagnostic and prognostic tool for MDS because myeloid and progenitor cells can exhibit abnormal differentiation patterns and aberrant antigen expression. Although progress has been made, the techniques, the antibody panels used, and their interpretation have not been rigorously standardized, and thus the use of flow cytometry cannot be routinely recommended for this purpose.

Flow cytometry may be helpful, however, if large granular lymphocytosis (LGL) disease is suspected. Patients with LGL leukemia frequently manifest cytopenias, particularly neutropenia, and it should be suspected if morphologically characteristic cells are seen in the peripheral blood or marrow, as well as in patients with a history of rheumatologic disorders and those with palpable splenomegaly.

Small populations of PNH clones can be found in approximately 20% of patients with aplastic anemia and MDS, particularly those with low-grade disease (without excess blasts). Flow cytometry is the preferred diagnostic test for PNH using antibodies against GPI-anchored proteins (i.e., CD55 and CD59), which are deficient in the granulocytes and erythrocytes in patients with PNH. Sensitivity is

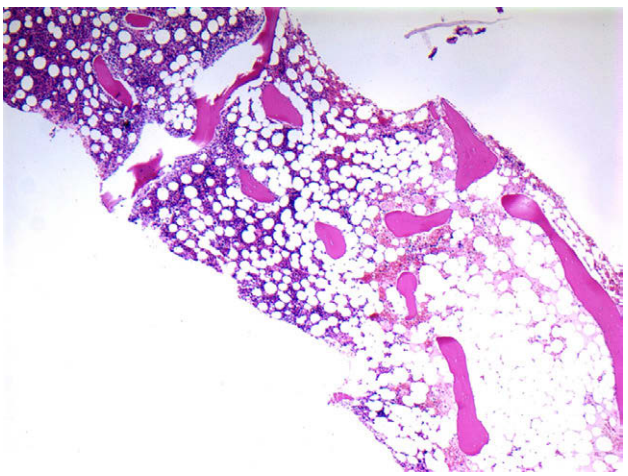


Figure 14.2 Variable cellularity. This bone marrow biopsy is subcortical and shows variable cellularity ranging from less than 5% cellularity (directly subcortical) to 40% cellularity. (Color plate 14.2)

(*Continued*)

increased further by the use of multiparameter flow cytometry using a FLAER assay.

PNH in the setting of a bone marrow failure syndrome is typically subclinical and not associated with overt hemolytic disease. The clinical significance of the PNH clone remains unclear. Although not entirely consistent across studies, there is a suggestion of a greater benefit for IST with antithymocyte globulin and/or cyclosporine in patients with MDS and selected characteristics such as the presence of a PNH clone, marrow hypoplasia, HLA-DR15 histocompatibility type, younger age, normal cytogenetics, and low-grade MDS.

Case study 14.6

A 65-year-old male is found to be anemic with a hemoglobin of 7.6 g/dL. His WBC count is 3500/μl, and his platelet count is 512,000/μl. Bone marrow aspirate differential reveals 23% ringed sideroblasts, normal cytogenetics, and adequate iron stores. He has been given the diagnosis of refractory anemia with ringed sideroblasts (RARS).

1. What other test(s) should be ordered to further classify this patient?

A. PCR for *JAK2*V617F mutation
B. Gene sequencing for TET2 mutations
C. A FISH–MDS panel

This patient fulfills the criteria for RARS with thrombocytosis (RARS-T), a provisional entity in the revised WHO classification of myeloid disorders. It is currently classified as an MDS/MPD because it shares characteristics of both MDS and essential thrombocytosis (ET) as well as myelofibrosis to a lesser extent. Patients typically present with anemia and unusually high platelet counts (≥450,000/μl). Bone marrow aspirates show dyserythropoiesis with an increased number of ring sideroblasts (≥15%). The WBC count and BM cellularity may also be increased. Proliferation of large megakaryocytes, a feature commonly seen in ET or PMF, is required for the diagnosis.

Approximately one-half of patients with RARS-T will carry the *JAK2*V617F mutation. The likelihood of finding a *JAK2* mutation in patients with RARS increases proportionally with the degree of thrombocytosis. Platelet counts <400,000/μl are usually enough to exclude the disorder.

Reports to date have shown survival rates for patients with RARS-T to be intermediate between those of RARS and ET but with a higher propensity of thrombosis compared with RARS and a higher risk of leukemia compared with ET. The prognostic significance and therapeutic implications of the *JAK2* mutation in patients with RARS-T are currently unclear.

Other molecular changes have recently been described in MDS, and many are implicated as modifiers of epigenetic regulation by either DNA methylation (TET2, IDH, and DNMT3A) or histone alteration (EZH2 and ASXL1). Mutations in genes encoding for components of the RNA-splicing machinery have been recently discovered to be prevalent in MDS patients, particularly those with increased ring sideroblasts. In particular, SF3B1 mutations have been described in up to 60–70% of patients with RARS. TET2 mutations were found in 26% of RARS-T cases. We do not routinely perform testing for most genetic aberrations given the lack of clear diagnostic or clinical import.

Although conventional cytogenetic analysis to detect chromosomal abnormalities is an invaluable tool in the diagnosis and risk stratification of MDS, it is only helpful in the approximately 40% of cases in which it is abnormal. Over the past decade, the availability and utilization of FISH probes in bone marrow samples done for MDS have become increasingly common. Due to its ability to target interphase cells, FISH has an improved yield over metaphase karyotyping in malignancies with a low proliferative rate such as multiple myeloma and chronic lymphocytic leukemia. In MDS, however, the utility of FISH is not supported by our experience or the literature. Pitchford *et al*. (2010) performed FISH for −5/−5q, −7/−7q, +8, and del(20q) on 137 MDS cases. In 102 cases with normal cytogenetics, the FISH was abnormal in only one case (showing +8). In 35 patients with abnormal cytogenetics, only one showed a minor discrepancy. Other reported studies have generally been consistent with these findings. Due to its low yield and minimal added clinical benefit, we do not recommend the routine use of FISH for MDS except in cases of karyotype failure.

Case study answers

Case study 14.1

Question 1: Answer B
Question 2: Answer C, D, and E

Case study 14.2

Question 1: Answer B

Case study 14.3

Question 1: Answer A

Case study 14.4

Question 1: Answer A, B, and D
Question 2: Answer A

Case study 14.5

Question 1: Answer C
Question 2: Answer A

Case study 14.6

Question 1: Answer A

Selected reading

Halfdanarson TR, Kumar N, Li CY, *et al*. Hematological manifestations of copper deficiency: a retrospective review. Eur J Haematol. 2008;80:523–31.

Hellstrom-Lindberg E, Cazzola M. The role of JAK2 mutations in RARS and other MDS. Hematology Am Soc Hematol Educ Program. 2008;52–9.

Pitchford CW, Hettinga AC, Reichard KK. Fluorescence in situ hybridization testing for −5/5q, −7/7q, +8, and del(20q) in primary myelodysplastic syndrome correlates with conventional cytogenetics in the setting of an adequate study. Am J Clin Pathol. 2010;133:260–4.

Vardiman JW, Thiele J, Arber DA, *et al*. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2008;114:937–51.

Wimazal F, Fonatsch C, Thalhammer R, *et al*. Idiopathic cytopenia of undetermined significance (ICUS) versus low risk MDS: the diagnostic interface. Leuk Res. 2007;31:1461–8.

CHAPTER 15

Cytogenetics and prognostic models in myelodysplastic syndromes

Uma Borate and Harry P. Erba

University of Alabama at Birmingham, Birmingham, AL, USA

MDS cytogenetics and prognosis

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders that are characterized by peripheral blood cytopenias due to ineffective hematopoiesis and dysplastic morphologic changes with or without clonal chromosomal abnormalities. MDS has an increased risk of progression to acute myeloid leukemia (AML). The prognosis of patients with this disease varies significantly based on both patient and disease characteristics. However, currently cytogenetics plays a central role in the different prognostic systems. Our knowledge of both somatic mutations and epigenetic abnormalities in this disease is increasing rapidly. These findings are likely to be incorporated into future prognostic models and may help guide therapeutic options.

Case study 15.1

A 65-year-old white woman is referred by her internist to the hematology clinic for evaluation of worsening symptomatic anemia. She required hospitalization last week for dyspnea and was found to have hemoglobin of 6.9 g/dL. She received 2 units of packed red blood cells (PRBC) for the first time with resolution of her acute symptoms and improvement in her performance status. Gastrointestinal blood loss and nutritional deficiencies were excluded. Her physical exam is unremarkable except for an S3 gallop. Her hemoglobin is 7.3 gm/dl, her mean corpuscular volume (MCV) is 104, her white blood cell (WBC) count is 5500/μL with a normal differential, and her platelet count is 270,000/μL. Her absolute reticulocyte count is 15,000/μL. There is moderate red blood cell anisopoikilocytosis on the peripheral smear. Serum erythropoietin is 10 IU/mL. A bone marrow aspirate and biopsy demonstrate dysplastic features in 20% of the erythroid precursors. Blasts account for 2% of marrow nucleated cells. Iron stores are adequate with less than 5% ring sideroblasts. A fluorescent in situ hybridization panel showed no abnormalities of chromosomes 5q, 7q, 8, or 20q. The cytogenetic analysis showed a normal female karyotype in all 20 metaphases (46XX). She was diagnosed with MDS.

- **How will you classify her disease?**

The clinical behavior of MDS, in terms of rate of progression of marrow failure, transfusion dependence, risk of progression to AML, and overall survival, varies greatly among patients with this disease. Various classifications have been proposed over the years in an attempt to better prognosticate patient outcomes. The French-American-British (FAB) classification is the oldest scheme for the classification of MDS (Table 15.1). It divides MDS into five subtypes based on the bone marrow and peripheral blood morphology, namely, the percentage of blasts in the peripheral blood and bone marrow, peripheral blood absolute monocytosis, and the presence or absence of ring sideroblasts. She has refractory anemia (RA). However, other features of the disease, including cytogenetic abnormalities, were not included, mostly due to our very limited knowledge of these changes when the FAB classification system was developed.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 15.1 FAB classification of myelodysplastic syndromes (Source: Bennett JM, *et al*. Br J Haematol. 1982;51(2):189–99. Reproduced with permission of John Wiley & Sons Ltd).

	Peripheral blood	Bone marrow
Refractory anemia (RA)	Blasts $\leq$1% Monocytes $\leq 1 \times 10^9$/l	Blasts <5% Ringed sideroblasts $\leq$15%
Refractory anemia with ringed sideroblasts (RARS)	Blasts $\leq$1% Monocytes $\leq 1 \times 10^9$/l	Blasts <5% Ringed sideroblasts >15% of erythroid precursors
Refractory anemia with excess blasts (RAEB)	Blasts <5% Monocytes $\leq 1 \times 10^9$/l	Blasts $\geq$5–$\leq$20%
Chronic myelomonocytic leukaemia (CMML)	Monocytes $> 1 \times 10^9$/l Blasts <5%	Blasts $\leq$20%
Refractory anemia with excess blasts in transformation (RAEB-t)	Blasts $\geq$5% Or Auer rods	Or blasts >20–$\leq$30% Or Auer rods

The World Health Organization (WHO) reclassified MDS in 2000 and 2008 (Table 15.2) based on clinical data, but the system remained predominantly a morphologic classification. The WHO 2008 classification system subclassifies the low-grade MDS (i.e., less than 5% marrow blasts) based on the number of lineages demonstrating dysplastic changes. Patients with refractory cytopenia with unilineage dysplasia (RCUD), including RA, refractory neutropenia, refractory thrombocytopenia, and RA with ring sideroblasts (RARS), have a more favorable outcome compared with those low-grade MDS patients with multilineage dysplasia, including refractory cytopenias with multilineage dysplasia (RCMD) and RCMD with ring sideroblasts. It lowers the blast threshold for the diagnosis of AML from 30% to 20%, eliminating the diagnosis of refractory anemia with excess blasts in transformation (RAEB-t) by FAB criteria. Refractory anemia with excess blasts has been subdivided into RAEB1 (5–9% marrow blasts) and RAEB2 (10–19% marrow blasts), again based on differences in prognosis. The 2008 WHO classification also adds a category for unclassifiable cases that do not fit into other categories and for atypical presentations of MDS, such as those with extensive fibrosis. The WHO classification does include one genetically defined subtype, MDS with isolated del(5q). She has RA by the WHO classification as well.

However, aside from marrow morphology, both the FAB and WHO systems do not include factors that have been

Table 15.2 WHO classification of myelodysplastic syndromes.

Disease	Blood findings	Bone marrow findings
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	$\geq$15% ringed sideroblasts Erythroid dysplasia only <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods $< 1 \times 10^9$/L monocytes	Dysplasia in $\geq$10% of the cells of two or more myeloid cell lines <5% blasts in marrow No Auer rods <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods $< 1 \times 10^9$/L monocytes	Dysplasia in $\geq$10% of the cells in two or more myeloid cell lines $\geq$15% ringed sideroblasts <5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB1)	Cytopenias <5% blasts No Auer rods $< 1 \times 10^9$/L monocytes	Unilineage or multilineage dysplasia 5–9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB2)	Cytopenias 5–19% blasts Auer rods $\pm$ $< 1 \times 10^9$/L monocytes	Unilineage or multilineage dysplasia 10–19% blasts Auer rods $\pm$
Myelodysplastic syndrome—unclassified (MDSU)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia: one myeloid cell line <5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count <5% blasts	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

(Source: Vardiman JW, Thiele J, Arber DA, et al. T Blood. 2009;114(5):937–51. Reproduced with permission of American Society of Hematology. Adapted from Swerdlow, SH, Campo, E, Harris, NL, Jaffe, ES, Pileri, SA, Stein, H, Thiele, J, Vardiman, JW. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon, 2008).

(*Continued*)

shown to affect the course of MDS. Many features have been shown to influence MDS outcome, including patient age, comorbid conditions, performance status, transfusion dependence, LDH, cytogenetics, and marrow fibrosis. Multivariate analyses have demonstrated the significant impact of marrow cytogenetic abnormalities on the prognosis of patients with MDS.[1] A clonal abnormality is defined by the International System for Human Cytogenetic Nomenclature as two or more cells with the same chromosome gain or structural rearrangement, or three cells with the same chromosome loss.

The most widely accepted MDS risk assessment model is the International Prognostic Scoring System (IPSS), which uses marrow blasts, cytogenetic changes, and the number of peripheral blood cytopenias to classify MDS cases into four prognostic subgroups: low risk (score: 0), intermediate-1 risk (score: 0.5–1.0), intermediate-2 risk (score: 1.5–2.0), and high risk (score: ≥2.5). The system was developed prior to the WHO classification and therefore still incorporated 21–30% marrow blasts. The cytogenetics were broadly divided into good, with normal, −Y, del(5q), and del(20q); poor, with complex (≥3 abnormalities) or chromosome 7 anomalies; and intermediate risk, which includes all other abnormalities. It is also important to realize that the model only applies to patients at the time of diagnosis with de novo MDS who received supportive care alone. Therapy-related MDS generally has a much worse prognosis than de novo disease.

These risk groups showed significantly different overall survival and risk of acute leukemia transformation. Median survival for low-risk patients was 5.7 years, and it was 3.5 years for intermediate-1 risk, 1.2 years for intermediate-2 risk, and 0.4 years for the high-risk disease group.

The IPSS has several limitations, the most important of which is that it does not characterize patients with lower-risk disease (IPSS low or intermediate-1 risk) very well in terms of prognosis. This group accounts for two-thirds of patients with MDS, some of whom may possibly benefit from early intervention. As this system was developed at initial diagnosis in patients with MDS, it cannot be used reliably during the course of the disease and its evolution. Furthermore, the model was based on cytogenetic information from only 816 patients, two-thirds of whom had a normal diploid karyotype. The prognostic significance of less common single or double cytogenetic changes [i.e., other than del(5q), chromosome 7 abnormalities, trisomy 8, del(20q), and −Y] could not be accurately assessed; these were arbitrarily included in the intermediate-risk karyotype group.

Schanz *et al*. (2011) evaluated a greater number of MDS cases (2902 patients) with cytogenetic data from several different groups, and they were able to propose a new comprehensive cytogenetic scoring system. This data set allowed the investigators to estimate the prognostic impact of less common single and double cytogenetic changes. Nineteen cytogenetic abnormalities were identified. Cytogenetic categories have a more significant effect on survival compared with marrow blast percentage. They divided these cytogenetic abnormalities into five prognostic subgroups: very good, good, intermediate, poor, and very poor.

This new cytogenetic scoring system provided the foundation for the revised IPSS (IPSS-R) (Table 15.3). The major differences between the IPSS-R and its predecessor include five cytogenetic subgroups rather than three, classification of the less common cytogenetic abnormalities, division of the lowest marrow blast subgroup into <2% blasts and 2 to <5% blasts, and weights for the degree of individual cytopenias. A significant proportion of patients within the IPSS lower-risk group (27%) would be "upstaged" in the IPSS-R classification, while 18% in the higher risk group would be "downstaged" by IPSS-R.

The score by IPSS-R correlated with the risk of dying and risk of leukemic transformation (Table 15.4).

Thus, based on the above classification systems, this patient would be classified as low risk with a total score of 0 by IPSS (blasts <5%, 0; normal cytogenetics, 0; and 0/1 cytopenia, 0) with a median survival of 5.7 years. Using the IPSS-R, she would have a score of 3.5, placing her in the intermediate-risk category with a predicted survival of 3 years. Her physician chooses to treat her with an erythropoietic stimulating agent, and she becomes transfusion independent.

Table 15.3 IPSS-R prognostic factors and weights (Source: http://www.mds-foundation.org/wp-content/uploads/2011/12/2-RevisedInternationalPrognosticScoringSystem.pdf).

	0	0.5	1	1.5	2	3	4
Cyto	Very good		Good		Intermediate	Poor	Very poor
Blasts	<2%		2–<5%		5–<10%	>10%	
Hemoglobin	≥10 g/dL		8–10 g/dL	<8 g/dL			
Platelet	≥100,000	50,000–100,000	<50,000				
Absolute neutrophil count	≥0.8	<0.8					

Table 15.4 IPSS-R and prognosis (Source: http://www.mds-foundation.org/wp-content/uploads/2011/12/2-RevisedInternational PrognosticScoringSystem.pdf).

	Very low (≤1.5)	Low (>1.5–3)	Intermediate (>3–4.5)	High (>4.5–6)	Very high (>6)
Overall survival (years)	8.8	5.3	3.0	1.6	0.8
Acute myeloid leukemia (AML) 25% (years)	NR	10.8	3.2	1.4	0.7

AML 25%, time to evolution to AML in 25% of the at-risk population.

Case study 15.2

A 79-year-old woman develops fatigue and transfusion-dependent anemia (2 units every 3–4 weeks). EGD and colonoscopy are negative. Her past medical history is significant for emphysema due to 40 pack-years of tobacco abuse and to osteoarthritis. She walks with a cane. She has a caregiver at home help her with all activities of daily living. She is sedentary much of the day. Physical exam is remarkable for decreased breath sounds and prolonged expiratory phase. She has neither adenopathy nor hepatosplenomegaly. Her WBC count is 5600/μL, her advanced neutrophil count (ANC) is 2600/μL, her hemoglobin is 9.4 gram/dL, and her platelet count is 174,000/μL. Bone marrow core biopsy is 20% cellular with clusters of unilobate atypical megakaryocytes and 4.5% blasts with increased fibrosis. Cytogenetic analysis showed 46XX, t(1;6)(p22;q23), del(5)(q13q33), 46XX.

- **How would you classify this patient?**

She has RA by the FAB classification and morphologic features of the 5q minus syndrome by WHO criteria, which has been associated with a more favorable prognosis. Based on the previous discussion, her IPSS would be intermediate-1 risk (<5% blasts, 0; intermediate risk karyotype, 0.5; single cytopenia, 0; and total score: 0.5). Her median survival is estimated to be 3.5 years. Based on the IPSS-R classification, she would be classified as low risk [2 to <5% blasts, 1; good cytogenetic category, 1; hemoglobin (HGB) 8–10 g/dL, 1; total score: 3]. Her median overall survival is predicted to be 3 years, and 25% of such patients will transform to AML in 10.7 years.

However, there are features in this patient that clearly have a negative impact on her prognosis but are not included in either the IPSS or IPSS-R, including advanced age, performance status, comorbid illnesses, transfusion dependence, abnormal marrow blast percentage, and marrow fibrosis. As transfusion requirements were found to be an independent prognostic factor in the survival of MDS patients, another scoring system that specifically takes into account the transfusion needs of the patient was developed. This scoring system uses the 2008 WHO MDS classification and is called the WHO classification-based Prognostic Scoring System (WPSS).[4] It divides patients into five risk groups as follows: very low (score = 0), low (score = 1), intermediate (score = 2), high (score = 3–4), and very high (score = 5–6). According to the WPSS, she has intermediate-risk disease with an estimated median survival of years. The WPSS can also be applied at any time during the course of the disease. However, one major limitation of the WPSS scoring system is the requirement of accurate information about prior transfusion requirements of the diagnosis of MDS, which is not always available. The WPSS classification has now been modified to include hemoglobin levels instead of transfusion requirements.

The global MD Anderson Cancer Center (MDACC) model can be used to evaluate patients with chronic myelomonocytic leukemia (CMML) and treatment-related myelodysplastic syndrome anytime during the course of the disease. These patients had been excluded from both the IPSS and IPSS-R. This scoring system incorporates age, performance status, and transfusion requirement, which adversely affect the prognosis of MDS patients but are not included in the IPSS or IPSS-R. The degree of anemia, thrombocytopenia, and leukocytosis (for CMML) is also included in the model. The global MDACC model has not been validated but is intended to evaluate all MDS patients anytime during the course of their disease without WHO classification of their disease pathology. Patients with 0 to 4 points had a median survival of 54 months and a 3-year survival rate of 63%. Patients with 5 and 6 points had a median survival of 23 to 30 months and a 3-year survival rate of 30% to 40%. Patients with 7 to 8 points had a median survival of 13 months and a 3-year survival rate of 13% to 19%. Patients with 9 or more points had a median survival of 5 to 10 months and a 2% 3-year survival rate. She has a combined score of 8 due to performance status 2 (2), age over 65 years (2), platelet count 50,000 to 199,000/μL (1),

(*Continued*)

hemoglobin less than 12 g/dL (2), and transfusion dependence (1).

Patients with lower-risk MDS remain quite heterogeneous in terms of prognosis. These patients have a wide range of disease behaviors and outcomes. To address this issue and better prognosticate in this category, Garcia-Manero *et al*. (2008) evaluated outcomes in a series of 856 patients with low-risk or intermediate-1 risk disease by IPSS seen at the MDACC over a 30-year period (1976–2005). Using multivariate analysis, they developed a risk assessment model for patients with lower-risk MDS. Unfavorable karyotype included all karyotypes except for del(5q) alone and normal diploid. Patient age, degree of cytopenias, and elevation of the bone marrow blast above 4% were included in the model. The model has been validated by Bejar *et al*. (2012). By the prognostic score for lower-risk MDS patients of Garcia-Manero *et al*. (2008), she had a score of 6, consistent with median survival of 16 months and 4-year survival <10%. Her survival varies significantly from that predicted by either the IPSS or the IPSS-R. Finally, the prognostic significance of marrow fibrosis has been extensively debated. One potential explanation of the absence of fibrosis from the various prognostic models is the difficulty in reproducibly grading the degree of marrow fibrosis in these patients as well as the variability in performance of reticulin stains.

The patient was started on lenalidomide 10 mg daily (refer to Chapter 16 for the treatment of MDS). Within 1 month, she had a good response with a WBC of 5300, ANC of 800, HGB of 8.5 gram/dL, and platelet count of 128,000. Her lenalidomide was held for 2 weeks due to grade 3 neutropenia and restarted at 5 mg daily with a good response and no side effects. She subsequently became red blood cell transfusion independent in 2 months and continued doing well for one year, at which time she had recurrent pancytopenia. A repeat bone marrow biopsy was diagnostic of progression to acute myeloid leukemia, with 30–40% cellularity and 20% myeloblasts. There was no evidence of clonal evolution by cytogenetic analysis. She enrolled in a clinical study with clinical benefit for 6 months followed by hospice care. Her outcome appears to have been better predicted by the model for lower-risk MDS developed by Garcia-Manero and the MDACC global MDS risk assessment model than by either the IPSS or IPSS-R.

Case study 15.3

A 64-year-old woman with multiple medical problems, including diabetes mellitus type 2, hypertension, coronary artery disease status post bypass graft surgery, chronic obstructive pulmonary disease, depression, and opiate and alcohol dependence, presented to the hospital with severe fatigue and dyspnea. She was hypotensive with a multifocal pneumonia. Her labs were significant for a WBC count of 3500, an ANC of 2500, an HGB of 5.3 g/dL, an MCV of 102, and a platelet count of 85,000. She received 4 units of PRBC. A bone marrow biopsy was 40% cellular with erythroid aplasia, small megakaryocytes with hypolobate nuclei, shift to immaturity in granulocytes, and 6.0% blasts. Flow cytometry detected a myeloblast population, accounting for 7% of the nucleated cells, and expressing CD13, CD33, CD34, CD45, and CD117. Cytogenetic analysis revealed a clonal abnormal karyotype with both structural and numeric changes: 46XX, del(1)(q12q44), −3, der(5)t(1;5)(q12;q11.2), der(7)t(3;7)(q13;q32), +12, 0–1 markers [cp5]. The der(5)t(1;5) results in deletion of 5q.

- **How would you risk stratify this patient?**

Her composite score by IPSS is 2.0, consistent with intermediate-2 risk (5–10% blasts, 0.5; poor risk karyotype, 1.0; two cytopenias, 0.5). As MDS is a disease of older patients, most will have a significant number of comorbidities. None of the scoring systems discussed in this chapter take into account the effect of comorbidities on the natural history and treatment of MDS patients. Several groups have developed comprehensive scoring systems to include comorbidity indices with the IPSS scores in order to get a more accurate picture of a patient's prognosis. Comorbid illnesses, poor performance status, and advanced patient age will limit the ability of a higher-risk patient to undergo potentially curative therapy for MDS. She received azacitidine, achieving a complete remission after six cycles (see Chapter 16 for the treatment of MDS). Her disease relapsed after one year of azacitidine. She received decitabine followed by clofarabine without response. She died within 2 years of her diagnosis.

Over the last 2–3 years, several new and clinically significant somatic mutations have been identified in varying frequencies in MDS (Table 15.5). Some of these appear to affect the prognosis of the disease. TET2 is one of the most frequently mutated genes in MDS; TET2 mutations appear to be prognostically favorable in MDS. The 5-year overall survival is 76.9% in mutated versus 18.3% in unmutated patients ($P = 0.005$). The 3-year leukemia-free survival is 89.3% in TET2 mutated versus 63.7% in unmutated patients ($P = 0.035$). In multivariate analysis, the presence of TET2 mutation was an independent favorable prognostic factor irrespective of the MDS subtype. RUNX1 point mutations have been identified in MDS and MDS-related AML. About 20% of MDS patients may have these mutations, with a higher incidence in secondary MDS compared to de novo

disease. This mutation is associated with a worse prognosis compared with those without the mutation. ASXL1 mutations are a poor prognostic factor for overall survival independent of other established risks in multivariate analyses. Mutations of the EZH2 gene located on chromosome 7 have been discovered in several myeloid malignancies, including MDS.[5] Overexpression of the EZH2 gene is generally associated with poor prognosis in MDS, especially in lower-risk cases.[5] DNMT3A mutations are found in approximately 8% of de novo MDS cases. DNMT3A mutations may occur early in the course of MDS, and patients with DNMT3A mutations have worse overall survival and an increased risk of progression to acute leukemia. IDH1/2 genes are mutated in approximately 10% of MDS patients. In MDS with sole del(5q) cytogenetic abnormality, mutant IDH has been associated with poor overall and leukemia-free survival. The prognostic effects of IDH1 and IDH2 mutations among patients with MDS in association with IPSS-R showed an adverse prognostic effect of mutant IDH1, but not mutant IDH2, on both overall and leukemia-free survival. Mutations in the components of the RNA-splicing machinery also play an important role in the pathogenesis of MDS. Genes involved in the spliceosome like U2AF1, SRSF2, and SF3B1 are frequently mutated in MDS. SF3B1 is mutated in most patients with MDS with increased ring sideroblasts (84.9%). In some studies, patients with SF3B1 mutations had fewer cytopenias and better event-free survival, but other studies found that the SF3B1 mutation had no additional prognostic value in MDS. Mutation of one of the following five genes has a negative impact on the prognosis of MDS patients predicted by the IPSS: TP53, EZH2, ETV6, RUNX1, and ASXL1.

Table 15.5 Somatic mutations in MDS (Source: Data from Bejar R, *et al*. N Engl J Med. 2011;364(26):2496–506; Itzykson R, *et al*. Leukemia. 2011;25(7):1147–52; Papaemmanuil E, *et al*. N Engl J Med. 2011;365(15):1384–95; Makishima H, *et al*. Blood. 2012;119(14):3203–10; and Thol F, *et al*. Blood. 2012;119(15):3578–84).

Mutation	Chromosome location	Frequency (%)	Function	Clinical significance in mutated cases
TET2	4q	20–26	Control of cytosine hydroxymethylation	Inconsistent impact on survival: improved response to azacitidine
RUNX1	21q	Up to 20	Transcription factor	Decreased survival
ASXL1	20q	10–15	Epigenetic regulator	Decreased survival
EZH2	7q	2–6	Polycomb group protein	Decreased survival
DNMT3A	2p	Up to 8	Transcription factor	Decreased survival and increased risk of sAML
CBL	11q	1	Signal transduction	Unknown
IDH1/IDH2	2 q/15q	5–10	As IDH1 and cell metabolism; epigenetic regulation	Decreased survival (unknown for IDH2)

Conclusion

At present, the most widely accepted prognostic models in MDS are based predominantly on marrow morphology, cytogenetics, and cytopenias. Patient-specific features, such as age, performance status, and comorbid illness, affect prognosis as well as choice of therapy, but they are not considered in the IPSS or IPSS-R. Because the marrow karyotype is normal in over 50% of MDS patients, the usefulness of the IPSS and IPSS-R is limited. Fifty percent of MDS patients with normal karyotype will have somatic mutation in at least one of a few genes. Many of these genes encode proteins involved in the epigenetic modulation of gene transcription, such as components of the RNA-splicing machinery, regulators of DNA methylation, and enzymes of histone modification. These somatic mutations will likely soon be incorporated into the next generation of MDS prognostic models.

However, prognostic models are only valid in the context of available therapies. Although the IPSS was developed from patients receiving only supportive care, the risk as assessed by IPSS has been shown to impact outcome with hypomethylating agents and allogeneic hematopoietic stem cell transplantation. These prognostic models have limited utility, basically just identifying patients with high-risk disease who should proceed to allogeneic hematopoietic stem cell transplantation, if possible. We need to assess whether mutations are associated with response to specific therapies (i.e., they are predictive, not just prognostic). In this way, we will be better able to choose treatment for our patients. Finally, true progress will be realized only as we understand the biologic effects of these somatic mutations

and can effectively target the disrupted cellular mechanisms that lead to MDS.

Selected reading

Greenberg PL, Tuechler H, Schanz J, *et al*. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–65.

Haase D, Germing U, Schanz J, *et al*. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood. 2007;110(13):4385–95.

Malcovati L, Germing U, Kuendgen A, *et al*. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25(23):3503–10.

Schanz J, Steidl C, Fonatsch C, *et al*. Coalesced multicentric analysis of 2,351 patients with myelodysplastic syndromes indicates an underestimation of poor-risk cytogenetics of myelodysplastic syndromes in the international prognostic scoring system. J Clin Oncol. 2011;29(15):1963–70.

Xu F, Li X, Wu L, *et al*. Overexpression of the EZH2, RING1 and BMI1 genes is common in myelodysplastic syndromes: relation to adverse epigenetic alteration and poor prognostic scoring. Annals of Hematology. 2011;90(6):643–53.

CHAPTER 16

Management of myelodysplastic syndromes

Vu H. Duong[1], Alan F. List[2], and Rami S. Komrokji[2]

[1]University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA
[2]H. Lee Moffitt Cancer Center, Tampa, FL, USA

1. What is the general approach to the treatment of newly diagnosed myelodysplastic syndrome (MDS)?

Therapy should be tailored to each patient according to the specific risk profile, and whenever possible, patients should be treated on a clinical trial. Chapter 15 has defined the prognostic stratification in MDS. A general overview of treatment is summarized in Figure 16.1.

2. Which patients are good candidates for treatment with erythropoiesis-stimulating agents (ESAs) such as epoetin alpha or darbepoietin?

ESAs are an appropriate initial treatment for anemia in lower-risk MDS patients. A simple, validated decision model was developed by the Nordic MDS Group for the use of epoetin alpha and granulocyte colony-stimulating factor (G-CSF) in patients with lower-risk MDS based on their pretreatment serum erythropoietin (EPO) level and the number of red blood cell (RBC) transfusions administered each month. Patients are assigned +2, +1, and −3 points for EPO levels of <100, 100–500, or >500 U/L, respectively. Similarly, patients who require fewer than two units of packed RBCs (pRBCs) each month are assigned +2 points, and those who require at least two units each month are assigned −2 points. Patients with a combined score that was greater than +1 had a 74% probability of response, compared to 23% for those with a score between −1 and +1 and 7% for those with scores less than −1. Darbepoetin appears to be equivalent to epoietin alpha, and the use of either agent is reasonable. We typically recommend a 6–8-week trial of ESAs, followed by continuation of treatment in responders (the median duration of response is 12–18 months). We reserve the addition of G-CSF for patients who do not respond after a 6–8-week trial of an ESA, a method that has been employed with modest success in multiple prospective trials.

3. Which patients are good candidates for treatment with immunosuppressive therapy (IST)?

In the phase III trial of antithymocyte globulin and cyclosporine versus best supportive care in patients primarily with lower-risk MDS, IST was shown to increase hematologic response rates significantly by 6 months (29% vs. 9%, respectively), but neither 2-year progression-free survival (46% vs. 55%) nor overall survival (49% vs. 63%) was significantly improved. Based on their previous experiences with IST, the National Institutes of Health (NIH) developed and validated a predictive score for response based on age, the presence of a human leukocyte antigen (HLA)-DR15 class II phenotype, and the duration of RBC transfusion dependence. The patient's age in years is added to the duration of RBC transfusion dependence in months. A sum $\leq$57 predicts a high probability of response for patients in whom HLA-DR15 is absent, while a sum of $\leq$71 predicts higher responses for patients in whom HLA-DR15 is present. In addition to the above factors, other studies have reported that bone marrow hypocellularity, the presence of a paroxysmal nocturnal hemoglobinuria clone, and a low CD4:CD8 ratio correlate with improved response rates. We wait 4–6 months after therapy to assess response, and we closely observe for treatment-related toxicity such as infections and cyclosporine toxicity.

4. What is the best starting dose for lenalidomide in lower-risk patients with RBC transfusion dependence and a chromosome 5q deletion [del(5q)]?

The US Food and Drug Administration (FDA)-approved starting dose for lenalidomide in MDS is 10 mg daily continuously or for 21 days every 4 weeks based on the MDS-003 phase II registration trial conducted exclusively in transfusion-dependent patients with del(5q). A subsequent phase III trial randomized patients to placebo or two

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

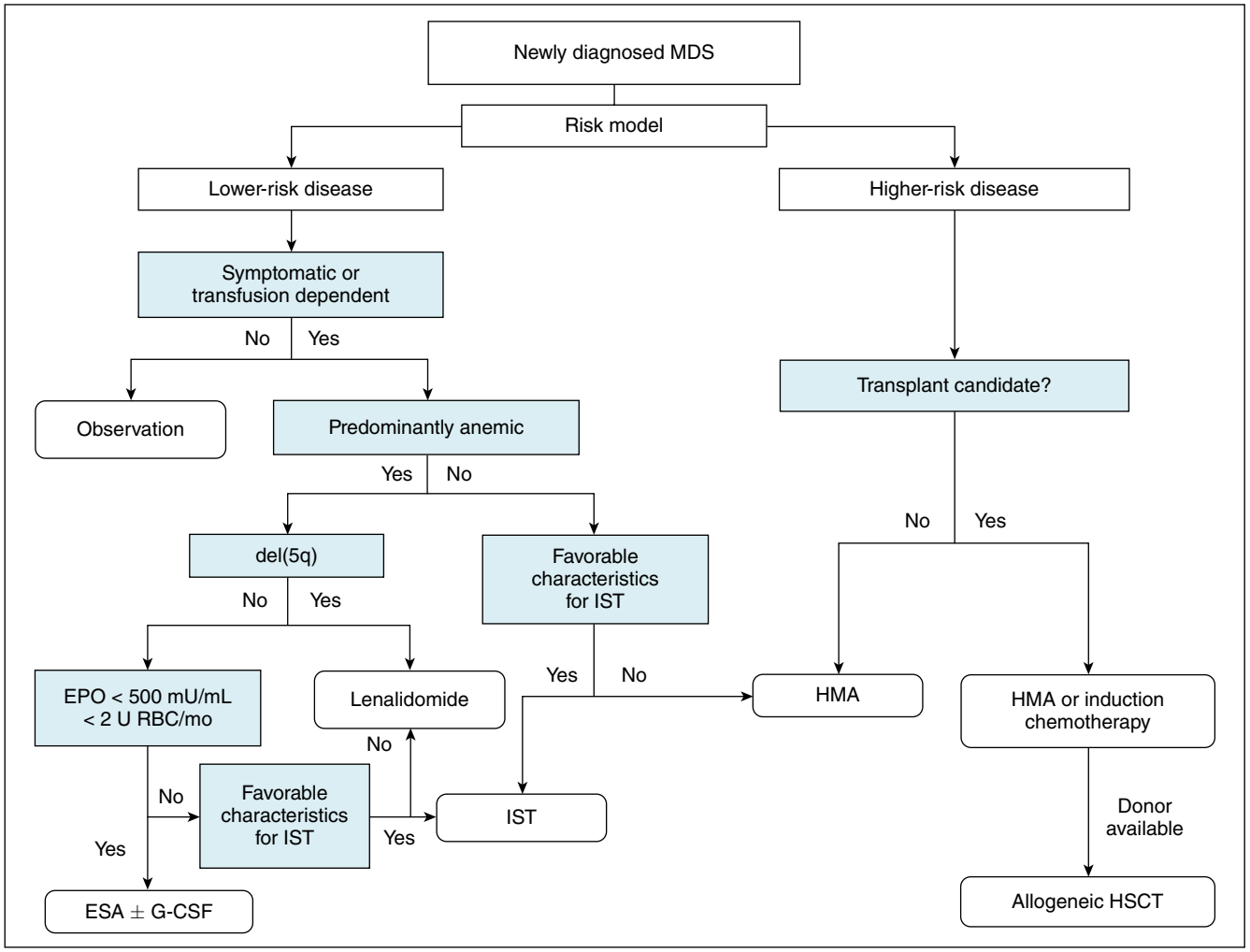


Figure 16.1 General approach to the treatment of newly diagnosed myelodysplastic syndrome. Del(5q), chromosome 5q deletion; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; RBC, red blood cell.

different doses of lenalidomide: 5 mg daily on days 1–28 and 10 mg daily on days 1–21 of a 28-day cycle. This trial was not designed to detect differences in the two lenalidomide arms, but higher rates of transfusion independence and cytogenetic response were seen in the 10 mg arm. In the phase II MDS-003 trial in patients with del(5q), patients were also originally treated with 10 mg on days 1–21, but shortly after activation, the schedule was amended to 10 mg continuous daily dosing in light of the faster times to response observed in the pilot trial. Forty-six patients received the day 1–21 schedule, and 102 received continuous daily dosing, which resulted in a slight trend toward higher erythroid response rates (72% vs. 77%, respectively; $P = 0.26$) and faster median time to response (4.7 weeks vs. 4.3 weeks). The 10 mg continuous dosing is associated with more frequent neutropenia and thrombocytopenia, but the development of these events is also associated with a higher probability of transfusion independence. Based on the available data, we initiate patients on the 10 mg continuous daily dosing schedule with weekly blood counts for the first 8 weeks. Approximately 80% of patients will require a drug holiday after a median duration of 3 weeks for myelosuppression. Treatment is held for an average of 3 weeks, then the dose is reduced to 5 mg daily. G-CSF can be used to accelerate neutrophil recovery and preempt neutropenia. The median time to response is 4 weeks, and the median duration of response is approximately 3 years.

5. Can lenalidomide be used in lower-risk patients with anemia and karyotypes other than del(5q)?

The use of lenalidomide in MDS without the del(5q) abnormality is considered off-label; however, a multicenter phase II trial (MDS-002) demonstrated some activity of this agent

in lower-risk, transfusion-dependent MDS patients without this specific cytogenetic abnormality. In that trial, 26% of patients achieved RBC transfusion independence that lasted a median of 41 weeks. An additional 17% of patients had at least a 50% reduction in transfusion requirement, for an overall response rate of 43%. The median time to response (4.8 weeks) in this trial appears similar to the results in patients with del(5q). Unlike the MDS-003 study, however, there were very few cytogenetic responses. Further comparisons between the MDS-002 and MDS-003 trials show a shorter median duration of transfusion independence and a less robust median increase in hemoglobin in patients without the del(5q) abnormality. The exact role of lenalidomide in this specific population of patients is currently under investigation in a phase III study. Until the results of this trial are available, we consider this as a treatment alternative in lower-risk patients requiring frequent transfusions of RBCs who have failed ESAs, have adequate platelet and neutrophil counts, and otherwise do not have favorable characteristics for immunosuppressive therapy. The National Comprehensive Cancer Center Network (NCCN) guidelines for management of MDS list lenalidomide as an option for treatment of anemia in non-del(5q) lower-risk MDS.

6. Can patients with higher-risk disease and del(5q) be treated with lenalidomide rather than hypomethylating agents (HMAs)?

Lenalidomide treatment of higher-risk MDS with del(5q) should be considered investigational, and in our practice we use lenalidomide exclusively in lower-risk patients. A phase II study of daily lenalidomide in 47 higher-risk MDS patients with del(5q) reported a 27% response rate, including seven complete remissions (CRs). Most responses were rapid, but the duration of response was only 6.5 months. Patients with an isolated del(5q) were more likely to respond compared with those with additional chromosomal abnormalities. While this study utilized lenalidomide at the currently approved dose of 10 mg daily, dose escalation may improve response rates.

7. Does lenalidomide increase the risk of progression to acute myeloid leukemia (AML)? Should patients be monitored for clonal evolution while on lenalidomide therapy?

As seen in the long-term follow-up of 42 European patients treated in the MDS-003 trial, 15 patients (36%) progressed to AML and 17 (40%) had karyotypic evolution. Patients who failed to achieve a response to lenalidomide appeared to have a higher rate of AML progression compared to those who responded. These rates of AML progression in this isolated subset of patients may seem higher than historical controls, but patients in the MDS-003 trial were all transfusion dependent, which is a known poor prognostic factor for disease progression. In addition, recent studies indicate that TP53 gene mutations are demonstrable in approximately 20% of del(5q) MDS patients, expand over time, and are associated with higher risk of disease progression and lower frequency of cytogenetic response to lenalidomide. The rate of AML progression can be as high as 80% in patients with del(5q) and more than 5% blasts; thus, the apparent tendency toward leukemic transformation may actually be a reflection of the natural history of disease in this subset of patients with greater AML potential. A more recent study from the International Working Group on MDS with del(5q) evaluated 295 lenalidomide-treated patients on the MDS-003 and -004 studies along with 125 untreated, lower-risk, RBC-transfusion-dependent patients with del(5q) from a registry. The median follow-up was over 4 years in each cohort. Despite a higher RBC transfusion burden in the lenalidomide cohort, the 2-year cumulative AML progression risk was similar between cohorts [hazard ratio (HR) 0.969], but lenalidomide-treated patients had a significant improvement in survival (HR 0.597). In the phase III trial of lenalidomide versus placebo in del(5q) MDS, almost all patients who were randomized to placebo crossed over to the lenalidomide arm; thus, truly randomized prospective data with long-term follow-up are lacking, and the issue of whether lenalidomide truly increases the risk of AML progression remains unclear. Nonetheless, responding patients have a lower frequency of AML than nonresponders, suggesting that a drug effect is unlikely. No formal guidelines currently exist for monitoring cytogenetics in patients on lenalidomide, and we do not routinely perform karyotyping or fluorescent in situ hybridization on our responding patients.

8. How does one manage MDS patients with isolated thrombocytopenia? Are romiplostim or eltrombopag reasonable options?

Currently, the only available treatment modalities that can potentially improve platelet counts are IST and the HMAs. The use of the thrombopoietin receptor agonists romiplostim and eltrombopag in patients with MDS remains investigational. Romiplostim decreased the rate of clinically significant bleeding events and platelet transfusions compared to placebo in a randomized trial of patients with lower-risk MDS and thrombocytopenia. Despite these promising results, the trial was halted prematurely when data emerged showing an apparent increase in peripheral blasts and AML transformation in the romiplostim arm. Longer follow-up showed a lower hazard ratio for progression to AML than was originally reported. Eltrombopag is a noncompetitive thrombopoietin receptor agonist that was shown to be cytotoxic to leukemic myeloblasts in preclinical studies, and it is currently being studied in several

early-phase trials in patients with MDS. The interim results of one study were recently presented, showing significantly increased platelet counts and decreased bleeding or transfusion events in patients treated with eltrombopag compared to placebo, with no patients progressing to AML in the treatment arm. Additional data regarding the efficacy and safety of this agent are needed before it can be incorporated routinely into practice.

9. In lower-risk patients, what schedule of azacitidine should be given?

In our practice, we administer 5 days of azacitidine at 75 mg/m^2 every 28 days in patients with lower-risk disease. A multicenter community-based study randomized patients (most of whom had lower-risk MDS) to three different schedules of azacitidine: (i) a 5–2–2 schedule (75 mg/m^2 subcutaneously for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days), (ii) a 5–2–5 schedule (50 mg/m^2 subcutaneously for 5 days, followed by 2 days of no treatment, then 50 mg/m^2 for 5 days), or (iii) a 5-day schedule (75 mg/m^2 subcutaneously for 5 days). Differences in response rates were not statistically significant, but there was a trend toward a higher rate of hematologic improvement and RBC transfusion independence in patients treated on the 5-day schedule, with comparable (and perhaps even reduced) hematologic toxicity. It should be noted that 75 mg/m^2 for 7 days, which showed survival benefit in higher-risk patients, was not one of the arms in this study. The first randomized phase III study from the Cancer and Leukemia Group B (CALGB), however, used the 7-day schedule and allowed patients with lower-risk disease to be enrolled. Analysis of the whole study population showed only a trend toward survival benefit over best supportive care. Although it can be argued that the crossover design of the study may have confounded the results, definitive survival benefit from azacitidine using the current FDA-approved schedule has never been shown in lower-risk patients.

10. How does one manage intermediate-risk patients by the Revised International Prognostic Scoring System (IPSS-R)?

Most clinical trials in MDS have risk-stratified patients based upon the original IPSS score, dividing patients into lower-risk (low and intermediate-1) and higher-risk (intermediate-2 and high) categories. The development of the Revised IPSS (IPSS-R) resulted in five risk categories (very low, low, intermediate, high, and very high), leaving uncertainty regarding the treatment of patients in the intermediate category. Patients in this risk category had a median survival of 3.0 years and a median time to 25% AML evolution of 3.2 years. Although cohorts from differing eras were used to develop the two risk models, these data appear to be closer to those for IPSS intermediate-1 patients (3.5 years and 3.3 years, respectively) than those for IPSS intermediate-2 patients (1.8 years and 1.1 years, respectively). At this point, therapy must be individualized to the patient by considering additional factors such as age, the presence of specific gene mutations, the presence of bone marrow fibrosis, and disease tempo.

11. Which HMA should be used for higher-risk MDS patients?

Both azacitidine and decitabine are approved by the FDA for management of MDS, but they have not been directly compared in a prospective, randomized study. Only azacitidine, however, has been shown to confer overall survival benefit over conventional care regimens in patients with higher-risk disease, including those with refractory anemia with excess blasts in transformation (RAEB-t). In the AZA-001 trial, patients with higher-risk MDS by IPSS treated with azacitidine had a median survival of 24.5 months compared to 15.0 months in patients treated with intensive chemotherapy, low-dose cytarabine, or best supportive care. In contrast, in two phase III trials of decitabine versus best supportive care, only a trend toward overall survival benefit was seen despite the lack of active treatment in the control arm. In both trials of decitabine, however, treatment was not continued until disease progression, which likely affected survival outcomes. In addition, the highest complete response rate ever reported for an HMA (39%) was in patients receiving the 5-day 20 mg/m^2/d intravenous decitabine regimen. While both agents have clinical activity, we favor azacitidine in our practice given its documented overall survival benefit, a practice that is supported by current NCCN guidelines.

12. What are the optimal schedules and routes of administration of azacitidine and decitabine in higher-risk MDS patients?

In contrast to patients with lower-risk disease, we administer 75 mg/m^2 of azacitidine subcutaneously on days 1–7 of a 28-day cycle in higher-risk patients whenever possible, as this is the only dose, route of administration, and schedule combination ever shown to improve overall survival. When weekend dosing is not feasible in the community, we generally recommend the 5–2–2 schedule. Although pharmacokinetic data are available showing similar bioavailability between intravenous and subcutaneous administration, only one prospective study has been published evaluating the efficacy of intravenous azacitidine. When given for 5 consecutive days every 28 days, the overall response rate was 27% and the median survival was only 14.8 months. An oral form of azacitidine is also currently

under development. The initial FDA-approved schedule for decitabine, based on the phase III trial, was 15 mg/m^2/dose given intravenously every 8 h for 3 consecutive days every 28 days. This schedule is often inconvenient for patients and requires inpatient hospitalization; thus, many clinicians, including ourselves, use the alternative FDA-approved schedule of a 20 mg/m^2 dose given intravenously once daily for 5 consecutive days. As stated in Question 11, this schedule is associated with a high CR rate, and it may be less toxic than the 3-day schedule due to the lower cumulative dose.

13. When treating higher-risk patients with HMAs, how should doses be modified for cytopenias?

Cytopenias are the most frequent adverse event associated with HMA therapy, and clinical practice varies widely. The package insert for azacitidine recommends dose reductions of up to 67% of the initial dose depending on nadir absolute neutrophil, white blood cell, and platelet counts. However, dose reductions or delays to allow recovery of counts may be associated with lower efficacy. A consensus panel of experts recommends against dose modifications during the first three cycles even in the presence of severe cytopenias, except in cases of life-threatening infections. Eighty-six percent of patients in the AZA-001 trial did not require dose modifications, and despite the higher incidence of grade 3 or 4 neutropenia and thrombocytopenia compared to best supportive care, there was no increase in the incidence of infections or bleeding. In addition, improvement in cytopenias may occur with subsequent cycles, in particular anemia and thrombocytopenia. The use of G-CSF to improve neutropenia has not been studied systematically and was not allowed on the AZA-001 trial; thus, we do not routinely use this agent to hasten neutrophil recovery after treatment with HMAs. If dose adjustments are needed after the first three cycles, we generally dose-delay rather than dose-reduce therapy.

14. In patients who have had a sustained response to HMA therapy, can cycles be given less frequently than every 4 weeks or even stopped?

In the absence of toxicities, we attempt to stay on schedule with the administration of HMAs, and we do not stop therapy in responders unless there is evidence of loss of response or disease progression. In circumstances when patients are adamant about prolonging the interval between cycles for quality-of-life purposes, we have a frank discussion regarding the risks of this approach, and we almost never increase the dosing interval beyond 6 weeks. In the AZA-001 trial, the median duration of therapy for responders was 14 months and continued treatment with azacitidine after first response led to higher-quality responses in 48% of patients, suggesting that the benefits of HMAs are greater with prolonged exposure. Loss of response after discontinuation can be rapid, and retreatment results in inferior quality and duration of responses compared to initial treatment.

15. Should induction chemotherapy (with an anthracycline and cytarabine) ever be used for higher-risk patients?

Compared to AML, induction chemotherapy for MDS generally results in lower CR rates and shorter responses, but it was one of the few options available to higher-risk patients prior to the age of HMAs. In particular, younger patients with favorable karyotypes appeared to derive the most benefit. Although azacitidine was shown to be superior to conventional care regimens that included induction chemotherapy in the AZA-001 trial, fit patients in whom allogeneic stem cell transplantation was planned were excluded from the trial. As expected, only 14% of patients in the control arm underwent induction chemotherapy, but this resulted in slightly higher remission rates compared to azacitidine (40% vs. 29%, respectively), although this was not statistically significant. Although achievement of a complete response is prerequisite to extension in survival with induction chemotherapy, this is not the case for azacitidine. Thus, its role has clearly diminished in the last decade, but induction chemotherapy may still have value only in a highly select group of MDS patients.

16. Some patients develop therapy-related MDS, but they have lower-risk disease by various prognostic scores. How should these patients be managed?

The World Health Organization collectively considers therapy-related MDS, therapy-related AML, and therapy-related myelodysplastic/myeloproliferative neoplasms as a distinct clinical entity. This group of diseases generally has a worse prognosis than their de novo counterparts. It should be noted that the IPSS, WHO classification–based Prognostic Scoring System (WPSS), and IPSS-R (but not the global MD Anderson MDS risk model) excluded patients with therapy-related MDS; thus, risk scores calculated within these systems must be interpreted with caution. In all phase III trials of both azacitidine and decitabine, therapy-related MDS patients either were excluded or accounted for a very small fraction of the study population; thus, it is unclear whether the benefits of therapy extend to this group of patients. Several retrospective studies, however, have demonstrated response rates of approximately 40% using these agents; thus, we feel their use is justified, and we routinely use azacitidine in this population. Radiation-induced myeloid neoplasms behave more like de novo MDS and should be treated accordingly. The

outcome of therapy-related myeloid neoplasms is predominantly driven by disease karyotype; thus, we tailor therapy based on karyotype where we may apply a stepwise approach in those with a more favorable karyotype but pursue allogeneic stem cell transplantation in those with poor-risk disease.

17. What treatment options are available for patients who have failed or progressed on HMAs?

Patients who have initial failure, progress on therapy, or lose initial response to HMAs have a very poor prognosis, with a median survival measured in months. One small trial evaluated the utility of switching to decitabine after azacitidine failure, demonstrating a response in 4 out of 14 patients (28%), but the duration of response was very short. Whenever possible, these patients should be referred for treatment on a clinical trial. Some agents that appear to have promising results in higher-risk patients include rigosertib, tosedostat, sapacitabine, and clofarabine.

18. What is the role of HMAs prior to allogeneic hematopoietic stem cell transplantation?

The screening process prior to allogeneic stem cell transplantation can often span several months; thus, HMAs are commonly used as bridging therapy, a practice that is supported by NCCN guidelines. This strategy may be helpful in halting disease progression with limited toxicity, allowing more patients to proceed to transplant, but no prospective studies are available. A large retrospective study comparing azacitidine to induction chemotherapy or both prior to transplant suggests that overall survival, event-free survival, relapse rate, and nonrelapse mortality are similar between azacitidine and induction chemotherapy. There was a trend toward poorer overall survival in patients who received both therapies, but this may be a reflection of aggressive disease requiring multiple therapies. The optimal timing of transplantation during HMA therapy is also controversial and is further complicated by the long duration of therapy before the best response is attained. Although patients with lower blast counts at the time of transplantation have better outcomes than those with higher disease burden, the value of cytoreduction prior to transplant remains unclear. From a practical standpoint, most patients receive at least two or three cycles of azacitidine before a donor is available and the pre-transplant workup is complete. In our practice, patients who have stable disease on azacitidine with no improvement in peripheral blood counts or bone marrow proceed to transplant as soon as possible. In patients who appear to be responding early, we hold transplantation until the maximal response is gained. The role of posttransplant azacitidine maintenance is emerging, with early studies suggesting benefit. A dose-finding study found that 32 mg/m^2 given for 5 days for at least four cycles was safe and associated with one-year event-free survival and overall survival rates of 58% and 77%, respectively.

19. What is the value of iron chelation therapy, and when should it be used?

Although transfusion dependence and elevated ferritin levels are known to correlate with poorer outcomes in patients with MDS, to date no randomized trial has shown a definitive benefit for iron chelation therapy in patients with MDS. Two large phase II studies have shown that deferasirox decreases serum ferritin levels as well as labile plasma iron in lower-risk MDS patients, but both studies also had high rates of discontinuation, mainly due to gastrointestinal, renal, or hepatic toxicities. The potential benefit on the morbidity and mortality of higher-risk patients is uncertain and likely minimal given the overall poor prognosis of these patients. A large, multicenter, placebo-controlled phase III study evaluating deferasirox in IPSS-defined low-risk or intermediate-1-risk MDS patients with a baseline serum ferritin >1000 mcg/L (TELESTO) is currently accruing. Until the results of this study are available, we generally consider iron chelation therapy in patients with lower-risk disease, long life expectancy, and serum ferritin >1000 mcg/L or other clinical evidence of iron overload. There are also emerging data about the use of iron chelation for patients who will proceed to allogeneic stem cell transplantation.

20. What is the role of prophylactic antimicrobial, antifungal, and antiviral agents in patients treated with HMAs?

Routine infectious prophylaxis in patients with MDS has not been studied extensively. A single retrospective study of patients receiving decitabine reported a lower incidence of febrile episodes in patients who were treated with prophylactic oral antimicrobial agents compared to those who were not. Randomized studies evaluating antibacterial and antifungal prophylaxis in leukemia patients rarely included patients with MDS, and those who were included underwent induction chemotherapy rather than treatment with HMAs. In our practice, we give quinolone, posaconazole, and aciclovir prophylaxis to patients with MDS undergoing induction chemotherapy in accordance with current guidelines. In patients treated with HMAs, we reserve quinolone and aciclovir prophylaxis for patients who have severe baseline neutropenia and other risk factors for infection. We also give secondary prophylaxis to patients who have previously had neutropenic fevers or documented infections while on therapy.

Selected reading

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, *et al*. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10:223–32.

Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, *et al*. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003;120:1037–46.

Kantarjian H, Issa J-PJ, Rosenfeld CS, *et al*. Decitabine improves patient outcomes in myelodysplastic syndromes. Cancer. 2006;106:1794–803.

List A, Dewald G, Bennett J, *et al*. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006;355:1456–65.

Passweg JR, Giagounidis AAN, Simcock M, *et al*. Immunosuppressive Therapy for Patients With Myelodysplastic Syndrome: A Prospective Randomized Multicenter Phase III Trial Comparing Antithymocyte Globulin Plus Cyclosporine With Best Supportive Care SAKK 33/99. Journal of Clinical Oncology. 2010;29:303–9.

CHAPTER 17

Management of therapy-related myeloid neoplasms

Jagoda K. Jasielec and Richard A. Larson
The University of Chicago, Chicago, IL, USA

Introduction

Therapy-related myeloid neoplasms (t-MNs) are clonal disorders of hematopoietic stem cells that occur following prior treatment with cytotoxic chemotherapy and/or ionizing radiation. This clinical syndrome is a spectrum of disorders that includes myelodysplastic syndrome (t-MDS), acute myeloid leukemia (t-AML), and myelodysplastic and myeloproliferative neoplasms (t-MDS/MPN). It is distinct from secondary leukemias that arise from antecedent hematologic disorders, such as primary MDS or myelofibrosis, or those leukemias that are second cancers appearing in the absence of prior cytotoxic exposure. t-MNs are estimated to represent approximately 10–20% of all newly diagnosed cases of MDS, AML, MDS/MPN, although the precise incidence is unknown. The latency period between first exposure and development of bone marrow dysfunction varies depending on the specific cytotoxic agents (alkylators, topoisomerase-II inhibitors, antimetabolites, or radiation) used, as well as the intensity and duration of exposure. The outcomes for patients with t-MN are inferior compared to those for patients with primary MDS or de novo AML; the median survival overall is approximately 9–10 months. The causes for increased mortality are many and include a higher incidence of unfavorable cytogenetics, persistence of the primary malignancy, chronic organ injury and poor bone marrow reserve from prior therapies, alloimmunization affecting further transfusion support, as well as chemotherapy resistance related to prior exposures. In this chapter, we discuss the diagnosis and management of t-MN, which are illustrated by commonly encountered scenarios in clinical practice.

Case study 17.1 Presentation with pancytopenia

A 62-year-old man was treated for stage IIIA diffuse, large, B-cell lymphoma with six cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), after which he achieved a complete response. Approximately one year later, his disease relapsed, and he received treatment with R-ICE (rituximab, ifosfamide, cyclophosphamide, and etoposide) followed by filgrastim [granulocyte colony-stimulating factors (G-CSF)] to mobilize autologous stem cells for collection. He underwent an autologous stem cell transplantation following conditioning with BEAM (carmustine, etoposide, cytarabine, and melphalan). His blood counts recovered to normal. Now 4 years later, he presents with macrocytic anemia and thrombocytopenia on routine bloodwork. The peripheral blood smear shows trilineage dysplasia with extensive dysgranulopoiesis (hypogranular neutrophils), poikilocytosis, and oval macrocytes. Bone marrow aspiration and biopsy reveal 7% myeloblasts with myelodysplastic changes. Cytogenetic analysis shows a complex karyotype, including del(5q) and monosomy 7, in the majority of metaphase cells. No lymphoma is seen.

Supported in part by grants CA40046 and CA14599 from the National Cancer Institute of the National Institutes of Health, USA, and from the Cancer Research Foundation.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

• **Who is at risk for t-MN?**

By definition, t-MNs occur after cytotoxic exposures. These neoplasms are thought to be the direct consequence of mutational events induced by the prior therapy. However, the exact role of the cytotoxic exposure in the development of t-MN remains unclear. The possibilities include (i) a mutational event or series of mutations entirely due to the specific DNA-damaging agent, (ii) an entirely stochastic event (i.e., happening by chance), or (iii) a host susceptible to the development of myeloid neoplasms regardless of exposures. Evidence in support of the pivotal role of cytotoxic agents includes characteristic recurring cytogenetic abnormalities induced by specific cytotoxic exposures with unique mechanisms of action. However, various germline genetic factors likely impact an individual's susceptibility to t-MN. The functions of many of the genes known to be involved in hereditary cancer susceptibility, such as *TP53*, *BRCA1*, and *BRCA2*, are in various DNA repair pathways that play an important role in maintaining DNA integrity in the face of damaging exposures, whether natural and environmental or iatrogenic and therapeutic.

t-MN occurs at every age but is more commonly seen in older patients (the median age is about 61 years). Patients at risk include anyone who has previously received chemotherapy or radiotherapy (RT) alone or in combination, with the greatest relative risk observed in those treated with combined-modality therapy. The majority of patients who received RT alone had received radiation to large fields of active hematopoiesis, including the central skeleton and pelvis. Approximately half of t-MN patients have been previously treated for hematologic disorders, about 40% have had solid tumors, and a small fraction were treated for nonmalignant conditions such as autoimmune diseases, or had undergone a solid organ transplant.

• **What agents have been associated with t-MN?**

Alkylating agents are most commonly associated with t-MN, followed by topoisomerase-II inhibitors, such as etoposide and doxorubicin; leukemogenic potency varies between agents. t-MN has also been reported in patients who received mitoxantrone for multiple sclerosis, with an estimated incidence of 0.21%; therapy-related promyelocytic leukemia accounts for 30% of these cases. Other agents associated with therapy-related leukemia include antimetabolites such as fludarabine. Azathioprine has been linked to t-MN after use in solid-organ transplantation or for inflammatory conditions. The routine use of G-CSFs as an adjunct to chemotherapy also increases the risk of t-MN.

• **What are the clinical features of t-MN?**

The clinical presentation of t-MN is variable but generally resembles that of primary MDS or de novo AML. Although sometimes discovered serendipitously during routine follow-up from prior treatments, patients more often present with symptoms related to pancytopenia, including fatigue, fever, infections, easy bruising, and bleeding. The presentation also differs depending on the prior exposures. The latency period for patients previously treated with alkylating agents or RT is typically 5–7 years after the first exposure but may extend to as long as 10 years after the last exposure. In these patients, t-MN most often presents with a more insidious course resembling primary MDS with increasing pancytopenia and bone marrow failure with trilineage dysplasia. In contrast, those who previously received a topoisomerase-II inhibitor have shorter latencies, often only 1–3 years. These patients sometimes present with overt acute leukemia and high white blood cell (WBC) counts.

• **How would you evaluate this patient?**

The diagnosis of t-MN is made based on the assessment of peripheral blood and bone marrow samples. The bone marrow aspirate specimen should be evaluated by flow cytometry and sent for cytogenetic analysis of metaphase cells and molecular diagnostic studies. Although fluorescence in situ hybridization (FISH) assays (using a limited panel of specific DNA probes) will identify some of the more common clonal abnormalities, full karyotyping is strongly recommended. For younger patients who may be candidates for allogeneic hematopoietic cell transplantation (HCT), human leukocyte antigen (HLA) typing should be performed. Marrow blast counts of greater than or less than 20% are sometimes used to divide t-AML from t-MDS, respectively, but have no importance with regard to confirming the diagnosis of t-MN.

Case study 17.2 Recurring clonal chromosomal abnormalities

A 45-year-old woman was diagnosed and treated for limited-stage, "triple-negative" breast cancer with four cycles of adriamycin plus cyclophosphamide followed by paclitaxel and chest wall radiation; G-CSF was given as primary prophylaxis. One year later, she is found to have anemia and a WBC count of 80,000/μl; 95% are monoblasts. Cytogenetic analysis demonstrates 46XX, t(9;11) in 20 out of 20 metaphase cells analyzed from the blood.

• What are the recurring cytogenetic abnormalities associated with t-MNs?

Approximately 80% of patients with t-MNs have clonal cytogenetic aberrations; some are quite complex in nature, involving multiple chromosomes. In several large series, most abnormalities involved loss, deletion, or rearrangement of chromosome 5, chromosome 7, or both. Deletion of the long arm of chromosome 7, or monosomy 7, is often associated with mutations in *RUNX1* and abnormalities of *RAS* or *P53*. Whereas abnormalities of chromosomes 5 and 7 are strongly associated with prior exposure to alkylating agents, cases associated with topoisomerase-II inhibitors more often present with balanced translocations. These include translocations involving the *MLL* gene at chromosome band 11q23, *PML–RARA*, *RUNX1*, *CBFB*, and *NUP98*. Rearrangements associated with RT alone include inv(16) and t(15;17), although loss or deletion of chromosome 5 and/or 7 is more common. Approximately 20% of patients may present with a normal karyotype by conventional cytogenetics but, similar to de novo AML, mutations in *FLT3*, *NPM1*, *RAS*, *MLL*, and *RUNX1* genes may be detected in these cases. Whether these leukemias have arisen de novo, thus representing primary events, rather than from mutations induced by prior cytotoxic therapies is uncertain.

• What are the prognostic implications of cytogenetic abnormalities in t-MN?

Cytogenetic abnormalities are the strongest predictors of outcome in patients with t-MN. The cytogenetic risk stratification used in de novo MDS and AML has similar prognostic value in therapy-related disease, although overall outcomes are generally inferior when compared to de novo AML with the same cytogenetic profile. t-MN patients with t(8;21), inv(16), t(16;16), or t(15;17) carry a more favorable prognosis, whereas those with abnormalities in chromosomes 5 or 7, 11q23, 3q21q26, trisomies 8 or 13, or complex karyotypes carry an unfavorable prognosis. Normal karyotype, t(9;11), and other abnormalities not otherwise listed in the favorable or unfavorable groups are considered intermediate risk. Among patients receiving intensive induction chemotherapy for t-AML, the median survivals in one series for favorable-, intermediate-, and unfavorable-risk groups were 26.7, 15.5, and 5.6 months, respectively.

• What is the optimal treatment for patients with t-MN?

Because patients with t-MN have generally been excluded from large, front-line clinical trials, there is a lack of prospective data on best treatments. Therefore, we encourage enrollment onto clinical trials whenever possible. In cases where a clinical trial is not available, or where patients choose not to participate, treatment strategy should be based on similar factors as in de novo leukemia, taking into account one's age, performance status, underlying comorbidities, and disease characteristics, and heavily weighting any cytogenetic abnormalities. Other unique factors in this population that must be taken into account are persistence of the primary malignancy, a lower hematopoietic stem cell reserve in heavily pretreated patients, and prior alloimmunization to blood products that compromises future supportive care. In general, patients with good performance status and adequate organ and bone marrow function should receive standard AML induction chemotherapy and then be considered for allogeneic HCT. Those with underlying comorbidities or persistent primary malignancy may benefit from supportive care or less aggressive chemotherapy, such as one of the hypomethylating agents. Patients with poor performance status are not good candidates for chemotherapy and may survive longer and better with supportive care alone.

Multiple choice questions

What is the most appropriate treatment for the following patients?

1. A 58-year-old man previously treated for metastatic non-small-cell lung cancer developed t-MN with a complex karyotype. He has a performance status of 3 and is currently not receiving any further treatment for his lung cancer.

A. Standard induction chemotherapy with cytarabine and anthracycline
B. Hypomethylating agent
C. Allogeneic hematopoietic stem cell transplant
D. Supportive care

This patient is likely to have a very poor outcome from induction chemotherapy and short survival given his poor performance status and underlying metastatic malignancy. He should be recommended supportive care with blood products, hydration, and hydroxyurea as needed.

2. A 63-year-old man with diabetes, compensated heart failure, chronic renal insufficiency, and prior combination chemotherapy for diffuse large cell lymphoma developed pancytopenia. Bone marrow exam reveals myelodysplasia with 5% myeloblasts. Cytogenetics reveals a clone with 46XY, del(20q), −7, +8.

A. Standard induction chemotherapy with cytarabine and anthracycline
B. Hypomethylating agent
C. Allogeneic stem cell transplantation in first remission
D. Supportive care

Hypomethylating agents, such as decitabine and azacitidine, have been shown to be effective in some patients with MDS and AML, including those with unfavorable cytogenetics. Although these agents have not been prospectively evaluated in many patients with t-MNs, in one retrospective study of 34 patients with t-MDS and 16 patients with t-AML treated with azacitidine, the overall response rate was 42%, with 21% of patients achieving a complete remission, 4% partial remission, and 17% hematologic improvement. In another series of patients with high- to intermediate-risk MDS treated with azacitidine, the response rate in 61 patients with t-MDS was approximately 43% with a median duration of response of 7.1 months, which was not statistically different from that of other higher risk MDS. This patient has an unfavorable karyotype, and unfortunately he is not a candidate for intensive chemotherapy or stem cell transplantation due to underlying comorbidities. Hypomethylating agents are better tolerated and may still yield a clinical benefit for this patient.

3. A 35-year-old man previously treated for testicular cancer presents with leukocytosis (WBC count: 23,000/μl) and is diagnosed with t-AML with t(8;21).

A. Standard induction chemotherapy with cytarabine and anthracycline followed by high-dose cytarabine consolidation
B. Hypomethylating agent
C. Standard induction chemotherapy followed by allogeneic stem cell transplantation in first remission
D. Supportive care

This patient is young, without underlying comorbidities, and has t-MN with a cytogenetically favorable prognosis. He should be treated with curative intent using standard intensive remission induction chemotherapy followed by high-dose cytarabine consolidation. Hypomethylating agents achieve lower rates of complete response and should be reserved for patients who cannot otherwise tolerate standard chemotherapy. The role of allogeneic transplantation in first remission for t-MN patients with a favorable karyotype, including t(15;17), inv(16), t(16;16), and t(8;21), is controversial due to a paucity of prospective clinical trial data. Following standard induction and consolidation therapies, these patients appear to have comparable response rates to their de novo counterparts. Thus, allogeneic transplantation is usually reserved in the event of relapse. However, all patients should be HLA-typed at diagnosis so that a stem cell donor could be found quickly if necessary.

4. A 52-year-old man was treated for stage IIIB Hodgkin lymphoma 7 years ago with six cycles of escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone) chemotherapy, after which he achieved a complete response without any recurrence. He now presents with newly diagnosed t-MN with leukocytosis (WBC count: 66,000/μl), 80% myeloblasts in the bone marrow, and a normal karyotype by conventional cytogenetics. Molecular analysis demonstrates a mutation in *FLT3* with an internal tandem duplication (ITD).

A. Standard remission induction and consolidation chemotherapy
B. Hypomethylating agent
C. Standard remission induction followed by allogeneic stem cell transplantation
D. Supportive care

The relative importance of an *FLT3* -ITD mutation (either mono-allelic or bi-allelic) in patients with t-MN is unknown. Our first recommendation would be to enroll this patient onto a clinical trial evaluating one of the *FLT3* inhibitors currently under study, either alone or in combination with chemotherapy. Most patients with cytogenetically normal AML with a *FLT3* -ITD mutation will achieve remission after standard induction chemotherapy. However, we would HLA-type the patient and initiate a donor search so that an allogeneic transplant could be considered either early in first remission or in the event of a later relapse.

Case study 17.3 t-MN with more favorable cytogenetics

A 35-year-old man was diagnosed with stage IIB Hodgkin lymphoma and achieved a complete response after six cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) followed by radiation to the residual mediastinal mass. Two years later, he complained of fatigue and was found to have a macrocytic anemia; several blasts were seen in the peripheral blood smear. A bone marrow exam demonstrated AML with 50% myelomonoblasts. Abnormal eosinophils with large blue-black granules were noted. Cytogenetics showed 46XY, inv(16)(p13q22) in 75% of the metaphase cells.

- **What cytogenetic abnormality would you expect in this patient?**

Given the relatively short latency after combined modality therapy, acute presentation, and the presence of characteristic abnormal eosinophils, it is not unexpected that this t-MN patient has an inv(16)(p13q22) resulting in a *CBFB–MYH11* fusion gene. This recurring abnormality is found in about 8% of AML occurring de novo, where it indicates a favorable prognosis. Although sometimes seen in t-MN after RT alone, this rearrangement also occurs after exposure to alkylating agents, topoisomerase-II inhibitors, or combined-modality therapy (as in this case).

- **What is the recommended treatment for this patient?**

He is young, lacks significant comorbidities, and has a cytogenetically favorable prognosis for AML. He should be treated with standard intensive remission induction chemotherapy that includes cytarabine and an anthracycline. Postremission therapy should include several courses of high-dose cytarabine. In one case series, 85% of patients with t-AML with inv(16) achieved a complete remission following standard chemotherapy, which is comparable to response rates in de novo disease. Patients under the age of 55 years had a median survival of longer than 3 years, which supports the utilization of a standard, curative chemotherapy regimen in this patient. In another series of t-MN patients of all ages with an inv(16), the 5-year survival rate after intensive induction and consolidation therapy was 62% compared with 78% ($P = 0.33$) for those with de novo AML and inv(16). Although this young adult might be a candidate for an allogeneic HCT in first remission, it is not clear that this intervention provides any better long-term outcome.

Case study 17.4 Therapy-related acute promyelocytic leukemia

A 30-year-old woman had received mitoxantrone for relapsing multiple sclerosis. She now presents with gum bleeding and bruising. Her WBC count is 2000/μl, and the platelet count is 12,000/μl. Her blood smear demonstrates a small number of malignant promyelocytes. The fibrinogen level is 100 mg/dl, and the international normalized ratio is 1.8.

- **What is the most likely diagnosis?**

Based on her previous treatment with mitoxantrone and the hematologic findings, this woman has most likely developed therapy-related acute promyelocytic leukemia (t-APL). The diagnosis can be confirmed by the presence of t(15;17) with conventional metaphase cytogenetics and/or *PML–RARA* by FISH or a real-time polymerase chain reaction assay.

- **How should this patient be treated?**

We recommend that patients with t-APL should be treated in the same way as those with de novo APL, using either all-trans retinoic acid (ATRA; tretinoin) plus an anthracycline, or ATRA plus arsenic trioxide (ATO) for remission induction. In a review of 106 cases of t-APL, the rate of complete response was 87% in patients who received ATRA-based therapy. Of those who achieved a complete response, only 10% relapsed. The 8-year survival was estimated to be 59%, and this statistic included those patients who died before receiving therapy. In a smaller study of 51 patients with t-APL treated with the AIDA regimen of ATRA plus idarubicin, the rates of complete response, leukemia-free survival, and overall survival were similar to those of patients with de novo APL (97% vs. 93%, 65% vs. 68%, and 85% vs. 78%, respectively). Recent data suggest that omitting cytotoxic chemotherapy and treating with only ATRA plus ATO alone may be more tolerable and yield comparable rates of complete response (89% vs. 70%) and similar overall survival compared to t-APL patients treated with ATRA and an anthracycline. In a recent review from the Mayo Clinic, patients with t-APL treated with ATRA and ATO had significantly lower rates of complete response compared to those with de novo APL (64% vs. 93%). However, this was attributed to a higher induction mortality rate in t-APL (36% vs. 8%). Among those patients who achieved a complete response, none relapsed.

Multiple choice answers

Question 1: Answer D
Question 2: Answer B
Question 3: Answer A
Question 4: Answer C

Selected reading

Godley LA, Larson RA. Therapy-related myelodysplastic syndrome and myeloid leukemia. In: Steensma DP, editor. Myelodysplastic syndrome: pathology and clinical management. New York: Informa Healthcare; 2008. p. 173–194.

Itzykson R, Thépot S, Quesnel B, *et al*. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood. 2011;117(2):403–11.

Larson, RA. Cytogenetics, not just previous therapy, determines the course of therapy-related myeloid neoplasms. J Clin Oncol. 2012;30(19):2300–2.

Larson, RA. Etiology and management of therapy-related myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2007;453–9.

Swerdlow SH, Campo E, Harris NL, *et al*. World Health Organization classification of tumors of hematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.

CHAPTER 18

Hematopoietic cell transplantation in myelodysplastic syndromes

Antonio Di Stasi, Armin Ghobadi, and Partow Kebriaei

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 18.1

The patient is a 65-year-old Caucasian male, in good health, with a coincidental finding of neutropenia [absolute neutrophil count (ANC): $1.07 \times 10^3/\mu L$] and macrocytic anemia [hemoglobin (Hgb): 10.5 g/dL; mean corpuscular volume (MCV): 102 fL]. He reports no known prior exposure to toxins. His other laboratory parameters, including platelet (PLT) and absolute reticulocyte counts, iron studies, and serum erythropoietin (EPO), red cell folate, and copper levels, were all unremarkable. However, since his plasma vitamin B_{12} level was slightly below the lower normal limit, he was given vitamin B_{12} supplementation without improvement in his macrocytic anemia. Additionally, his test for HIV was negative. Bone marrow biopsy revealed a bone marrow with low cellularity for age (20%), with 9% blasts, abnormal nuclear lobulation of granulocytes, normal iron stores, and no increase in reticulin. His karyotype did not reveal any cytogenetic abnormalities. Finally, his flow cytometry analysis excluded large granular lymphocytic disease and paroxysmal nocturnal hemoglobinuria. The patient is sent to your hematopoietic stem cell transplantation (HSCT) clinic for evaluation for transplant.

- **What is the best next step in management?**

This patient is affected by myelodysplastic syndrome (MDS), which is consistent with refractory anemia with excess blasts-2 (RAEB-2) and an International Prognostic Scoring System (IPSS) score of 1.5 (intermediate-2). The IPSS is based on the percentage of blasts, number of cytopenias and cytogenetics, and median survival ranges from 5.7 years for low risk (IPSS: 0) to 0.4 years for high risk (IPSS: 2.5–3.5), while the 25% estimated progression to acute myeloid leukemia (AML) ranges from 9.4 to 0.2 years, respectively. Allogeneic HSCT is the only curative modality for MDS. However, for patients with low-risk and intermediate-1 MDS, delayed HSCT maximizes overall survival, whereas for patients with intermediate-2 and high-risk MDS, HSCT at diagnosis maximizes overall survival, with 35–50% long-term disease-free survival. For patients in the intermediate-1 or low-risk group, a transplant is to be considered in the case of development of poor risk factors, such as low performance status, advanced age, a drop in blood counts, an increased number of blasts, cytogenetic abnormalities, or failure to respond to hypomethylating agents. Our patient is an ideal candidate for HSCT: age range <75 years, IPSS: 1.5, Karnofsky performance status: 90%, and no comorbidities. Furthermore, he has no uncontrolled infections at present, and organ functions are appropriate. Importantly, high-resolution human leukocyte antigen (HLA) typing revealed that one sibling was fully matched with the patient.

- **Is induction therapy indicated prior to transplant? And if so, what is the optimal induction regimen?**

The American Society for Blood and Marrow Transplantation (ASBMT) has not provided recommendations regarding the optimal intensity of the induction regimen, such as high-

Authors' disclosure: The clinical cases in this chapter do not refer to actual patients. All of the recommendations are in accordance with the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) "Myelodysplastic Syndromes," version 2.2013, unless otherwise specified.

Acknowledgments: A.D. is thankful to Drs. S-K. Tey and L-M. Poon for scientific critical discussions.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

intensity chemotherapy (AML-like) or milder, hypomethylating agents before HSCT. Published data seem to favor a transplant performed with minimal burden of disease, especially in reduced-intensity conditioning (RIC) regimens that most heavily rely on the graft-versus-leukemia (GVL) effect. One possible "bias" is that remission induction selects responsive patients. Some data show that induction therapy may not be associated with superior outcome; however, this may be related to the stage of disease and/or cytogenetic risk, which are "critical" in reporting and analyzing results in HSCT clinical trials involving a biologically heterogeneous disease such as MDS. Therefore, randomized clinical trials or more homogeneous series are needed to answer this question. In addition, the optimal debulking therapy is an area of debate. There are limited data to conclude whether therapy with hypomethylating agents is superior to cytotoxic induction chemotherapy, although one interesting publication by Gerds *et al*. (2012) showed that 5-azacytidine compared with induction chemotherapy prior to HSCT was associated with a better one-year overall survival rate (57 vs. 36%, $P = 0.24$), lower nonrelapse mortality, and a lower relapse rate, but only the hazard for relapse was significantly lower. However, after adjustment for cytogenetic risk, IPSS score, and donor, the rates of post-HCT relapse for the two cohorts were similar. It also seems that an allogeneic HSCT performed earlier in the course of disease leads to better outcomes. For this patient, we decided to adopt cytoreductive therapy with 5-azacytidine, and restaging performed after the first cycle showed complete remission of disease. Peripheral blood hematopoietic stem cells from the matched related donor were collected and cryopreserved.

• **What is the most appropriate intensity of the transplant conditioning regimen?**

The lower relapse rate of myeloablative conditioning (MAC) regimens is counterbalanced by a higher degree of regimen-related toxicity and transplant-related mortality (TRM) precluding this option for older patients, who are frequently affected by MDS–AML. Although large retrospective studies have reported comparable results between MAC and RIC regimens in MDS (and AML), randomized controlled trials are undergoing comparing MAC and RIC regimens (e.g., NCT01339910). Although this study is based on a few different regimens, its results will shed light on this controversy. Alatrash *et al*. (2011) have previously demonstrated that the development of a busulfan–fludarabine MAC regimen with low TRM allowed transplantation in patients through the eighth decade of life. This patient received a matched related donor HSCT after a MAC regimen. We used peripheral blood hematopoietic progenitor cells that are granulocyte colony-stimulating factor mobilized; these cells have been associated with survival benefit, as compared with bone marrow progenitor cells, in patients undergoing MRD–HSCT for myeloid malignancies. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and mini-dose methotrexate.

Case study 18.2

A 56-year-old man presents to the clinic with anemia (Hgb: 8.2g/dL; MCV: 96fL). His ANC was $1.0 \times 10^3/\mu L$, but PLT counts and the EPO level were within normal limits. A bone marrow biopsy showed a hypercellular marrow with increased red cell precursors, consistent with refractory cytopenia with multilineage dysplasia. Fluorescent in situ hybridization (FISH) analysis revealed del(5q) (IPSS: 0.5). He was treated with lenalidomide for 2 years, and had an erythroid response with an increase in Hgb level to 13g/dL. However, at his next follow-up his counts dropped, with an ANC of $0.45 \times 10^3/\mu L$ and no blasts in the peripheral blood; Hgb was 7.5g/dL and MCV was 104fL. The PLT count was $20 \times 10^3/\mu L$, requiring blood product transfusion support. The bone marrow biopsy aspirate revealed 11% blasts, with a FISH analysis revealing del(5q) and monosomy 7. The ferritin level was found to be elevated at >2500ng/mL.

• **What is the most appropriate next step in management?**

Lenalidomide has proved effective in MDS with del(5q), where about two-thirds of patients become transfusion independent, with a median response duration of 2.2 years. It has also been shown to be effective in non-del(5q) MDS. However, in this patient with progressive disease, as evidenced by cytogenetic progression and worsened cytopenias, it is now reasonable to consider HSCT. The ferritin level was found to be markedly elevated, and apart from red blood cell transfusions, the release of toxic iron radicals by the treatment itself or ineffective hematopoiesis leads to growth factor (GDF15) overexpression, which inhibits hepcidin and iron absorption. We do not routinely use iron-chelating agents prior to transplant; however, it is important to reduce the usage of glutathione-depleting agents, such as acetaminophen, in the early posttransplant period to minimize liver toxicity. Elevated ferritin levels pre-HSCT have been recognized as a poor prognostic factor in patient receiving HSCT. Thus, during the posttransplant period, phlebotomy or iron chelation in patients with high ferritin levels and tissue iron deposition, as evaluated by magnetic resonance imaging, may be useful to consider.

A donor search was performed, and a matched related or matched unrelated donor was not identified. In the interim,

(*Continued*)

the patient suffered repeated infectious episodes. A donor search finally identified two HLA 4/6 (B, C, DRB1 matches) umbilical cord blood (UCB) units with a combined cell dose of 1.5×10^7 nucleated cells/kg. A related haploidentical donor was also identified. Donor anti-HLA antibody testing revealed antibodies detected against the B allele of one UCB unit.

• What is the best donor to use for transplant?

If a matched related or matched unrelated donor is unavailable, transplant from a UCB or haploidentical donor is reasonable in very high-risk cases. Results from randomized trials are not yet available in guiding this choice. Two parallel phase II trials studying RIC alternative-donor HSCT, in acute leukemias and lymphomas, showed that although NRM was higher after UCB transplantation (UCBT; UCB 24% vs. haploidentical 7%), the relapse rate was higher with haploidentical HSCT (UCB 31% vs. haploidentical 45%). The one-year DFS was comparable at 45%. The two modalities are undergoing randomized comparison in a Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) trial (NCT01597778). To note, at least one retrospective study has shown comparable survival among UCBT and matched unrelated donor HSCT as well as in acute leukemias. However, currently there are limited data regarding AML–MDS to draw any definitive conclusion. The main non-HLA favorable factors to consider when choosing a donor are cytomegalovirus (CMV)-negative serology (for CMV-negative patients), male sex, younger age, ABO compatibility, lower parity in female donors, and larger body weight. Regarding HLA factors, one study showed that single mismatches at HLA-B or -C were better tolerated than mismatches at HLA-A or DRB1 in UCBT (relative risk for survival: 1.18; 95% confidence interval: 1.01–1.37; $P = 0.04$). Noninherited maternal HLA matching has been associated with lower treatment-related mortality and higher overall survival. However, this matching requirement may delay transplantation.

Considering the remission state of disease, the infectious risk of our patient, the cell dose of the UCB units available, and the presence of anti-UCB donor HLA antibodies (the latter associated with graft failure), we decided to proceed with haploidentical HSCT rather than UCBT. For haploidentical HSCT, we used a T-cell-replete marrow graft followed by in vivo T-cell depletion with cyclophosphamide after transplant; tacrolimus and mycophenolate mofetil were additionally used for GVHD prophylaxis. This approach, pioneered by the Johns Hopkins group and replicated at MD Anderson Cancer Center, appears to result in effective GVHD control and better immune reconstitution, resulting in improved overall survival as compared with traditional T-cell-depleted haploidentical HSCT.

Case study 18.3

You are the attending physician of a stem cell transplantation unit, and you are consulted by the lymphoma department about a 46-year-old female initially diagnosed with stage IIIA Hodgkin lymphoma 7 years ago. She achieved complete remission (CR) after six cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). She was doing fine until 3 months ago, when she developed gradually worsening shortness of breath. Her ANC was $1.2 \times 10^3/\mu L$, Hgb: 9.7 g/dL, MCV: 95 fL, and PLT: $90 \times 10^3/\mu L$. The bone marrow biopsy showed normal cellularity, 6% myeloblasts, and multilineage dyspoiesis with no evidence of involvement by Hodgkin lymphoma. Cytogenetic analysis showed a complex karyotype with multiple abnormalities, including monosomy 7 and monosomy 5. Whole-body positron emission tomography showed no evidence of Hodgkin lymphoma. Her Eastern Cooperative Oncology Group (ECOG) performance score was 1, without significant comorbidities.

• How would you choose between standard chemotherapy versus HSCT?

The patient is affected by secondary MDS resulting from previous chemotherapy with alkylator agents. Secondary MDS is a disease that develops following prior immunosuppressive or cytotoxic therapy, or as evolution from an antecedent hematologic disorder (such as inherited bone marrow failures or aplastic anemia). Secondary MDS is an absolute indication for allogeneic HSCT, in light of the poor prognosis of this disease, regardless of IPSS (or revised IPSS) score. Molecular characteristics of the disease are sought to potentially more precisely allow prognostication. Because the risk of relapse is still high, especially in high-risk MDS–AML, new therapeutic strategies are warranted. Interestingly, preliminary results from heavily pretreated patients have shown that *WT1* passive immunotherapy is able to induce durable responses in relapsed AML–MDS. Thus, both active and passive adoptive immunotherapy clinical trials need to be encouraged, as they may positively affect the natural history of the disease.

Case study 18.4

A 36-year-old man was diagnosed with MDS after prodromal episodes of abdominal pain, and intermittent cytopenias (Hgb: 8 g/dL; PLT: $60 \times 10^3/\mu L$; and ANC: $0.5 \times 10^3/\mu L$). A bone marrow biopsy showed hypocellularity (12%), with 8% blasts, multilineage dysplasia, and increased reticulin staining. The patient has remained transfusion independent. Cytogenetics showed monosomy 7, and an HLA–MRD was not available. The patient was started on treatment with antithymocyte globulin and cyclosporine without response. The patient does not have any relationship with his one living sibling.

- **What is the most appropriate management?**

Hypoplastic MDS offers an intriguing problem in terms of diagnosis and treatment. Because it is characterized by poor prognosis, hypocellular MDS is regarded in many centers as an indication for early allogeneic HSCT, especially in younger individuals with an available matched related or matched unrelated donor. The presence of monosomy 7 or increased fibrosis is associated with poor prognosis as well.

An unrelated donor search was started. However, considering the high risk of disease, expectant management would not be warranted. Considering the tempo to HSCT, our patient was enrolled on a clinical trial with SB939 (hydroxamic acid–based histone deacetylase inhibitor) in combination with 5-azacitidine for two cycles with complete remission. A matched unrelated donor was not found; however, two 4/6 (HLA B, C, DRB1 matches) UCB stem cell sources were identified, with a total cell dose of 5.3×10^7 nucleated cells/kg. Furthermore, the patient consented to proceed with an unrelated UCB transplant after a MAC regimen, and GVHD prophylaxis consisted of antithymocyte globulin, tacrolimus, and mycophenolate mofetil. Significant progress has been made in UCBT, especially in regard to more rapid engraftment and faster immune reconstitution.

Case study 18.5

You are consulted on the leukemia floor regarding an 18-year-old patient treated elsewhere with a 7/8 matched unrelated donor HSCT for secondary MDS with MLL (myeloid–lymphoid) gene rearrangement. She had received treatment, including etoposide, 6 months earlier for Ewing sarcoma. Her posttransplant period was complicated by *Pseudomonas aeruginosa* lung infection resolved after antibiotic therapy. She remained on standard post-HSCT antimicrobial prophylaxis and tacrolimus targeting a plasma level of 5 to 10 ng/mL. Sixty days post-transplant, she presented to the emergency department with a maculopapular skin rash involving <50% body surface area, abdominal pain, and diarrhea more than 1000 mL/daily. She was admitted to the floor and resuscitated with intravenous fluids, and symptomatic management was implemented. Stool cultures were negative, including *Clostridium difficile* toxins. Endoscopy revealed an erythematous colon mucosa, and histology reported GVHD grade 3/4 in both skin and colon biopsies.

- **What is the most appropriate initial treatment?**

The patient is affected by acute GVHD (aGVHD) grade III, and was treated with topical steroids and systemic methylprednisolone 2 mg/kg/day, with resolution of the symptoms and signs of aGVHD on day 3 post-treatment. She was maintained also on tacrolimus, and her steroids were tapered starting day 6 from treatment initiation.

Topical steroids is an appropriate choice for skin aGVHD up to stage II (<50% body surface area). For higher stages and/or visceral aGVHD, treatment with methylprednisolone at 2 mg/kg/day or prednisone at 2.0 to 2.5 mg/kg/day has long been accepted as a standard first-line systemic therapy, as recently published in ASBMT guidelines. An exception is aGVHD of the upper gastrointestinal tract, which is more responsive to lower-dose systemic corticosteroids and topical steroid therapy. Although ursodiol is commonly used as adjunct therapy in the prophylaxis or therapy of liver GVHD, combined treatment with multiple agents should be limited to patients who agree to participate in well-designed phase II or phase III studies. The optimal rate for tapering steroid doses has not been defined. Tapering of steroid doses should begin as soon as aGVHD manifestations show major improvement. Inappropriately rapid taper rates carry a risk of aGVHD exacerbation or recurrence, whereas inappropriately slow taper rates increase the risk of steroid-related complications. The taper schedules provided in national multicenter trials for aGVHD, such as BMT–CTN 0302 and 0802, reflect current practice. The aggregated results of standard treatment with prednisone showed an overall CR rate of 48%, an overall CR and partial remission rate of 64%, and a weighted 6-month survival estimate of 0.66, and therefore alternative strategies are explored in refractory patients.

(*Continued*)

Evaluation of response rate and survival does not support or exclude any of the agents tested as second-line therapy thus far, namely, mycophenolate mofetil, denileukin diftitox, extracorporeal photopheresis, pentostatin, antithymocyte globulin, alemtuzumab, infliximab, etanercept, and sirolimus. Prospective trials, or validated prognostic factors and new treatments, will allow improvement of the outcome of steroid-refractory GVHD. Cellular therapies in the form of donor T cells can be modified to express a suicide gene such that GVL can potentially be augmented while GVHD is abrogated. T-regulatory cells, which have a direct immunosuppressive effect, and mesenchymal stromal cells (which have immunomodulatory and reparative effects), are under intense investigation and hold great promise.

Selected reading

Bejar R, Stevenson K, Abdel-Wahab O, *et al*. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364(26):2496–506.

Cutler C. Patient selection for transplantation in the myelodysplastic syndromes. Hematol Oncol Clin North Am. 2010;24(2):469–76.

Cutler CS, Lee SJ, Greenberg P, *et al*. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104(2):579–85.

Raaijmakers MH, Mukherjee S, Guo S, *et al*. Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Nature. 2010;464(7290):852–7.

CHAPTER 19

Acquired aplastic anemia

Valeria Visconte and Ramon V. Tiu
Cleveland Clinic, Cleveland, OH, USA

Case study 19.1

A 34-year-old female is complaining of increased skin bruising, dyspnea on exertion, palpitations, and petecchiae for a duration of 2 weeks. Her vital signs are significant for tachypnea (respiratory rate = 23), tachycardia (heart rate = 118 beats/min), and fever (102 °F). On physical examination, she has blood blisters in her mouth, and small petecchiae and ecchymoses on both lower extremities; the patient has no palpable lymphadenopathies or organomegalies. A complete blood count (CBC) shows a hemoglobin (Hgb) of 7.8 g/dL, a mean corpuscular volume (MCV) of 102 fL, a leukocyte [white blood cell (WBC)] count of 800/μL, an absolute neutrophil count (ANC) of 215/μL, an absolute lymphocyte count (ALC) of 600/μL, and a platelet (PLT) count of 9000/μL. Her absolute reticulocyte count (ARC) is 23,000/μL. A bone marrow (BM) biopsy is performed and shows a BM cellularity of <5% with some mild erythroid dysplasia. The megakaryocytes are absent with no dysplastic changes. Metaphase cytogenetics (MC) shows no growth. The fluorescence in situ hybridization (FISH) for MDS is unremarkable. The patient is concerned that she has myelodysplastic syndrome (MDS) and would like to know if there is another test that can help clarify her diagnosis.

1. Which laboratory technique may be helpful to clarify the patient's diagnosis?

A. Spectral karyotyping
B. Paroxysmal nocturnal hemoglobinuria (PNH) flow cytometry
C. Testing for a *JAK2V617F* mutation
D. Single nucleotide polymorphism array (SNP-A) karyotyping

An important variant of MDS called hypocellular MDS can present with a hypocellular BM similar to aplastic anemia (AA) as well as other clinicopathologic features of MDS. Morphologic criteria for MDS and persistent cytogenetic abnormalities characteristic of MDS, including −7 and −7q, can be helpful in differentiating between both diseases (Maciejewski and Selleri 2004). However, the distinction between AA and hypocellular MDS can be sometimes difficult. This is especially true in cases of minimal dysplasia with no other overt morphologic MDS-related changes and when the MC and FISH for MDS show a normal karyotype. A study using SNP-A karyotyping showed chromosomal abnormalities in 30% of AA patients with previously normal karyotype by MC at presentation (Afable *et al*. 2011). This technique may be useful in distinguishing between hypocellular MDS and AA (Afable *et al*. 2011). Flow cytometry to quantify the percentage of granulocytes, monocytes, and red cells deficient in glycosyl-phosphatidylinositol (GPI)-linked proteins (CD55, CD59, CD14, CD24, and CD52) can be used to diagnose the presence of PNH. Although PNH clones are more frequently found in AA patients, they also can be found in MDS patients and they are not helpful in differentiating between hypocellular MDS and AA. *JAK2V617F* mutations are primarily seen in myeloproliferative neoplasms (MPNs) and are less commonly found in MDS. Spectral karyotyping is a molecular cytogenetic technique that utilizes fluorophores binding to each chromosome to identify structural chromosomal abnormalities in cancer cells. Its clinical application in AA is still unclear.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

2. She also inquired about whether she may have an inherited type of AA. What additional tests may be helpful to exclude congenital causes of AA?

A. Chromosome breakage testing with mitomycin C
B. Chromosome breakage testing with diepoxybutane
C. Telomere length (TL) measurements
D. All of the above

The majority of AA patients, regardless of age, have acquired idiopathic immune-mediated AA (Visconte 2012; Young 2005). However, a small proportion of patients has inherited AA. Most cases of inherited AA are due to Fanconi anemia (FA), dyskeratosis congenita (DC), Shwachman–Diamond syndrome, and amegakaryocytic thrombocytopenia and are diagnosed between the ages of 2 and 5 years. FA is the most common type of inherited AA (Alter 2007). Patients can present with congenital malformations, early cancers, and variable degrees of cytopenias. The diagnosis is made based on the presence of increased chromosome breakage in lymphocytes cultured with either mitomycin C or diepoxybutane. DC is commonly associated with the triad of leukoplakia, dystrophic nails, and a hyperpigmented rash. However, the vast majority of patients do not have these clinical features. Clinical history and physical examination for associated anomalies together with genetic testing can be helpful in the diagnosis of some cases. TL analysis can also be helpful in some cases with a strong clinical suspicion. The finding of TL <1 percentile for age in three different lymphocyte subsets may be useful in the diagnosis.

Case study 19.2

A 54-year-old man is evaluated for fatigue and intermittent dyspnea. On physical examination, he has small petecchiae on both lower extremities; the rest of the examination is unremarkable. CBC shows a Hgb of 8.0 g/dL, MCV of 92 fL, a (WBC) count of 1000/μL, with an ANC of 300/μL and a PLT count of 13,000/μL. No blasts are detected. A BM biopsy shows a BM cellularity of 10%, 0% blasts, and no evidence of dysplasia. His megakaryocytes are decreased and normal in morphology. Standard metaphase karyotyping shows 46XY.

1. What is the best treatment approach for this patient?

A. Horse antithymocyte globulin alone
B. Alemtuzumab
C. Horse antithymocyte globulin plus cyclosporine
D. Rabbit antithymocyte globulin plus cyclosporine

The treatment strategy for patients with AA depends on the patient's age and disease severity at presentation. In younger patients (<40 years old), a matched-sibling allogeneic hematopoietic cell transplant (MS-allo-HCT), if available, is the recommended therapeutic approach; while for older patients (>40 years of age) or for younger patients with no MS donors, the preferred approach is to give immunosuppressive therapies (ISTs). ISTs used in AA include antithymocyte globulin (ATG), cyclosporine (CsA), alemtuzumab, and cyclophosphamide. The best studied and most effective regimen is a combination of ATG plus CsA. A long-term study (a median follow-up of 11 years) of AA patients treated with ATG plus CsA showed overall response rates of 60–80%, an overall survival rate of 58%, a relapse rate of ~35%, and a risk of clonal evolution of 6–15%. Two preparations of ATG derived from different host animals (rabbit and horse) are available that stimulate different T-cell antigens (Risitano 2012). Both formulations are available in the United States. Horse ATG (hATG) plus CsA is the preferred IST for the front-line treatment of newly diagnosed severe AA patients, and it leads to response rates of 60–75%, with higher responses in younger patients (60–75%) compared to adults (~50%). The standard protocol uses a dose of 40 mg/kg/day of hATG for 4 days. A second preparation of ATG in the form of rabbit ATG (rATG) is also currently available. It is given at a dose of 3.5 mg/kg/day intravenously (IV) for 5 days while CsA is given at 12–15 mg/kg in divided doses twice daily. Both agents are potent at inducing lymphotoxicity. A randomized study showed that hATG plus CsA is superior to rATG plus CsA in terms of response rate (68% vs. 37%; $P < 0.001$) and survival rate at 3 years (96% vs. 76%; $P = 0.04$), excluding stem cell transplantation, and without censoring eventual stem cell transplantation (94% vs. 70%; $P = 0.008$) at 6 months. Further studies also showed that rATG was inferior to hATG. Response rates and time to response are better with hATG plus CsA compared to hATG alone in severe AA patients (65% vs. 31%, $P = .011$; 60 vs. 82 days, $P = .019$). Conversely, the response rate to single-agent alemtuzumab is only 19% in the treatment of naïve severe AA.

2. Which clinicopathological factors can predict for response to IST in severe AA patients?

A. Age >40 years old
B. Short telomeres
C. Presence of a PNH clone
D. ANC of >200/μL

IST using ATG with CsA can benefit two-thirds of newly diagnosed severe AA patients. Several factors that can influence response to IST in AA patients have been studied. Multivariate analysis showed improved response rates to IST in patients who have one or more of the following clinical findings: (i) younger age (<18 years old), (ii) baseline ARC of ≥25,000/μL, (iii) baseline ALC of ≥1000/μL, and/or (iv) short telomeres.

Case study 19.3

A 60-year-old female presented with neutropenic fever and epistaxis. Work-up was consistent with a diagnosis of severe AA. She was successfully treated with hATG and CsA and achieved a complete hematologic response. She was maintained on CsA 125 mg twice daily orally, but she decided to stop her dose abruptly without consulting her hematologist 7 months into her treatment. Three months after stopping her CsA treatment, she developed multiple petecchiae in both her lower extremities and palpitations. Her CBC showed a Hgb of 6.8 g/dl, an MCV of 90 fL, and a (WBC) count of 920/μL, with an ANC of 167/μL and a PLT count of 11,000/μL. A BM biopsy showed findings consistent with relapsed AA. She has no matched sibling or unrelated donors.

1. Which pharmacologic therapies can be used as a salvage treatment for her relapsed AA?

A. Single-agent alemtuzumab
B. Rabbit ATG plus cyclosporine
C. Both
D. None of the above

Approximately 30% of severe AA patients who have been successfully treated with IST can relapse. This is particularly true in patients who abruptly discontinue their CsA dose. Patients with relapse severe AA who do not have suitable BM donors can still be successfully salvaged with other IS regimens. Single-agent alemtuzumab given at 10 mg/dose/day via IV infusion over 2 hours for 10 days resulted in response rates of 56%, while rabbit ATG with CsA given at a dose of 3.5 mg/kg/day IV for 3 consecutive days together with CsA led to responses in 50–70% of patients.

2. Patients with relapsed or refractory severe AA treated with alemtuzumab are at increased risk for which of the following?

A. Clinically significant cytomegalovirus (CMV) Epstein–Barr virus (EBV) reactivation with disease
B. Clinically significant EBV reactivation with disease
C. Subclinical CMV reactivation
D. Subclinical EBV reactivation
E. A and B
F. C and D

Patients who had primary infection with CMV and EBV in the past are at risk for reactivation and subsequent disease development. This is particularly true in patients who receive IS agents. Alemtuzumab is a potent lymphotoxic agent that can deplete both T- and B-lymphocyte populations. Subclinical reactivations for both CMV (21%) and EBV (92%) can occur in seropositive patients treated with alemtuzumab; however, no EBV or CMV disease developed.

Case study 19.4

A 44-year-old male was diagnosed with AA 6 months prior. He was treated with standard-dose hATG and CsA but did not achieve any hematologic response. The decision was made to initiate eltrombopag.

1. What type of response can the patient expect from this treatment?

A. Improvement in Hgb
B. Improvement in ANC
C. Improvement in PLT
D. All of the above

Eltrombopag is an orally bioavailable nonpeptide thrombopoietin (TPO) agonist. It interacts selectively with the TPO receptor inducing the JAK–STAT signaling and the differentiation of the megakaryocytes. It is currently approved by the US Food and Drug Administration for the treatment of patients with immune thrombocytopenic purpura and hepatitis C–associated thrombocytopenia. A phase II trial was conducted in patients with refractory AA treated with eltrombopag. The patients received a starting dose of 50 mg orally daily, which was escalated by 25 mg increments every 2 weeks to a maximum of 150 mg orally daily (Olnes *et al*. 2012).

2. Is there a concern for the development of increased BM fibrosis in refractory AA patients treated with eltrombopag?

A. Yes
B. No

TPO agonists have been shown to induce reversible BM fibrosis in animals. This is probably mediated by increased levels of transforming growth factor beta-1. A small proportion (<5%) of patients with immune thrombocytopenic purpura developed increased reticulin fibrosis in the BM after treatment with romiplostim and eltrombopag. Discontinuation of the TPO agonists led to resolution of reticulin fibrosis, and no case of myeloproliferative neoplasms progression was noted. In lower-risk MDS patients, no cases of BM fibrosis were noted in patients treated with romiplostim. Similarly, there was no increased BM fibrosis noted in patients with refractory severe AA who received eltrombopag (Olnes *et al*. 2012).

Case study answers

Case study 19.1

Question 1: Answer D
Question 2: Answer D

Case study 19.2

Question 1: Answer C
Question 2: Answer B

Case study 19.3

Question 1: Answer C
Question 2: Answer F

Case study 19.4

Question 1: Answer D
Question 2: Answer B ("No")

Selected reading

Afable MG, 2nd, Tiu RV, Maciejewski JP. Clonal evolution in aplastic anemia. Hematology Am Soc Hematol Educ Program. 2011;2011:90–95.

Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. Hematology Am Soc Hematol Educ Program. 2007;29–39.

Marsh JC, Bacigalupo A, Schrezenmeier H, *et al*. Prospective study of rabbit antithymocyte globulin and cyclosporine for aplastic anemia from the EBMT Severe Aplastic Anaemia Working Party. Blood. 2012;119:5391–6.

Olnes MJ, Scheinberg P, Calvo KR, *et al*. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2012;367:11–19.

Visconte V, Tiu RV. Rare bone marrow failure conditions. In: Raghavan D, Blanke C, Johnson DH, *et al*., editors. Text of uncommon cancer. 4th ed. Hoboken, NJ: Wiley-Blackwell; 2012. p. 627–35.

PART 4

Myeloproliferative Neoplasms

CHAPTER 20

Diagnostic approach in myeloproliferative neoplasms

Ayalew Tefferi
Mayo Clinic, Rochester, MN, USA

Introduction

Contemporary diagnosis in myeloproliferative neoplasms (MPNs) is according to the World Health Organization (WHO) system, which is primarily based on morphology but also includes information from cytogenetic and molecular studies. The WHO recognizes five major categories of myeloid malignancies: acute myeloid leukemia (AML), myelodysplastic syndromes (MDSs), myeloproliferative neoplasms, MDS–MPN overlap, and *PDGFR*- or *FGFR1*-rearranged myeloid and lymphoid malignancies associated with eosinophilia (Table 20.1). This chapter focuses on the WHO category of MPN that includes eight subcategories: chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis (SM), chronic eosinophilic leukemia-not otherwise specified (CEL-NOS), chronic neutrophilic leukemia (CNL), and MPN unclassifiable (MPN-U).

1. What are the typical clinical presentations of MPN?

The presence of MPN is usually suspected when a patient presents with peripheral blood (PB) cytosis (e.g., granulocytosis, erythrocytosis, thrombocytosis, and eosinophilia) or bone marrow (BM) mastocytosis. However, monocytosis or myeloid blastosis is usually a characteristic feature of MDS–MPN and AML, respectively, and not MPN. In addition, patients with MPN might also display marked splenomegaly (in PMF and CML); thrombo-hemorrhagic complications (PV, ET, and PMF); microvascular symptoms of erythromelalgia, paresthesia, and lightheadedness (PV and ET); pruritus (PV and PMF); profound constitutional symptoms and cachexia (PMF and CML); urticaria pigmentosa (SM); vasodilatory symptoms, including syncope (SM); symptoms of leukostasis (CML and CNL); anemia (PMF, CEL-NOS, CML, and SM); eosinophilic organopathy (CEL-NOS); and recurrent miscarriage (ET).

2. What are the disease-causing mutations in MPNs?

MPNs as a group represent clonal hematopoietic stem cell diseases, and all of them display abnormal myeloproliferation. The disease-causing mutations are unknown in most cases, with a few exceptions. *BCR–ABL1* is recognized as the disease-causing mutation in CML. In PV, ET, and PMF, the majority of patients harbor *JAK2* mutations, but their precise pathogenetic contribution is not clearly understood, although their presence appears to be a prerequisite for the phenotype of erythrocytosis. Similarly, *KIT* and *CSF3R* mutations are present in virtually all cases of SM and CNL, respectively, and their pathogenetic role is currently being investigated. In addition, many other nonspecific mutations are present across all the disease categories of MPN, including mutations involving *MPL*, *LNK*, *CBL*, *TET2*, *ASXL1*, *IDH*, *IKZF1*, *EZH2*, *DNMT3A*, *TP53*, *SF3B1*, *SRSF2*, and *SETBP1*. Clonal myeloproliferation in MPNs is accompanied by variable degrees of reactive inflammatory states with aberrant cytokine expression; bone marrow stromal changes, including collagen fibrosis and angiogenesis; and extramedullary hematopoiesis mainly involving the spleen and liver but also other organs.

3. How important is morphology in the diagnosis of MPNs?

Bone marrow morphology is the cornerstone of specific diagnosis in MPNs. According to the WHO system, the percentage of blasts in the BM or PB constitutes the first step to classify all myeloid malignancies as AML or chronic myeloid malignancy. AML is defined by the presence of ≥20% blasts in the BM or PB. AML can also be diagnosed

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

in the presence of <20% blasts if cytogenetic studies reveal t(8;21)(q22;q22), inv(16)(p13.1q22), t(16;16)(p13.1;q22), t(15;17)(q22;q12), or in the presence of extramedullary tumor consisting of myeloid blasts (i.e., granulocytic sarcoma).

Once AML is ruled out, the next step is to determine the presence or absence of morphologic dysplasia, including dyserythropoiesis or dysgranulopoiesis, in order to classify the process as MDS or MDS–MPN versus MPN. In MPN, there should be no or minimal cellular dysplasia. MDS is distinguished from MDS–MPN by the absence of peripheral blood cytosis. In other words, MDS–MPN overlap is characterized by the presence of both dyserythropoiesis–dysgranulopoiesis and granulocytosis [as in atypical CML (aCML)], thrombocytosis [as in refractory anemia with ring sideroblasts with marked thrombocytosis (RARS-T)], or monocytosis [as in chronic myelomonocytic leukemia (CMML)]. Table 20.1 lists the subcategories of MDS–MPN overlap. Diagnosis of RARS-T requires the presence of dyserythropoiesis (including ring sideroblasts that account for

Table 20.1 World Health Organization (WHO) classification of myeloid malignancies (Source: Tefferi A, et al. Cancer. 2009;1:3842–7. Adapted from Swerdlow, SH, *et al.* World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon, 2008).

1. **Acute myeloid leukemia (AML) and related precursor neoplasms***
2. **Myeloproliferative neoplasms (MPNs)**
   - **Classic MPNs**
     i. Chronic myelogenous leukemia, *BCR–ABL1* positive (CML)
     ii. Polycythemia vera (PV)
     iii. Primary myelofibrosis (PMF)
     iv. Essential thrombocythemia (ET)
   - **Nonclassic MPNs**
     i. Chronic neutrophilic leukemia (CNL)
     ii. Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
     iii. Mastocytosis
     iv. Myeloproliferative neoplasm, unclassifiable (MPN-U)
3. **Myelodysplastic syndromes (MDSs)**
   - Refractory cytopenia** with unilineage dysplasia (RCUD)
     i. Refractory anemia (ring sideroblasts <15% of erythroid precursors)
     ii. Refractory neutropenia
     iii. Refractory thrombocytopenia
   - Refractory anemia with ring sideroblasts (RARS; dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow erythroid precursors)
   - Refractory cytopenia with multilineage dysplasia (RCMD; ring sideroblast count does not matter)
   - Refractory anemia with excess blasts (RAEB)
     i. RAEB-1 (2–4% circulating *or* 5–9% marrow blasts)
     ii. RAEB-2 (5–19% circulating *or* 10–19% marrow blasts *or* Auer rods present)
   - MDS associated with isolated del(5q)
   - MDS, unclassifiable
4. **MDS–MPN**
   - Chronic myelomonocytic leukemia (CMML)
   - Atypical chronic myeloid leukemia, *BCR–ABL1* negative
   - Juvenile myelomonocytic leukemia (JMML)
   - MDS–MPN, unclassifiable
     i. *Provisional entity: Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T)*
5. **Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*,*** *PDGFRB*,*** or *FGFR1****
   - Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
   - Myeloid neoplasms with *PDGFRB* rearrangement
   - Myeloid and lymphoid neoplasms with *FGFR1* abnormalities

*AML–related precursor neoplasms include "therapy-related myelodysplastic syndrome" and "myeloid sarcoma."
**Either mono- or bicytopenia: hemoglobin level <10 g/dL, absolute neutrophil count $<1.8 \times 10^9$/L, or platelet count $<100 \times 10^9$/L. However, higher blood counts do not exclude the diagnosis in the presence of unequivocal histological and cytogenetic evidence for myelodysplastic syndrome.
***Genetic rearrangements involving platelet-derived growth factor receptor α/β (*PDGFRA–PDGFRB*) or fibroblast growth factor receptor 1 (*FGFR1*).

15% or more of all erythroid precursors), megakaryocyte proliferation and morphology that is similar to that seen in ET, and a platelet count $\geq 450 \times 10^9$/L.

Specific diagnosis in MPN is based on detailed megakaryocyte morphology, the presence or absence of granulocyte proliferation, or reticulin fibrosis. Megakaryocyte cluster formation is a characteristic feature of MPN, especially ET, PV, and PMF. Megakaryocyte morphology in ET consists of large, hyperlobulated, mature-appearing forms, whereas megakaryocytes in PMF display abnormal maturation with hyperchromatic, irregularly folded bulky nuclei, often accompanied by left-shifted granulocyte proliferation. In PV, trilineage proliferation is accompanied by both large and small megakaryocytes without maturation defects. Megakaryocytes in CML are characteristically small and hypolobulated. The aforementioned megakaryocyte morphology in PMF might (fibrotic PMF) or might not (prefibrotic MF) be accompanied by overt reticulin fibrosis.

4. When should the diagnosis of CNL be suspected?

CNL is considered in the presence of right-shifted granulocytosis, an absence of *BCR–ABL1*, an absence of dysgranulopoiesis, and a monocyte count $<1 \times 10^9$/L. Most recently, a highly prevalent *CSF3R* mutation has been discovered in CNL, and mutation screening should now be included in the diagnostic work-up of CNL. Differential diagnosis of CNL includes aCML, which is an MDS–MPN overlap entity that is characterized by left-shifted granulocytosis, dysgranulopoiesis, and an absence of *BCR–ABL1*. A PB monocyte count of $>1 \times 10^9$/L is consistent with CMML. WHO diagnostic criteria for CNL include the presence of $\geq 25 \times 10^9$/L PB leukocytes, >80% segmented neutrophils, <10% immature granulocytes, and <1% PB myeloblasts.

5. When should the diagnosis of CEL-NOS and hypereosinophilic syndrome be suspected?

Diagnosis of both CEL-NOS and hypereosinophilic syndrome (HES) requires the presence of $\geq 1.5 \times 10^9$/L PB eosinophil count and absence of *PDGFR–FGFR1* rearrangements. In addition, diagnosis of HES requires the presence of eosinophilia-associated organopathy and absence of phenotypically abnormal and/or clonal T lymphocytes. CEL-NOS is distinguished from HES by the presence of either a cytogenetic abnormality or greater than 2% PB blasts or >5% BM blasts (reviewed in Chapter 27).

6. How important are immunohistochemistry and molecular markers in the diagnosis of SM?

Diagnosis of SM requires demonstration of abnormal (spindle-shaped) BM mast cells staining for tryptase or CD117 and with abnormal phenotype. Normal mast cells are round and do not express CD25 or CD2. Clonal mast cells are spindle shaped and express CD25 and sometimes CD2. Mutation screening for *KIT*D816V and measurement of serum tryptase are complementary but not essential or adequate for the diagnosis of SM. A diagnosis of SM according to WHO criteria includes the presence of aggregates of morphologically abnormal mast cells or, in the case of diffuse infiltration or low mast cell content, the demonstration of abnormal mast cell expression of CD25 or the presence of *KIT*D816V.

7. What are frequent cytogenetics and molecular abnormalities in MPN?

Recurrent cytogenetic abnormalities are seen in approximately 33% of patients with PMF, 11% of patients with PV, and 7% of those with ET at the time of diagnosis. The incidence of cytogenetic abnormalities is estimated at 17% for CNL and 20% for SM, but it has not been systematically examined in CEL-NOS, although the majority are affected. The type of cytogenetic abnormalities seen in PMF, PV, and ET are listed in Table 20.2; the most frequent abnormalities are del(20q), del(13q), +8, +9, and chromosome 1 abnormalities. Abnormalities of +9 and del(13q) are relatively specific to MPN, whereas del(20q) is seen in both MPN and MDS. The presence of *BCR–ABL1* is a requirement for the

Table 20.2 Frequent cytogenetic abnormalities in PMF, PV, and ET (Source: Data based on Hussein K, *et al.* Eur J Haematol. 2009;82(4):255–9; Gangat N, *et al.* Eur J Haematol. 2008;80(3):197–200; and Gangat N, *et al.* Eur J Haematol. 2009;83:154–5).

Cytogenetic findings	PMF ($n = 109$)	PV ($n = 137$)	ET ($n = 402$)
Normal (including –Y)	73 (67%)	122 (89%)	374 (93%)
Abnormal (excluding –Y)	36 (33%)	15 (11%)	28 (7%)
del(20q), isolated (number of patients and % abnormal)	10 (28%)	2 (13%)	2 (7%)
del(13q), isolated (number of patients and % abnormal)	3 (8%)	1 (7%)	1 (4%)
+9, isolated (number of patients and % abnormal)	3 (8%)	2 (13%)	2 (7%)
+8, isolated (number of patients and % abnormal)	3 (8%)	4 (27%)	2 (7%)

ET, essential thrombocythemia; PMF, primary myelofibrosis; PV, polycythemia vera.

diagnosis of CML and is specific to CML in the context of a chronic myeloid malignancy. *JAK2*V617F is found in the majority of patients with polycythemia vera (95–97%), essential thrombocythemia (50–70%), or primary myelofibrosis (50–70%), and therefore is useful as a clonal marker in these settings. Recently, *CALR* mutations in exon 9 were reported in patients with ET or PMF who did not have *JAK2*V617F or MPL mutations. This mutation, which encodes for calreticulin, was observed in 67% and 88% of patients with ET and PMF, respectively. In ET, *CALR* mutations correlated with male sex, younger age, lower leukocyte count, lower hemoglobin level, higher platelet count and longer thrombosis-free survival. Resequencing in 1107 samples from patients with MPNs showed that *CALR* mutations were absent in PV. In systemic mastocytosis, the presence of *KIT*D816V is expected but not essential for diagnosis.

8. How do I approach establishing the diagnosis of MPNs?

CML diagnosis requires demonstration of *BCR–ABL1*, regardless of clinical or laboratory presentation. In the absence of *BCR–ABL1*, the differential diagnosis depends on the PB picture: primarily right-shifted granulocytosis suggests CNL, granulocytosis associated with dysgranulopoiesis suggests aCML, monocytosis suggests CMML, and the concomitant presence of erythrocytosis, thrombocytosis, or leukoerythroblastosis suggests PV, ET, or PMF, respectively. In general, current diagnosis in the latter three disorders is according to the WHO system (Table 20.3). Identification of the *CALR*-mutated gene in exon 9 should further enhance our ability to accurately diagnose ET and PMF.

Table 20.3 World Health Organization (WHO) system for the diagnosis of essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) (Source: Tefferi A, et al. Blood. 2007;110:1092–7. Adapted from Swerdlow, SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon, 2008).

2008 WHO Diagnostic Criteria						
		Polycythemia vera*		**Essential thrombocythemia***		**Primary myelofibrosis***
Major criteria	1	Hgb >18.5 g/dL (men) and >16.5 g/dL (women) *or***	1	Platelet count $\geq 450 \times 10^9$/L	1	Megakaryocyte proliferation and atypia*** accompanied by either reticulin and/or collagen fibrosis, *or*†
	2	Presence of *JAK2*V617F or *JAK2* exon 12 mutation	2	Megakaryocyte proliferation with large and mature morphology.	2	Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
			3	Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm	3	Demonstration of *JAK2*V617F or other clonal marker *or* no evidence of reactive marrow fibrosis
			4	Demonstration of *JAK2*V617F or other clonal marker *or* no evidence of reactive thrombocytosis		
Minor criteria	1	BM trilineage myeloproliferation			1	Leukoerythroblastosis
	2	Subnormal serum Epo level			2	Increased serum LDH level
	3	EEC growth			3	Anemia
					4	Palpable splenomegaly

BM, bone marrow; CML, chronic myelogenous leukemia; EEC, endogenous erythroid colony; Epo, erythropoietin; Hgb, hemoglobin; Hct, hematocrit; MDS, myelodysplastic syndromes; LDH, lactate dehydrogenase; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

*PV diagnosis requires meeting either both major criteria and one minor criterion *or* the first major criterion and two minor criteria. ET diagnosis requires meeting all four major criteria. PMF diagnosis requires meeting all three major criteria and two minor criteria.

**Hgb or Hct >99th percentile of reference range for age, sex, or altitude of residence *or* red cell mass >25% above mean normal predicted *or* Hgb >17 g/dL (men) and >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency.

***Small to large megakaryocytes with an aberrant nuclear–cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

† In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis (i.e., prefibrotic PMF).

PV is suspected when the hemoglobin level is >18.5 g/dL in men or 16.5 g/dL in women for Caucasians, or 17.5 g/dL in men and 16 g/dL in women for African Americans (or the equivalent in other races). PV is also suspected if there is a documented and sustained increase of at least 2 g/dL from an individual's baseline value, especially when accompanied with PV characteristic features such as pruritus, thrombosis, splenomegaly, or panmyeloproliferation. Diagnostic evaluation begins with a PB *JAK2*V617F mutation screen and the measurement of serum erythropoietin (Epo) levels. The presence of *JAK2*V617F clinches the diagnosis for all practical purposes. Serum erythropoietin level is most useful in guiding additional evaluation in the absence of *JAK2*V617F; if subnormal, the possibility of a *JAK2* exon 12 mutation should be considered. BM examination is not necessary to make a diagnosis of PV.

ET remains a diagnosis of exclusion. The platelet threshold for the diagnosis of ET is 450×10^9/L. After excluding reactive thrombocytosis on clinical grounds, PB screening for *JAK2*V617F is appropriate because the particular mutation is detected in the majority of patients with ET. However, the presence of *JAK2*V617F confirms clonal thrombocytosis but not necessarily ET; specific diagnosis is made after careful review of bone marrow histology and after distinguishing ET from CML, RARS-T, and prefibrotic MF. The diagnostic possibility of CML is easily ruled out by demonstrating the absence of *BCR–ABL1*. Similarly, PB mutation screening for *SF3B1* might help increase the suspicion of RARS-T because the specific mutation is present in >80% of patients with RARS-T but <1% in those with ET. BM morphology remains the most reliable method to distinguish ET from prefibrotic MF.

PB clues to the diagnosis of PMF include leukoerythroblastosis and increased LDH. BM examination is indicated when PMF is suspected, and one should also order cytogenetic studies and mutation screening for *JAK2*V617F. Bone marrow fibrosis associated with the presence of either *JAK2*V617F or trisomy 9/del(13q) is highly suggestive of PMF. In addition, close examination of megakaryocyte morphology and distribution should help exclude the possibility of reactive bone marrow fibrosis or clonal myelofibrosis associated with MDS, CMML, MDS–MPN, SM, or any other myeloid malignancy.

CNL is suspected in the presence of right-shifted granulocytosis, in the absence of *BCR–ABL1*. When CNL is suspected, mutation screening for *CSF3R* and *SETBP1* is indicated, and the presence of the *CSF3R* mutation confirms the diagnosis for all practical purposes. Differential diagnosis includes CML and aCML. The latter is associated with dysgranulopoiesis, which is absent in CNL. One must also exclude CMML and assure that the PB monocyte count is $<1000 \times 10^9$/L.

CEL-NOS is suspected in the presence of PB eosinophilia. Differential diagnosis for PB eosinophilia includes myeloid and lymphoid neoplasms associated with eosinophilia and *PDGFR* or *FGR1* rearrangements, clonal eosinophilia associated with an otherwise WHO-defined myeloid malignancy, "lymphocytic variant hypereosinophilia," and idiopathic eosinophilia, including HES and CEL-NOS. Diagnostic evaluation should start with PB mutation screening for *FIP1L1–PDGFRA* and, in its absence, a BM examination with cytogenetic studies. The absence of *PDGFRA/B* mutations or chromosome 5q33 or 8p11 abnormalities rules out the possibility of myeloid or lymphoid neoplasms associated with eosinophilia and *PDGFR* or *FGR1* rearrangements. In addition, BM morphological examination also helps exclude the possibility of SM, CMML, or any other WHO-defined myeloid malignancy. CEL-NOS is distinguished from idiopathic eosinophilia and HES by the presence of a cytogenetic abnormality, greater than 2% peripheral blood blasts, or greater than 5% bone marrow blasts. In addition, diagnosis of HES requires the presence of $\geq 1.5 \times 10^9$/L PB eosinophil count for at least 6 months, evidence for organ involvement, and exclusion of "lymphocytic variant hypereosinophilia," which is defined by the presence of clonal or phenotypically abnormal (e.g., $CD3^-$ and $CD4^+$) T cells.

SM is suspected in the presence of urticaria pigmentosa or other clinical features of mastocytosis such as flushing, syncope, diarrhea, or osteopenia. BM examination is necessary for accurate diagnosis and should be accompanied by tryptase staining, mast cell flow, and *KIT*D816V mutation screening. Diagnosis of SM requires the presence of aggregates of morphologically abnormal mast cells, the demonstration of abnormal mast cell expression of CD25, or the presence of *KIT*D816V.

Selected reading

Barbui T, Thiele J, Carobbio A, *et al*. Discriminating between essential thrombocythemia and masked polycythemia vera in JAK2 mutated patients. American Journal of Hematology. 2014; Feb 18.

Klampfl T, Gisslinger H, Harutyunyan AS, *et al*. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379–90.

Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia. 2010;24(6):1128–38.

Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia. 2008;22(1):14–22.

Tefferi A. Primary myelofibrosis: 2013 update on diagnosis, risk-stratification, and management. American Journal of Hematology. 2013 Feb;88(2):141–50.

CHAPTER 21

Chronic myeloid leukemia: chronic phase

Jerald P. Radich

Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Introduction

Tyrosine kinase inhibitors (TKIs) have irrevocably changed the care of chronic myeloid leukemia (CML) patients, dramatically changing the natural history of this disease. With multiple TKIs available, we now have an "embarrassment of riches" in treatment options. Below are some common questions and clinically relevant answers for patients with chronic-phase CML.

Multiple choice and discussion questions

1. Is there one best TKI that is preferred over others for patients with chronic-phase CML?

The choices are imatinib, and the more potent second-generation TKIs nilotinib and dasatinib. Here are some basic considerations for selection of therapy: (i) What are the treatment goals? For instance, for someone in their 70s, it may be appropriate to extend survival without concerns of potential serious toxicities. For someone much younger, it may be appropriate to achieve "deeper responses" with counseling about the management of concurrent, manageable side effects in order to allow discontinuation of a particular TKI (see question 4, this chapter). (ii) Conduct an avid evaluation of preexisting comorbidities. It may not be best to prescribe dasatinib or nilotinib, respectively, to a patient with cardiopulmonary problems or vascular disease, given the emerging evidence of pulmonary hypertension and peripheral vascular occlusion, respectively, associated with these medications. (iii) Another important consideration is as follows: is the chronic-phase disease status at the time of diagnosis a low or high Sokal (or Hasford) risk? If the patient seems to be on the verge of transition to an accelerated or blast phase, there may be a reason to start therapy with a more potent TKI. (iv) The personal experience and comfort level of a physician in managing various side effects of specific TKIs remain crucial in the decision-making process (Table 21.1).

All things being equal, the second-generation TKIs do yield superior progression-free survival (PFS) compared to imatinib. Three separate randomized trials showed that nilotinib or dasatinib yielded more frequent complete cytogenetic remissions (CCyRs) and major molecular responses (MMRs) by 12 months, as well as fewer progressions to the accelerated or blast phase, compared to imatinib (1–3). To date, however, no randomized trial has shown a benefit in overall survival (OS) of nilotinib or dasatinib over imatinib.

2. In the modern era, what are the strengths and weaknesses of the Sokal, Hasford, and Euro scores?

Table 21.2 displays the variables used in these clinical scores. The Sokal score was created to predict the natural history of CML in the era of hydroxyurea and busulfan therapy; Hasford was based on the experience of patients treated with interferon; and the Euro score is based on modern experience with TKI therapy. Because we do not ever know how long patients have had CML prior to their diagnosis, the scores are a rough measure of time of Bcr–Abl exposure [since, e.g., the spleen size and white blood cell count presumably were normal at the time the patient acquired the Philadelphia (Ph) chromosome]. All of these scores are effective at predicting the behavior of CML and the response to therapy. Predictably, patients with low-risk scores do best with TKIs, whereas patients with high-risk disease have worse achievement of treatment milestones.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 21.1 Some consideration for the selection of tyrosine kinase inhibitor (TKI) therapy in chronic myeloid leukemia.

TKI	Advantage	Disadvantage
Imatinib	Long-term data available Less expensive	Lower rates of complete cytogenetic remission (CCyR) compared to second-generation TKIs Fluid retention Musculoskeletal aches and pains
Dasatinib	• 10% higher CCyR compared to imatinib • ~2× higher rates of major molecular response (MMR)	Pleural effusion Pulmonary arterial hypertension Thrombocytopenia Hemorrhage
Nilotinib	>10% higher CCyR compared to Imatinib ~2× higher rates of MMR	Cumbersome dosing schedule Skin rash Pancreatitis QT prolongation Dyslipidemia or hyperglycemia Peripheral arterial disease

3. Peripheral blood– and bone marrow aspirate–retrieved cytogenetic and molecular studies provide unusually concordant results in the majority of patients. Can they preclude the need for bone marrow biopsy every 3 months?

A. Yes
B. No

Peripheral blood monitoring of the Bcr–Abl transcript is a sensitive and accurate method of following disease burden in CML. The peripheral blood value correlates well with bone marrow Bcr–Abl testing, as well as cytogenetic chromosomal karyotyping. Bone marrow chromosomal testing is important at diagnosis, because it is needed to identify both the Ph chromosome and other cytogenetic changes that would change the diagnosis to the accelerated phase. However, once therapy is initiated, National Comprehensive Cancer Network (NCCN) guidelines call for q3 month peripheral blood polymerase chain reaction (PCR) testing alone, with bone marrow reserved for cases that do not meet treatment milestones or have evidence of relapse.

4. How hard should we push for an MMR?

In the original IRIS study comparing imatinib to interferon and Ara-C, MMR was defined as a 3 log reduction in Bcr–Abl levels compared to a standard diagnostic baseline averaged from a number of patients. More lately, the assay has been standardized, so that MMR is now 0.1% on the International Scale (IS). Several studies have shown that MMR is a "safe haven": that is, it is very unusual for patients who achieve an MMR to suffer a relapse or progression of their disease.

Sometimes, patients become "stuck" with a best TKI response of a CCyR (which roughly corresponds to a Bcr–Abl level of 1% IS) but not quite an MMR. The obvious temptation is to change drugs to another TKI. It is not clear, however, that this switching will do the trick. Indeed, several clinical trials are testing whether switching to a more potent TKI, or adding another agent to an existing TKI, will force a dive into an MMR. Physicians and patients are encouraged to enroll in these important trials. The decision then to switch TKIs in order to achieve an MMR should be made in consideration of treatment goals. Are you just trying to improve survival? Achieving CCyR may be enough, and there may not be value in switching if the initial drug is well tolerated. In contrast, the goals for a young patient may be to protect from the advanced phase for years, or even possibly qualify for discontinuation trials. In this case, a more aggressive approach may be warranted.

5. What does complete molecular response (CMR) mean? No evidence of leukemia? No disease?

Like complete response in acute leukemia, CML patients in CMR still have disease. The PCR assay for Bcr–Abl is very sensitive, with the ability to detect roughly one CML cell in a background of 100,000 normal cells. However, because there are billions of CML cells at diagnosis, there are likely many CML cells still present in patients for whom the PCR assay is "negative." Thus, no evidence of CML does *not* mean no CML.

One must be very careful when interpreting a negative Bcr–Abl PCR result, as this can arise from (at least) three (not mutually exclusive) causes. First, the patient may indeed have CML levels below the detection of a good, sensitive, reproducible assay. Second, the sample could be poor (due to, e.g., an inadequate cell number) or degraded, so that the ability to detect the Bcr–Abl mRNA target is greatly impaired. Thus, if a lab reads a result as negative, it should also report how many cell equivalents it could read. A negative Bcr–Abl assay from a test that assayed 100,000 cells is much more reassuring than a negative test that assayed 10 cells, for (an absurdly exaggerated) example. Last, the test is fairly complex, and the lab may be doing a lousy job (a false negative). This happens.

6. How do I approach a patient with CHR and CCyR but a "rising BCR–ABL to ABL ratio"?

This depends on where it is rising from, and how high and fast it is rising. The exact level of rising that is significant

Table 21.2 Posttransplant use of tyrosine kinase inhibitors (TKIS) in patients with chronic myeloid leukemia (CML) (adapted from Bar M, *et al.* J Natl Comp Cancer Network. 2013;11(3):308–15).

Reference	*N* pts.	Indication	TKI	Median dose	Significant toxicity	Outcome
Kantarjian *et al.*[a]	28	Relapse	Imatinib	600 mg	Grade 3–4 hematologic toxicity Grade 3–4 liver toxicity	CHR: 74% (CP: 100%, AP: 83%, BP: 43%) CgR: 58% (CP: 63%, AP: 63%, BP: 43%) CCgR: 35%
Olavarria *et al.*[b]	128	Relapse	Imatinib	400 mg (CP) 600 mg (AP/BP)	N/A	CCgR: 44% (CP: 58%, AP: 48%, BP: 22%) CMR:26% (CP: 37%, AP: 33%, BP: 11%) CP: 2y OS 100% AP: 2y OS 86% BP: 2y OS 12%
DeAngelo *et al.*[c]	15	Relapse	Imatinib	600 mg	Grade 3–4 liver toxicity	CCgR: 11/15 (73%) CMR: 7/15 (47%)
Hess *et al.*[d]	44	Relapse	Imatinib	400 mg	Grade 3–4 hematologic toxicity	CCgR: 73% CMR: 62%
Palandri *et al.*[e]	16	Relapse	Imatinib	400 mg	Grade 3–4 hematologic toxicity	CCgR:88% CMR:75%
Klyuchnikov *et al.*[f]	11	Relapse	Dasatinib	50 mg BID	Thrombocytopenia-related gastrointestinal bleeding	Stable response in 4 pts (2 with extramedullary relapse)
Wright *et al.*[g]	22	Relapse	Imatinib (20), Dasatinib (6)	Imatinib 400 mg Dasatinib 140 mg	Grade 3–4 hematologic toxicity	CHR: 86% (AP/BP-79%) CCgR: 77% (AP/BP-71%) CMR: 64% (AP/BP-57%)
Carpenter *et al.*[h]	22	Prophylaxis	Imatinib	400 mg	Grade 1–3 nausea, emesis, Liver toxicity	CCgR: 5/7 CMR: 5/7
Olavarria *et al.*[i]	22	Prophylaxis	Imatinib	400 mg	Not noted	68% relapse at median of 17 month after HCT

CCyR, complete cytogenetic response; CgR, cytogenetic response; CHR, complete hematologic response; CMR, complete molecular response.

[a]Kantarjian HM, *et al.* Blood. 2002;100:1590–5.
[b]Olavarria E, *et al.* Leukemia. 2003;17:1707–12.
[c]DeAngelo DJ, *et al.* Clin Cancer Res. 2004;10:5065–71; and DeAngelo DJ, *et al.* Clin Cancer Res. 2004;10:1–3.
[d]Hess G, *et al.* J Clin Oncol. 2005;23:7583–93.
[e]Palandri F, *et al.* Bone Marrow Transpl. 2007;39:189–91.
[f]Klyuchnikov E, *et al.* Acta Haematol. 2009;122:6–10.
[g]Wright MP, *et al.* Biol Blood Marrow Transpl. 2010;16:639–46.
[h]Carpenter PA, *et al.* Blood. 2007;109:2791–3.
[i]Olavarria E, *et al.* Blood. 2007;110:4614–17.

is not known. Some labs prefer a 2× change, whereas others more conservatively choose a 10× change (note that this is always confirmed by a repeat assay). Several things influence how much increase we tolerate before worry sets in. It depends on both the reproducibility of the assay (which is different from lab to lab) and the actual Bcr–Abl level. For example, a 5× change associated with the loss of MMR is far more concerning than a case where the Bcr–Abl goes from undetectable to 0.0001%. The latter example represents an infinite increase in the measured disease burden, but to a level that is exceedingly low and has no clinical meaning.

That being said, in the case of a rising Bcr–Abl, it would be wise to repeat the peripheral blood Bcr–Abl in one month. If it is still rising, one should (i) discuss compliance with the patient: is the Bcr–Abl climbing because they have given themselves a drug holiday? Then one should (ii) obtain a bone marrow for morphology and cytogenetics if the level has increased above MMR; and (iii) perform Abl mutation testing.

7. When do I consider switching to a different TKI?

NCCN and the European Leukemia Network (ELN) have established online treatment recommendations, which include monitoring guidelines and robust treatment outcome endpoints. Fortunately, the NCCN and ELN guidelines are quite similar. Patients should have at least a bone marrow minor cytogenetic response or a peripheral blood BCR–ABL level of <10% by 3–6 months, and by 12 months, all patients should achieve a CCyR. Failure to achieve established milestones, or recurrence of disease after reaching these goals, is considered a failure of the TKI therapy, and it warrants alteration in therapy to a different TKI. Fluorescent in situ hybridization testing for BCR–ABL should be done at diagnosis only for those cases that have inaspirable bone marrows, or for monitoring, in the rare circumstance when peripheral blood for PCR testing is not available.

8. How do I select a second-generation drug for resistant disease?

There are now four second-generation TKIs approved for resistant chronic-phase CML: nilotinib, dasatinib, bosutinib, and ponatinib. If a patient is started on imatinib, it makes sense to switch to a second-generation TKI; if a patient needs to switch from initial therapy to a second-generation therapy, then switching to another TKI is justified, but in general changing to a less potent TKI (e.g., imatinib) is probably not the best option. The same criteria for picking the initial therapy (see question 1, this chapter) apply here as well. Consider the specific side effect profile, comorbidities of the patient, and comfort level with a given TKI. However, an additional important consideration is the presence of ABL point mutations, which confer resistance in about 50% of cases presenting with relapsed CML. There are hundreds of possible point mutations, but the most common have had in vitro testing performed, and ample literature exist showing which particular mutation is sensitive to which TKI. Ponatinib is unique among these agents, as it is the only TKI that is effective in patients with the T315I mutation. Moreover, it seems to be effective across the entire range of known ABL mutations. Time will tell if it becomes the first choice for resistant disease.

9. How is TKI intolerance defined?

When there was only imatinib, there were complicated schemes to try to keep patients on the drug in the face of its side effects. Now that we have a total of five TKIs approved by the US Food and Drug Administration, the easier course in patients with any toxicity that potentiates drug discontinuation or reduction is to simply switch TKIs. Fortunately, the available agents appear to be "cross-tolerant"; that is, if a patient has a particular side effect on one TKI, he or she is relatively unlikely to have it on another TKI. This phenomenon is likely a product of the genetic polymorphism and the different spectra of kinases being targeted. Because CML is often diagnosed with a relative absence of symptoms, patients may actually feel worse taking a TKI than they did before they were diagnosed. This is a recipe for poor adherence, and several studies have demonstrated a shockingly poor compliance to the scheduled dosing of these TKIs. This is especially problematic because adherence is strongly associated with the ability to achieve important endpoints such as MMR and complete molecular response (CMR; see question 11, this chapter).

10. Is adherence to TKI a problem?

One would think that adherence to a TKI regimen in CML would be a snap—after all, these are oral agents, have a very palatable side effect profile, and are amazingly efficacious. But one would be wrong. Several studies have shown three important features of adherence: (i) in self-reporting, patients dramatically inflate their own adherence; (ii) in contrast, subjective measures (pill counting, etc.) in the same patients show remarkably low adherence (busted!); and (iii) adherence to >90% of prescribed doses yields great results in achieving CCyR, MMR, and CMR. Nothing beats the benefit of actually taking the medicine.

11. Are we ready to safely discontinue therapy after achievement of a specific milestone?

It was first thought that patients would need to stay on TKIs forever, because in vitro work showed that the putative CML stem cell survived in the presence of BCR–ABL inhibition. However, several studies have shown that approximately 40% of patients who are in a CMR can successfully discontinue TKI therapy and stay in CMR for several years. Most patients relapse within 6 months after discontinuation, and so far all patients have responded when rechallenged with a TKI, although not all have returned to CMR. There are many things we don't know about discontinuation, and these are the subjects of several ongoing and future studies. First, can we predict who can be discontinued safely? So far, the data suggest that patients

with low-risk chronic-phase CML have the best chance for successful discontinuation. Second, how long should someone be in CMR before discontinuation, and is the effect the same for all the TKIs? Lastly, in the cases that relapse, has the absence of TKI inhibition allowed rare clones to begin the process of ABL-independent progression? If so, it might take many years for this resistant or progression clone to emerge. Until these questions are answered, no patient should have their TKI discontinued outside the context of a clinical trial.

Multiple choice answer

Question 3: Answer A

Selected reading

Kantarjian H, Shah NP, Hochhaus A, *et al.* Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260–70.

Radich JP. How I monitor minimal residual disease in CML. Blood. 2009;114:3376–81.

Saglio G, Kim DW, Issaragrisil S, *et al.* Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251–9.

Selected websites

www.nccn.org
www.leukemia-net.org

CHAPTER 22

Blast crisis of chronic myeloid leukemia

Michael J. Mauro

Memorial Sloan Kettering Cancer Center, New York, NY, USA

1. How common is blast crisis of chronic myeloid leukemia (CML)?

Blast crisis of CML is commonly referred to as the "terminal phase" of CML—not, hopefully, due to its morbidity but given that it represents the final phase of a disease in which the majority of patients are diagnosed in a chronic phase and treatment is aimed at prevention of a penultimate accelerated phase or blast crisis. This principle begets the most obvious answer to this question: *prevention and better therapies have diminished it tremendously!* Although the prevalence of CML is increasing given the effectiveness of tyrosine kinase inhibitors (TKIs), the number of cases of transformation to blast crisis has fallen and management of blast crisis has changed accordingly; it still represents a frontier where advances are needed. Prior to the availability of current therapy options, transformation rates were as high as 20% of CML cases; this has fallen to ~1%. The rare patient who presents with de novo blast phase disease (not arising from chronic-phase CML) can be treated with lineage-specific regimens that nearly always incorporate TKI therapy; the patient who, despite good initial therapy in the chronic or accelerated phase with TKI therapy, progresses to blast crisis likely has a more complex dominant mechanism of resistance, and careful selection of therapy is warranted.

In clinical trials of chronic-phase CML treated with TKIs, including evolved (second-generation) TKIs, we still observe, albeit rarely, transformation to the blast phase even in the face of early response. Although early and efficient disease burden reduction has proven to be the key toward limiting progression to blast crisis, in some cases the likely unstable clones responsible for transformation preempt TKI therapy and relatively quickly exploit their growth advantage and appear.

Last, as global healthcare evolves and access is gained increasingly to diagnostics as well as to specific therapies such as TKIs for Philadelphia chromosome–positive (Ph+) leukemia, it is noted that the presentation of CML is possibly skewed more toward the accelerated and blast phase in countries such as India, as well as typical presentation as much as a decade younger than in other parts of the world. The causes of such differences remain to be elucidated.

2. What is the nature of blast phase CML?

The most prevalent phenotype of blast phase CML is indeed that evolved from chronic- or accelerated-phase CML, which is resistant to therapy and manifests as a clonal disease bearing ABL kinase domain mutations 50% or more of the time. De novo blast crisis still occurs and, as mentioned, may represent untreated chronic CML with rapid progression prior to the patient seeking medical attention, especially in developing countries. Common in accelerated phase and blast crisis are (i) a higher frequency of Abl kinase domain mutations and (ii) a spectrum of mutations skewed toward an increasing amount of cases with T315I and the so-called p-loop (phosphorylation loop, most commonly at positions 250, 252, 253, and 255) mutations.

In addition to kinase domain mutations, recent analyses have continued to show that clonal evolution—chromosome anomalies aside from the Ph chromosome in the CML clones, particularly via "major route" pathways [trisomy 8, an additional Ph chromosome, isochromosome 17 (17q), and trisomy 19]—is commonly observed in the setting of transformation to blast crisis. Additional findings include p53 mutations, recently characterized mutations such as ASXL1 and TET2, as well as altered

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

gene expression profiles with altered regulation of select sets of genes, which are potentially targetable for therapy at some point.

Clinically, the features of blast phase CML are akin to those of acute leukemia; first and foremost, the main delineator of stage, the blast cell count in the marrow or blood, registers at 20% or greater by newer definitions or 30% or greater by traditional definitions. Significant thrombocytopenia and progressive anemia are common objective findings; fatigue, night sweats, weight loss, bone pain, and abdominal symptoms from splenic enlargement are common subjective complaints. Bleeding is increased in the setting of thrombocytopenia, and complications from high leukocyte count—leukostasis and tumor lysis syndrome—are more frequent.

When CML terminates in blast phase, it is curious to many that it takes shape as either a lymphoid or myeloid phenotype; historically, it is twice as likely to develop as a myeloid transformation than a lymphoid type, and the ability to de-differentiate to either type, or a mixed type, speaks to the early stem cell origin of CML.

3. What are the best therapy options for blast crisis of CML?

Therapy for cases of blast crisis of CML is quite dependent on the clinical and prior treatment history. As mentioned in this chapter, de novo blast crisis may have different molecular underpinnings than blast crisis evolved from chronic-phase CML treated with current TKI options. Blast crisis treated over a decade ago at the outset of imatinib's availability taught us important lessons about the paradox of sensitivity and subsequent resistance. Myeloid blast crisis was relatively successfully treated with imatinib, however short-lived, with only rare patients experiencing long-term remission. Lymphoid blast crisis was noted to be remarkably sensitive to imatinib therapy, with the majority of patients responsive; however, by day 100 of treatment, nearly all patients had relapsed disease. Such response data reveal the instability of transformed CML and either the preexistence or rapid development of TKI-resistant clones.

If a blast crisis patient has not had prior TKI therapy, imatinib therapy is not unreasonable; however, available data would predict an overwhelming or complete expectation of relapse if response occurred. Primary therapy with subsequent-generation TKIs is understudied but might be either more effective or more durable. For patients with prior exposure to TKIs, it is imperative to assay for and follow sequentially Abl kinase domain mutation status; results from phase II trials that are available for all of the currently approved TKIs beyond imatinib (nilotinib, dasatinib, bosutinib, and ponatinib) as well as in vitro data provide reasonable guidance as to which agent would be most pragmatic in select situations. One of the clearest categories is the presence of the T315I mutation, which is amenable only to ponatinib. It is notable that the advantage of ponatinib in the setting of a T315I mutation is much greater in chronic-phase CML, which is likely due more to earlier identification, less prior therapy, and better drug exposure, perhaps again highlighting the instability of blast phase disease. Increased incidence of potential adverse events, including morbid vascular complications, has led to necessary greater scrutiny of the risk/benefit ratio of ponatinib; as well recent work has identified the potential for compound mutations (multiple mutations in a single clone) that may be more likely to develop in blast crisis and lead to greater challenges and limitations of TKI-based therapy. Other mutations offer direction as well, with mutations V299L, T315A, or F317L/V/I/C suggested to be more amenable to nilotinib, and Y253H, E255K/V, or F359V/C/I mutations more amenable to dasatinib. Bosutinib has a profile closest to dasatinib and should thus be used accordingly; aside from the T315I mutation, ponatinib's profile preclinically and with clinical trial data would suggest efficacy in the face of any mutation, and thus it should not be relegated to T315I cases only but to those where the risk/benefit ratio is acceptable.

The combination of TKI and steroids has had particular activity in Ph+ acute lymphoblastic leukemia (ALL) and has been studied by the GIMEMA group and reported by R. Foa and colleagues. Induction with dasatinib and prednisone, with two planned intrathecal methotrexate instillations, followed by taper of the steroids after 4–5 weeks and maintenance of the dasatinib alone, has yielded very high response rates and some durability, especially in cases where transcript reduction is rapid. Gradual relapse is common and predictably linked to the T315I mutation. Nonetheless, this regimen demonstrates the potential of a "nonchemotherapy" induction as a bridge to transplantation for many and a definitive treatment for some, and it will be the impetus for further TKI and steroid induction regimens.

Consideration of intrathecal sampling, followed by either prophylactic or necessary treatment with conventional therapies such as methotrexate or cytarabine, is recommended for many blast crisis patients. The risk and necessity of this component should be assessed by disease type (lymphoid > myeloid) and the presence or absence of symptoms. Available data show limited penetration and subtherapeutic concentrations of TKIs in the cerebrospinal fluid, and thus the importance of intrathecal prophylaxis and therapy.

Myeloid blast crisis does not have a particular conventional chemotherapy and TKI regimen that is considered superior, and thus a number of choices could be considered. Given the availability of multiple newer and more potent TKIs, it may be preferable to start first with a TKI alone or a TKI and low-risk chemotherapy option prior to

a conventional chemotherapy "induction" to reduce the risk of complications and the recovery needed prior to a definitive stem cell transplantation.

4. What is the role of transplantation in blast crisis of CML?

As a general axiom, transplantation should be part of the discussion of most cases of blast crisis CML. In the case of return to chronic phase or a more favorable deeper response, the challenge remains to ensure open discussion, timely assessment for donor availability and risk stratification during a window of opportunity to pursue definitive stem cell transplant. Disease control may be longer in a minority of patients, but durable remission after TKI, TKI plus chemotherapy, or conventional chemotherapy in the setting of blast crisis is the exception and not the rule. As mentioned, in the current era the ability to manage a patient with TKI therapy alone, with second- or third-generation agents used to combat resistance (even sequential resistance), is generally associated with modest or selective toxicity, reduced recovery time, and outpatient or "day hospital"–style management. The decision to proceed to stem cell transplantation while having blast phase CML either successfully treated or salvaged, in particular with more simple and "patient-friendly" options such as TKIs, is indeed a difficult one; the patient has limited exposure to traditional chemotherapy side effects, and in cases of remission, often rapid improvement in blood counts and general well-being. Given the modest response rates and persistent risk of relapse, a second chronic phase and excellent response should be viewed as an opportunity not to lose, rather than a return to the safe harbor that we associate with response for patients in the first chronic phase.

Careful management of drug–drug interactions is necessary in the patient with blast crisis needing supportive care and infection prophylaxis. The TKIs are all cleared via hepatic cytochrome p450 metabolism, and the issue of concomitant therapy either inducing or inhibiting this pathway can lead to TKI under- or overexposure or other drug side effects. Of particular note are azole antifungal agents used for prophylaxis of mold infections; the more potent of these generally warrant modified-dose TKIs to avoid overexposure. Also, given the requirement for normal (acid) stomach pH for absorption of dasatinib in particular (less so with nilotinib and other TKIs), the concomitant use of proton-pump inhibitors or histamine-2 (H2) blockade therapy for acid suppression is contraindicated.

5. Is blast crisis truly preventable?

Although TKI therapy is effective, albeit in a more limited fashion for CML in blast phase, evolution of the knowledge into mechanisms of resistance will likely continue, and it is likely that a more effective combination therapy of Bcr–Abl inhibition with inhibition of relevant pathways seen with disease transformation may increase our ability to salvage patients unlucky enough to either present with transformed disease or evolve to advanced disease. The complexity of resistance observed in the setting of TKI failure in blast crisis or Ph+ ALL is evolving, and novel observations of compound mutations as a pathway to pan-TKI resistance comprise a major concern. The solution and potentially greater advance, however, may have already occurred as the fraction of patients from chronic- or accelerated- phase CML who do transform is dramatically lower and may fall further with more aggressive initial therapy and/or careful risk-adapted therapy for these patients. Ponatinib, the first approved "third-generation" kinase inhibitor, continues as a viable option for many patients, including those with complex resistance and progressive disease. If it can more completely subvert resistance and further halt progression—including the inevitable cases still seen with nilotinib and dasatinib early after chronic-phase diagnosis and initiation of treatment—it could further prove its worth and add significantly to the quest to prevent blast crisis of CML.

Selected reading

Hehlmann R. How I treat CML blast crisis. Blood. 2012; 120(4):737–47.

Radich JP. The biology of CML blast crisis. Hematology Am Soc Hematol Educ Program. 2007;2007:384–91.

CHAPTER 23

Chronic myeloid leukemia and pregnancy

Michael J. Mauro

Memorial Sloan Kettering Cancer Center, New York, NY, USA

1. What about pregnancy in the setting of chronic myeloid leukemia (CML)?

Pregnancy is an important topic given the increased ability to treat CML into stable and long-standing remission. Although CML is typically a disease that strikes women at the end of or beyond the childbearing years, there remains a significant minority of patients in whom CML is diagnosed and fertility remains along with the desire to have children. So what to do? Assuming pregnancy is an elective option, it is wise for a patient to defer until well into a stable remission. Thus, proper initial therapy with the aim to achieve rapid and definitive cytogenetic and molecular response according to available guidelines is first. Trials reported to date for patients in remission on tyrosine kinase inhibitor (TKI) therapy who have discontinued treatment show the prognostic value of longer duration of therapy for the likelihood of "treatment-free remission." Consensus regarding current trials for deliberate (non-pregnancy-related) treatment cessation generally includes a 2-year period of complete molecular response (CMR; $\geq$4.5 log reduction below standard baseline) to maximize the odds of success off treatment. Thus, general principles of counseling for a younger woman who wishes to plan a family might include definitive TKI treatment as if participation in a treatment-free remission trial is planned, and at the point of 'eligibility', for instance when considered safe for consideration of treatment interruption, conception would be considered reasonable as well.

2. What if CML is diagnosed during pregnancy?

CML certainly may present in the setting of pregnancy and poses a particular challenge. The TKIs approved for use in CML are all assigned pregnancy category D status, thus advising against any use in pregnancy. Studies of pregnancy outcome with TKI exposure, with the bulk of cases in the literature describing exposure to imatinib, show a range of effects and do include the possibility of severe effects incompatible with survival of the fetus. Subsequent-generation TKIs are less well studied. Early development and TKI effects on germ cell layer and neural tube development may explain severe effects observed with very early exposure; exposure late in pregnancy (third trimester) may have much less potential for effect. Avoidance of TKI in pregnancy is thus the blanket recommendation. Rather than definitive treatment, control of CML in the setting of pregnancy may be more feasible; in particular interferon-alpha, a historic standard therapy for chronic-phase CML, now generally given in the pegylated form, can be deployed safely in pregnancy with disease control and in certain cases progress toward remission. First-trimester use of interferon may be associated with increased rates of spontaneous abortion, and timing of interferon is thus crucial. A simple goal of treatment during pregnancy might be to control blood counts to avoid placental blood flow issues and hemostatic and viscosity issues resulting from uncontrolled elevation in the leukocyte count at the time of delivery.

3. How could a woman who has CML plan to conceive?

As mentioned in this chapter, the initial advice is to defer pregnancy until a stable, high-quality remission has been achieved. Once this is the case, the woman would best be as knowledgeable as possible regarding her menstrual cycles and ovulation timing, and she can consider obstetrical consultation to ensure fertility. Male partners should have a low threshold to consider testing to avoid failure of conception and repeated attempts in the context of unrecognized male fertility issues. With confirmation of fertility

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

in both partners and knowledge of the woman's cycles and ovulation timing, therapy with TKI may continue until conception is felt likely to have occurred (or simply a well-timed and purposeful attempt at the peak of ovulation); TKI therapy can then be held awaiting rapid confirmation of pregnancy. If pregnancy is not confirmed, TKI therapy can resume until the next ovulatory cycle; if it is confirmed, TKI exposure has been minimized and therapy can continue to be held through pregnancy. Such an approach minimizes the additional "lead time" off treatment inherent in the strategy of continuous TKI interruption for the purpose of attempting conception.

Pregnancies between partners with CML, especially in the case of a woman treated for CML, should be managed by a higher-risk obstetrician given the unknown potential for therapy related or disease related factors that could affect the developing child. Such cases benefit also from leukemia- or moreover CML-specific hematology care given the risk of disease recurrence. As well, genetic counseling and utilization of full prenatal testing for chromosome anomalies and birth defects are recommended. Last, an important discussion needs to take place before any woman with CML considers pregnancy and the required treatment interruption regarding the risk of disease return, relapse, and even progression because retreatment during pregnancy may be delayed. Involvement of the partner is crucial, as the worst-case scenario of putting the mother's health in jeopardy needs to be understood and accepted. The goals of retaining fertility, achieving relevant remission on therapy to allow consideration for such an endeavor as parenting and the potential for 'treatment free remission' have coalesced into a reality for CML patients during TKI therapy, whereas with prior therapies such was not possible and with stem cell transplant rare. Given, the current climate of pursuit of treatment-free remission, consideration of treatment hold for pregnancy in the presence of a high quality remission seems entirely consistent philosophically and should be considered quite feasible and likely to have good odds of being uneventful from the perspective of the CML.

Selected reading

Apperley J. CML in pregnancy and childhood. Best Pract Res Clin Haematol. 2009;22(3):455–74.

Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. Semin Hematol. 2003;40(2 Suppl. 2):21–5.

CHAPTER 24

Polycythemia vera

Constantine S. Tam[1] and Srdan Verstovsek[2]

[1]Peter MacCallum Cancer Center, Melbourne, VIC, Australia
[2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

1. Is it possible to have polycythemia vera (PV) without a *JAK2* mutation?

In the era of widespread *JAK2* mutation testing, it is easy to forget that many laboratories only routinely test for the *JAK2V617F* mutation in exon 14, which is present in approximately 95% of patients with true PV. A further approximately 4% will have mutations at various codons within exon 12 of the *JAK2* gene, which can be tested for in some, but not all, academic centers and commercial labs. Rare mutations in other genes are described in patients with unexplained erythrocytosis, including mutations in LNK, and cooperating mutations or promoter hypomethylation in *SOCS* genes, *TET2*, or *EZH2*; testing for these mutations is not possible in everyday practice, and, therefore, it is possible to encounter a patient with true PV who is *JAK2* mutation negative.

2. What is the optimal therapeutic hematocrit target in patients with PV?

There was considerable uncertainty about the importance of "strict" hematocrit control of 45% as claimed in earlier studies. In the European Collaboration of Low-Dose Aspirin in PV (ECLAP) study, a multinational prospective study of 1638 patients with PV, only 48% of patients were maintained at the recommended hematocrit target of <0.45, with the remainder maintained at 0.45–0.50 (39%) and >0.50 (13%). Interestingly, in the ECLAP study there was no relationship found between hematocrit level and risk of thrombosis, as had been previously reported, although it can be argued that the entire ECLAP cohort was undertreated as a whole, as reflected by the high event rate (3.2% major thrombosis per year). Analysis of the historic PVSG-01 study also failed to show a relationship between thrombosis and hematocrit, albeit at a liberal hematocrit target of 0.52. These older studies predated the modern practice of routine aspirin prescription and risk stratification by age and prior thrombosis; nevertheless, their results gave plenty of ammunition to proponents of liberal hematocrit targets.

Fortunately, the question of target hematocrit is now definitively answered with the recent publication of the CYTO-PV study. In this study, 365 patients with PV were randomized to hematocrit targets of <0.45 (low hematocrit) or 0.45–0.50 (high hematocrit). Notable differences between the CYTO-PV study and previous studies included the use of aspirin in all patients (unless contraindicated), and a recommendation for the use of hydroxyurea in high-risk patients (those age $\geq$65 years *or* with prior thrombosis). After a median follow-up of 31 months, major thrombosis or cardiovascular death occurred in 9.8% of the high-hematocrit group, compared with 2.7% of the low-hematocrit group ($P = 0.007$)—a remarkable difference, considering that the median hematocrit differed by only 0.03 between the two groups (0.44 vs. 0.47). The annual rate of major thrombosis or cardiovascular (CV) death in the high-hematocrit group (4.4% per year) was similar to that of the ECLAP study (3.2% per year), despite the routine prescription of aspirin and the use of hydroxyurea in high-risk patients in the CYTO-PV study. These observations confirm the critical importance of hematocrit control in PV, and highlight the ineffectiveness of aspirin and hydroxyurea in failing to overcome the adverse consequences of poor hematocrit control.

3. Should the hematocrit target differ between male and female patients with PV?

Traditionally, a target of 0.42 is often recommended for female patients. In the CYTO-PV patients, the therapeutic target was identical for male and female patients, and with the caveat of small numbers in subgroup analyses, the

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

event rate in the high-hematocrit group was numerically higher in female (13%) than male (8%) patients. The CYTO-PV trial showed that reduction in hematocrit to physiological levels was important in preventing thrombosis, and if one extrapolates the physiological differences in hemoglobin in health to that in disease states, it would seem reasonable that the target for female patients should be lower than that of male patients. Although there is no prospective evidence at present to support this view, the judicious use of a lower hematocrit target (0.42) in female patients is unlikely to cause harm, and represents the authors' personal practice.

4. Should extreme thrombocytosis in a patient with well-controlled hematocrit be an indication for cytoreductive therapy in PV?

There is a reasonable argument for the use of cytoreduction in extreme thrombocytosis ($\geq 1500\times10^9$/L), due to the well-documented association between extreme thrombocytosis and bleeding risk from acquired von Willebrand factor deficiency. Unlike the situation with thrombosis risk, in which there are alternatives to cytoreduction (i.e., control of hematocrit and use of aspirin), the only therapeutic maneuver available to ameliorate the bleeding phenotype in extreme thrombocytosis is by cytoreduction; this practice is supported by expert opinions and consensus guidelines. The preferred choice of cytoreductive agent in this situation for younger patients would be interferon, while in older patients hydroxyurea is a standard of care.

5. Should leukocytosis with well-controlled hematocrit be an indication for cytoreductive therapy in PV?

The ECLAP study was able to provide insight into the association between white blood cell (WBC) count and thrombosis in PV. Two hundred and five thromboses occurred in 1638 patients followed for a mean of 2.7 years in the original ECLAP data set. Of these, 81 were first vascular events. Overall, the effect of leukocytosis was rather weak, being associated mainly with an increased risk of myocardial infarction when the WBC count exceeded 15×10^9/L. Aspirin is highly effective in the secondary prevention of recurrent vascular events in the general population, and data from ECLAP and studies of essential thrombocytosis suggest that aspirin use is associated with similar lowering of risk as a reduction in white cell count. In our view, these patients may well be equally served by aspirin therapy.

6. A patient develops a deep venous thrombosis (VTE) in the context of previously undiagnosed PV. What should be the duration of anticoagulation?

PV is a potent provoking factor for venous thromboembolism (VTE). Tight hematocrit control is clearly effective at ameliorating this risk, reducing the rate of major VTE to <0.5% per year. The American College of Chest Physicians (ACCP) guidelines state that in VTE provoked by a non-surgical transient risk factor, treatment with anticoagulation should be continued for 3 months. Expert opinions in cancer-related thrombosis suggest continuation of anticoagulation while a malignancy is "active." As the risk of thrombosis in PV is clearly related to the hematocrit, we regard stable control of hematocrit (<0.45 for males and <0.42 for females) as being sufficient to allow cessation of anticoagulation in most patients with standard DVT or PE, provided that they have been treated for at least 3 months, and that the clot had resolved completely on repeat imaging. As aspirin is effective in preventing recurrent thrombosis following cessation of anticoagulation in patients without PV, and as aspirin may have beneficial effects in PV, we routinely prescribe ongoing aspirin in patients who completed anticoagulation therapy for VTE.

A more difficult question arises when it comes to life- or limb-threatening thrombosis, or clots in unusual sites (e.g., the brain and the splanchnic circulation). When these occur in the general population outside of PV, the risk–benefit ratio often favors indefinite anticoagulation, providing that no contraindications to anticoagulation exist. To that extent, we note, for example, the European Leukemia Network recommendation of lifelong anticoagulation for patients with splanchnic vein thrombosis. For thrombosis in unusual but less critical sites (e.g., the upper limb), the duration of treatment depends on the individual risk–benefit ratio, but for most standard-risk patients we have tended to anticoagulate for 3 months and until the hematocrit is well controlled, and then bridge onto ongoing aspirin therapy.

7. Should reduction in *JAK2V617F* allele burden be a therapeutic goal in PV?

The short answer in clinical practice is "no." The major cause of morbidity and mortality in PV is thrombosis, which is related to the intensity of hematocrit control. Most PV-specific therapies (with the possible exception of interferon) fail to reduce the *JAK2V617F* burden, but result in survival prolongation through reduction of thrombotic risk.

However, as we improve our ability to prevent CV events through effective control of the hematocrit, the risk of clonal progression to AML and myelofibrosis becomes increasingly relevant. Multiple studies have documented an AML progression rate of approximately 0.8% per year in patients treated with venesection or hydroxyurea. This risk is now relatively important, considering that the risk of cardiovascular death or thrombosis is 1.1% per year in optimally controlled PV. Therefore, future studies will likely start to focus on reduction of the neoplastic clone as

a therapeutic endpoint, based on the premise (established from treatment of chronic myeloid leukemia) that suppression of the chronic-phase disease may reduce the subsequent risk of transformation.

8. How do we interpret the presence of significant bone marrow fibrosis in patients with PV?

It is a common misconception that the presence of marrow reticulin fibrosis in patients with PV represents transformation to post-PV myelofibrosis. In fact, approximately 30% of marrow specimens in patients with uncomplicated PV have varying degrees of reticulin fibrosis. Compared with patients without marrow fibrosis, patients with reticulin fibrosis are more likely to have palpable splenomegaly and transform to overt myelofibrosis, but they have similar overall and leukemia-free survival.

The consensus criteria for diagnosis of post-PV myelofibrosis have been published recently. Required criteria are (i) a documented history of PV, and (ii) significant marrow fibrosis (grade 2 to 3 on a 0–3 scale, or grade 3 to 4 on a 0–4 scale). In addition, the patient must have at least two clinical manifestations of myelofibrosis, as defined by (i) anemia or sustained loss of requirement of treatment for erythrocytosis, (ii) a leucoerythroblastic blood film, (iii) increasing or newly palpable splenomegaly, and (iv) development of constitutional symptoms (>10% weight loss, night sweats, and unexplained fever). Thus, post-PV myelofibrosis is a clinicopathological diagnosis, and not one based on marrow appearances alone.

9. Is hydroxyurea therapy truly devoid of leukemia risk?

Acute leukemia is a rare but devastating complication of PV. Early reports suggested a relationship between the occurrence of acute leukemia and exposure to mutagenic therapy, but the widespread use of alkylating agents and radiation-based treatment precluded a clear assessment of the underlying leukemia risk. It was not until the PVSG-01 study that the question of acute leukemia in relation to treatment was addressed definitively. This study randomized 431 patients (1:1:1) to treatment with venesection alone, with chlorambucil, or with radioactive phosphorus. At a median follow-up of 6.5 years, acute leukemia occurred in 1 (venesection), 9 (radioactive phosphorus), and 16 (chlorambucil) patients, respectively. PVSG-01 not only demonstrated the mutagenicity of radioactive phosphorus and alkylating agents, but also underscored the low inherent risk of leukemic transformation in non-exposed patients.

The ECLAP study provided further insight into the natural risk of leukemia in patients with PV. Among 1638 patients with PV followed for a median duration of 2.8 years, 22 cases of AML–MDS were diagnosed. Patients were managed according to local practices. Not surprisingly, high rates of AML–MDS were encountered in patients receiving radioactive phosphorus or alkylating agents at registration. The crude AML–MDS rates were 7.3% and 6.4%, respectively. Among patients not receiving treatment, or treated with venesection or interferon, AML–MDS occurred in 5 of 664 (0.8%) over the study period. This rate is the same as that of patients treated with hydroxyurea as the only cytoreductive drug (6 of 736, or 0.8%). Thus, with the caveat of short follow-up, ECLAP provides some degree of assurance that the leukemia risk of hydroxyurea is similar to that of the natural history of PV.

The French randomized study of pipobroman versus hydroxyurea as a first-line therapy of PV provides further evidence for the low risk of acute leukemia in patients receiving long-term hydroxyurea. This study randomized 285 patients younger than 65 years to (1:1) hydroxyurea or pipobroman, with a very mature median follow-up of 16.3 years. The actuarial risk of AML–MDS for patients treated exclusively with hydroxyurea was 7.3% at 10 years, 10.7% at 15 years, and 16.6% at 20 years (i.e., approximately 0.8% per year). Importantly, the AML–MDS risk of pipobroman was approximately double that of hydroxyurea at every time point.

Finally, a case–control study of 162 patients who developed AML–MDS in a nationwide myeloproliferative diseases cohort found that 25% of AML occurred in patients never exposed to cytoreductive therapy, and that there was no dose–response effect of hydroxyurea therapy on the subsequent risk of AML–MDS.

So is hydroxyurea free from leukemia risk? This question cannot be answered definitively on current evidence, except to note that with the exception of interferon, hydroxyurea is the safest cytoreductive drug with respect to leukemogenicity. In the context of risks associated with even moderately controlled PV, for example the approximately 3% per year risk of major thrombosis or CV death in inadequately treated patients, the risk–benefit ratio for hydroxyurea is justified in patients in whom alternate treatment fails to adequately control their hematocrit.

10. How do we advise a female with PV who wishes to pursue pregnancy?

PV predominantly occurs in older males, and it is relatively rare in females of reproductive age (incidence 0.04–0.25 per 100,000 at the ages of 20–39 years). For this reason, there is little information pertaining to pregnancy in patients with PV, with the largest review comprising only 36 pregnancies in 18 patients. Even in healthy individuals, pregnancy itself is a prothrombotic state. Not surprisingly, most complications that occur in patients with myeloproliferative diseases relate to thrombosis, whether placental (fetal loss and intrauterine growth retardation) or maternal (venous thromboembolism).

Harrison reviewed published literature on PV and pregnancy in 2005. Of 36 pregnancies published in reports, fetal loss occurred in 15 (42%). Maternal morbidity was substantial, with three VTE (one fatal), four preeclampsia, and one postpartum hemorrhage. Eleven pregnancies were managed on a formal protocol comprising venesection, aspirin, and prophylactic low-molecular-weight heparin, as well as interferon as appropriate. These 11 pregnancies resulted in 10 live births without intrauterine growth retardation or maternal complications.

Hence, successful pregnancies can occur in patients with PV, provided that the patient is managed jointly by an experienced team of a hematologist, obstetrician, and ultrasonographer, and meticulous attention is paid to thromboprophylaxis and control of the hematocrit. Patients should cease hydroxyurea for 3–6 months prior to conception, and receive aspirin prophylaxis throughout pregnancy, as well as low-molecular-weight heparin for 6 weeks postpartum. Venesections should either target a hematocrit of 0.36, or aim to maintain the hematocrit in the gestation-appropriate reference range. Patients at especially high risk (e.g., those with previous late-term loss or other severe pregnancy complications, platelets $>1500\times10^9$/L, or VTE within the past 6 months) should receive additional prophylaxis, including interferon and antenatal coverage with low-molecular-weight heparin. Iron supplementation should be avoided. In the postpartum period, women who are breastfeeding can continue to receive aspirin and low-molecular-weight heparin, but they should avoid hydroxyurea and interferon.

Selected reading

Landolfi R, Marchioli R, Kutti J, *et al*. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004; 350(2):114–24.

Marchioli R, Finazzi G, Landolfi R, *et al*. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol. 2005;23(10):2224–32.

Marchioli R, Vannucchi AM, Barbui T. Treatment target in polycythemia vera. N Engl J Med. 2013;368(16):1556.

Passamonti F. How I treat polycythemia vera. Blood. 2012; 120:275–84.

Spivak JL. Polycythemia vera: myths, mechanisms, and management. Blood. 2002;100(13):4272–90.

CHAPTER 25

Essential thrombocytosis

Paola Guglielmelli and Alessandro M. Vannucchi
The University of Florence, Florence, Italy

Case study 25.1

A 35-year-old, otherwise healthy woman presents with thrombocytosis, ranging from 495 $\times$ 10^9/L to 600 $\times$ 10^9/L, which is reproducibly detected in several complete blood counts (CBCs) performed over the last 3 years. Possible causes of reactive thrombocytosis were excluded, and the referring physician favored a diagnosis of essential thrombocythemia (ET).

1. Should the patient perform additional tests?

A. No, the diagnosis can be made as such, considering the exclusion of reactive causes and the persistence of thrombocytosis over the past 3 years
B. Yes, additional tests are needed before we can conclude that this is essential thrombocythemia

The revised 2008 World Health Organization (WHO) criteria for the diagnosis of ET require all of the following: (i) a confirmed platelet count >450 $\times$ 10^9/L; (ii) results of bone marrow biopsy showing normal or slightly reduced cellularity with no or little granulocyte or erythroid proliferation, accompanied by marked proliferation of large and mature-appearing megakaryocytes; (iii) exclusion of other myeloid disorders mimicking ET, including chronic myelogenous leukemia, polycythemia vera (PV), primary myelofibrosis (PMF), and some myelodysplastic syndromes (MDS); and (iv) demonstration of the *JAK*2V617 mutation or any other clonal marker, or, in the absence of a clonal marker, no evidence of reactive thrombocytosis. Therefore, we would recommend that this subject undergoes bone marrow biopsy and mutational analysis for *JAK*2V617F, bearing in mind that up to 40% of ET patients may be lacking the mutation. In specialized laboratories, mutations in the thrombopoietin receptor gene *MPL* (particularly at codon 515) can also be searched for; *MPL* mutations account for about 5% of ET patients without the *JAK*2V617F abnormality.

In 2013, mutations in the calreticulin (*CALR*) gene were discovered in 60–80% of patients with *JAK*2V617F and *MPL* unmutated patients (Klampfl *et al.*; Nangalia *et al.*) accounting for 15–25% of all patients with essential thrombocytosis. Therefore, search for *CALR* mutations represents a second line molecular test to be order in the *JAK*2V617F mutation test is negative in the diagnostic process for suspected thrombocytosis.

My patient, as above, performed bone marrow biopsy and the *JAK*2V617F mutation analysis; the latter was ranked as "positive" from the reference laboratory. However, I am aware that other laboratories also perform a quantitative analysis of the amount of mutated alleles (expressed as the ratio of mutated to wild-type alleles).

2. Do I need to perform this measurement in any patient with ET?

A. No
B. Yes

At present, there is no obvious clinical impact of measuring the *JAK*2V617F allele burden outside a clinical study. Usually, patients with ET have an allele burden in the lowest quartile (as opposed to patients with PV and PMF, in whom the median allele burden is in the second to fourth quartile),

Acknowledgments: Supported by the AIRC (Italian Association for Cancer Research) program "Special Program Molecular Clinical Oncology 5 $\times$ 1000" to the AIRC–Gruppo Italiano Malattie Mieloproliferative (AGIMM) group (project no. 1005; a detailed description of the AGIMM project is available at www.progettoagimm.it).

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

but this cannot be used as a criterion for differential diagnosis among the three classic MPNs, due to their significant overlapping. Furthermore, although several studies, including three meta-analyses, have shown that *JAK2*V617F-mutated ET patients are more prone to arterial and venous thrombosis than those with the wild-type counterpart, positivity for the *JAK2*V617F mutation is not (yet) accepted as a criterion for definition of "high-risk disease" and, consequently, for adjusting therapeutic management. Finally, although a higher allelic burden and/or its progressive increase have been associated with transformation to post-ET myelofibrosis, there is currently no recommendation to monitor changes in *JAK2*V617F allelic burden over time.

Case study 25.2

A 66-year-old man with a history of asymptomatic ET for the last 23 years came to my attention after almost 5 years of not seeing a hematologist. In recent months, he developed night sweats, occurring at least twice per week, and had lost appetite and almost 5 kg of body weight. His family doctor ordered a CBC and routine biochemical tests. The leukocyte count was 12×10^9/L, the automated differential count was reported as normal, the platelet count had dropped from the usual 700–850 $\times 10^9$/L to 235 $\times 10^9$/L, and his hemoglobin was 10.1 g/dL. Routine biochemistry was within normal range, except for a modest increase of transaminases. Physical examination revealed splenomegaly, 5 cm from the left costal margin. I examined his blood smear and found 3% myelocyte, 2% erythroblasts, and abnormalities of red blood cell morphology with a few dacryocytes.

- **How should I interpret these findings?**

These findings are very suggestive of a myelofibrotic transformation. According to the criteria established by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), a suspicion of post-ET MF should be corroborated by the two "required" findings [a previous diagnosis of ET according to WHO criteria, and a grade 2–3 (according to the European classification) or grade 3–4 (according to standard classification) fibrosis in bone marrow biopsy] and at least two of the following "additional" criteria: anemia or a $\geq$2 g/dL decrease from baseline hemoglobin level, a leukoerythroblastic peripheral blood picture, increasing splenomegaly of at least 5 cm from the left costal margin or the appearance of a newly palpable splenomegaly, a lactate dehydrogenase value above reference level, and the development of at least one of three constitutional symptoms (night sweat, >10% body weight loss in 6 months, and/or unexplained fever). Therefore, this patient should undergo bone marrow biopsy to corroborate the clinical suspicion.

Case study 25.3

I have a totally asymptomatic patient with thrombocytosis (ranging from 850 to 1000 $\times 10^9$/L), normal Hb level, and minimal leukocytosis (10 to 11.2 $\times 10^9$/L). His *JAK2*V617F mutation is positive, and his BCR–ABL is negative. Physical examination is negative, with no spleen enlargement. I made a suspicion of essential thrombocythemia and, to fulfill the 2008 WHO criteria, I prescribed bone marrow biopsy. However, unexpectedly, I got back a diagnosis of "prefibrotic myelofibrosis" from the histopathologist. I have no experience on this topic.

- **What should I do?**

Prefibrotic myelofibrosis is considered a distinct entity from classical, or "true," essential thrombocythemia based on histological features that include a hypercellular, age-matched appearance, usually with increased granulocytopoiesis and reduced erythropoiesis; these findings differ from those of classical essential thrombocythemia, in which cellularity is normal or slightly decreased and there is no significant change in myeloid or erythroid representation. However, the most compelling changes involve the megakaryocytic lineage: in prefibrotic myelofibrosis, megakaryocytes appear as organized in dense or loose clusters, are medium to large size, and have irregular nuclei with a bulbous or staghorn appearance; in essential thrombocythemia, megakaryocytes are dispersed and of late-maturing appearance. In both conditions, there is no or insignificant increase of reticulin fibers. The reproducibility of differential diagnosis and the existence of prefibrotic myelofibrosis as a distinct entity have been questioned by several experts. However, at least two large series have highlighted the clinical relevance of such a differential diagnosis. In a large multicenter European study that included 891 and 190 patients with essential thrombocythemia and prefibrotic myelofibrosis, respec-

(*Continued*)

tively, the latter group of patients showed significantly greater risk of transformation to myelofibrosis (incidence was 1.0 vs. 0.5 per 100 patient-years) or acute leukemia (0.6 vs. 0.1 per 100 patient-years), and a rate of death that was double (2.7 vs. 1.3 per 100 patient-years). The overall survival of the entire cohort of prefibrotic myelofibrosis patients was significantly reduced compared to that of those with essential thrombocythemia, which in turn was very close to that of a normal population. Finally, although there was no difference in thrombosis between the two groups, the rate of hemorrhage was significantly increased in prefibrotic myelofibrosis (1.4 vs. 0.8 per 100 patient-years). In a multivariable analysis, predictors of bleeding included a diagnosis of PMF [hazard ratio (HR): 1.74], leukocytosis (HR: 1.74), previous hemorrhage (HR: 2.35), and aspirin therapy ($P = 0.001$; HR: 3.16). However, there is as of yet no substantiated evidence that clinical behavior should differ in prefibrotic myelofibrosis as compared to essential thrombocythemia. Therefore, conventional management of patients with prefibrotic myelofibrosis does not differ substantially from that of those with essential thrombocythemia. However, because the aforementioned studies revealed that major bleeding episodes may occur more frequently in prefibrotic myelofibrosis as opposed to WHO-defined ET, some caution should be exerted in indiscriminately prescribing aspirin to these subjects. Finally, some early studies suggest that treatment with interferon may retard progression, but such potentially relevant observations need to be confirmed prospectively.

• Should all patients with WHO-defined essential thrombocythemia receive some treatment?

Survival in ET does not differ significantly from that of the control population, and no drug yet has been shown to alter the course of the disease. Therefore, the leading criteria for management are related to the risk of thrombosis associated with the individual. In fact, thrombosis represents the leading cause of morbidity and mortality. Age older than 60 years and a history of thrombosis are the criteria used to classify patients into a "high-risk" (when either or both of these is present) or "low-risk" (when both are absent) category. Therapy must be tailored accordingly.

• Does this mean that abnormally increased platelet count is not considered a good reason to start therapy?

Yes, although counterintuitively, there is no evidence that thrombotic risk is associated with increased platelet count. Therefore, platelet count is not a reason to start treatment in an otherwise young, asymptomatic subject with essential thrombocythemia and no previous history of thrombosis. However, "extreme" thrombocytosis (in excess of 1500×10^9/L) is associated with increased risk of hemorrhages, possibly due to an acquired von Willebrand–like disorder. Paradoxically, a platelet count greater than 1000×10^9/L was found to exert a protective effect on thrombosis, supporting previous evidence that thrombosis is not directly associated with a high platelet count.

• Should I use aspirin in all subjects with essential thrombocythemia independent of risk category?

Fatal cardiovascular events represent the commonest cause of death in essential thrombocythemia. Arterial thrombosis, including myocardial infarction, and ictus and peripheral arterial occlusions account for 60–70% of events; venous occlusions may present as peripheral deep venous thrombosis, pulmonary embolism, and splanchnic vein thrombosis. Additional vascular manifestations are represented by microcirculatory disturbances, presenting as erythromelalgia, hearing and visual impairment, headache, dizziness, and recurrent miscarriages, the latter attributed to impaired placental microcirculation and thrombosis. These considerations represent the background for a possible indication to the use of aspirin in essential thrombocythemia. Microvessel manifestations usually respond well to aspirin, which may have a dramatic effect on reversing pain due to erythromelalgia attack; therefore, in patients with clinically significant microvascular manifestations that impair quality of life, prophylactic low-dose aspirin (800–1000 mg daily) is recommended. The migraine or erythromelalgia attacks may require a full aspirin dose that should be limited to a few days (and not as routine attack prophylaxis) due to the risk of hemorrhages. However, whether all low-risk and asymptomatic patients should indiscriminately receive prophylactic low-dose aspirin is a matter of debate. In a retrospective study of 517 low-risk ET patients, the rate of major vascular complications was around 1.5–2.0 per 100 patient-years, which significantly contrasts with a 3% rate per 100 patient-years in the low-risk patients with PV in the ECLAP trial and a 0.54% rate in the healthy subject populations in the Antithrombotic Trialist Collaboration study. The prospective ECLAP study has firmly established the favorable net risk–benefit ratio in PV patients with no clear indication to aspirin, thus supporting the use of aspirin in all risk categories in PV. While these conclusions are simply mutuated in the approach to high-risk ET patients (to whom aspirin is routinely prescribed), it is definitely unclear whether the same applies to low-risk patients as well. One prospective observational trial in low-risk ET is ongoing, and results will very likely help to clarify this issue. Current guidelines from the British Committee for Standards in Hematology suggest that all patients with ET should receive low-dose aspirin unless otherwise contraindicated. However, contrasting results have been reported in a retrospective study of 300 low-risk ET patients either treated with antiplatelet therapy ($n = 198$) or observed only ($n = 102$). Results from that study indicated that there was no significant advantage in using aspirin except in patients who were *JAK2*V617F mutated (where the rate of venous thrombosis was around fourfold greater in the absence of antiplatelet therapy) and

in those who had cardiovascular risk factors and in whom arterial thromboses were increased 5.4-fold. Thus, it is concluded that aspirin treatment should eventually be reserved to the above-delineated category of patients but should not be given as routine primary prophylaxis in all low-risk ET patients. As a matter of fact, ET is also characterized by a paradoxical hemorrhagic tendency that may be unmasked by the use of aspirin, with a double incidence of severe bleeding (from 0.6 to 1.26 per 100 patient-years) in those treated with aspirin. In brief, no evidence-based recommendations can be given. Personally, I do not treat with aspirin low-risk asymptomatic patients younger than 40 with no cardiovascular risk factors. If present, I aggressively pursue a correction of diabetes, hypertension, obesity, and lipid abnormalities and strongly advise patients to immediately stop smoking and refrain from the use of oral contraceptives; in these subjects, however, I recommend low-dose aspirin irrespective of younger age. Most patients tolerate aspirin well, but in cases of gastric symptoms and in those with a history of gastric ulcer, I recommend the addition of a proton pump inhibitor. Currently, there is no experience to favor the use of antiaggregating agents other than aspirin in ET; in particular, the higher gastric bleeding rate seen in subjects receiving clopidogrel versus aspirin plus esomeprazole suggest that such drug combinations may be safer also in patients with a previous history of gastric bleeding when using aspirin alone.

Case study 25.4

My 77-year-old patient with essential thrombocythemia was doing pretty well under hydroxyurea, 1 g daily, for 7 years; her platelet count was steady at 400–500 $\times$ 10^9/L without toxicity on white blood cells (7.9 $\times$ 10^9/L; normal differential count) or hemoglobin (11.3 g/dL). However, she recently presented with bilateral leg ulcers, which appeared 3 months apart and were progressively worsening and very painful. An ecoscan of leg veins and arteries was normal, without significant abnormalities in blood flow; there is no diabetes and no uncontrolled hypertension, and she referred no local trauma in the history.

- **How should I interpret these findings and manage the patient?**

Hydroxyurea is a remarkably well-tolerated cytotoxic drug; however, some patients may develop intolerance to hydroxyurea. Specific criteria for defining a patient as "intolerant" to hydroxyurea have been developed as a consensus statement from a group of experts from the European Leukemia Network (ELN). Intolerance may present as gastrointestinal side effects (nausea, intestinal cramping, and diarrhea; these manifestations are relatively infrequent and usually short-lasting, very rarely forcing one to stop treatment), hydroxyurea-related fever, pulmonary manifestations (exceptionally unusual), or cutaneous toxicities, as in the case of your patient. The latter are quite common (up to 5% of cases) and include alopecia, skin atrophy, squamous dysplasia, hyperpigmentation (especially in sun-exposed areas), nail hyperpigmentation, dermatomyositis-like eruption, and actinic keratosis. The most compelling manifestations (apart from the possibly higher rate of nonmelanoma squamous cell carcinoma attributable to the use of hydroxyurea) are cutaneous ulcers, which are typically located in the perimalleolar or pretibial region, often multiple, and usually very painful. Patients should be alerted about the possibility of this side effect at the time they start hydroxyurea; while ulcers usually appear after several years of hydroxyurea usage, no clear relationships with time of exposure and total drug dose have been found. Local abnormalities and/or systemic diseases may contribute to and facilitate ulcer development. Particular care should be paid to avoid local infections, but there is no standard of care; nurses experienced in ulcer management should be involved in the management from the very beginning. Topical drugs and patches, wound surgical toilette, application of activated platelet rich-plasma preparations, and hyperbaric oxygen therapy are among the most commonly exploited remedies, but their efficacy is unpredictable. In most cases, hydroxyurea must be stopped, because the healing of the ulcers may be significantly delayed (a process that usually requires months to complete), and second-line therapy must be instituted. Considering the age of your patient, and according to the recommendations from the ELN experts, I would shift the patient to busulfan, starting with a low dose (2 mg daily) and adjusting it based on blood cell counts. Anagrelide may be an option, too, but the possibility of cardiac side effects in the aged population should be considered.

Case study 25.5

I was asked by a young woman with *JAK2*V617F-positive essential thrombocythemia, diagnosed soon after she delivered a healthy baby, whether her disease could be passed to her daughter. She read on the web about familiar forms of myeloproliferative neoplasms in general, including essential thrombocythemia.

• What is the best reply?

This anxious mother can be reassured that at present, there is no evidence that the *JAK2*V617F mutation can be inherited. There is one published report of a family with thrombocytosis associated with an inherited *JAK2*V617 mutation, but this was different from the classical VF (it was a V617I amino acid shift), and it did not represent a true MPN. Other inherited forms of thrombocytosis may be associated with the germline transmission of a *MPL*S505N mutation, and these can also quite infrequently be found in apparently sporadic cases of MPN. Also, families with germline transmission of a classical myeloproliferative disorder have been well characterized, but in these families different MPN phenotypes and the presence or absence of the *JAK2*V617F mutation can be encountered. On the other hand, there is epidemiologic evidence that the risk of having a myeloproliferative disorder is increased about sevenfold in the relatives of affected subjects, as shown in a large study from the Swedish registry including more than 37,000 subjects. Both family cases and the epidemiologic observations support the existence of additional mutations other than the *JAK2*V617F mutation as well as inherited predisposition alleles. Genome-wide association studies have resulted in the identification of such a predisposition allele, located in the same *JAK2* gene on chromosome 9, and called 46/1 or GGCC. This haplotype is strongly associated with the *JAK2*V617F and *JAK2* exon 12 mutations and, less strongly, also to *MPL* mutations, suggesting that it can indeed represent a predisposition allele for classical MPN (but not chronic myelogenous leukemia). This said, at present there is no indication (or rationale) to screen for the *JAK2* haplotype or *JAK2* mutations in the relatives of MPN patients unless they have other clinical clues suggestive of MPN.

Case study 25.6

One 31-year-old woman, who had essential thrombocythemia diagnosed 8 years before, was asymptomatic, and was regularly followed in the clinic without any ongoing treatment, came asking if she can become pregnant. In particular, she asked about the risks associated with the pregnancy and the risks for the baby. She is usually around 1 million platelets.

• What is known in regard to this, and how should I manage this pregnancy?

The issue of a pregnancy plan is indeed relatively common among ET patients, who are usually younger than those with other myeloproliferative neoplasms such as polycythemia vera and primary myelofibrosis. Any such request should be handled in the most accurate way, of course, but the woman should feel comfortable in taking the decision to become pregnant after a wise and open discussion with the referring physician. First, the dangers for the mother are minimal, if at all; severe complications have been reported very rarely. However, the woman should be informed that the rate of pregnancy failure is higher than expected in age-comparable healthy women. Up to 50–70% of ET women may expect successful live births; however, first-trimester loss occurs in about 25–40% and late-pregnancy loss in 10% of cases. The rate of abruptio placentae may be about fourfold higher than in the general population (1%) as well as intrauterine growth retardation. Usually, ET women are suggested that they should take low-dose aspirin during the pregnancy, and that it is even better if they start before the planned conception and continue for all the pregnancy, although there is no direct proof that this is really necessary and improves the outcome. According to most experts, even in low-risk patients, low-molecular-weight heparin (4000 U daily) should be started from the 16th week and continued for 6 weeks after delivery. A previous thrombotic history, or repeated ($\geq$3) unsuccessful pregnancies, may require, in selected cases, the addition of low-molecular-weight heparin to aspirin, but the risk of bleeding should also be considered. The platelet count usually decreases in the second trimester, which is similar to but more evident than in healthy women, but platelets usually return to basal levels, or sometimes even greater for a while, after delivery. In cases in which there is a need for cytoreductive therapy, such as in symptomatic disease, elevated leukocytes, or extreme thrombocytosis, interferon can be used. There is no information about anagrelide that it is not allowed during pregnancy.

Case study answers

Case study 25.1

Question 1: Answer B ("Yes")
Question 2: Answer A ("No")

Selected reading

Barbui T, Barosi G, Birgegard G, *et al*. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011;29:761–70.

Barbui T, Thiele J, Vannucchi AM, *et al*. Problems and pitfalls regarding WHO-defined diagnosis of early/prefibrotic primary myelofibrosis versus essential thrombocythemia. Leukemia. 2013;27(10):1953–8.

Barosi G, Mesa R, Finazzi G, *et al*. Revised response criteria for polycythemia vera and essential thrombocythemia: a ELN and IWG-MRT consensus project. Blood. 2013;121(23):4778–81.

Harrison CN, Bareford D, Butt N, *et al*. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol. 2010;149:352–75.

Klampfl T, Gisslinger H, Harutyunyan AS, *et al*. Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms. New England Journal of Medicine. 2013;369:2379–90.

Nangalia J, Massie CE, Baxter EJ, *et al*. Somatic CALR Mutations in Myeloproliferative Neoplasms with Nonmutated JAK2. New England Journal of Medicine. 2013;369:2391–405.

Tefferi A, Barbui T. Personalized management of essential thrombocythemia—application of recent evidence to clinical practice. Leukemia. 2013;27(8):1617–20.

CHAPTER 26

Primary myelofibrosis

Ayalew Tefferi
Mayo Clinic, Rochester, MN, USA

Introduction

Primary myelofibrosis (PMF) is listed under the World Health Organization (WHO) classification category of myeloproliferative neoplasms (MPNs). The operational subcategory of "*BCR–ABL1*-negative MPN" includes PMF, polycythemia vera (PV), and essential thrombocythemia (ET). All three disorders are characterized by stem cell–derived clonal myeloproliferation and the presence of somatic mutations involving *JAK2* (in the majority of patients) and *MPL* or other somatic mutations (in the minority) (Table 26.1). The pathogenetic relevance of *JAK2* or other mutations in MPN is poorly understood and currently under investigation. Regardless, clonal myeloproliferation in PMF is associated with putatively reactive bone marrow (BM) fibrosis, osteosclerosis, angiogenesis, extramedullary hematopoiesis (EMH), and abnormal cytokine expression.

1. How is a diagnosis of PMF established?

PMF is diagnosed according to the WHO system. Post-PV or post-ET MF is diagnosed according to criteria set by the International Working Group for MPN Research and Treatment (IWG-MRT) (Barosi *et al*. 2008). Diagnosis of PMF is suspected in the presence of peripheral blood (PB) leukoerythroblastosis (LES; i.e., the presence of nucleated red cells, immature granulocytes, and dacryocytes). However, LES can result from any form of BM infiltration, including metastatic cancer or lymphoma. Therefore, a BM examination is always indicated in the presence of unexplained LES. BM morphology is key in diagnosing PMF and distinguishing it from reactive bone marrow fibrosis or other myeloid malignancies. In addition, the presence of *JAK2V617F* or of trisomy 9 and del(13q) is highly suggestive of the diagnosis.

2. What are the differences between the International Prognostic Scoring System (IPSS), dynamic IPSS (DIPPS), and DIPSS-plus?

Current prognostication in PMF is best accomplished by the use of the IPSS, DIPSS, or DIPSS-plus. The IPSS is applicable at the time of initial diagnosis and uses five independent predictors of inferior survival: age >65 years, hemoglobin <10 g/dL, leukocyte count $>25 \times 10^9$/L, circulating blasts ≥1%, and the presence of constitutional symptoms. The presence of 0, 1, 2, and ≥3 adverse factors defines low-risk, intermediate-1 risk, intermediate-2 risk, and high-risk disease, respectively. The corresponding median survivals were 11.3, 7.9, 4, and 2.3 years. DIPSS and DIPSS-plus are applicable at any time during the disease course. DIPSS assigns two, instead of one, adverse points for hemoglobin <10 g/dL, and risk categorization is accordingly modified: low (0 adverse points), intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points), and high (5 or 6 points). The median survival was not reached in low-risk patients; it was 9.8 years in intermediate-1, 4.8 years in intermediate-2, and 2.3 years in high risk.

DIPSS-plus includes three additional DIPSS-independent risk factors: platelet count $<100 \times 10^9$/L, red cell transfusion need, and unfavorable karyotype. The four DIPSS-plus risk categories based on the aforementioned eight risk factors (Table 26.2) are low (no risk factors), intermediate-1 (one risk factor), intermediate-2 (two or three risk factors), and high (four or more risk factors), with respective median survivals of 15.4, 6.5, 2.9, and 1.3 years. An unfavorable karyotype for the DIPSS-plus system includes a complex

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 26.1 World Health Organization (WHO) diagnostic criteria for polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PM) (Source: Tefferi A, *et al*. Blood. 2007;110:1092–7).

2008 WHO Diagnostic Criteria						
		Polycythemia vera[a]		**Essential thrombocythemia**[a]		**Primary myelofibrosis**[a]
Major criteria	1	Hgb >18.5 g/dL (men) Hgb >16.5 g/dL (women) *or*[b]	1	Platelet count ≥450 × 10^9/L	1	Megakaryocyte proliferation and atypia[c] accompanied by either reticulin and/or collagen fibrosis, *or*[d]
	2	Presence of *JAK2V617F* or *JAK2* exon 12 mutation	2	Megakaryocyte proliferation with large and mature morphology	2	Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasms
			3	Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasms	3	Demonstration of *JAK2V617F* or other clonal marker *or* no evidence of reactive marrow fibrosis
			4	Demonstration of *JAK2V617F* or other clonal marker *or* no evidence of reactive thrombocytosis		
Minor criteria	1	BM trilineage myeloproliferation			1	Leukoerythroblastosis
	2	Subnormal serum EPO level			2	Increased serum LDH level
	3	EEC growth			3	Anemia
					4	Palpable splenomegaly

BM, bone marrow; CML, chronic myelogenous leukemia; EEC, endogenous erythroid colony; EPO, erythropoietin; Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; PMF, primary myelofibrosis; PV, polycythemia vera.
[a]PV diagnosis requires meeting either both major criteria and one minor criterion *or* the first major criterion and two minor criteria. ET diagnosis requires meeting all four major criteria. PMF diagnosis requires meeting all three major criteria and two minor criteria.
[b]Hgb or Hct >99th percentile of reference range for age, sex, or altitude of residence; *or* red cell mass >25% above mean normal predicted; *or* Hgb >17 g/dL (men) or >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency.
[c]Small to large megakaryocytes with an aberrant nuclear–cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.
[d]In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis (i.e., prefibrotic PMF).

Table 26.2 Risk stratification and risk-adapted therapy in primary myelofibrosis (PMF)

DIPSS-plus[a] risk groups PMF	Median survival	Management of PMF
Low risk (no risk factors)[b]	~15.4 years	Observation *or* conventional drugs[c]
Intermediate-1 risk (1 risk factor)[b]	~6.5 years	Observation *or* conventional drugs[c] *or* experimental drugs
Intermediate-2 risk (2 or 3 risk factors)[b]	~2.9 years	Allo-HCT *or* experimental drugs
High risk (≥4 risk factors)[b]	~1.3 years	Allo-HCT *or* experimental drugs

DIPSS, Dynamic International Prognostic Scoring System.
[a]Information in this column from Gangat N *et al*. J. Clin Oncol. 2011;9(4):392–7.
[b]DIPSS-plus uses eight risk factors for inferior survival: age >65 years, hemoglobin <10 g/dL, leukocyte count >25 × 10^9/L, circulating blasts ≥1% , presence of constitutional symptoms, presence of unfavorable karyotype, platelet count <100 × 10^9/L and presence of red cell transfusion need. Please note that a transfusion-dependent patient automatically has two risk factors because of transfusion need (one risk point) and hemoglobin <10 g/dL (one risk point).
[c]Androgen preparations or thalidomide with prednisone for anemia; hydroxyurea for symptomatic splenomegaly.

karyotype or sole or two abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement. DIPSS-plus was recently further enhanced by the identification of patients with AML-like prognosis, defined by the presence of monosomal karyotype, inv(3) and i(17q) abnormalities, or any two of the following: circulating blasts >9%, leukocytes $\geq 40 \times 10^9$/L, or another unfavorable karyotype. Leukemic transformation in PMF is predicted by unfavorable karyotype and platelet count $<100 \times 10^9$/L. Emerging data suggest an additional adverse prognostic effect from certain molecular markers (e.g., *IDH*, *EZH2*, *SRSF2*, or *ASXL1* mutations) and increased serum interleukin 8 (IL-8) and IL-2 receptor levels or serum-free light chain levels. Interestingly, the additional prognostic value of somatic mutations was studied in 879 PMF patients and identified *ASXL1* mutations as a DIPSS-plus independent risk factor. The combined consideration of *CALR* and *ASXL1* mutations in PMF was also recently highlighted by showing the best survival in the presence of *CALR* and absence of *ASXL1* mutation (i.e. *CALR+ASXL1-*) and worst survival in patients with *CALR–ASXL1+* mutational status.

3. Does diagnosis of PMF always warrant therapy?

Treatment in PMF is based on risk category per DIPSS-plus (see Table 26.2 and Figure 26.1). In general, asymptomatic patients with low-risk or intermediate-1 risk disease can be observed without any type of treatment intervention. Specific symptoms dictate the type of therapy in symptomatic patients with low- or intermediate-1 risk disease. Accordingly, symptomatic anemia might be managed with androgen preparations [e.g., testosterone enanthate 400–600 mg IM weekly, oral fluoxymesterone 10 mg three times daily (TID); side effects include hepatotoxicity or virilizing effects], prednisone (0.5 mg/kg/day), danazol (600 mg/day), thalidomide (50 mg/day; side effects include peripheral neuropathy) ± prednisone, or lenalidomide (10 mg/day; works best in the presence of 5q−, and side effects include myelosuppression) ± prednisone (10 mg/day). Erythropoiesis-stimulating agents (ESAs) are best avoided because of their potential to exacerbate splenomegaly. One can expect a response rate of 10% to 30% with the use of the aforementioned drugs for PMF-associated anemia, and one can expect a response duration of 6 to 24 months. PMF-associated splenomegaly might not need therapy as long as it is asymptomatic. Otherwise, hydroxyurea is the first-line drug of choice. Side effects of hydroxyurea include myelosuppression and mucocutaneous ulcers. Usually, the degree of splenomegaly in low or intermediate-1 risk patients is not severe enough to require any other therapy, including ruxolitinib, splenectomy, or radiotherapy.

4. What is the best way to treat a DIPPS-plus-defined high-risk or intermediate-2 risk group of patients?

High or intermediate-2 risk patients with PMF should always be considered for either investigational drug therapy or allogeneic hematopoietic cell transplant (allo-HCT). Because ruxolitinib [the new Janus kinase (JAK)

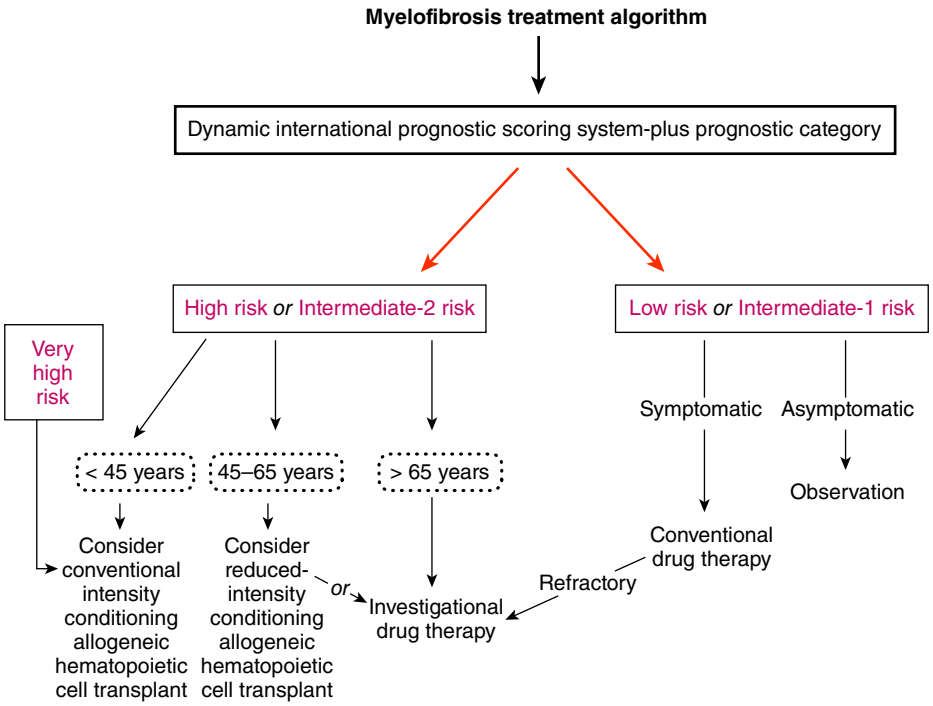


Fig. 26.1 Treatment algorithm for primary myelofibrosis. High-risk, intermediate-2, intermediate-1, and low-risk categories are according to the Dynamic International Prognostic Scoring System (DIPSS)-plus. A very high-risk group includes patients with monosomal karyotype, inv(3) and i(17q) abnormalities, or any two of the following: circulating blasts >9%, leukocytes $\geq 40 \times 10^9$/L, or another unfavorable karyotype. CIC, conventional intensity conditioning; RIC, reduced-intensity conditioning; allo-HCT, allogeneic stem cell transplant.

inhibitor approved for use in PMF] does not modify the natural history of the disease and does not favorably affect bone marrow fibrosis or clonal myeloproliferation, patients with high-risk or intermediate-2 risk disease are best served by participation in clinical trials or consideration of allo-HCT. As outlined in Figure 26.1, allo-HCT is the preferred treatment for "very-high-risk" disease, which is defined by the presence of monosomal karyotype, inv(3) and i(17q) abnormalities, or any two of the following: circulating blasts >9%, leukocytes $\geq 40 \times 10^9$/L, or another unfavorable karyotype. However, the risk of transplant-related complications might not be justified in those patients in whom median survival is expected to be >5 years, and such patients are best managed with experimental drug therapy.

5. Which group of patients may benefit from ruxolitinib therapy in PMF?

Ruxolitinib is a *JAK1–JAK2* inhibitor, which was approved (on November 16, 2011) by the U.S. Food and Drug Administration for use in patients with high- or intermediate-risk disease. The drug was initially evaluated in 153 patients with PMF or with post-PV or post-ET MF, in a phase I/II study where dose-limiting toxicity (DLT) was thrombocytopenia and the maximum tolerated dose (MTD) was established as 25 mg twice daily or 100 mg once daily. Drug-associated adverse events included thrombocytopenia, anemia, and a "cytokine rebound reaction" upon drug discontinuation, which is characterized by acute relapse of symptoms and splenomegaly. In this original study, grade 3/4 thrombocytopenia or anemia occurred in 39% and 43% of patients, respectively. Drug benefits included a ≥50% decrease in palpable spleen size in approximately 44% of the patients and the alleviation of constitutional symptoms in the majority of patients. The drug had no remarkable effect on the *JAK2V617F* allele burden or bone marrow fibrosis. The mechanism of action is currently believed to be related to the drug's ability to downregulate proinflammatory cytokines.

The above-mentioned observations were recently confirmed by two randomized studies comparing ruxolitinib with either placebo or best available therapy. In the placebo-controlled COMFORT-1 trial, the spleen response rate was approximately 42% for ruxolitinib versus <1% for placebo, and 46% of patients derived symptomatic relief. However, the benefit of the drug was undermined by ruxolitinib-associated anemia (31% vs. 13.9% for placebo) and thrombocytopenia (34.2% vs. 9.3% for placebo). In the best available therapy-controlled COMFORT-2 trial, the spleen response was 28.5% with ruxolitinib versus 0% otherwise, but the drug was again associated with thrombocytopenia (44.5% vs. 9.6%), anemia (40.4% vs. 12.3%), and diarrhea (24.0% vs. 11.0%). Furthermore, the treatment discontinuation rate was very high, ranging from 50% to 92% in the first 2 years, and upon treatment discontinuation, "ruxolitinib withdrawal syndrome" might ensue and is characterized by acute relapse of disease signs and symptoms and occasional hemodynamic decompensation.

6. Is there a role of splenectomy in PMF?

Indications for splenectomy in PMF include drug-refractory and severely symptomatic splenomegaly, symptomatic portal hypertension, severe thrombocytopenia, and frequent red blood cell transfusions. In general, symptomatic relief is expected in the majority of splenectomized patients with MF, and about 50% of those requiring red blood cell transfusions become transfusion independent after splenectomy. In a recent report of 314 splenectomized patients with MF, more than 75% benefited from the procedure and the benefit lasted for a median of one year. Procedure-associated complications occurred in 28% of the patients and included infections, portal vein thrombosis, and bleeding. The perioperative mortality rate was 9%. Approximately 10% of patients experienced progressive hepatomegaly and 29% thrombocytosis after splenectomy. Median survival after splenectomy was 19 months. Leukemic transformation was documented in 14% of patients, whose survival was not different from that of patients without "leukemic transformation."

7. What is the role of radiotherapy in PMF?

Radiotherapy in PMF is most successful in the treatment of nonhepatosplenic EMH, which might involve the vertebral column, lymph nodes, and pleura and peritoneum; treatment consists of low-dose radiotherapy at 100–1000 cGy in 5 to 10 fractions. Diagnosis of PMF-associated pulmonary hypertension is confirmed by technetium-99m sulfur colloid scintigraphy, and treatment with single-fraction (100 cGy) whole-lung irradiation has been shown to be effective. A single fraction of 100 to 400 cGy involved-field radiotherapy has also been shown to benefit patients with PMF-associated extremity pain. Splenic irradiation (100 cGy in 5–10 fractions) induces transient reduction in spleen size but can be associated with severe pancytopenia.

8. What is the role of allogeneic hematopoietic cell transplantation (allo-HCT) in PMF?

In general, allo-HCT is a treatment modality whose benefits should be carefully balanced against its risks. In regard to its role in MF, according to one of the largest relevant studies, 5-year disease-free survival and treatment-related mortality were 33% and 35% for matched related and 27% and 50% for unrelated transplants, respectively, and the outcome did not appear to be favorably affected by reduced-intensity conditioning (RIC). The respective

chronic graft-versus-host disease and relapse rates for matched related transplants were 40% and 32%, respectively, and history of splenectomy did not affect outcome. However, it should be noted that the reports from more recent studies were more promising, with a 100-day mortality rate of 13%, a relapse rate of 11%, and a 7-year survival of 61%. Regardless, allo-SCT remains a difficult treatment option in terms of treatment-related mortality and morbidity, and the timing of transplantation in patients with PMF continues to be debated (the topic is covered in detail in Chapter 30).

9. What are some of the investigational drugs in development?

Pomalidomide, other JAK-inhibiting adenosine triphosphate (ATP) mimetics, and other novel drugs (e.g., mTOR inhibitors) are currently being tested in patients with PMF. Pomalidomide is a thalidomide analog. In the initial phase II randomized study, anemia response was 25% with 2 mg/day of the drug alone or 0.5 or 2 mg/day in combination with prednisone. In a subsequent phase II study, pomalidomide used alone at 0.5 mg/day induced an anemia response of 24% in the presence of *JAK2V617F* and 0% in its absence; in addition, marked splenomegaly was associated with inferior response (11% vs. 38% in the absence of marked splenomegaly). Pomalidomide had no effect on spleen size, but platelet response was seen in 58% of patients with a platelet count of $<100 \times 10(9)/L$. The drug was very well tolerated with very infrequent neuropathy or myelosuppression. *JAK2* inhibitor ATP mimetics other than ruxolitinib include SAR302503, CYT387, lestaurtinib, SB1518, AZD1480, BMS911543, LY2784544, and XL019 (see www.ClinicalTrials.gov). A promising strategy of targeting human telomerase with imetelstat has demonstrated selective anti-clonal activity. Overall response rate of 44% in 33 patients in with high or intermediate-2 risk PMF has been demonstrated. The four (22%) CR patients experienced reversal of BM fibrosis and recovery of normal megakaryocyte morphology. Two CR patients were transfusion-dependent at baseline and became transfusion-independent. Complete molecular responses were documented in 2 CR patients. Among 13 patients with leukocytosis, 10 (77%) normalized their count or had >50% reduction. Eleven (61%) patients had complete or partial resolution of leukoerythroblastosis. The current study signifies the potential value of telomerase-based treatment strategies in PMF and identifies imetelstat as an active drug in that regard.

Selected reading

Gangat N, Caramazza D, Vaidya R, *et al*. DIPSS-Plus: a refined Dynamic International Prognostic Scoring System (DIPSS) for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count and transfusion status. J Clin Oncol. 2011;9(4):392–7.

Koch CA, Li CY, Mesa RA, *et al*. Nonhepatosplenic extramedullary hematopoiesis: associated diseases, pathology, clinical course, and treatment. Mayo Clinic Proc. 2003;78(10):1223–33.

Mesa RA, Nagorney DS, Schwager S, *et al*. Palliative goals, patient selection, and perioperative platelet management: outcomes and lessons from 3 decades of splenectomy for myelofibrosis with myeloid metaplasia at the Mayo Clinic. Cancer. 2006;107(2):361–70.

Tefferi A, Jimma T, Gangat N, *et al*. Predictors of greater than 80% 2-year mortality in primary myelofibrosis: a Mayo Clinic study of 884 karyotypically annotated patients. Blood. 2011;118(17):4595–8.

Tefferi A, Litzow MR, Pardanani A. Long-term outcome of treatment with ruxolitinib in myelofibrosis. New Engl J Med. 2011;365(15):1455–7.

CHAPTER 27

Eosinophilic myeloproliferative disorders

Jason Gotlib

Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA, USA

Case study 27.1

A 54-year-old man with no significant medical history reports a 3-month history of mild fatigue during his annual routine checkup with his internist. The physical examination is unremarkable. A complete blood count (CBC) reveals a white blood cell (WBC) count of 9.6×10^9/L, with the manual differential revealing 45% neutrophils, 20% lymphocytes, 5% monocytes, and 25% eosinophils (absolute eosinophil count: 2.5×10^9/L). The hemoglobin and platelet count are normal.

1. Should the patient be referred to a hematologist for a bone marrow biopsy?

A. Yes

B. No

A systematic approach to the differential diagnosis of eosinophilia should be undertaken before assuming a bone marrow biopsy is immediately necessary to make a diagnosis in this case. The starting point is to recognize the cutoff for a normal eosinophil count. The upper limit of normal for the range of percentage of eosinophils in the peripheral blood is generally 3–5%, with a corresponding absolute eosinophil count (AEC) of $0.35–0.5 \times 10^9$/L. The severity of eosinophilia has been arbitrarily partitioned into mild (AEC from the upper limit of normal to 1.5×10^9/L), moderate (AEC: $1.5–5.0 \times 10^9$/L), and severe (AEC: $>5 \times 10^9$/L). In 2011, the Working Conference on Eosinophil Disorders and Syndromes proposed the term "hypereosinophilia (HE)" for persistent and marked eosinophilia (1.5×10^9/L).

The first step in the work-up of eosinophilia is to rule out reactive (secondary) causes. This requires a thorough history and physical examination to evaluate patient travel and exposures, new medications, and a review of prior blood counts to evaluate the temporality and severity of eosinophilia. In developing countries, eosinophilia most commonly derives from infections, particularly tissue-invasive parasites. In developed countries, allergy/atopy conditions, hypersensitivity conditions, and drug reactions are the most common causes of eosinophilia. Other secondary causes of eosinophilia to consider include collagen-vascular diseases (e.g., Churg-Strauss syndrome and systemic lupus erythematosus), pulmonary eosinophilic diseases (e.g., idiopathic acute or chronic eosinophilia pneumonia, tropical pulmonary eosinophilia, allergic bronchopulmonary aspergillosis, etc.), allergic gastroenteritis (with associated peripheral eosinophilia), and metabolic conditions such as adrenal insufficiency. Malignancies may be associated with secondary eosinophilia, which usually results from elaboration of eosinophilopoietic cytokines such as IL3, IL5, and GM-CSF from the tumor. Such cytokine-driven eosinophilia has been associated with various solid malignancies, Hodgkin and non-Hodgkin's lymphomas, and acute lymphoblastic leukemia.

Routine testing for secondary causes of eosinophilia typically involves ova and parasite testing, and sometimes stool culture and antibody testing for specific parasites (e.g., strongyloides and other helminth infections). The type and frequency of laboratory and imaging tests (e.g., chest X-ray, electrocardiogram and echocardiography, or computed tomography scan of the chest, abdomen, and pelvis) are guided by the patient's travel history, symptoms, and findings on physical examination. For patients with eosinophilia and signs or symptoms referable to lung disease, pulmonary function testing, bronchoscopy with bronchoalveolar lavage or biopsy, and serologic tests (e.g., aspergillus immunoglobulin E (IgE) to evaluate for allergic bronchopulmonary aspergillosis (ABPA)) may be considered.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

The internist finds no reactive causes for eosinophilia. Although a referral is placed to hematology, the patient does not follow up with this consultation. The patient returns 6 months later complaining of increasing shortness of breath with exertion. On physical examination, an S3 murmur is auscultated, the spleen is palpated 5 cm below the left costal margin, and 2+ lower extremity edema is present. The current CBC reveals a WBC count of 23×10^9/L with 32% eosinophils (absolute eosinophil count: $\sim 7.4 \times 10^9$/L). Myeloid immaturity is not present. An echocardiogram reveals a decreased ejection fraction (EF) of 45%. Endomyocardial biopsy reveals an extensive eosinophilic infiltrate. No new reactive causes of eosinophilia have emerged.

2. Does the patient meet the criteria for idiopathic hypereosinophilic syndrome (HES)?

A. Yes
B. No

Idiopathic HES is a diagnosis of exclusion whose criteria include an absolute eosinophil count $>1.5 \times 10^9$/L lasting for more than 6 months, signs of organ damage, and other causes of eosinophilia have been ruled out. Although no obvious causes of reactive eosinophilia have emerged, a work-up for primary (clonal) eosinophilia has not yet been undertaken (Figure 27.1).

The current World Health Organization classification of myeloid neoplasms provides guidance for approaching the

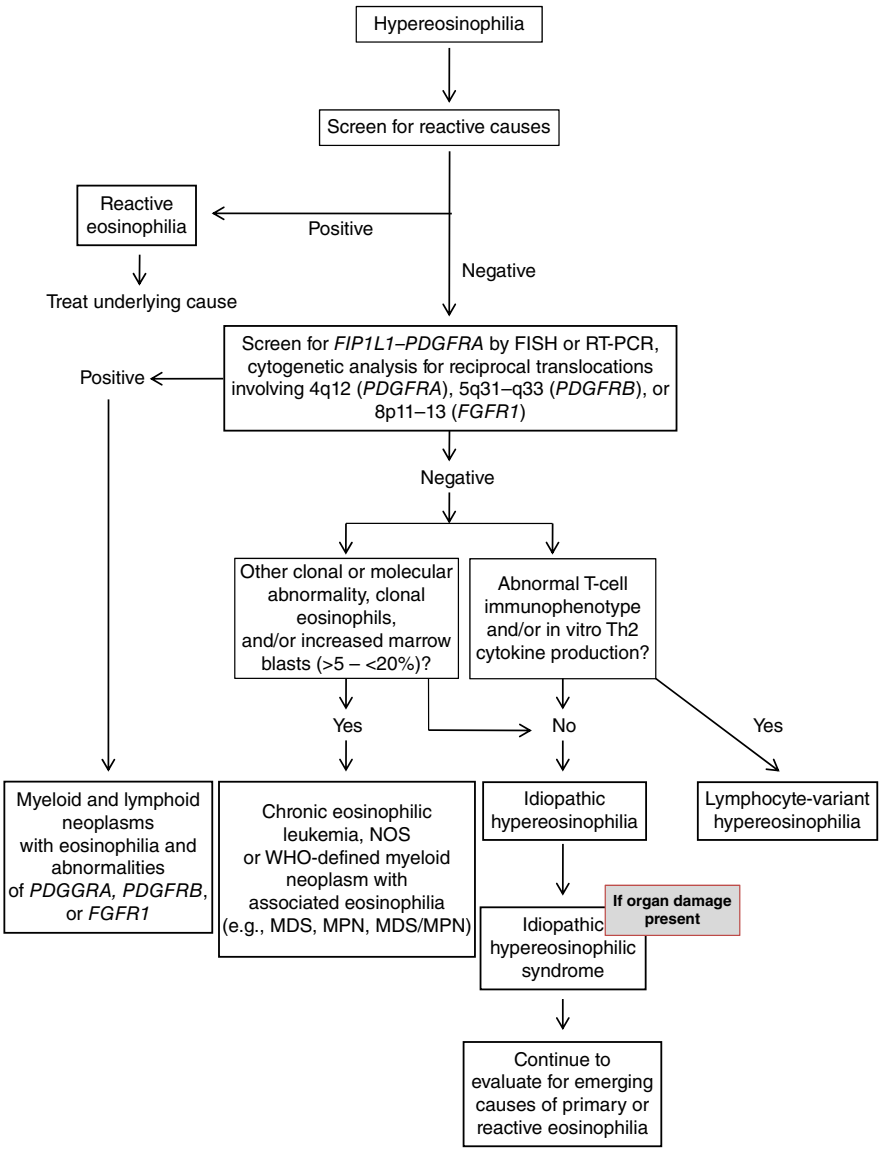


Figure 27.1 Diagnostic algorithm for evaluation of hypereosinophilia. FISH, fluorescent in situ hybridization; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NOS, not otherwise specified; RT-PCR, reverse transcription polymerase chain reaction; WHO, World Health Organization.

evaluation of primary eosinophilias. In the current edition, a new major category was added, "Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB), or fibroblast growth factor receptor 1 (FGFR1)" (Tables 27.1 and 27.2). "Chronic eosinophilic leukemia—not otherwise specified" (CEL-NOS) is another bone marrow–derived eosinophilic neoplasm, one of eight diseases within the World Health Organization (WHO) category of myeloproliferative neoplasms (MPNs) (Tables 27.1 and 27.2). CEL-NOS is defined by the absence of the Philadelphia chromosome or a rearrangement involving *PDGFRA/B* or *FGFR1*. It also excludes other WHO-defined acute and chronic myeloid neoplasms that may be associated with eosinophilia. CEL-NOS is characterized by an increase in blasts in the bone marrow or blood (but fewer than 20% to exclude acute leukemia as a diagnosis), and/or there is evidence for a nonspecific cytogenetic abnormality (e.g., trisomy 8) or other clonal marker (Table 27.2). If none of these entities are identified (including lymphocyte-variant hypereosinophilia; discussed further in this chapter), then the diagnosis of idiopathic hypereosinophilia (organ damage absent) or idiopathic hypereosinophilic syndrome (organ damage present) can be made (Table 27.2).

A time window of sustained eosinophilia for 6 or more months is no longer universally accepted as necessary criterion for HES. In part, this relates to the fact that modern evaluation of eosinophilia can usually proceed rapidly, and some patients may require immediate treatment. It is difficult to predict what duration and severity of eosinophilia will precipitate tissue damage in individual patients. HES is considered a provisional entity that may change to a specific diagnosis if a defined basis for eosinophilia emerges over time.

3. Which of the following genetic markers should be obtained from the peripheral blood as part of the initial work-up of primary eosinophilia in this patient?

A. *JAK2* V617F
B. *BCR–ABL1*
C. Fluorescent in situ hybridization (FISH) for *CHIC2* deletion
D. *FLT3* ITD or D835 mutation

Clues to the presence of a primary eosinophilia may emerge from the evaluation of the blood smear. Review of the peripheral smear for circulating blasts, dysplastic cellular morphology, monocytosis, and elevated serum B_{12} or serum tryptase level(s) in conjunction with bone marrow morphologic, cytogenetic, and immunophenotypic analyses will help identify whether a WHO-defined eosinophilia-associated myeloid neoplasm is present: acute myelogenous leukemia (AML) (esp. inv(16)(p13q22) or t(16;16)(p13;q22)), myelodysplastic syndrome (MDS), systemic mastocytosis (SM), the classic MPNs (chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis), and MDS–MPN overlap disorders (e.g. chronic myelomonocytic leukemia (CMML)) (Table 27.2).

Laboratory evaluation of primary eosinophilia should begin with screening of the peripheral blood for the

(*Continued*)

Table 27.1 2008 World Health Organization (WHO) classification of myeloid malignancies (Source: Swerdlow S, *et al.*, editors. World Health Organization Classification of Tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008).

1. **Acute myeloid leukemia and related disorders**
2. **Myeloproliferative neoplasms (MPN)**
   - Chronic myelogenous leukemia, *BCR-ABL1* positive
   - Chronic neutrophilic leukemia
   - Polycythemia vera
   - Primary myelofibrosis
   - Essential thrombocythemia
   - Chronic eosinophilic leukemia, not otherwise specified
   - Mastocytosis
   - Myeloproliferative neoplasms, unclassifiable
3. **Myelodysplastic syndromes (MDS)**
   - Refractory cytopenia with unilineage dysplasia
     - Refractory anemia
     - Refractory neutropenia
     - Refractory thrombocytopenia
   - Refractory anemia with ring sideroblasts
   - Refractory cytopenia with multilineage dysplasia
   - Refractory anemia with excess blasts (RAEB)
     - RAEB-1
     - RAEB-2
   - Myelodysplastic syndrome with isolated del(5q)
   - Myelodysplastic syndrome, unclassifiable
4. **MDS/MPN**
   - Chronic myelomonocytic leukemia
     - CMML-1
     - CMML-2
   - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
   - Juvenile myelomonocytic leukemia
   - MDS/MPN, unclassifiable
   - Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) (provisional entity)
5. **Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1***
   - Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
   - Myeloid neoplasms associated with *PDGFRB* rearrangement
   - Myeloid and lymphoid neoplasms associated with *FGFR1* abnormalities

Table 27.2 2008 World Health Organization classification of eosinophilic disorders (Source: Swerdlow S, *et al.*, editors. World Health Organization Classification of Tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008).

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*

Diagnostic criteria of an MPN[1] with eosinophilia associated with *FIP1L1–PDGFRA*
A myeloproliferative neoplasm with prominent eosinophilia
and
Presence of a *FIP1L1–PDGFRA* fusion gene[2]

Diagnostic criteria of MPN associated with the *ETV6–PDGFRB* fusion gene or other rearrangement of *PDGFRB*
A myeloproliferative neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis
and
Presence of t(5;12)(q31∼q33;p12) or a variant translocation[3] *or* demonstration of an *ETV6-PDGFRB* fusion gene or rearrangement of *PDGFRB*

Diagnostic criteria of MPN or acute leukemia associated with an *FGFR1* rearrangement
A myeloproliferative neoplasm with prominent eosinophilia and sometimes with neutrophilia or monocytosis
or
Acute myeloid leukemia or precursor T-cell or precursor B-cell lymphoblastic leukemia or lymphoma (usually associated with peripheral blood or bone marrow eosinophilia)
and
Presence of t(8;13)(p11;q12) or a variant translocation leading to *FGFR1* rearrangement demonstrated in myeloid cells, lymphoblasts, or both

Chronic eosinophilic leukemia, not otherwise specified (NOS)

1. There is eosinophilia (eosinophil count $>1.5 \times 10^9$/L).
2. There is no Ph chromosome, *BCR–ABL* fusion gene, other myeloproliferative neoplasms (PV, ET, PMF, or systemic mastocytosis), or MDS/MPN (CMML or atypical CML).
3. There is no t(5;12)(q31∼q35;p13) or other rearrangement of *PDGFRB*.
4. There is no *FIP1L1–PDGFRA* fusion gene or other rearrangement of *PDGFRA*.
5. There is no rearrangement of *FGFR1*.
6. The blast cell count in the peripheral blood and bone marrow is less than 20%, and there is no inv(16)(p13q22) or t(16;16)(p13;q22) or other feature diagnostic of AML.
7. There is a clonal cytogenetic or molecular genetic abnormality, or blast cells are more than 2% in the peripheral blood or more than 5% in the bone marrow.

Idiopathic hypereosinophilic syndrome (HES)

Exclusion of the following:
1. Reactive eosinophilia
2. Lymphocyte-variant hypereosinophilia (cytokine-producing, immunophenotypically aberrant T-cell population)
3. Chronic eosinophilic leukemia, not otherwise specified
4. WHO-defined myeloid malignancies associated eosinophilia (e.g., MDS, MPNs, MDS/MPNs, or AML)
5. Eosinophilia-associated MPNs or AML/ALL with rearrangements of *PDGFRA*, *PDGFRB*, or *FGFR1*
6. The absolute eosinophil count of $>1500/mm^3$ must persist for at least 6 months, and tissue damage must be present. If there is no tissue damage, idiopathic hypereosinophilia is the preferred diagnosis.

[1]Patients presenting with acute myeloid leukemia or lymphoblastic leukemia/lymphoma with eosinophilia and a *FIP1L1–PDGFRA* fusion gene are also assigned to this category.

[2]If appropriate molecular analysis is not available, this diagnosis should be suspected if there is a Ph-negative MPN with the hematological features of chronic eosinophilic leukemia associated with splenomegaly, a marked elevation of serum vitamin B_{12}, elevation of serum tryptase, and increased bone marrow mast cells.

[3]Because t(5;12)(q31∼q33;p12) does not always lead to an *ETV6–PDGFRB* fusion gene, molecular confirmation is highly desirable. If molecular analysis is not available, this diagnosis should be suspected if there is a Ph-negative MPN associated with eosinophilia and with a translocation with a 5q31–33 breakpoint.

FIP1L1–PDGFRA gene fusion by reverse transcription polymerase chain reaction (RT-PCR) or interphase or metaphase FISH (Figure 27.1). Probes are available that hybridize to the region between the *FIP1L1* and *PDGFRA* genes where the *CHIC2* gene is located; its deletion is a surrogate for the cytogenetically occult 800 kb deletion on chromosome 4q12 that results in the *FIP1L1–PDGFRA* fusion. If testing for *FIP1L1–PDGFRA* is not available, evaluation of the serum tryptase level may be a useful ancillary test since increased levels have been associated with the presence of the *FIP1L1–PDGFRA* fusion or other myeloproliferative disorders with hypereosinophilia. Genetic rearrangement of *PDGFRA* (fusion partners besides FIP1L1), *PDGFRB*, and *FGFR1* can usually be inferred by their abnormal karyotype equivalent: rearrangement of 4q12 (*PDGFRA*), 5q31–33 (*PDGFRB*), or 8p11–13 (*FGFR1*). Over 20 gene fusion partners of *PDGFRB* have been described. Eosinophilic myeloid neoplasms related to fusions involving the *FGFR1* gene are similarly rare. In these cases, the association of the t(8p11–13) breakpoint with lymphoblastic lymphoma with eosinophilia and myeloid hyperplasia was first described in 1995. More than 10 fusion partners of *FGFR1* have been reported, with *ZNF198–FGFR1* being the most common.

Although eosinophilia can accompany *BCR–ABL1*-positive chronic myeloid leukemia (CML) (and acute lymphoblastic leukemia (ALL)), as well as *JAK2* V617F–positive MPNs, and these mutation tests can be drawn simultaneously with FISH for the *CHIC2* deletion, there are no other clinicopathologic findings in this particular case to steer the physician to these diagnoses. *FLT3* mutations (ITD or D835) are found primarily in AML and confer a worse prognosis. Interestingly, however, MPN cases of primary eosinophilia associated with reciprocal translocations involving FLT3 (e.g., *ETV6–FLT3*) and JAK2 (e.g., *PCM1–JAK2*) have been published.

The patient undergoes peripheral blood testing with FISH for the *CHIC2* deletion, which is positive in 96/200 cells (48%).

4. What treatment should be initiated?

A. Hydroxyurea
B. Corticosteroids (prednisone 1 mg/kg)
C. Imatinib
D. Imatinib + with an initial course of prednisone 1 mg/kg

Imatinib is first-line therapy in patients with *FIP1L1–PDGFRA*-positive disease and the rare patients with alternate *PDGFRA* fusions or rearranged *PDGFRB*. The hematologic benefit of empiric imatinib in myeloid neoplasms associated with eosinophilia was identified in several early studies before the therapeutic target *FIP1L1–PDGFRA* was identified by Cools *et al*. (2003). Molecular remissions were first reported by the NIH group by PCR testing of the peripheral blood in five of six *FIP1L1–PDGFRA*-positive patients after 1–12 months of imatinib therapy. Several reports have now described rapid induction of molecular remission in imatinib-treated *FIP1L1–PDGFRA*-positive patients. Although 100 mg daily may be sufficient to achieve a molecular remission in some patients, others may require higher maintenance doses in the range of 300–400 mg daily. Maintenance dosing of 100–200 mg weekly may be sufficient to achieve a molecular remission in some patients. The optimal maintenance dose of imatinib that sustains a molecular remission has not been defined.

The natural history of imatinib-treated *FIP1L1–PDGFRA*-positive myeloid neoplasms was evaluated in an Italian prospective cohort of 27 patients with a median follow-up period of 25 months (range: 15–60 months). Patients were dose escalated from an initial dose of 100 mg daily to a final dose of 400 mg daily. Complete hematologic remission was achieved in all patients within 1 month, and all patients became PCR negative for *FIP1L1–PDGFRA* after a median of 3 months of treatment (range: 1 to 10 months). Patients continuing imatinib remained PCR negative during a median follow-up period of 19 months (range: 6–56+ months). Another European study prospectively assessed the natural history of molecular responses to imatinib doses of 100–400 mg daily. Among 11 patients with high pretreatment transcript levels, all achieved a 3-log reduction in transcript levels by one year of therapy, and 9 of 11 patients achieved a molecular remission.

In patients with rearrangements of *PDGFRB* or *PDGFRA* variants other than *FIP1L1–PDGFRA*, case reports and series indicate that imatinib, usually at doses of 400 mg daily, can produce durable hematologic and cytogenetic remissions. Similar to *FIP1L1–PDGFRA*, FISH can be used to assess response to imatinib in *PDGFRB*-rearranged cases.

Cardiogenic shock has been reported in a few *FIP1L1–PDGFRA*-positive patients after initiation of imatinib. Steroids during the first 7–10 days of imatinib treatment is recommended for patients with known cardiac disease and/or elevated serum troponin levels, which may be related to eosinophil-mediated heart damage or other cardiac comorbidities. In this patient with a biopsy-proven cardiac eosinophilic infiltrate and signs of heart failure, it would be prudent to begin this individual on a combination of imatinib and prednisone, with tapering of the latter if there is less concern for cardiac decompensation.

The patient commences imatinib 400 mg daily and achieves a complete hematologic remission within 1 month. Splenomegaly has resolved, but he is maintained on heart failure medications with a repeat echocardiogram (echo) showing an ejection fraction (EF) of 50%. After 3 months, FISH testing for the *CHIC2* deletion from the peripheral blood is negative. The patient is lost to follow-up and comes back to clinic

(*Continued*)

one year later with complaints of night sweats, a 20 pound weight loss, and progressive dyspnea on exertion. The patients reports having stopped imatinib 6 months ago because he "felt well." On exam, splenomegaly 15 cm below the left costal margin is noted. A repeat echo shows a restrictive cardiomyopathy with an EF of 35%. The CBC now reveals a WBC count of 47×10^9/L, hemoglobin 8.5 g/dL, and platelet count 94×10^9/L. The differential reveals 15% neutrophils, 5% bands, 10% lymphocytes, 52% eosinophils, 12% immature myeloids (myelocytes and metamyelocytes), and 6% blasts. The smear reveals occasional teardrop and nucleated red blood cells. A bone marrow biopsy shows marked hypercellularity and eosinophilia, 8% myeloblasts, and MF-2 reticulin fibrosis. Cytogenetics reveals trisomy 8 and del (20q).

5. What is the next step in management?

A. Switch to prednisone.
B. Multi-agent AML-type (idarubicin–cytarabine) chemotherapy
C. *JAK2* V617F mutation testing
D. Sequence analysis of *PDGFRA* to evaluate for resistance mutation(s)

Despite in-depth and durable molecular remissions, discontinuation of imatinib often leads to disease relapse. In a dose de-escalation trial of imatinib in five patients who had achieved a stable hematologic and molecular remission at 300–400 mg daily for at least one year, molecular relapse was observed in all patients after 2–5 months of either imatinib dose reduction or discontinuation. Molecular remissions were reestablished with re-initiation of imatinib in all patients at a dose range of 100–400 mg daily. In a cohort of patients evaluated by the Mayo Clinic, hematologic relapse occurred only several weeks after discontinuation of imatinib in four patients. These data indicate that imatinib does not cure *FIP1L1–PDGFRA*-positive disease and argue for ongoing imatinib therapy to suppress the abnormal clone.

FIP1L1–PDGFRA-positive patients can develop resistance to imatinib, mostly involving the T674I mutation within the ATP-binding domain of *PDGFRA*. T674I *PDGFRA* is analogous to the T315I *ABL1* mutation in CML, which confers pan-resistance to the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. However, unlike CML, secondary resistance is much less common (less than 10 cases are reported in the literature), and is almost exclusively observed during advanced phases of the disease.

Options for second-line treatment for T674I imatinib resistance are limited. One patient with the *FIP1L1–PDGFRA* T674I mutation in blast crisis responded briefly to sorafenib, but this was followed by rapid emergence of a pan-resistant *FIP1L1–PDGFRA* D842V mutant. Other reports have demonstrated either in vitro or in vivo activity of sorafenib, midostaurin (PKC412), or nilotinib against the T674I mutant. The ability of alternative tyrosine kinase inhibitors to elicit durable clinical remissions (despite in vitro data demonstrating inhibitory activity against mutated fusions) has been disappointing.

In this case, it would be premature to use induction chemotherapy since the patient does not have a diagnosis of AML; however, the patient is demonstrating signs of disease progression and may soon require higher intensity therapy such as induction chemotherapy or allogeneic transplantation if a suitable donor can be identified. However, his cardiac function may preclude such options. Although the patient has marked splenomegaly and marrow fibrosis, his diagnosis is not myelofibrosis, and the *JAK2* V617F mutation is unlikely to be present except in rare cases as a tandem mutation. Steroids would not be helpful in this clonal myeloid disorder showing evolution toward AML.

Case study 27.2

A 46-year-old man reports a 4-month history of fevers, night sweats, weight loss, and progressive swelling of lymph nodes in the bilateral cervical, axillary, and inguinal areas. An excisional left inguinal lymph node biopsy reveals T-cell lymphoblastic lymphoma. A CBC reveals a WBC count of 33×10^9/L, with 49% neutrophils; 5% bands; 13% metamyelocytes, myelocytes, and promyelocytes; 4% lymphocytes; 10% monocytes; and 19% eosinophils. A bone marrow biopsy reveals myeloid hyperplasia and moderate eosinophilia. Testing for *BCR–ABL1* and *JAK2 V617F* is negative. Marrow cytogenetics reveal t(8;13)(p11;q12), and sequencing of the partner genes reveals a *ZNF198–FGFR1* fusion.

1. What is the treatment recommendation and prognosis?

A. Imatinib; excellent prognosis
B. FGFR1 tyrosine kinase inhibitor; excellent prognosis
C. AML or ALL-type induction chemotherapy; poor prognosis
D. Hydroxyurea; poor prognosis

This patient has a myeloid neoplasm associated with eosinophilia with rearrangement of *FGFR1* according to the WHO classification. This condition has been alternatively referred to as "8p11 myeloproliferative syndrome" or "stem cell leukemia/lymphoma." The natural history of patients

with myeloid or lymphoid disease with rearranged *FGFR1* follows an aggressive course, usually terminating in AML in 1–2 years. Therefore, intensive chemotherapy with regimens such as hyper-CVAD (directed to treatment of T- or B-cell lymphoma), followed by early allogeneic transplantation, is recommended. The data for use of small molecule inhibitors for patients with *FGFR1*-rearranged disease are minimal. The small-molecule midostaurin (PKC412) inhibited the constitutively activated *ZNF198–FGFR1* fusion in vitro, and elicited a hematologic response in a patient with the fusion.

Case study 27.3

A 61-year-old woman presents with progressive fatigue and crampy abdominal pain with moderate diarrhea. Mild splenomegaly is present on examination. A CBC reveals a WBC count of 28×10^9/L, hemoglobin 8.4 g/dL, and platelet count 82×10^9/L. The differential shows 57% eosinophils without increased blasts or myeloid immaturity. Endoscopy reveals a moderate eosinophil infiltrate on gastric and small duodenal biopsies. No causes for reactive eosinophilia are found. A bone marrow shows a cellularity of 60% with marked eosinophilia and minimal fibrosis without evidence for dysplasia. Cytogenetics is normal. Testing is negative for *BCR–ABL1* and *JAK2* V617F, and there is no evidence for rearrangement of *PDGFRA/B* or *FGFR1*. T-cell receptor gene rearrangement is negative, and immunophenotyping of the bone marrow aspirate reveals a heterogeneous B- and T-lymphocyte population without aberrant markers. A diagnosis of idiopathic HES is made.

1. Which first-line treatment do you recommend?

A. Prednisone
B. Hydroxyurea
C. Interferon-alpha
D. A or B

Corticosteroids (e.g., prednisone 1 mg/kg) are recommended as first-line treatment for HES. Steroids have potent anti-eosinophil activity and can produce rapid reductions in eosinophil count. In a retrospective analysis of 188 patients, 141 HES patients on corticosteroids as first-line monotherapy achieved a complete remission (CR) or partial remission (PR) after one month, with duration of therapy ranging from 2 to 20 years and a median maintenance dose of 10 mg/day. As symptoms improve and eosinophil counts normalize, a steroid taper can be instituted, particularly given the long-term treatment side effects of steroids.

Hydroxyurea at 500–1000 mg daily is also an effective first-line option for HES, with the understanding that, like corticosteroids, hydroxyurea is palliative and does not change the natural course of the disease. Hydroxyurea can be used as monotherapy or in combination with corticosteroids. In the same retrospective study, 64 HES patients (34%) received hydroxyurea monotherapy, with 13 (72%) achieving CR or PR. One should note that for CEL-NOS and steroid-refractory idiopathic HES, hydroxyurea has been used as a first-line treatment.

Interferon alpha (IFNα) has been used effectively to induce hematologic and cytogenetic remissions in patients with HES and CEL-NOS who are refractory to either steroids or hydroxyurea, or administered in addition to corticosteroids as a steroid-sparing agent. Of the 188 patients in a retrospective study, 46 were treated with IFNα in combination with steroids, with response rates ranging from 50% to 75%, respectively. IFNα remissions have been associated with improvement in clinical symptoms as well as occasional improvement or reversion of end-organ injury, including hepatosplenomegaly and cardiac and thromboembolic complications. The optimal starting or maintenance dose of IFNα has not been well defined, but the initial dose required to control eosinophil counts often exceeds the doses required to sustain a remission. Initiation of therapy at 1 million units by subcutaneous injection three times weekly (tiw) and gradual escalation of the dose to 3–4 million units or higher tiw may be required to control the eosinophil count. Treatment of four HES patients with pegylated interferon alpha 2b (PEG-IFNα-2b) among a larger cohort of *BCR–ABL1*-negative MPN patients resulted in one CR and one PR, but side effects required that the initial study dose be reduced from 3 to 2 mcg/kg/week. A lower starting dose of 90 mcg/kg/week (e.g., 1–1.5 mcg/kg/week) is better tolerated based on the experience of PEG-IFNα-2a (Pegasys) in PV and ET. Side effects of short- and longer-acting formulations of IFNα are usually dose dependent and can include fatigue and flu-like symptoms, transaminitis, cytopenias, depression, hypothyroidism, and peripheral neuropathy. IFNα is considered safe for use in pregnancy.

Second- and third-line agents for the treatment of HES have included vincristine, cyclophosphamide, etoposide, 2-chlorodeoxyadenosine alone or in combination with cytarabine, and cyclosporin-A. Imatinib has been used empirically in *PDGFRA/B*-rearrangement-negative patients (e.g., with HES or CEL-NOS). At doses of 400 mg or higher, partial hematologic responses are sometimes observed, but are more often transient and may reflect drug-related myelosuppression.

(*Continued*)

Other treatment options for HES have included the anti-CD52 monoclonal antibody alemtuzumab, based on the expression of the CD52 antigen on eosinophils. In patients with HES who were refractory to other therapies, infusion of alemtuzumab one to three times weekly produced a hematologic remission in 10 of 11 patients (91%), but responses were not sustained when alemtuzumab was discontinued. Longer-term follow-up of patients receiving maintenance therapy on this study was recently reported. Other antibody treatment approaches to HES include the use of mepolizumab, an anti-IL5 humanized monoclonal antibody that inhibits binding of IL5 to the alpha chain of the IL5 receptor found on eosinophils. Mepolizumab has been evaluated in a large, randomized, double-blinded, placebo-controlled trial of 85 HES patients (e.g., *FIP1L1–PDGFRA*-negative patients). Patients were randomized to intravenous mepolizumab 750 mg or placebo every 4 weeks for 36 weeks. No adverse events were significantly more frequent with mepolizumab compared to placebo. A significantly higher proportion of mepolizumab-treated HES patients versus placebo were able to achieve the primary efficacy endpoint of a daily prednisone dose of $\leq$10 mg daily for at least 8 consecutive weeks. Therefore, mepolizumab has a potential role as a steroid-sparing agent for these patients. Mepolizumab has not yet been approved by the US Food and Drug Administration, but is currently available on a compassionate use basis (ClinicalTrials.gov Identifier NCT00244686) for individuals with life-threatening HES who have failed three prior therapies.

Case study 27.4

A 45-year-old man reports a recurrent macular skin rash. A biopsy reveals a mixture of lymphocytes and increased eosinophils in the dermis, but a specific diagnosis is not rendered. A CBC reveals a WBC count of 18×10^9/L with 45% eosinophils. Primary and secondary causes of eosinophilia are ruled out. T-cell receptor gene rearrangement of the peripheral blood is positive. Immunophenotyping of the peripheral blood reveals a population of CD3− CD4+ T-lymphocytes.

1. Does this patient meet the diagnostic criteria for lymphocyte-variant hypereosinophilia?

A. Yes
B. No
C. Additional information is required

If both secondary and primary causes of eosinophilias are excluded, lymphocyte-variant hypereosinophilia should be considered next in the diagnostic algorithm before making a diagnosis of HES. Patients with lymphocyte-variant hypereosinophilia often have cutaneous signs and symptoms as the primary disease manifestation. Although patients' skin disease can by symptomatic, the natural history of this condition is typically indolent, with rare patients progressing to T-cell lymphoma or Sézary syndrome. A clonal T-cell receptor gene rearrangement and/or T-cells with an aberrant immunophenotype are characteristic of lymphocyte-variant hypereosinophilia. Abnormal cell populations that have been described include double-negative immature T-lymphocytes (CD3+, CD4−, and CD8−), an absence of CD3 (CD3− and CD4+), an elevated expression of CD5 on CD3− CD4+ cells, and loss of surface CD7 and/or expression of CD27. Elevated serum IgE levels are also commonly described. Research-based analyses have reported T-cell production of cytokines (e.g., IL5, IL4, and IL13) consistent with a T-cell helper type 2 (Th2) cytokine profile, and production of TARC, a chemokine in Th2-mediated diseases. This syndrome represents a mixture of clonal and reactive processes resulting in the expansion of a clone of T-lymphocytes that produce cytokines that drive eosinophilia. Although these laboratory findings constitute basic elements of this syndrome, neither the WHO nor other consensus panels have established specific diagnostic criteria for this condition. The finding of isolated T-cell clonality by PCR without T-cell immunophenotypic abnormalities or demonstration of Th2 cytokine production is not adequate to make a diagnosis of this variant. In an analysis of patients diagnosed with HES, 18/42 (43%) subjects exhibited a clonal T-cell receptor gene rearrangement by PCR. However, the biologic relevance of such clonal T-cell populations to eosinophilia was not established. Therefore, whether such patients should still be referred to as HES or as lymphocyte-variant hypereosinophilia remains a matter of debate.

2. Which of the following has not been associated with relatively worse outcomes in eosinophilic diseases and MPNs?

A. Cardiac disease
B. Corticosteroid refractoriness
C. Height of eosinophilia
D. Presence of *FIP1L1–PDGFRA*

Older case series identify cardiac disease as the primary etiology of premature death. A review of 57 HES cases published through 1973 reported a median survival of 9 months, and the 3-year survival was only 12%. Patients usually presented with advanced disease, with congestive heart failure

accounting for 65% of deaths at autopsy. In addition to cardiac involvement, peripheral blood blasts and a WBC count greater than 100×10^9/L were poor prognostic factors. A later report of 40 HES patients cited a 5-year survival rate of 80%, which decreased to 42% at 15 years. Factors predictive of a worse outcome included the presence of a myeloproliferative neoplasm, corticosteroid-refractory hypereosinophilia, cardiac disease, male sex, and the height of eosinophilia. It is possible that male sex was identified as a poor prognostic factor because we have learned that almost all patients diagnosed with *FIP1L1-PDGFRA*-positive eosinophilic neoplasms are male. The basis for this gender predominance is unknown. Before the availability of imatinib for such patients, it is quite likely that these individuals experienced poor outcome because their myeloid neoplasms were unsuccessfully treated.

In WHO-defined myeloid malignancies, the prognostic importance of associated eosinophilia has been studied in only a few diseases. In a series of 123 patients with systemic mastocytosis, eosinophilia was prevalent in 34% of cases, but it was prognostically neutral and was not affected by exclusion of *FIP1L1–PDGFRA*-positive cases. In a study of 1008 patients with de novo MDS, eosinophilia (and basophilia) predicted a significantly reduced survival without having a significant impact on leukemia-free survival. A retrospective analysis of 288 individuals with newly diagnosed MDS revealed that significantly higher numbers of patients with eosinophilia or basophilia (compared to patients with neither) had chromosomal abnormalities carrying an intermediate or poor prognosis. In addition, the overall survival rate was significantly lower and a higher rate of evolution to AML was observed.

Case study answers

Case study 27.1

Question 1: Answer B ("No")
Question 2: Answer B ("No")
Question 3: Answer C
Question 4: Answer D
Question 5: Answer D

Case study 27.2

Question 1: Answer C

Case study 27.3

Question 1: Answer D

Case study 27.4

Question 1: Answer C
Question 2: Answer D

Selected reading

Bain BJ, Gilliland DG, Horny H-P, *et al*. Chronic eosinophilic leukaemia, not otherwise specified. In: Swerdlow S, Harris NL, Stein H, *et al*., editors. World Health Organization classification of tumours. pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008. p. 51–3.

Gotlib J. World Health Organization-defined eosinophilic disorders: 2014 update on diagnosis, risk stratification, and management. Am J Hematol. 2014;89:325–37.

Gotlib J, Cools J. Five years since the discovery of the FIPL1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias. Leukemia. 2008;22:1999–2010.

Klion AD, Robyn J, Maric I, *et al*. Relapse following discontinuation of imatinib mesylate therapy for FIP1L1/PDGFRA-positive chronic eosinophilic leukemia: implications for optimal dosing. Blood. 2007;110:3552–6.

Verstovsek S, Tefferi A, Kantarjian H, *et al*. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. Clin Cancer Res. 2009;15:368–73.

CHAPTER 28

Chronic myelomonocytic leukemia

Mrinal M. Patnaik
Mayo Clinic, Rochester, MN, USA

Case study 28.1

A 55-year-old male presented with a one-year history of progressive effort intolerance, 10-pound weight loss, early satiety, and left upper abdominal quadrant fullness. On a physical examination, he was found to have moderate splenomegaly. His bloodwork revealed hemoglobin of 8.0 gm/dl, a mean corpuscular volume of 96 fL, a white blood cell (WBC) count of 9.2×10^9/L, and a platelet count of 100,000/ml. His absolute neutrophil count (ANC) was 3.4×10^9/L, while the absolute monocyte count (AMC) was 2.6×10^9 /L. A peripheral blood smear was remarkable for monocytosis with occasional hypogranular neutrophils.

On reviewing a prior complete blood count (CBC) from a year ago, his hemoglobin was 9.2 gm/dl, his WBC count was 7.8×10^9/L, and his AMC was 1.8×10^9/L.

A bone marrow biopsy revealed a cellularity of 70% with trilineage hyperplasia and associated dysplasia. The megakaryocytes were markedly abnormal with hypolobated forms. There were increased butyrate esterase–positive monocytes and dual esterase–positive cells. The myeloblasts were estimated at 5% by morphology and immunohistochemistry. The cytogenetics were diploid: 46XY. Fluorescent in situ hybridization (FISH) studies for *BCR–ABL1*, *PDGFRA*, and *PDGFRB* abnormalities were negative.

1. What are the definition and the differential diagnosis for peripheral blood monocytosis?

Absolute monocytosis is defined by a peripheral blood AMC $>1 \times 10^9$ cells/L. The differential diagnosis is categorized into clonal versus reactive. Reactive monocytosis is common and is most often seen in association with viral infections. Chronic infections and inflammatory conditions such as tuberculosis, brucellosis, leishmaniasis, sarcoidosis, and connective tissue disorders can be associated with monocytosis. Monocytosis is also one of the early signs of a recovering bone marrow (BM) following myelosuppression. Clonal monocytosis is often persistent and is associated with hematopoietic stem cell disorders such as chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), and myeloid disorders, with overlapping features between myelodysplastic syndromes (MDSs) and myeloproliferative neoplasms (MPNs).

2. What are the World Health Organization (WHO) definition and subcategorization for CMML?

CMML is a clonal hematopoietic stem cell disorder with overlapping features of MDS and MPN. It is characterized by:

i. Persistent peripheral blood monocytosis $>1 \times 10^9$/L

ii. Absence of the Philadelphia chromosome and the *BCR–ABL1* fusion oncogene

iii. Absence of the *PDGFRA* or *PDGFRB* gene rearrangements

iv. Less than 20% blasts and promonocytes in the peripheral blood and bone marrow

v. Dysplasia involving one or more myeloid lineages.

If myelodysplasia is absent or minimal, the diagnosis of CMML can still be made if the other requirements are met and one of the following applies: an acquired, clonal, or molecular genetic abnormality is present in the hematopoietic cells, or the monocytosis has persisted for at least 3 months and other causes of monocytosis have been excluded.

CMML is further subclassified into CMML-1 (<5% circulating blasts and <10% BM blasts) and CMML-2 (5–19% circulating blasts and 10–19% BM blasts, or when Auer rods are present irrespective of the blast count), with the median overall survival (OS) being approximately 20 and 15 months, respectively.

3. What are the epidemiology, clinical features, and presenting symptoms of patients with CMML?

The incidence of CMML has been approximated at 12.8 cases per 100,000 people per year, with the median age of

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

presentation being 65–75 years. Patients with CMML have features overlapping between those of MDS and MPN. Those with a MDS phenotype present with or develop peripheral blood cytopenias, effort intolerance, easy bruisability, and transfusion dependence. Those with a MPN phenotype present with or develop leukocytosis, monocytosis, hepatomegaly, splenomegaly, and features of myeloproliferation.

4. What are the typical bone marrow morphological findings in patients with CMML?

The bone marrows are often hypercellular with granulocytic hyperplasia and dysplasia. Monocytic proliferation can be present but is often difficult to appreciate, and immunohistochemical studies that aid in the identification of monocytes and their precursors are recommended. Almost 80% of patients will demonstrate micro-megakaryocytes with abnormal nuclear contours and lobations, and 30% of patients can have an increase in BM reticulin fibrosis. Twenty percent of patients can demonstrate nodules composed of mature plasmacytoid dendritic cells.

5. What are the typical immunophenotypic and cytochemical bone marrow findings in patients with CMML?

On immunophenotyping, the abnormal BM cells often express myelomonocytic antigens such as CD13 and CD33, with variable expression of CD14, CD68, and CD64. Markers of aberrant expression include CD2, CD15, and CD56 or decreased expression of CD14, CD13, HLA-DR, CD64, or CD36. The presence of myeloblasts can be detected by expression of CD34. The most reliable markers on immunohistochemistry include CD68R and CD163. The monocytic cells are often positive for nonspecific esterases and lysozyme, while the granulocytic precursors are often positive for lysozyme and chloroacetate esterase.

6. What are the cytogenetic abnormalities seen in patients with CMML?

Cytogenetic abnormalities in CMML can be detected by conventional karyotyping or FISH studies. Clonal cytogenetic abnormalities are seen in approximately 20–40% of patients with CMML. Frequent aberrations include +8, monosomy 7, del7q, and recurring abnormalities of chromosome 12p. In a large Spanish cytogenetic study ($n = 304$), the karyotype was normal in 73% of patients. The most frequent abnormalities included +8, del5q, +10, del11q, del12p, add17p, +19, +21, abnormalities of chromosome 7, and complex karyotypes. Cytogenetic abnormalities were more frequent in patients with increased peripheral blood and BM blasts, and those who demonstrated dyserythropoiesis and dysgranulopoiesis. Based on these findings, the Spanish cytogenetic risk stratification system was developed, categorizing patients into three groups; high risk (+8, chromosome 7 abnormalities, or complex karyotype), intermediate risk (all chromosomal abnormalities except for those in the high- and low-risk categories), and low risk (normal karyotype or –Y), with 5-year OS of 4%, 26%, and 35% respectively.

7. What is the importance of detecting *PDGFRA* and *PDGFRB* gene rearrangements in patients suspected to have a diagnosis of CMML?

The platelet-derived growth factor receptors alpha and beta (*PDGFRA* chromosome *4q12* and *PDGFRB* chromosome *5q31–q32*) are type III receptor tyrosine kinases that are involved in the development of myeloid malignancies. The clinical phenotype in both cases involves prominent blood eosinophilia and marked responsiveness to imatinib mesylate. These abnormalities can be detected by karyotyping and FISH techniques, and given their unique response to imatinib they are no longer classified as CMML. Patients presenting with a clinical phenotype of CMML, especially with eosinophilia, should be assessed for t(5;12) (q31–q32;p13), giving rise to the *ETV6(TEL)–PDGFRB* fusion oncogene. Gene rearrangements involving *PDGFRA* are less common, but nevertheless due to their imatinib responsiveness should be evaluated.

8. What is the current understanding with regard to CMML disease biology?

The advent of next-generation sequencing technology has led to the identification of molecular aberrations in ~90% of patients with CMML. These can broadly be divided into four categories:

i. Mutations involving epigenetic regulator genes, such as *EZH2*, *ASXL1*, *TET2*, *DNMT3A*, *IDH1*, and *IDH2*.

ii. Mutations involving the spliceosome machinery, such as *SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*, *SF3A1*, *PRPF40B*, *U2AF65*, and *SF1*.

iii. Mutations involving DNA damage response genes, such as *Tp53*.

iv. Mutations involving genes regulating cellular and receptor tyrosine kinases and transcription factors, such as *JAK2*, *KRAS*, *NRAS*, and *RUNX1*.

Thus far, in CMML, *ASXL1*, mutations have been associated with a shorter OS and leukemia-free survival (LFS).

9. Discuss the role of *RAS* gene mutations in CMML.

Mutations involving the *KRAS* and *NRAS* genes are common in patients with CMML (~40%), and they are often associated with a myeloproliferative phenotype with monocytosis. The expression of mutated *RAS* in mice has been associated with an MPN phenotype with monocytosis. Although univariate analysis studies have demonstrated inferior outcomes in CMML patients with *RAS*

mutations, these observations have not held in multivariate models.

10. What are the clinical relevance and prognostic impact of spliceosome mutations in CMML?

Mutations in genes of the splicing machinery are common in patients with myeloid malignancies, including CMML. *SF3B1* mutations have a high prevalence (~80%) in MDS and ring sideroblasts (RS), can be seen in patients with CMML and RS (<10%), and do not influence either OS or LFS. *SRSF2* is the most commonly mutated spliceosome gene in CMML (28–47%) and has been associated with increased age, less pronounced anemia, and a diploid karyotype. Thus far, *SRSF2* mutations have not demonstrated an independent prognostic impact. *U2AF1* mutations are seen in ~10% of patients with CMML and have not been associated either with inferior OS or with LFS.

11. What are the currently available prognostic scoring systems for CMML? Describe their advantages and disadvantages.

Numerous prognostic systems have attempted to better define and stratify the natural history of CMML. The Bournemouth system, Lille system, and International Prognostic Scoring System (IPSS) are limited by the fact that they were mainly designed for patients with MDS and excluded patients with CMML who had a proliferative phenotype (WBC $> 12 \times 10^9$/L).

The MD Anderson Prognostic Scoring System (MDAPS) was developed on a cohort of 213 CMML patients and identified a hemoglobin level <12 gm/dl, the presence of circulating immature myeloid cells (IMCs), an absolute lymphocyte count (ALC) $>2.5 \times 10^9$/L, and ≥10% BM blasts as independent predictors for inferior survival. This model identified four subgroups of patients with median survivals of 24, 15, 8, and 5 months for low-risk, intermediate-1 risk, intermediate-2 risk, and high-risk disease, respectively.

The MDAPS was then analyzed in 212 CMML patients in the Dusseldorf registry. In a univariate analysis, circulating IMCs had no prognostic impact, while in a multivariate analysis, elevated LDH, BM blast count >10%, male gender, hemoglobin <12 gm/dl, and ALC $>2.5 \times 10^9$/L were independently prognostic. The Dusseldorf score classified patients into three risk categories, with a median survival of 93 (low), 26 (intermediate), and 11 (high) months, respectively.

The Spanish cytogenetic risk stratification system analyzed the role of karyotype abnormalities in patients with CMML. This stratification system did not, however, predict for the long term.

In 2008, the global prognostic model for patients with de novo MDS, secondary MDS, and CMML was proposed. On multivariate analysis, independent factors included older age, poor performance status, thrombocytopenia, anemia, increased BM blasts, leukocytosis ($>20 \times 10^9$/L), chromosome 7 or complex cytogenetic abnormalities, and a prior history of red blood cell transfusions. Four prognostic groups were identified with median survivals of 54 (low), 25 (intermediate-1), 14 (intermediate-2), and 6 months (high), respectively. This model was validated in 176 patients with CMML and leukocytosis ($>12 \times 10^9$/L).

Some, but not all, studies have demonstrated a negative prognostic impact for *ASXL1* mutations in patients with CMML. Notably, a Mayo Clinic study analyzed several clinical and laboratory parameters, including *ASXL1* mutations, in 226 patients with CMML; on multivariable analysis, risk factors for survival included hemoglobin <10 gm/dL, platelet count <100 × 10(9)/L, AMC >10 × 10(9)/L and the presence of IMC. In this study *ASXL1* mutations were detected in 49% of patients and did not impact either overall ($P = 0.08$) or leukemia-free ($P = 0.4$) survival. The study resulted in the development of the Mayo prognostic model, with three risk categories; low (0 risk factors), intermediate (1 risk factor) and high (≥2 risk factors), with median survivals of 32, 18.5 and 10 months, respectively.

In contrast to the findings from the above-discussed Mayo Clinic study, a GFM (Groupe Francais des Myelodysplasies) study demonstrated an adverse prognostic effect for *ASXL1* mutations in 312 patients with CMML; additional risk factors on multivariable analysis included age >65 years, white blood count (WBC) >15 × 10(9)/L, platelet count <100 × 10(9)/L and hemoglobin level <10 gm/dL in females and <11 gm/dL in males. The GFM prognostic model assigns 3 adverse points for WBC >15 × 10(9)/L and 2 adverse points for each one of the remaining risk factors, resulting in a three-tiered risk stratification: low (0–4 points), intermediate (5–7 points) and high (8–12 points), with respective median survivals of 56, 27.4 and 9.2 months. It should be noted that all nucleotide variations (missense, nonsense and frameshift) were regarded as *ASXL1* mutations in the Mayo study, whereas only nonsense and frameshift *ASXL1* mutations were considered in the French study.

12. Discuss the management strategies for a patient with CMML.

The treatment for CMML can be broadly divided into two categories: supportive care and directed or targeted therapy.

Supportive care: Supportive care focuses on symptom management and palliation, and it comes into play when patients are ineligible for, or have failed, directed therapy. Hydroxyurea, a myelosuppressive agent, is very helpful in palliating symptoms related to massive splenomegaly and in controlling elevated blood counts. Other agents that have been used with less efficacy and tolerability

include etoposide, low-dose cytarabine, topotecan, and 9-nitro-campothecin. Erythropoietin analogs can be used in patients with anemia; however, granulocyte colony-stimulating factor should be used with caution, given the risk for splenic rupture in patients with proliferative disease. Recommendations for supportive transfusional care, infectious disease prophylaxis, and iron chelation therapy are similar to those for patients with MDS, and data for their specific use in CMML do not exist.

Directed and targeted therapy: The hypomethylating agents 5-azacitidine and decitabine have been approved by the US Food and Drug Administration (FDA) for use in patients with MDS. Given the overlapping MDS–MPN phenotype and the presence of similar genetic and methylation abnormalities in CMML, these agents have been used in CMML with varying success. There currently are no phase III randomized clinical trial data. Based on phase II studies, the overall response rates vary between 20% and 30%, with CR rates generally being <15%. Similar to MDS, these medications generally take a minimum of four cycles before response assessment can be made. On starting these medications, the worsening of preexisting cytopenias and transfusion dependence is very likely. Other agents that have been tried, either alone or in conjunction with hypomethylating agents, include histone deacetylase inhibitors (panobinostat and vorinostat), immunomodulatory drugs such as lenalidomide, and farnesyl transferase inhibitors (tipifarnib and lornafarnib). GSK 212 is an oral MEK inhibitor that is currently being evaluated in phase II clinical studies in patients with *RAS*-mutated CMML and has demonstrated encouraging responses.

13. Discuss the role for allogeneic stem cell transplantation (allo-SCT) in CMML.

Allo-SCT remains the only curative option for patients with CMML. This technique is, however, fraught with complications, such as graft rejection, nonrelapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD), organ injury, and disease relapse in the posttransplant period. There are no randomized studies comparing allo-SCT with other modalities of care. The advent of reduced-intensity conditioning (RIC) allo-SCT and the greater availability of matched unrelated donors and alternative donor stem cell sources (umbilical cord blood and haploidentical donors) have made SCT available to more people. Eissa *et al*. reported outcomes on 85 patients with CMML who underwent allo-SCT (32% RIC SCT, 62% peripheral blood stem cell grafts). After a median follow-up of 5.2 years, 49 (58%) had died, 20 from disease relapse and 29 from nonrelapse causes; 26% developed grade II–IV acute GVHD; and 40% developed chronic GVHD. A multivariate model identified increasing age, a high SCT comorbidity index, and poor risk cytogenetics as independent prognosticators for poor survival. A more recent European study evaluated SCT in 73 patients with CMML (61% CMML-1 and 43 RIC SCT). The 3-year OS was 32%, the NRM was 36%, and the cumulative incidence of relapse was 35%. OS was not influenced by the CR status, BM blast percentage at allo-SCT, prior treatments, and chronic GVHD. Twenty-eight percent and 34% of patients developed acute grade II–IV and chronic GVHD, respectively. For young patients with high-risk disease, poor prognostic scores, high-risk karyotypes, and increased BM blasts, early stem cell transplantation strategies should be pursued. For the elderly, the transplant ineligible, and patients with limited donor options, clinical trials or off-label use of hypomethylating agents can be considered.

14. Discuss the diagnosis and treatment approach in the above-mentioned case.

The patient in the above-mentioned case meets the 2008 WHO diagnostic criteria for CMML-1 and has presented with a proliferative phenotype. He is symptomatic from his disease and has developed anemia, which is very likely to necessitate red blood cell transfusions. Given his younger age, I would HLA-type the patient and his siblings. If there are no sibling matches, unrelated and alternate donor sources should be investigated. If we can identify a suitable stem cell source, and if his pre-transplantation evaluation, including the SCT comorbidity index, is satisfactory, I would give him the option of proceeding with an allo-SCT. In the event that he does not have a stem cell source, or if he is transplant ineligible, I would look to enroll him in clinical trials or attempt therapy with hypomethylating agents.

Selected reading

Eissa H, Gooley TA, Sorror ML, *et al*. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia: relapse-free survival is determined by karyotype and comorbidities. Biol Blood Marrow Transplant. 2011;17(6): 908–15.

Gelsi-Boyer V, Trouplin V, Adelaide J, *et al*. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. Br J Haematol. 2009;145(6):788–800.

Kantarjian H, O'Brien S, Ravandi F, *et al*. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer. 2008;113(6):1351–61.

Patnaik MM, Parikh SA, Hanson CA, Tefferi A. Chronic myelomonocytic leukaemia: a concise clinical and pathophysiological review. Br J Haematol. 2014 Jan 28.

Such E, Cervera J, Costa D, *et al*. Cytogenetic risk stratification in chronic myelomonocytic leukemia. Haematologica. 2011; 96(3):375–83.

CHAPTER 29

Hematopoietic cell transplantation in chronic myeloid leukemia

Jerald P. Radich

Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Tyrosine kinase therapy has revolutionized the therapy of chronic myeloid leukemia (CML). A mere decade ago, the only way to produce long-term, disease-free outcomes in CML was through stem cell transplantation. The advent of imatinib has pushed transplantation to the role of salvage therapy in CML. Still, patients treated in the chronic phase fail imatinib. Second-generation tyrosine kinase inhibitors (TKIs) have been approved, and these will place some patients back into a remission, although the duration of these remissions is unclear. Some cases of resistant CML will progress to advanced-phase disease (accelerated and blast phase), and these cases are ultimately tougher to treat with any modality, including transplantation. The challenge in these patients is to decide which patients will benefit from transplant, and when.

There are now three TKIs approved for upfront chronic-phase CML (imatinib, dasatinib, and nilotinib), and four approved for cases refractory or intolerant to TKI therapy (generally in the context of imatinib failure: dasatinib, nilotinib, ponatinib, and bosutinib). With such an embarrassment of riches, how does the physician decide which drug to start with? Which to use if trouble occurs? This chapter will present several clinical stories to outline some of the questions faced in treating CML cases. Most of them do not have "cut-and-dried" answers, but rather fall into the category of the "art" of medicine.

Case study 29.1

A 31-year-old male rodeo clown has recently been diagnosed with chronic-phase CML. He is intermediate risk by both the Sokal and Hasford classification schemes. He has three siblings. Surprisingly, insurance coverage for rodeo clowns is good (especially for traumatic injuries), so there is not a problem with obtaining either TKI therapy or transplantation. Being a risk taker, he is attracted to transplantation since it is "one and done" rather than a potential lifetime of therapy.

1. All things considered, what do you recommend?

A. Tyrosine kinase therapy
B. Allogeneic transplantation
C. Clinical trial

The question here is whether transplantation should ever be offered as upfront therapy for newly diagnosed chronic-phase CML. In this setting, treatment with any TKI will yield 10-year survival of ~90. Compare this to the pre-TKI years, where the median survival for this group would be ~6 years. Allogeneic transplantation for chronic-phase CML would expect to yield ~85 disease-free survival (with either a matched related or unrelated donor), but it is associated with an upfront risk of morbidity and mortality. Thus, regardless of whether the patient is a risk taker or not, allogeneic transplant should be reserved for those patients who are intolerant or fail multiple TKI agents, or who progress to the accelerated or blast phase. In the past, patients who acquire the T315I mutation were also candidates for transplantation, but the recent approval of ponatinib, which is

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

highly effective against all Abl mutations, now has become the preferred initial approach for these cases.

After discussion, the above patient decides that he will try a TKI after all. He has no other medical history of relevance in considering a choice of imatinib versus nilotinib versus dasatinib. However, from your discussion, it becomes clear that the life of the rodeo clown may come into play in your decision. Besides the considerable "bumps" of the job, the schedule is hectic, with irregular eating, and the lifestyle not altogether monastic.

2. After much consideration, what do you decide on?

A. Imatinib
B. Dasatinib
C. Nilotinib

How do we decide which TKI to use? Three randomized phase III studies have shown that nilotinib and dasatinib have better short-term (12 m) efficacy, measured by cytogenetic response, molecular response, and progression rates, but thus far neither have shown a survival advantage. It is not clear if this is because there will be no survival advantage of the second-generation TKI versus imatinib, or if the survival with any regimen is so good that one would need a huge study, with longer follow-up, to see the effect.

Given that this patient presents with intermediate-risk disease by the Sokal and Hasford scores, many physicians would lean toward starting therapy with the more potent dasatinib or nilotinib, hoping that the more potent inhibition would better prevent progression to advanced-phase disease. However, the second-generation TKIs have more hematopoietic toxicity, especially grades 3–4 thrombocytopenia (e.g., ~10% grade 3–4 with imatinib versus 20% with dasatinib in the US Intergroup trial). Given this consideration and the patient's occupational propensity to collide with one-ton hoofed animals, you and the patient decide to start therapy with imatinib (A) (Table 29.1).

He starts on 400 mg a day, and while you have advised him to take off work, he has rejoined the rodeo circuit. He returns to your office 3 months later. He has normalized his complete blood count. He refuses to have a bone marrow aspiration for cytogenetics ("My back side is sore enough already, Doc!"). His peripheral blood polymerase chain reaction (PCR) shows a Bcr–Abl of 12% IS (there is no baseline test). When asked if he is taking his medication, he replies "mostly."

3. After furrowing your brow, what do you decide?

A. Continue on imatinib
B. Switch to nilotinib or dasatinib
C. Refer to allogeneic transplantation

What does early response mean, especially in the context of questionable compliance? A growing body of data suggest that early (3 m) response predicts outcome, and that patients who do not have a BCR–ABL <10% IS at 3 m have an inferior outcome (cytogenetic, molecular, and survival) compared to patients with a better response. This relationship seems to hold for both upfront CML and those patients who switch to a second-generation TKI after poor tolerance or efficacy to imatinib. Thus, some experts would advocate switching to an alternative TKI with such a poor 3 m BCR–ABL PCR result, even though there are not data suggesting that switching in these patients will actually change their natural history. The story is complicated here by the suspicion that the patient is not compliant. Adherence to the prescribed dose schedule of imatinib is surprisingly poor; not surprising is that if one does not take imatinib, it doesn't work. Thus, adherence to at least 90% of the prescribed imatinib dose is associated with a far superior outcome in reaching treatment milestones. Thus, for this patient, it is reasonable to continue on imatinib, with close follow-up.

He continues on imatinib, and while he says he understands your concern and promises to return in 3 months, he misses his next appointment. After 9 months without contact, you receive a postcard from him from the Calgary Stampede rodeo. It states, "Dear Doc. All is going well. Maybe some bruising lately, but it's been a tough week in the pen. Some fevers as well. Guess I caught a bug. See you in a week. Wish

Table 29.1 12 m responses in the ENESTnd, DASISION, and US Intergroup trials (Source: Data from Saglio G, *et al.* N Engl J Med. 2010;362:2251–9; Kantarjian H, *et al.* N Engl J Med. 2010;362:2260–70; Radich JP, *et al.* Blood; 2012;120:3898–905).

Response	NIL300bid (ENESTnd)	NIL400bid (ENESTnd)	IM 400 (ENESTnd)	DAS 100 (DASISION)	IM 400 (DASISION)	DAS 100 (US Intergroup)	IM 400 (US Intergroup)
CCyR	80%	78%	65%	83%	72%	84%	69%
MMR	44%	43%	22%	46%	28%	59%	43%
AP/BC	0.7%	0.4%	4.2%	1.9%	3.5%	1%	3%

AP/BC, patients progressing to accelerated phase and blast crisis; CCyR, complete cytogenetic remission; MMR, major molecular response.

(*Continued*)

you were here." He arrives a week later with a white blood cell count >100k, with 17% peripheral blood myeloblasts, an enlarged spleen, and 10 lbs of weight loss.

4. As he is now in accelerated phase, what do you recommend?

A. Switch to nilotinib, dasatinib, or ponatinib and watch response
B. Start on second-generation TKI, then move to allogeneic transplant
C. AML induction therapy, then TKI, then transplant

What do you do with the rare patients who, from either poor compliance (bad idea) or aggressive disease (bad luck), progress to aggressive CML? While patients who fail TKI and progress to accelerated phase can control their disease and sometimes achieve even a complete cytogenetic remission, their long-term disease survival is poor. Thus, transplantation is their best alternative. If a patient is in accelerated phase, a trial of dasatinib or ponatinib (nilotinib is not approved for advanced-phase disease) is warranted while the patient is securing a donor. Hopefully, by this time he and his siblings have been typed (you did think to do that, right?).

Case study 29.2

You are referred a 45-year-old female clothing inspector ("No. 6") who recently presented in what appeared to be chronic-phase CML. However, her cytogenetic exam showed the Ph in 15/20 metaphases, with five metaphases showing an additional clonal change of del17p (the location of the *p53* tumor suppressor gene). She started 3 weeks ago on imatinib 400 mg per day by her local general practitioner, and her counts are falling appropriately. She has no siblings.

1. Based on this story, what do you recommend?

A. Imatinib 400 mg/d
B. Imatinib 600–800 mg/d
C. Second-generation TKI
D. URD work-up with transplantation ASAP

What does clonal evolution mean in chronic-phase disease? There is considerable debate about what the picture of morphological chronic phase, with clonal evolution, really means. In many clinical trials of TKIs for chronic-phase disease, these patients were not excluded, although in some CML classification schemes, such patients would be called accelerated phase. A scenario as described above occurs in ~5% or less of chronic-phase cases. The prognosis seems to be best for cases like this (normal blast count, with clonal evolution only), intermediate for cases with increased blast counts but no clonal evolution, and worst for cases with clonal and blast evolution. However, cases with clonal evolution do worse compared to standard chronic-phase CML, with slower times of response, and worse rates of CCyR (71% vs. 89%), MMR (67% vs. 86%), and failure-free survival (61% vs. 76%), but not overall survival by 6 years of follow-up.

Thus, it is reasonable to start a TKI. However, it would be wise to perform HLA typing on the donor, and at least do a preliminary "world book" search to assess how many donors might be available if needed. In regard to the TKI to pick, given her clonal evolution, a more potent second-generation TKI would seem most attractive. High-dose imatinib would provide good kinase inhibition, but is generally less well tolerated than the other choices.

You start her on dasatinib. At 3 m, her BCR–ABL is 9%. At 6 months, she has a shifting of her cytogenetics, as she now has normal XX metaphases in 4/20 preparations (good), the Ph in 10/20 metaphases (OK), and secondary clone now in 5/40 metaphases (bad). Her blast count remains at 5% in the marrow.

2. What should you do?

a. Continue dasatinib
b. Perform mutation testing and switch TKI
c. Start an official unrelated donor search
d. B and C

What do we do with high-risk cases with suboptimal response? This is an unusual case: technically, she is responding (though certainly not optimally), but the shift in her clonal composition is ominous. It is certainly reasonable to continue dasatinib over the short interval of time needed to get mutation analysis. No matter the result, she will need to be switched, but she may have a mutation sensitive to nilotinib. If, on the other hand, she has a T315I mutation, then ponatinib would be clearly indicated. It is important to begin an unrelated donor search, since salvage to a complete cytogenetic remission with a durable response seems unlikely in this scenario, and transplant may be stacking up to be her best curative chance.

She indeed is positive for the T315I mutation, and she is placed on ponatinib while her unrelated search begins. After 3 months of therapy, her peripheral blood BCR–ABL is 5% IS, and her bone marrow still has the appearance of morphological chronic phase. Her cytogenetics is now XX in 14/20 metaphases, and the other 6/20 have the Ph with the iso 17q.

She has yet to find a donor given some initial insurance problems followed by a donor issue. Thus, she continues on ponatinib. Three months later, her BCR–ABL has risen to 15% IS; her bone marrow now shows an increase in blasts to 10%, and her cytogenetics have changed with 7/20 XX, 10/10 with the Ph iso17q, and now three new metaphases showing an additional change of a del 8. She now has a donor available.

3. What is your next step?

A. Both curse and praise the heavens
B. Enroll in a clinical trial
C. Move to transplant

While there is always merit in enrolling in a clinical trial, it would have to be especially attractive to outweigh the potential merits of moving to transplant.

Case study 29.3

A 57-year-old male driftwood sculpture with chronic-phase CML, diagnosed 3 years earlier, wishes to transfer to your care. At diagnosis he had no insurance (apparently, driftwood artists have a weaker union than rodeo clowns), but he was able to enroll on a randomized phase III trial and has been receiving a second-generation TKI. He had a remarkable response, achieving a complete molecular response (CMR) by 18 months, and has remained in CMR until 36 m. His first question to you is if he can now stop taking his TKI. He believes he is "cured," as evidenced by the CMR, and hates the "negative vibe" associated with being on therapy.

1. How should you reply?

A. Discontinue his TKI, increasing your own karma considerably
B. Discourage discontinuation
C. Enroll him on a discontinuation trial

Can we safely discontinue TKI in responding patients? CML "stem cells" are remarkably resistant to TKIs in vitro, and thus the assumption was that patients would have to remain on them forever. This assumption appears to be wrong. Several trials have now demonstrated that patients who have achieved and maintained a CMR for several years can discontinue TKI and remain in CMR. The largest trial has shown a continued CMR rate of ~40% up to 2 years after the discontinuation.

These results have to be taken cautiously, however. Thus far, all of the patients who have relapsed after discontinuation (usually within 3 months) have responded to restarting the TKI, though not all have again achieved a CMR. The danger is what may have happened in the months off therapy. If unopposed BCR–ABL activity promotes genetic instability and progression to advanced-phase disease, it is possible that some clone has become launched down the progression pathway. This pathway is often tyrosine kinase independent; that is, this clone might survive the reintroduction of the TKI. It would take years for a single cell to proliferate to a point of clinical danger; thus, these patients on discontinuation trial may not be "out of the woods" for some time. For this reason, if this patient wants to discontinue a drug, it should only be in the context of a clinical trial.

Case study 29.4

A 44-year-old male former investment banker now turned freestyle jumper was diagnosed two years ago with low-Sokal-risk CML. He has cycled through imatinib, dasatinib, and nilotinib, all with the same story: he has a good treatment response, but cannot tolerate the medications due to a series of odd but serious side effects. He does not have insurance (his agent seized when hearing about the freestyle jumping), and he is worried that his considerable saved financial resources will be drained by years of TKI therapy. Thus, he wants a transplant from his HLA-matched sibling.

He has read up and is curious about pursuing a nonmyeloablative transplant rather than a full transplant, as he suspects the latter approach will sooner return him to his risky and thrilling lifestyle (like an allogeneic transplant wouldn't!).

1. What should you do?

A. Send him to another clinic since well-informed patients scare you
B. Promote an allogeneic transplant
C. Offer a nonmyeloablative transplant
D. Suggest entering a trial comparing allogeneic versus nonmyeloablative transplant

When do we use a "full" versus a "mini" transplant? As opposed to standard "ablative" transplants (so called since

(*Continued*)

the preparative regimen of chemotherapy +/− total body irradiation (TBI) destroys the hematopoiesis, so that the patient must be rescued by a donor hematopoietic stem cell infusion), the nonmyeloablative (NMA) transplant uses far less preparative therapy, aiming to cripple rather than destroy the host hematopoietic and immune system. As such, the NMA relies on the graft-versus-leukemia effect to control and destroy the host leukemia.

NMA transplants were first offered for patients unable to receive a full transplant because of advanced age or other medical conditions that would make a full preparative regimen too toxic. However, the regimen proved to be more successful in combating disease and now is used much more routinely. A few things can be said about the NMA compared to the standard ablative transplant: (i) the regimen-related toxicity is less, with <10% at 100 days and <20% at 2 years posttransplant; (ii) however, relapse rates tend to be higher; and (iii) graft-versus-host disease (GVHD) rates and severity are similar. As such, for most diseases, survival for NMA is quite comparable to ablative transplants.

Early results using NMA for CML were troubled by high rates of graft rejection (especially with unrelated donors), since in CML the immune system had not been previously exposed to the immunosuppressive effects of chemotherapy. However, with improved protocols, NMA has been used with excellent results with regiment-related mortality, and with ∼40% patients achieving a molecular remission. However, thus far trials have been composed of very heterogeneous populations of patient phases, donors, and so on, so we clearly do not know how the NMA approach directly compares with the ablative treatment. Since we do not know what regimen is best, it is perfectly reasonable to suggest a randomized trial.

The patient is randomized to the full myeloablative protocol. He engrafts by day 28. He has full donor chimerism, he is in marrow remission by morphology and cytogenetics, and his peripheral blood BCR–ABL is low positive at 0.04% IS. He develops grade II GVHD of the skin, which is treated successfully with steroids. On his day 80 discharge work-up, he is still in remission, he has no active GVHD, and his peripheral blood BCR–ABL is now 0.8% IS.

2. What do you decide to do?

A. Wait and watch, and repeat PCR in 3 m
B. Immediately discontinue all immunosuppressive medications
C. Start a TKI
D. Give donor leukocyte infusions (DLIs)

What do you do about "molecular relapse"? Many studies have shown that the presence of BCR–ABL posttransplant is associated with subsequent relapse. In general, (i) d28 appears to have less consequence than later time points; (ii) disease at 2–12 months is associated with subsequent relapse; and (iii) low levels of BCR–ABL are often (in ∼10–25% of cases) at very low levels, and appear not to be associated with high risks of relapse. A major caveat is in the setting of a T-cell-depleted transplant; in this setting, without a GVL effect, any BCR–ABL at any time point is suggestive of subsequent relapse.

BCR–ABL molecular relapse has been treated with interferon, DLI, and, more recently, TKI (see Table 29.2). The treatment of molecular relapse with TKI is very effective. The response to TKI reflects the stage of disease, and complete hematological response was seen in >90% of chronic-phase cases, >50% of accelerated-phase cases, and >20% of cases in blast crisis. A complete cytogenetic remission occurred in >40% of all cases, with response rates considerably higher in chronic phase. Most of the data are from the use of imatinib; dasatinib seems to be associated with greater toxicity in this setting, particularly from bleeding complications. This should be expected given that in the nontransplant setting, thrombocytopenia is a greater problem with dasatinib compared to imatinib.

Imagine the same patient as above, but now he is transplanted for accelerated-phase disease. Before transplant, he had no ABL mutation. He engrafts at day 28 and has no GVHD.

3. What do you do?

A. Wait for his day 28 BCR–ABL to decide what to do
B. If his BCR–ABL is negative, watch
C. Start prophylactic TKI
D. Give TKI or DLI only if his BCR–ABL is highly positive

Should we give prophylactic TKI? While chronic phase is associated with a low risk of relapse, transplantation for accelerated- or blast-phase CML, or Ph+ ALL, is of sufficient high risk to warrant prophylactic administration of a TKI. Published trials are limited, but they suggest that imatinib can be given safely at engraftment without significant effects on hematological counts. The ability to give dasatinib or nilotinib in the prophylactic setting is currently under investigation. Because of the potential stronger effect on the hematopoietic system, some clinical trials give imatinib at engraftment, switching to a second-generation TKI at later dates (e.g., ∼day 100).

Phase I and II trials of prophylactic TKI suggest no negative effects on GVHD. It does seem to prevent molecular relapse. Twenty-two patients (7 CML and 15 Ph+ ALL) were treated with imatinib after engraftment, and 19 completed the planned course of 1 year of treatment. At a median follow-up of one and a half years, 5/7 of the CML patients and 12/15 of the Ph+ ALL cases were in a molecular remission.

Lastly, one continuing issue is whether or not the presence of a pretransplant mutation should have an effect on the

Table 29.2 Posttransplant use of tyrosine kinase inhibitors (TKIs) in patients with chronic myeloid leukemia (CML) (Source: Bar M, *et al.* J Natl Comp Cancer Network. 2013;11(3):308–15).

Reference	*N* pts.	Indication	TKI	Median dose	Significant toxicity	Outcome
Kantarjian *et al.*[a]	28	Relapse	Imatinib	600 mg	Grade 3–4 hematologic toxicity Grade 3–4 liver toxicity	CHR: 74% (CP: 100%, AP: 83%, BP: 43%) CgR: 58% (CP: 63%, AP: 63%, BP: 43%) CCgR: 35%
Olavarria *et al.*[b]	128	Relapse	Imatinib	400 mg (CP) 600 mg (AP/BP)	N/A	CCgR: 44% (CP: 58%, AP: 48%, BP: 22%) CMR:26% (CP: 37%, AP: 33%, BP: 11%) CP: 2y OS 100% AP: 2y OS 86% BP: 2y OS 12%
DeAngelo *et al.*[c]	15	Relapse	Imatinib	600 mg	Grade 3–4 liver toxicity	CCgR: 11/15 (73%) CMR: 7/15 (47%)
Hess *et al.*[d]	44	Relapse	Imatinib	400 mg	Grade 3–4 hematologic toxicity	CCgR: 73% CMR: 62%
Palandri *et al.*[e]	16	Relapse	Imatinib	400 mg	Grade 3–4 hematologic toxicity	CCgR:88% CMR:75%
Klyuchnikov *et al.*[f]	11	Relapse	Dasatinib	50 mg BID	Thrombocytopenia-related gastrointestinal bleeding	Stable response in 4 pts (2 with extramedullary relapse)
Wright *et al.*[g]	22	Relapse	Imatinib (20), Dasatinib (6)	Imatinib 400 mg Dasatinib 140 mg	Grade 3–4 hematologic toxicity	CHR: 86% (AP/BP-79%) CCgR: 77% (AP/BP-71%) CMR: 64% (AP/BP-57%)
Carpenter *et al.*[h]	22	Prophylaxis	Imatinib	400 mg	Grade 1–3 nausea, emesis, Liver toxicity	CCgR: 5/7 CMR: 5/7
Olavarria *et al.*[i]	22	Prophylaxis	Imatinib	400 mg	Not noted	68% relapse at median of 17 month after HCT

CCyR, complete cytogenetic response; CgR, cytogenetic response; CHR, complete hematologic response; CMR, complete molecular response.
[a]Kantarjian HM, *et al.* Blood. 2002;100:1590–5.
[b]Olavarria E, *et al.* Leukemia. 2003;17:1707–12.
[c]DeAngelo DJ, *et al.* Clin Cancer Res. 2004;10:5065–71; and DeAngelo DJ, *et al.* Clin Cancer Res. 2004;10:1–3.
[d]Hess G, *et al.* J Clin Oncol. 2005;23:7583–93.
[e]Palandri F, *et al.* Bone Marrow Transpl. 2007;39:189–91.
[f]Klyuchnikov E, *et al.* Acta Haematol. 2009;122:6–10.
[g]Wright MP, *et al.* Biol Blood Marrow Transpl. 2010;16:639–46.
[h]Carpenter PA, *et al.* Blood. 2007;109:2791–3.
[i]Olavarria E, *et al.* Blood. 2007;110:4614–17.

selection of a posttransplant TKI. If a patient harbors an imatinib-resistant mutation, does giving imatinib make any sense? Perhaps. First, resistance is likely a multiclonal phenomenon, so even in the case of imatinib resistance, there may be the presence of imatinib-sensitive clones. Anecdotal reports offer that patients sometimes relapse posttransplant with different clones than those that immediately preceded transplant.

He is started on imatinib 400 mg/d. His blood counts tolerate this well. He gets no GVHD. At discharge on day 100,

(*Continued*)

he now has a cytogenetic relapse, with the Ph in two of 20 metaphases. The peripheral blood BCR–ABL is 2.5% IS. Mutation analysis shows an E255V mutation.

4. What do you do?

A. Discontinue immunosuppressives
B. Change to dasatinib
C. Give DLI
D. All of the above

When do we need to give DLI? This patient has a cytogenetic relapse with an imatinib-resistant mutation. A reasonable option would be to taper immunosuppression rapidly, while starting dasatinib (nilotinib is also ineffective with the E255V mutation). The patient's response can be followed by peripheral blood PCR. If the patient gets GVHD, then DLI cannot be given, and one should maintain dasatinib; if no GVHD occurs, gauge the response to dasatinib alone—if his disease is disappearing, maintain dasatinib; and if it is still stable or increasing, DLI is appropriate.

DLI is effective in CML, and many studies demonstrate cytogenetic complete response rates of 50–100% in patients treated for clinically relapsed chronic-phase CML. Response rates are best for patients in early cytogenetic relapse, and worst for those who have progressed to advanced-phase disease. The two major complications of DLI are transient marrow failure (seen in cases of frank hematological relapse without adequate residual donor hematopoiesis), and the development of GVHD, which occurs in ~50% of cases. There is a close correlation between the development of GVHD and the achievement of complete responses to DLI.

Case study answers

Case study 29.1

Question 1: Answer A
Question 2: Answer A
Question 3: Answer A
Question 4: Answer B

Case study 29.2

Question 1: Answer C
Question 2: Answer D
Question 3: Answer C

Case study 29.3

Question 1: Answer C

Case study 29.4

Question 1: Answer D
Question 2: Answer C
Question 3: Answer C
Question 4: Answer D

Selected reading

Crawley C, Szydlo R, Lalancette M, *et al*. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood. 2005;106:2969–76.

Gratwohl A, Stern M, Brand R, *et al*. Risk score for outcome after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. Cancer. 2009;115:4715–26.

Kerbauy FR, Storb R, Hegenbart U, *et al*. Hematopoietic cell transplantation from HLA-identical sibling donors after low-dose radiation-based conditioning for treatment of CML. Leukemia. 2005;19:990–7.

Wright MP, Shepherd JD, Barnett MJ, *et al*. Response to tyrosine kinase inhibitor therapy in patients with chronic myelogenous leukemia relapsing in chronic and advanced phase following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2010;16:639–46.

CHAPTER 30

Hematopoietic cell transplantation in primary myelofibrosis

Irum Khan and Damiano Rondelli

University of Illinois Hospital & Health Sciences System, Chicago, IL, USA

1. Is there a cure for myelofibrosis?

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative therapy for patients with primary myelofibrosis (PMF), myelofibrosis secondary to polycythemia vera (PV-MF), or essential thrombocythemia (ET-MF). The effect of transplant relies both on the initial activity of the preparative regimen in reducing disease burden in the marrow and extramedullary sites, and on an immunological effect mediated by T-lymphocytes in the graft against clonal hematopoietic cells. This graft-versus-tumor effect was initially demonstrated by a 5-year survival of 54% for patients receiving an unmanipulated human leukocyte antigen (HLA)-matched related graft compared to 26% for those receiving a T-cell-depleted graft or a graft coming from an alternative donor. Complete normalization of marrow fibrosis, restoration of normal hematopoiesis, and reduction of splenomegaly to within normal limits usually occur over 12–24 months following transplantation.

2. Who is a candidate for allogeneic HSCT?

Given the marked heterogeneity in the clinical course of myelofibrosis and possible risks associated with transplantation, it is vital to have a reliable prognostic system to select patients who will benefit most. All the transplant studies reported to date utilized the Lille scoring system based on anemia, leukopenia, or leukocytosis, classifying patients as low, intermediate, or high risk.

An International Prognostic Scoring System (IPSS) was recently proposed and encompassed five independent risk factors at diagnosis: age >65 years, WBC $>25 \times 10^9$/L, Hb <10 g/dl, peripheral blood blasts >1%, and constitutional symptoms. A stratification of patients at any time point of the disease was obtained after finding that the development of anemia had double the adverse impact on survival and assigning it a score of 2 in the dynamic IPSS (DIPSS). Unfavorable cytogenetic abnormalities were shown to significantly impact posttransplant survival as well as risk of leukemic transformation in myelofibrosis. DIPSS was modified (DIPSS Plus) to include red cell transfusion dependency, platelet count $<100 \times 10^9$/L, and unfavorable karyotype. Based on the presence of 0 to 4 or more factors, patients at low-, intermediate-1, intermediate-2, and high-risk disease have a median survival of 15.4, 6.5, 2.9, and 1.3 years, respectively. Recently, a mortality rate >80% at 2 years was detected in patients with monosomal karyotype, inv(3) and i(17q) abnormalities, or any two of the following factors: peripheral blast percentage >9%, white blood count 40×10^9/l, or other unfavorable karyotype.

The DIPSS was retrospectively applied to a cohort of transplant patients in two separate analyses with similar results, confirming the prognostic value of this system in a transplant setting.

Leukemic transformation (LT) is often a catastrophic event in myelofibrosis, and chances of success with chemotherapy are dismal, with a median survival of 2.7 months. A scoring system to predict LT, including high-risk karyotype, peripheral blasts >2%, and platelets $<50 \times 10^9$/L, has been proposed. Transplant at the time of LT has poor outcome; however, in a small series of 13 patients transplanted in the blast phase, 49% patients were alive after a median follow-up of 31 months.

3. What factors are associated with transplant outcome?

Progress in HSCT over the past 2 decades was mostly related to the development of novel hematopoietic cell transplantation (HCT) preparative regimens at reduced intensity, improved antimicrobial prophylaxis, and improved graft-versus-host disease (GVHD) prophylaxis. A number of

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

nondisease factors such as age, donor type, and comorbidities impact outcome following HSCT in myelofibrosis.

In initial studies with myeloablative conditioning (MAC) regimens, patient age at the time of transplantation represented an important prognostic factor, with a 5-year survival of only 14% in PMF patients older than 45 years compared with 62% in younger patients. Retrospective studies both from the Nordic and the Australia–New Zealand cooperative groups confirmed the adverse prognostic impact of age on the outcome of allogeneic stem cell transplantation (allo-SCT). Transplant-related mortality significantly decreased upon introduction of reduced-intensity conditioning (RIC). However, multiple factors have been suggested as independent prognostic factors for toxicity in RIC transplants. In contrast with previous reports, Alchalby *et al*. (2010) initially showed that patients with wild-type *JAK2*V617F had an inferior survival after allogeneic HCT. In a following study from the same group, *JAK2* status, constitutional symptoms, and age >57 years independently predicted poor survival. The recently discovered calreticulin (CALR) mutation seen in 30% of MF cases has demonstrated predictive potential in transplant outcomes. Patients with mutated CALR had a better OS after ASCT than with wild-type CALR (4-year OS 82 vs 56%, respectively, $P = 0.043$). More specifically, patients with mutated CALR had the best prognosis, patients with JAK2 or MPL mutations had an intermediate prognosis and triple negative patients had the worst prognosis. Another single-center study demonstrated that spleen size >22 cm, transfusion history >20 units, and any donor other than a matched sibling donor (MSD) (e.g., a matched or mismatched unrelated donor, or a mismatched related donor) predicted an adverse outcome. Analysis of the French stem cell transplantation registry showed that factors favorably affecting engraftment were splenectomy before HCT, a human leukocyte antigen (HLA)-matched sibling donor, peripheral stem cell use as a source of stem cells, and the absence of pretransplant thrombocytopenia. In the GITMO experience, a longer interval between diagnosis and transplant negatively impacted survival after HSCT.

4. Is there a difference in outcome based on donor?

Several studies, including a large prospective trial, have reported similar outcomes in patients undergoing matched related (MRD) and matched unrelated donor (MUD) transplants, while outcomes of mismatched donors were significantly inferior. Contrary to this, using myelofibrosis retrospective data from the Center for International Blood and Marrow Transplant Research, Ballen *et al*. (2010) showed a 1-year nonrelapse mortality (NRM) rate of 27% for an HLA-identical HCT and 43% for an HLA-matched unrelated HCT. GITMO data also revealed a reduction in NRM associated with the choice of a matched sibling donor. The SFGM-TC registry, including patients with myelofibrosis transplanted between 1997 and 2008, showed engraftment probability and overall survival (OS) to be significantly inferior in nonsibling donors compared to matched sibling donors. An Italian study also indicated that having a donor other than a matched sibling was an independent poor prognostic factor. The ambivalent results from these different studies could be attributable to small sample sizes, retrospective design, patient heterogeneity, and the different chemotherapy regimens utilized. In a prospective study of RIC-HSCT in 66 patients, with a median follow-up of 24 months, 78% in the related group are alive compared to 44% in the unrelated group at 12 month follow-up. Possible interpretation of these different results could be the conditioning regimen utilized, the combination of older age and more advanced disease in the unrelated group, or the degree of HLA compatibility. At this time, for patients <65 years of age, in good overall condition, and with intermediate-2 or high-risk disease, a transplant from an MRD or MUD is indicated due to their poor prognosis. In a small study of 14 patients with marrow fibrosis secondary to different disorders, including PMF, cord blood was shown to be a feasible alternative graft source but only in the setting of a clinical trial at this time.

5. Is splenectomy indicated prior to transplant?

Significant splenomegaly at the time of transplant may adversely impact time to engraftment, so the question of whether splenectomy should be offered to these patients has been addressed. A previous analysis at Mayo Clinic showed a 27.7% risk of perioperative complications and a 6.7% mortality rate for splenectomy in myelofibrosis patients. Conflicting results have been reported on the survival benefit of pretransplant splenectomy. The European Group for Blood and Marrow Transplantation (EBMT) study reported a threefold increased risk of relapse after splenectomy, although it is argued that this may have been a reflection of more advanced disease. In contrast, an Italian study reported a reduced risk of relapse in patients who were splenectomized before HSCT. Review of the data from the Fred Hutchinson Cancer Center showed that after adjustment for DIPSS score and the Hematopoietic Cell Transplant Comorbidity Index (HCT-CI), patients who had a splenectomy were at lower risk for mortality compared with patients who had not (HR = 0.44). Retrospective data from the Center for International Blood and Bone Marrow Transplant Research (CIBMTR) and two other studies failed to show an effect of splenectomy on disease-free survival (DFS) or OS. Postulated setbacks of splenectomy in the setting of HSCT include a worsened severity of GVHD due to altered immunomodulation and an excess risk of acute myeloid leukemia transformation.

In the absence of any intervention for splenomegaly, successful engraftment can still occur. In a study of 10 patients with extensive splenomegaly, a progressive reduction of splenomegaly within 12 months post RIC transplant was

demonstrated, and it paralleled the reduction of marrow fibrosis. Given the absence of strong favorable evidence and inherent operating risks, at this time routine splenectomy is not advocated prior to transplant.

6. Myeloablative or reduced-intensity conditioning?

Conventional myeloablative conditioning (MAC) regimens for PMF or PV- or ET-MF resulted in a 3-year OS of 33–53% with a considerable NRM of 27–48%. Kerbuay *et al*. (2007) demonstrated that targeted busulfan in combination with cyclophosphamide led to a higher probability of survival than other regimens. However, the NRM remains high, and in the initial European study the 5-year OS for the patients >45 years of age was only 14%. Deeg *et al*. (2003) reported that intermediate- and high-risk patients were likely to have increased relapse and nonrelapse mortality. Patients with a low Lille score had an 80% OS rate at 3 years after transplantation, whereas patients with intermediate- or high-risk scores had 45% and 25% 3-year OS, respectively.

This led to the introduction of RIC regimens, with the potential reduction in NRM making allogeneic transplantation accessible to older patients and those with more advanced disease. In the early 2000s, several retrospective studies showed successful engraftment with stable full-donor hematopoietic chimerism and reversal of marrow fibrosis with RIC transplants in older patients. These studies used matched sibling donors as well as MUDs. Conditioning regimens included mostly fludarabine-based regimens. A retrospective study of 21 patients by the Myeloproliferative Disorders-Research Consortium (MPD-RC) observed an OS of 85% and event-free survival of 76% with a median follow-up of 31 months, despite a median patient age of 54 years and all patients having intermediate- or high-risk disease according to the Lille score system. These encouraging findings suggested that myelofibrosis is highly responsive to donor T-cell alloantigen recognition eliciting a graft-versus-tumor effect.

This data led to a pilot study using RIC with busulfan (10 mg/kg), fludarabine (180 mg/qm), and antithymocyte globulin (ATG) followed by allogeneic stem cell transplantation from related ($n = 8$) and unrelated donors ($n = 13$) in 21 myelofibrosis patients with median age of 53 years; in these patients, hematological response was seen in 100%, and after a median follow-up of 22 months, the 3-year estimated OS and DFS were 84% [95% confidence interval (CI): 67–100%]. This was followed by a phase II multicenter prospective trial conducted by the European Group for Blood and Marrow Transplantation (EBMT) using a busulfan (10 mg/kg)–fludarabine (180 mg/m^2)-based RIC regimen followed by allogeneic stem cell transplantation from related ($n = 33$) or unrelated donors ($n = 70$). Acute GVHD (aGVHD) grade 2 to 4 occurred in 27% of the patients, and chronic GVHD in 43%. Cumulative incidence of NRM at 1 year was 16%, but it was significantly higher in HLA-mismatched cases. The cumulative incidence of relapse at 3 years was 22% (95% CI: 13–31%) and was influenced by Lille score and splenectomy. The estimated 5-year event-free survival and OS rates were 51% and 67%, respectively. The MPD-RC undertook another prospective phase II study in the United States and Europe using a reduced-intensity regimen with fludarabine–melphalan (FluMel) ± ATG followed by allogeneic stem cell transplantation in patients with PMF or MF secondary to essential thrombocythemia (ET-MF) or polycythemia vera (PV-MF). Of 66 patients, 63 were at intermediate or high risk according to the Lille scoring system, and 3 were at low risk with thrombocytopenia. Interim results, after a median follow-up for survivors of 24 months, showed that NRM was 18% in MRD recipients and 53% in the unrelated group. Median survival time has not been reached in the related transplant group and is 7 months in the unrelated group.

There have been several comparisons of myeloablative conditioning versus RIC in myelofibrosis. Ninety-two patients with myelofibrosis in chronic phase underwent allo-HSCT in nine Nordic transplant centers. A MAC regimen was given to 40 patients, and a RIC regimen was used in 52 patients. When adjustment for age differences was made, the survival of the patients in the RIC group was significantly better ($P = 0.003$). These patients, in fact, experienced significantly less acute GVHD. The Swedish experience comparing MAC with RIC at six transplant centers ($n = 27$) showed that NRM was 10% in the RIC and 30% in the MAC group after a median follow-up of 55 months. In a review of 46 patients who underwent MAC or RIC over a 7-year period, Gupta *et al*. (2009) reported a reduced risk of GVHD, more rapid engraftment, and reduced hospitalization within the first 100 days with a RIC regimen. No difference in relapse rate or rate of histologic regression was noted. There was a trend toward improved DFS and OS in the RIC group at a median follow-up of 50 months. Retrospective studies from the GITMO and four major French transplant centers failed to demonstrate any improvement in survival or NRM using RIC over MAC.

Allogeneic HSCT with a MAC regimen may be a valid therapeutic option for young patients (<45 years). However, NRM after HSCT with RIC regimens, especially in an MRD setting, is in the range of 10–20%, and the risk of relapse in most studies does not exceed that seen with myeloablative conditioning. It appears, therefore, that the majority of patients with myelofibrosis should be conditioned with RIC regimens.

7. What are the main complications of HSCT?

Hepatotoxicity

The most common etiologies of abnormal liver function tests after HSCT are hepatic GVHD, drug-induced hepatitis, and iron overload, whereas severe hepatotoxicity (aminotransferase >1500 U/L) is mediated mainly by

veno-occlusive disease (VOD) and hypoxia. Patients with myelofibrosis are at a significantly higher risk of early hepatoxicity after HSCT compared to matched controls ($n = 53$) undergoing transplant for other indications. A history of portal hypertension, biopsy-proven hepatic iron overload, or splanchnic vein thrombosis strongly predicted for moderate or severe hyperbilirubinemia ($P = .02$). Importantly, moderate or severe hyperbilirubinemia or transaminitis was associated with inferior survival at 12 months ($P = .02$) in the myelofibrosis group. In light of these risk factors and their impact on survival, some groups are screening for portal hypertension prior to transplantation, and risk stratification for VOD is recommended prior to transplantation.

Graft-versus-host disease

The incidence of GVHD must be interpreted in the context of the conditioning regimen, T cell depletion, donor type, and source of stem cells. Rates of aGVHD differ with MAC or RIC regimens, and they depend on the use of T-cell immune-modifying agents. The Fred Hutchinson Cancer Center MAC experience revealed a 68% incidence of aGVHD. Use of RIC with ATG appeared to lower the rate of acute grade II–IV GVHD to 27%. Several retrospective comparisons provided conflicting results about the role of RIC in reducing a GVHD. Gupta *et al*. (2009) reported a day 100 cumulative incidence of aGVHD of 78% in the MAC-HSCT group versus 18% in the RIC-HSCT recipients, most likely because 70% of the RIC patients received ATG or alemtuzumab. The Nordic data showed 72% of patients undergoing RIC to be free of aGVHD compared to 24% of those undergoing MAC-HSCT. This was not confirmed by the British transplant data, in which aGVHD occurred in 29% and 38% of patients in the myeloablative and RIC groups, respectively, even though 70% RIC patients received an in vivo T-cell depletion. Chronic GVHD was reported in 40–59% of cases and predicted for improved OS, underscoring the importance of the graft-versus-tumor effect of allogeneic transplantation. In a retrospective study of 73 patients, relapse incidence was significantly higher in the absence of chronic GVHD ($P = 0.006$).

Regarding GVHD prophylaxis, prospective experience at the City of Hope has shown that tacrolimus–sirolimus $+/-$ methotrexate is superior to cyclosporine–mycophenolate mofetil (CsA–MMF) $+/-$ methotrexate. The estimated 2-year OS for the CsA–MMF cohort was 55.6%, and for the tacrolimus–sirolimus cohort it was 92.9% ($P = .047$). The probability of grade III or IV acute GVHD was 60% for the CsA–MMF patients, and 10% for the tacrolimus–sirolimus group ($P = .0102$).

Incidence of GVHD in some studies of myelofibrosis exceeds that in other hematologic malignancies. This has been postulated to be due to elevated proinflammatory cytokines enhancing dendritic cell activation of T cells. An interesting observation in this regard is that the *JAK2* inhibitor CP-690550 abrogated acute GVHD-related mortality in murine models; this effect was largely related to the suppression of donor CD4 T-cell-mediated interferon (IFN)-gamma production. Moreover, ruxolitinib has also been shown to reduce the levels of proinflammatory cytokines in PMF patients dramatically. It remains to be seen what effect ruxolitinib and other *JAK* inhibitors will have on the cytokines mediating GVHD.

Graft failure

Concern about graft failure caused initial reluctance to carry out transplants in patients with myelofibrosis. Previous data showed that graft failure was a problem in only 5–25% of patients, particularly those who received transplants from "alternative" (i.e., other than MSD) donors. The MPD-RC prospective study, however, reported a high rate of rejection in patients transplanted with unrelated donors and conditioned with fludarabine–melphalan and ATG.

8. Is there a marker of posttransplant minimal residual disease (MRD)?

In addition to its prognostic role, the *JAK2*V617F mutation can also be used as a marker for MRD. A study monitoring patients after transplantation with a quantitative polymerase chain reaction assay for *JAK2*V617F demonstrated that of 15 *JAK2*-positive patients analyzed, three relapsed clinically shortly after the *JAK2* gene mutation was detected in the peripheral blood. Kroger *et al*. (2007) demonstrated that 78% of patients with the *JAK2* mutation undergoing a RIC allo-SCT achieved a molecular response after a median of 89 days following transplantation. This achievement of molecular response 6 months after HSCT predicted for a reduced risk of relapse (5% vs. 35%). There is controversy surrounding the prognostic value of the *JAK2* allele burden in PMF. In nontransplant patients, low levels of the mutation seemed to predict a worse survival with a higher risk for bone marrow failure. However, in the setting of an allo-SCT, the allele burden on day 28 post transplantation discriminated two prognostic groups, with patients having >1% being at significantly higher risk for relapse and having an inferior overall survival. Other molecular markers that have been studied in primary and secondary myelofibrosis include the MPL W515L/K mutation.

9. Is there a role for donor lymphocyte infusions (DLIs) or second allograft in relapse post HSCT?

An immunologic graft-versus-tumor effect can be achieved with DLIs in myelofibrosis patients relapsing after HSCT.

The timing of a DLI, whether as a preemptive or salvage therapy, is debatable. In the salvage setting, responses were observed in 10 of 26 patients. Notably, all 10 responders achieved stable remissions and required no additional treatment. In a series of 17 patients where DLI was used

preemptively in 8 patients and as salvage in 9, complete molecular response rate was superior in the preemptive group (68% vs. 44%). The role of lymphodepleting chemotherapy prior to DLI has been explored. In preclinical models, lymphodepletion potentiates T-cell expansion and function by decreasing competition for cytokines and growth, elimination of regulatory T cells, and enhancement of antigen-presenting cell function.

In a recent study, 17 patients underwent a second HSCT at a median interval of 17 months from the first allograft due to relapse ($n = 13$), graft rejection ($n = 3$), and transformation to blast phase ($n = 1$). Fifteen patients were transplanted with cells from alternative donors, and two patients from the same donor. The response rate was 80%, and 1-year OS and PFS were 82% and 70%, respectively.

10. Will new agents available for myelofibrosis change the role of HSCT?

With the advent of *JAK* inhibitors into the clinical armamentarium for myelofibrosis, there is increasing debate on whether and when to refer a patient with myelofibrosis to the transplant physician. It is interesting to speculate whether improvement in the DIPSS score due to cytokine inhibition mediated by *JAK* inhibitors will allow physicians to modify the transplant strategy. It may be that the DIPSS score will be valid only in the absence of therapy with *JAK* inhibitors or similar compounds. By improving constitutional symptoms and splenomegaly, *JAK* inhibitors might turn out to be very useful in the pretransplant setting and favor a more rapid engraftment, and possibly reduce the rates of rejection and/or GVHD. A retrospective experience from Germany demonstrated an improved performance status and spleen size with Ruxolitnib therapy for a median duration of 97 days before RIC-HSCT Ruxolitinib did not appear to adversely affect early outcomes including engraftment. However the prospective French JAK ALLO study reported severe tumor lysis syndrome and fatal cardiac failure upon withdrawal of the Ruxolitinib prior to transplant supporting the need for further controlled studies and longer follow-up. A new study within the MPD-RC is prospectively testing the use of ruxolitinib in patients undergoing HSCT (NCT01790295) and will possibly address the questions discussed here.

Conclusion

The decision to opt for an allogeneic HSCT for patients with myelofibrosis is currently based on multiple considerations. Controversies continue to surround the timing, type of donor, and conditioning regimen.

- Comparisons of myeloablative and reduced-intensity regimens are retrospective and spread over many decades. However, RIC-HSCT has been shown to be safe and effective in patients of all ages.
- Although patients with intermediate-2 and high-risk disease, adverse cytogenetics, or transfusion dependence should unequivocally proceed to transplant, there is controversy about transplanting low-risk patients. Low-risk patients with an MRD should be monitored closely for any sign of progression as they can have an 80% survival rate if transplanted early in the course of disease.
- Close monitoring of MRD has become feasible in myelofibrosis, and the outcome of posttransplant strategies has consequently improved. Strategies of using *JAK1/2* inhibitor therapy in combination with transplantation will be explored in the near future.

Selected reading

Alchalby H, Yunus DR, Zabelina T, *et al*. Risk models predicting survival after reduced-intensity transplantation for myelofibrosis. Br J Haematol. 2012;157:75–85.

Gupta V, Gotlib J, Radich J, *et al*. JAK inhibitors and allogeneic stem cell transplantation for myelofibrosis. BBMT. 2014 (accepted for publication)

Hoffman R, Prchal JT, Samuelson S, *et al*. Philadelphia chromosome-negative myeloproliferative disorders: biology and treatment. Biol Blood Marrow Transplant. 2007;13:64–72.

Kroger N, Holler E, Kobbe G, *et al*. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2009;114:5264–70.

Rondelli D, Goldberg J, Marchioli, R, *et al*. Results of Phase II Clinical Trial MPD-RC 101: Allogeneic Hematopoietic Stem Cell Transplantation Conditioned with Fludarabine/Melphalan in Patients with Myelofibrosis. ASH Annual Meeting Abstracts. 2011;118:1750.

PART 5

Chronic Lymphocytic and Other Leukemias

CHAPTER 31

Prognostic markers and management of chronic lymphocytic leukemia

Courtney D. DiNardo and Susan O'Brien

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Multiple choice questions

1. Which of the following "classical" prognostic factors are associated with improved survival in chronic lymphocytic leukemia (CLL)?

A. Lymphocyte doubling time <6 months
B. Elevated β2-microglobulin
C. Eastern Cooperative Oncology Group Performance Status 2 or greater
D. Nodular pattern of bone marrow infiltration

In addition to the standard Rai and Binet clinical staging systems (Tables 31.1 and 31.2), there are established traditional prognostic markers that can be used to predict overall prognosis and to estimate the extent of tumor burden. A lymphocyte doubling time of less than 12 months, an elevated serum β2-microglobulin level (usually considered to be greater than twice the upper limit of the normal laboratory range), poor performance status, and a diffuse (as opposed to an interstitial and/or nodular) bone marrow histologic pattern have all been independently associated with worse outcome in CLL.

2. An asymptomatic 63-year-old man has lymphocytosis noted on routine blood work and is diagnosed with CLL, Rai stage 0, after appropriate diagnostic evaluations. Which of the following molecular results would be associated with an inferior prognosis in CLL?

A. Mutated immunoglobulin gene (IgVH)
B. Positive ZAP70 expression
C. Negative CD38 expression

Mutations of the immunoglobulin variable heavy-chain gene (IgVH) are thought to occur in postgerminal B-lymphocytes having undergone normal IgVH gene somatic hypermutation. Patients with mutated IgVH genes, commonly defined as a >2% difference in the nucleotide sequence compared to germline DNA, enjoy an improved survival and lower risk of disease relapse following treatment. CLL cells with low CD38 expression (considered <30% expression) by flow cytometry often co-associate with mutated IgVH status, and are also associated with an improved prognosis. ZAP70 is a tyrosine kinase protein normally expressed by T- and NK-cells, which is abnormally expressed in a subgroup of CLL patients with poor prognosis. While IgVH mutational status and ZAP70 and CD38 expression have all been independently associated with CLL prognosis, all three molecular tests are subject to some criticism. The optimal cutoff for CD38 positivity is debated, and the IgVH and ZAP70 tests are technically difficult assays for standard laboratories to perform. While the optimal method to integrate these molecular findings into patient care remains an unanswered question, we believe in the importance of incorporation of these molecular findings to provide improved risk stratification and risk-based decision making.

3. Which of the following cytogenetic abnormalities identified via a standard CLL fluorescent in situ hybridization (FISH) panel is associated with a favorable prognosis?

A. 11q deletion
B. 13q deletion
C. 17p deletion
D. Trisomy 12

Although only 40–50% of CLL patients have karyotypic abnormalities detectable by conventional cytogenetics, approximately 80–90% of the CLL population has identifiable abnormalities by FISH. This has led to the advent of "CLL FISH panels" to detect the most common

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 31.1 Modified Rai Clinical Staging System (Source: Adapted from Rai KR, *et al.* Blood 1975:46:219–34).

Risk	Stage	Description
Low	0	Lymphocytosis in blood or bone marrow
Intermediate	I	Lymphocytosis + enlarged lymph nodes
	II	Lymphocytosis + hepatomegaly or splenomegaly with or without lymphadenopathy
High	III	Lymphocytosis + anemia (hemoglobin <11 g/dL) with or without hepatomegaly, splenomegaly, or lymphadenopathy
	IV	Lymphocytosis + thrombocytopenia (platelet count <100/uL) with or without anemia, hepatomegaly, splenomegaly, or lymphadenopathy

Table 31.2 Binet Staging System (Source: Adapted from Binet JL, *et al.* Cancer 1981;48:198–206).

Stage	Description
A	Enlargement of ≤2 lymphoid-bearing areas
B	Enlargement of >3 lymphoid-bearing areas
C	Presence of anemia (hemoglobin <10 g/dL) or thrombocytopenia (platelet count <100,000/uL)

abnormalities. In seminal work performed by Dohner *et al.*, which has since been independently verified, CLL prognosis is independently associated with the above karyotypic abnormalities (Figure 31.1). Median overall survival with del(17p) was 32 months, del(11q) was 79 months, and with trisomy(12) was 114 months. A negative FISH panel conferred a median overall survival of 111 months. Patients with del(13q) had an uniquely improved overall survival, at 133 months.

4. A 57-year-old man is referred for a new diagnosis of CLL, which was diagnosed after presentation to medical attention for several months of unintentional weight loss, fatigue, and night sweats. Imaging reveals bulky abdominal lymphadenopathy, and his CLL FISH panel reveals del(11q). Which of the following is true regarding the initial management in this patient?

A. He should be immediately referred for allogeneic stem cell transplantation given his poor prognosis.
B. Standard front-line fludarabine, cyclophosphamide, and rituximab (FCR) immunochemotherapy is appropriate.
C. Watchful waiting with a return visit in 3 months is appropriate.

Deletion of 11q22–23, leading to loss of the ATM gene, is one of the most frequent chromosomal aberrations seen in CLL, and del(11q) is historically associated with reduced progression-free survival (PFS) after therapy and poor overall survival. For unclear reasons, it is more frequently seen in patients that are young, are male, and have more advanced clinical stages and symptomatology. Patients with del(11q) appear to be particularly sensitive to alkylating agent therapy (i.e., cyclophosphamide). With the advent of FCR immunochemotherapy, the poor prognosis related to the del(11q) abnormality has been greatly reduced, and FCR is an appropriate first-line treatment option. However, PFS is shorter in del(11q) patients, and they are excellent candidates for the consideration of trials involving maintenance therapy in CLL. Given his significant systemic symptoms, watchful waiting is not appropriate.

5. True or false? The use of novel molecular and cytogenetic prognostic markers in early-stage CLL allows a high-risk early-stage CLL cohort to be identified, and early treatment of these high-risk patients improves patient survival.

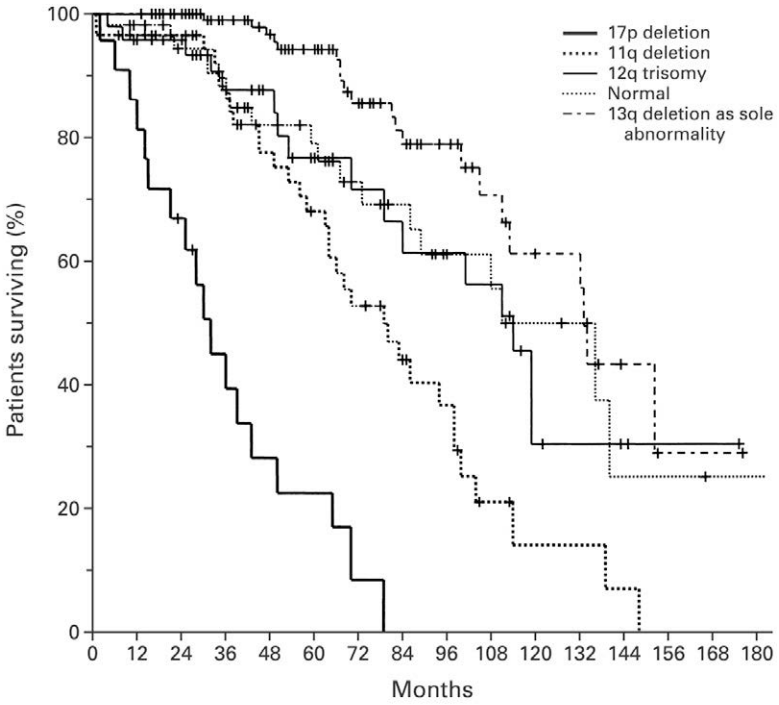
A. True
B. False

The decision to initiate treatment in CLL at this time is guided by disease stage (i.e., the Rai or Binet staging system) and systemic symptoms attributable to CLL (i.e. "B" symptoms or progressive lymphadenopathy or splenomegaly). Importantly, recent molecular and cytogenetic advances have improved our ability to predict which early stage patients are at higher risk of disease progression and poorer overall survival. However, there is no evidence at this time that early treatment of high-risk, early-stage patients leads to improved patient survival. Prospective trials of early intervention in high-risk patients are ongoing. Apart from treatment as part of a clinical trial, treatment for asymptomatic early-stage CLL patients with high-risk prognostic markers cannot be recommended.

6. A previously untreated 71-year-old female patient with CLL has progressive symptomatic anemia and cervical lymphadenopathy, and her lymphocyte count rises from 22,000 to 48,000 over several months. She has a history of benign hypertension and hyperlipidemia that are well controlled on medical therapy. A decision to initiate treatment is made. Which of the following agents is the most appropriate for first-line therapy?

A. FCR
B. Chlorambucil monotherapy
C. Bendamustine monotherapy
D. Fludarabine monotherapy

In one of the first randomized CLL treatment trials, fludarabine monotherapy was shown to improve overall



Number AT RISK

17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1	0

Figure 31.1 Overall survival in chronic lymphocytic leukemia (CLL) based on cytogenetic abnormalities at diagnosis (Source: Dohner H *et al.*, NEJM 2000; 343:1910–16. Reproduced with permission of Massachusetts Medical Society).

survival as compared to chlorambucil single-agent therapy. Subsequently, fludarabine as a combination with either cyclophosphamide (FC) or rituximab (FR) both demonstrated improvement in response rates and overall survival compared to fludarabine alone. Most importantly, the best outcomes reported in the literature thus far are with the three-drug regimen of fludarabine, cyclophosphamide, and rituximab (FCR), which has been shown to prolong both PFS and overall survival compared to FC in the phase III randomized trial of the CLL8 Protocol by the German CLL Study Group (GCLLSG) (Figure 31.2). Physically fit patients up to age 81 were eligible for this trial, and patients between 70 and 80 years of age who met the eligibility criteria of creatinine clearance >70 ml/min and a Cumulative Illness Rating Scale (CIRS) score ≤6 had no greater incidence of toxicity than those patients younger than 70 years. BR appears comparable to FCR in several early-phase clinical trials; a front-line GCLLSG single-arm BR trial reported inferior outcomes, with an overall response rate of 88% and a 24% complete remission (CR) rate, compared to those seen with FCR, but it incorporated a higher-risk CLL cohort. A front-line randomized trial of BR to FCR is ongoing. Bendamustine monotherapy, however, would not be an appropriate first-line option.

7. A 57-year-old man is diagnosed with symptomatic Rai stage III CLL. Evaluation at the time of diagnosis reveals CD38 positivity, unmutated IgVH gene status, and deletion of chromosome 11q23. He is treated with first-line FCR and attains a CR. Unfortunately, 9 months later he notes abdominal distention, and evaluation reveals relapsed disease with recurrent abdominal lymphadenopathy. At this time, is the best choice of therapy for this patient retreatment with FCR, given his excellent initial response to this therapy?

A. Yes

B. No

FCR immunochemotherapy has greatly reduced the poor prognosis historically related to CLL patients with del(11q). However, patients with del(11q) are unfortunately still at risk of relapsing soon after achieving a remission, and indeed more than 40% of patients with early relapse to FCR exhibit a deletion of 11q23. In patients who relapse

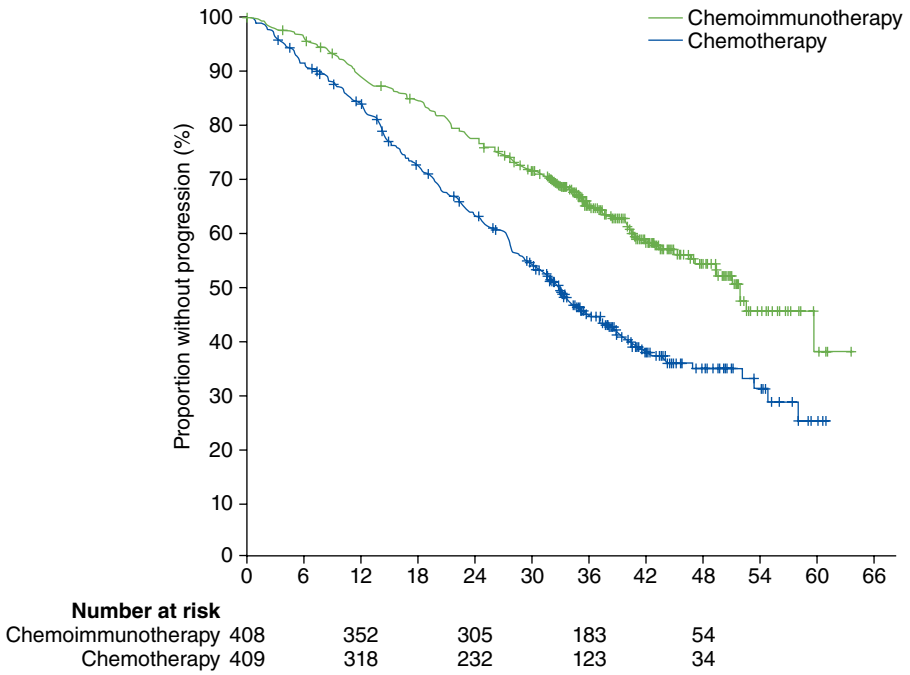


Figure 31.2 Overall survival of fludarabine, cyclophosphamide, and rituximab compared to fludarabine and cyclophosphamide in the phase III randomized controlled trial by the German CLL Study Group (Source: Hallek M *et al.*, Lancet Oncology; 376:1164–74. Reproduced with permission of Elsevier).

shortly after treatment with alkylating agents, retreatment with the same regimen is unlikely to induce another CR. Consideration of an allogeneic stem cell transplantation or participation in a clinical trial would be most appropriate for this patient. Ofatumumab would be another reasonable consideration, although as an off-label indication.

8. A 67-year-old female with CLL was treated approximately 2 years ago with bendamustine and rituximab (BR) combination therapy and attained a complete remission. She is presenting emergently to your office today with complaints of profound malaise, generalized pain, and recurrent fevers. You note both axillary and inguinal lymphadenopathy on exam. Laboratory results reveal an elevated lactate dehydrogenase (LDH) of 2500 IU/L. You are concerned about the possibility of Richter's transformation, and you are considering ordering a fluorodeoxyglucose positron emission tomography (FDG–PET) scan and/or obtaining a core biopsy of a lymph node for evaluation of this possibility. Which of the following is the best next step in her management?

A. Order FDG–PET alone
B. Order core lymph node biopsy alone
C. Order both FDG–PET and core lymph node biopsy
D. Neither FDG–PET or biopsy—retreat with FCR

Richter's transformation is the development of an aggressive large-cell lymphoma in the setting of underlying CLL. This rare but devastating phenomenon occurs in approximately 5% of CLL patients, often within the first 2–4 years from CLL diagnosis, and it carries a poor prognosis with a median survival of only 6 months. Suspicion for Richter's is raised in the setting of rapid clinical decline, progressive systemic "B" symptoms, elevated LDH, and increasing lymphadenopathy at one or more sites.

Biopsy-proven large-cell transformation is required for diagnosis. Importantly, FDG–PET scanning in patients suspected of Richter's transformation has become increasingly used to guide and assist in the evaluation. In a recent study of 328 patients with concurrent FDG–PET imaging and biopsy, a standardized uptake values (SUV) cutoff of 10 showed the highest discriminatory power for identifying patients with Richter's transformation, and it similarly identifies an optimal location for a subsequent biopsy. At the brightest point, the median SUV was 17.9 for patients with biopsy-proven Richter's and 3.6 with patients with no evidence of transformation on biopsy. Prospective studies to validate the role of FDG–PET in the evaluation and management of CLL patients for Richter's are ongoing.

9. True or false? CLL patients treated with FCR have a higher risk of secondary malignancies than with other standard first-line CLL treatment regimens.

A. True
B. False

The increased frequency of secondary malignancies in CLL patients is well known, related to both the underlying disease process and the antineoplastic therapies received. The question has been raised as to whether there is an increased risk of secondary malignancies, in particular of MDS and AML, in patients receiving FCR. After extended follow-up of >800 patients treated on the randomized phase III CLL8 trial of FCR versus FC (median follow-up: 5.9 years), the frequency of secondary malignancies was independent of the treatment given. 9.9% of patients in the FCR group and 12.1% of patients in the FC group developed a secondary malignancy, and this difference was not statistically significant. Of those patients who did develop malignancy, 52% developed a solid tumor, 37% experienced Richter's transformation, and 13% had MDS or AML, with a mean time to onset of 2.4 years. These results help confirm the utility of FCR as a front-line therapy.

10. A 59-year-old man is diagnosed with Rai stage IV disease. He has massive lymphadenopathy and evidence of progressive marrow failure with anemia and thrombocytopenia. Diagnostic work-up reveals trisomy(12) on a CLL FISH panel, a mutated IgVH gene, and lack of CD38 expression on flow cytometry. He is treated with six cycles of bendamustine and rituxan (BR) front-line therapy, which he tolerates well. At the completion of therapy, his peripheral counts have normalized, his lymphadenopathy has resolved, and he has no evidence of a clonal B-cell population by flow cytometry. However, FISH is still positive for trisomy(12) in 23 of 200 cells analyzed. What is the appropriate response to minimal residual disease (MRD) results in CLL at the completion of therapy?

A. Provide an additional two cycles of BR therapy
B. Switch to FCR chemotherapy for six cycles due to lack of response to BR therapy
C. This is an indication for maintenance therapy with monthly rituximab for 6 months
D. Continue close observation with clinic visits and laboratory monitoring every 3–6 months, with consideration of clinical trials if available

As many as 60% of all patients treated with chemoimmunotherapy have evidence of MRD at the completion of treatment. It has been shown that lower MRD levels after therapy are associated with longer PFS and overall survival, and thus eradicating MRD may lead to improved outcomes and delay the time to next treatment. While the achievement of an MRD-negative remission is a therapeutic goal, there is no evidence at this time that treatment of MRD-positive status or maintenance therapy will improve outcomes. Initially encouraging results with alemtuzumab were seen in the MRD-positive setting, although increased toxicity was also noted. Trials of alternative schedules of alemtuzumab, rituximab, lenalidomide, and ofatumumab, among others, are ongoing.

11. A 57-year-old man is referred to you for a new diagnosis of CLL, Rai stage III, which was diagnosed after evaluation for thrombocytopenia. He was initially diagnosed with idiopathic thrombocytopenic purpura that has been refractory to prednisone 60 mg daily and IVIG therapy 1 g/kg daily for 2 days, but now has bone marrow progression with 92% diffuse infiltration by CLL cells. He is ZAP-70 positive, has unmutated IgVH, and is CD38 positive, with a 17p deletion. Which of this patient's high-risk features affects your treatment decision?

A. 17p deletion
B. Positive ZAP-70
C. Unmutated IgVH
D. Positive CD38
E. Autoimmune cytopenias

Consistently decreased rates of response to all first-line treatments are unfortunately seen in patients with del(17p), with a median survival of less than 3 years irrespective of treatment choice. In patients with del(17p), a chromosomal aberration that results in deletion of the *p53* tumor suppressor gene, first-line treatment on clinical trials of novel induction regimens should be considered. Additionally, patients with del(17p) should be considered for allogeneic stem cell transplantation in first remission, as remission durations are short and disease response after first relapse is poor. CD38, ZAP-70, and IgVH status bear no relevance to the initial choice of chemotherapy. A history of immune-related CLL complications does suggest the particular usefulness of rituximab for treatment of ongoing autoimmune cytopenias, although this is a common complication in CLL (10–20% of patients) and does not connote high-risk disease behavior.

Multiple Choice Answers

Question 1: Answer D
Question 2: Answer B
Question 3: Answer B
Question 4: Answer B
Question 5: Answer B
Question 6: Answer A
Question 7: Answer B ("No")

Question 8: Answer C
Question 9: Answer B ("False")
Question 10: Answer D
Question 11: Answer A

Selected reading

Dohner H, Stilgenbauer S, Benner A, *et al.* Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910–6.

Fischer K, Cramer P, Busch R, *et al.* Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012;30:3209–16.

Hallek M, Fischer K, Fingerle-Rowson G, *et al.* Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376:1164–74.

Rassenti LZ, Jain S, Keating MJ, *et al.* Relative value of ZAP-70, CD38, and immunoglobulin mutation status in predicting aggressive disease in chronic lymphocytic leukemia. Blood. 2008;112:1923–30.

Tsimberidou AM, Tam C, Abruzzo LV, *et al.* Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer. 2009;115:373–80.

CHAPTER 32

Hematopoietic cell transplantation in chronic lymphocytic leukemia

Michael R. Bishop

The University of Chicago, Chicago, IL, USA

Case study 32.1

A 56-year-old male presented for his annual physical examination. Over the past year, he has done well but had noted slight fatigue, which he attributed to increased stress at work; he was otherwise asymptomatic. A complete blood count (CBC) demonstrated a white blood cell (WBC) count of 33,000 with 87% mature-appearing lymphocytes on peripheral smear, a hemoglobin (Hb) level of 13.7 g/dL, and a platelet count of 278,000. On physical examination he was noted to have mild (1–2 cm) cervical and axillary adenopathy; the spleen tip and liver edge were not palpable. A peripheral blood sample was sent for flow cytometric analysis and demonstrated a monoclonal B-lymphocyte population expressing CD5, CD19, CD20, CD22(dim), CD23, CD79(dim), and SmIg(dim); they were negative for CD38 and FMC7. A bone marrow examination demonstrated 40% lymphocytes with a diffuse histopathologic pattern. Cytogenetic analysis revealed a normal 46XY karyotype; however, fluorescence in situ hybridization (FISH) studies demonstrated an 11q deletion in 79% of cells. IgVH (immunoglobulin heavy-chain variable-region) mutational status was not performed. The patient was diagnosed as having B-cell chronic lymphocytic leukemia (CLL) and staged as Rai stage 0. It was recommended that the patient be closely observed with follow-up every 3 months. At a follow-up visit 6 months later, the patient complained of increased fatigue and occasional night sweats. On physical examination, his adenopathy had increased in both size and extent. A CBC demonstrated a WBC of 78,000 with 92% mature-appearing lymphocytes on peripheral smear, an Hb of 12.3 g/dL, and a platelet count of 213,000. A decision was made to begin treatment with the FCR regimen (fludarabine, cyclophosphamide, and rituximab) of which he received six cycles. At the completion of therapy, his adenopathy had almost completely resolved, and a CBC demonstrated a WBC of 6700 with 13% lymphocytes on peripheral smear, an Hb level of 14.3 g/dL, and a platelet count of 303,000. The decision was made to closely observe. The patient did well for approximately 11 months, at which time he called the office to say that he could palpate his cervical lymph nodes. He was found to have significant cervical adenopathy (3–4 cm) as well as diffuse adenopathy documented by a computed tomography (CT) scan. A CBC demonstrated a WBC of 59,000 with 89% mature-appearing lymphocytes on peripheral smear. The patient was treated with bendamustine plus rituximab for four cycles, resulting in a complete response. On follow-up 15 months later, a CBC demonstrated evidence of recurrent disease with a WBC of 29,000 with 72% mature-appearing lymphocytes on peripheral smear. He was also found to have a new left inguinal lymph node. An excisional lymph node biopsy demonstrated small lymphocytic lymphoma and no evidence of Richter's transformation. The patient was referred to a tertiary center for treatment options, including hematopoietic stem cell transplantation (HSCT). The patient has three living siblings who are in good health. A decision is made to treat the patient with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

• Is it appropriate to consider HSCT for the patient at this time?

The patient has been treated with a fludarabine-based regimen and second-line treatment with a bendamustine-based regimen. He is relatively young and has high-risk

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

features, with an 11q deletion and relatively short response durations to his two lines of treatment. Taken together, it is appropriate to *consider* transplantation as a treatment option. Whether the patient is an appropriate transplantation candidate is dependent on a number of factors, including the patient's response to third-line therapy, the availability of a donor, and ultimately whether the patient is willing to accept the toxicities associated with HSCT.

• If the patient does not have a responsive disease, is transplantation contraindicated?

Chemotherapy sensitivity is known to be an important prognostic factor; however, there are patients who lack chemotherapy sensitivity, generally defined as at least a partial response (PR), who can achieve long-term remissions and survival with allogeneic HSCT. Pavletic and collaborators (2000) at the University of Nebraska and Vanderbilt University reported on the results of 23 CLL patients who underwent myeloablative allogeneic HSCT, including 14 patients with chemotherapy-refractory disease, 12 of which were refractory to fludarabine. At the time of this report, 14 (61%) patients were alive and disease free, including eight patients with chemotherapy-refractory disease at a median follow-up of 26 months (range: 9–115 months). In univariate analysis, chemotherapy sensitivity was not significant ($P = 0.853$) relative to overall survival.

The Chronic Leukemia Working Party of the European Blood and Marrow Transplantation Group (EBMT) reported on the results of 77 CLL patients from 29 EBMT centers who underwent allogeneic HSCT using reduced-intensity conditioning. In a multivariate analysis, they observed that patients who had less than PR at the time of transplantation were at increased risk for relapse (hazard ratio = 3.5 (1.4–8.70; $P < 0.01$); however, it was a nonsignificant factor relative to overall survival. Similarly, Khouri and colleagues at the MD Anderson Cancer Center (2011) reviewed the results of 86 patients with relapsed and refractory CLL who were enrolled on sequential nonmyeloablative allogeneic HSCT protocols at their institution. In multivariate analysis, disease status at transplantation did not have a significant impact upon outcome, which may have been affected by the use of posttransplant immunomodulation in their treatment strategy.

In summary, lack of chemotherapy sensitivity is not an absolute contraindication to allogeneic HSCT. It does appear that results are improved, particularly in regard to progression-free survival (PFS), in patients who have chemotherapy-sensitive disease, and it is desirable to enter into transplant with as low a disease burden as possible. In my own practice, I have found that patients with truly progressive disease at the time of transplant rarely, if ever, benefit from HSCT, and I advise against transplantation for these patients. However, I will offer patients with stable disease the option of allogeneic HSCT, explaining that the risk of relapse is increased.

• What if the patient does not have a human leukocyte antigen (HLA)-matched sibling? Are the results significantly worse with a well-matched volunteer unrelated donor?

Similar to results in the acute leukemias, there are reports that outcomes are worse with unrelated donors. However, subsequent studies have demonstrated that outcomes are equivalent and possibly even superior with unrelated donors. The Cooperative German Transplant Study Group reported on 30 patients with advanced B-cell CLL who underwent reduced-intensity allogeneic HSCT. Fifteen patients received cells from HLA-related donors, and the other 15 from HLA-matched unrelated donors. After a median follow-up of 2 years, the probability of overall survival and PFS at 2 years for all patients was 72% and 67%, respectively. Acknowledging that the numbers were small, there was no difference in PFS between recipients of related and unrelated donors (70% vs. 67%; $P = 0.6735$).

The Seattle transplantation group performed an outcomes analysis on 64 patients with advanced CLL treated with nonmyeloablative allogeneic HCST; 44 were from related donors, and 20 were from unrelated donors. The 2-year rates of overall and disease-free survival were 60% and 52%, respectively. Recipients of unrelated donors were observed to achieve higher complete remission and lower relapse rates than recipients of related donors, suggesting more effective graft-versus-leukemia activity. These data are intriguing and suggest that although they may result in higher treatment-related morbidity and mortality, the use of unrelated donors can result in similar outcomes as measured by PFS and overall survival.

• Is there a stage of disease at which HSCT is no longer of any benefit?

This is an essential question and can be looked at from several perspectives. "Stage of disease," as defined by chemotherapy sensitivity, was addressed above. From another perspective, it comes down to an issue of timing. Again, using the acute leukemias (and, to a similar degree, our previous experience with chronic myeloid leukemia), it has been observed that the earlier in the patient's disease course that transplantation is utilized, the better the outcomes. There is some evidence to support similar observations in patients with CLL who have undergone allogeneic HSCT, yet there are data that contradict this assumption. In their admittedly small patient population ($n = 30$), the Cooperative German Transplant Study Group did not observe any difference in PFS among patients who had three or fewer prior therapies as compared to patients who had received more

than three prior chemotherapy regimens (75% vs. 56%; $P = 0.4454$).

Similar results were reported from the German CLL Study Group CLL3X trial. This prospective, multicenter phase II trial was designed to investigate the long-term outcome of reduced-intensity conditioning allogeneic HSCT in patients with poor-risk CLL. One hundred eligible patients were enrolled, and 90 patients proceeded to allogeneic HSCT. At a median follow-up of 46 months (range: 7–102 months), the 4-year event-free survival and overall survival rates were 42% and 65%, respectively. In univariate analysis, neither the time interval from diagnosis to allogeneic HSCT (≥5 years vs. <5 years; $P = 0.14$) nor the number of previous regimens (≥3 vs. <3; $P = 0.85$) was found to correlate with overall survival. It is of note that in this trial, chemotherapy-refractory disease did adversely correlate with overall survival ($P = 0.023$) in multivariate analysis. Based on these data, it does not appear that the use of allogeneic HSCT later in the disease course of CLL patients significantly affects outcomes.

• What is the quality of life like for CLL patients who undergo allogeneic HSCT?

This is the question asked by almost everyone thinking of referring a patient for transplantation, and it is an essential question for all patients. There is a tremendous amount of literature on the outcomes and quality of life (QOL) in long-term survivors following allogeneic HSCT, a primary concern being the effects of chronic graft-versus-host disease (GVHD). There is, however, only a limited amount of data on the QOL of CLL patients who have undergone allogeneic HSCT. Gill and colleagues from the Peter MacCallum Cancer Centre in East Melbourne evaluated the clinical outcomes and measures of QOL in 13 CLL patients from the transplant database at the Royal Melbourne Hospital. Seven of 13 patients (54%) achieved a complete remission (CR), of whom four remained in continuous CR at 30–77 months posttransplant. They reported that three out of five patients, who were still alive at last follow-up, had resumed part- or full-time employment. The Mayo Clinic retrospectively reviewed the outcomes of 12 consecutive CLL patients who had undergone allogeneic HSCT at their institution prior to July 2004. The median patient age was 44 years (range: 18–55). All but one patient had received a myeloablative conditioning regimen. At the time of this report, six patients (50%) had died, including four early deaths from infection. A CR was documented in eight patients (66.7%) posttransplant, of which six were still alive. All surviving patients were reported as displaying excellent performance status without ongoing chronic GVHD. In counseling patients, it is important to emphasize possible long-term complications as well as the equal likelihood that they have the potential to resume a relatively normal life.

• Is there any role for autologous HSCT in patients with relapsed CLL?

Based on the success of high-dose chemotherapy and autologous HSCT in other hematologic malignancies, there had been a high degree of interest in applying this treatment in CLL. However, these early efforts were associated with a high incidence of relapse and a lack of clear clinical benefit. The Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) and Groupe Français d'étude de la Leucémie Lymphoïde Chronique (GFLLC) jointly conducted a prospective, randomized trial of autologous HSCT in 241 previously untreated CLL patients. They all received three courses of mini-CHOP (reduced-dose cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by three courses of fludarabine. Patients in CR were then randomized to autologous HSCT or observation, whereas the other patients were randomized to receive dexamethasone, cytarabine, and cisplatin as second-line therapy followed by either autologous HSCT or three courses of fludarabine plus cyclophosphamide (FC). After upfront treatment, 105 patients entered CR and were randomized between autologous HSCT ($n = 52$) and observation ($n = 53$); their respective 3-year EFS rates were 79.8% and 35.5%. The 94 patients who did not enter CR were randomized between autologous HSCT ($n = 46$) and FC ($n = 48$); their respective 3-year EFS rates were 48.9% and 44.4%. There was no difference in overall survival between the two response subgroups.

The German CLL Study Group conducted the CLL3 trial, which was designed to study intensive treatments, including autologous HSCT, as part of first-line therapy in patients with CLL. After a median observation time of 8.7 years (range: 0.3–12.3 years), the median PFS, time to retreatment, and overall survival of 169 evaluable patients, including 38 patients who did not proceed to autologous HSCT, was 5.7, 7.3, and 11.3 years, respectively. When 110 CLL3 patients were compared with 126 matched patients from the FCR arm of the CLL8 trial, 4-year time to retreatment (75% vs. 77%) and overall survival (86% vs. 90%) were similar, despite a significant PFS benefit for autologous HSCT. The authors concluded that autologous HSCT can provide very effective disease control in poor-risk CLL, although its clinical benefit, relative to overall survival, over intensive fludarabine-based regimens remains uncertain.

In an accompanying editorial to the French study, it was concluded, "It seems, therefore, that the game for ASCT in CLL is indeed over." They further went on to speculate whether other forms of cellular therapy could be efficacious or offer some additional benefit to current or forthcoming

(*Continued*)

chemoimmunotherapy regimens, such as FCR. This latter statement was likely based on ongoing studies with chimeric antigen receptors, which have subsequently demonstrated highly encouraging responses in refractory CLL patients.

• What if the patient had Richter's transformation? Is there any role for HSCT?

The results with conventional therapies for patients with Richter's transformation have been relatively disappointing. The EBMT conducted a retrospective analysis to evaluate the outcomes after autologous or allogeneic HSCT in patients with Richter's transformation. Fifty-nine patients were identified among EBMT centers; 34 patients had received autologous HSCT, and 25 had received allogeneic HSCT. The overwhelming majority of autologous recipients had chemotherapy-sensitive disease; 36% of allogeneic recipients had chemotherapy-refractory disease. A reduced-intensity conditioning regimen was used in 18 of the allogeneic transplant recipients. The 3-year estimates of overall survival and relapse-free survival (RFS) were 36% and 27%, respectively, for allogeneic HSCT and 59% and 45%, respectively, for autologous HSCT. Taking into account the limitations set by the low number of adverse events and age younger than 60 years, chemotherapy-sensitive disease and use of a reduced-intensity conditioning regimen were found to be associated with superior RFS after allogeneic HSCT in multivariate analysis. The authors concluded that patients with Richter's transformation who have chemotherapy-sensitive disease appear to benefit from consolidation with transplantation strategies, and prolonged survival was observed in a significant proportion of patients.

As for our patient, he achieved a partial response to R-CHOP and proceeded to a reduced-intensity allogeneic HSCT from an HLA-matched sibling. His early posttransplant was uncomplicated, but he developed limited chronic GVHD of the skin and eyes, which were controlled with localized treatments. He eventually achieved a molecular complete remission (CR) by one year posttransplant, which illustrates that responses after allogeneic HSCT may be delayed.

Case study 32.2

A 67-year-old male sought medical attention from his primary care physician for the recent development of "lumps" above his left axilla and right supraclavicular region. Upon questioning, he acknowledged progressive fatigue over the preceding 2 months and occasional fevers and night sweats over the past 2 weeks. He palpated the masses approximately a week ago and called at his wife's insistence. On physical examination, he had palpable bilateral cervical, right supraclavicular, bilateral axillary (left greater than right), and bilateral inguinal adenopathy. The spleen tip was palpable 2 cm below the left costal margin with deep inspiration; the liver edge was not palpable. A CBC demonstrated a WBC of 42,700 with 90% mature lymphocytes with occasional prolymphocytes, an Hb of 10.8 g/dl, and platelets of 103,000. He was referred to a hematologist, who sent his blood for flow cytometric analysis, which demonstrated a monoclonal B-cell population that expressed CD5, CD19, CD20(dim), CD22(dim), CD23, CD38, and CD79(dim); they were negative for CD10 and SmIg. The cells were also positive for ZAP70, and IgVH was unmutated. A bone marrow examination demonstrated a hypercellular marrow with 70–80% replacement by lymphocytes; 10% were prolymphocytes. Cytogenetic analysis demonstrated a deletion of the short arm of chromosome 17 in 19 of 20 metaphases analyzed; this was confirmed by FISH. A CT scan of the chest, abdomen, and pelvis demonstrated diffuse adenopathy and splenomegaly. The patient was offered participation in a clinical trial for induction chemotherapy, and it was suggested that he and his two siblings have HLA typing performed.

• Is there a role for early HSCT in CLL?

In this particular situation, the patient has very poor prognostics features with a 17p deletion and an unmutated IgVH status. It has been suggested that patients with either of these abnormalities, and possibly the 11q deletion, are potential candidates for early transplantation, in light of the poor responses to conventional agents and short survival associated with each of these entities. Moreno and colleagues from two Spanish transplant centers (2005) investigated whether allogeneic HSCT may overcome the negative clinical impact of unmutated IgVH genes in CLL. They analyzed the transplant outcomes of 34 CLL patients who presented with unmutated IgVH genes (allogeneic HSCT = 14; autologous HSCT = 20) and compared them to 16 CLL patients who presented with mutated IgVH genes (allogeneic HSCT = 9; autologous HSCT = 7). The pretransplant tumor burden was assessed as being significantly higher in the allogeneic HSCT recipients, which was independent of the IgVH mutational status. The risk of relapse was significantly higher after autologous HSCT [5-year risk = 61%; 95% confidence interval (CI): 44–84%] than after allogeneic HSCT (5-year risk = 12%, 95% CI: 3–44%; $P < 0.05$). In the unmutated IgVH group, 13 of 20 autologous HSCT patients and 2 of 14 allogeneic HSCT patients experienced disease

progression, with a risk of relapse at 5 years of 66% (95% CI: 48–93%) versus 17% (95% CI: 5–60%), respectively ($P = 0.01$). The authors concluded that allogeneic HSCT may overcome the unfavorable effect of unmutated IgVH genes in patients with CLL.

Caballero and investigators from seven Spanish transplant centers (2001, 2002) evaluated the efficacy of reduced-intensity allogeneic HSCT in 30 CLL patients with poor prognostic features and/or high-risk molecular and cytogenetic characteristics. Eighty-three percent of patients had active disease at the time of transplant. Fourteen of the 23 patients analyzed (60%) had unmutated IgVH status. Eight of 25 patients (32%) had 11q−, with four of them also displaying unmutated IgVH; 6 patients (24%) had 17p−, five of which also had unmutated IgVH. At a median follow-up of 47.3 months, 22 patients were alive and disease free. The overall survival and event-free survival (EFS) at 6 years were 70% and 72%, respectively. According to molecular and cytogenetic characteristics, overall survival and EFS for unmutated IgVH CLL and/or with 11q− aberration ($n = 13$) were 90% and 92%, respectively, which is not significantly different from those patients who had normal cytogenetics by FISH, 13q− and +12, or mutated IgVH CLL ($n = 7$). All six patients with 17p deletion were transplanted with active disease, including three with refractory disease; all except one achieved CR after the transplant, and two were alive and disease free at the time of this report. The authors concluded that reduced-intensity allogeneic HSCT could overcome the adverse prognosis of patients with unmutated CLL as well as those with 11q− or 17p−.

The EBMT retrospectively reviewed the outcomes of 44 CLL patients in their registry with a 17p deletion who received allogeneic HSCT. Twenty-four patients underwent transplant from an HLA-matched sibling, and 20 had an alternative donor. The 17p deletion was determined by FISH in 82% of patients and by conventional banding in 18% of patients. The median age was 54 years. Before HCST, patients had received a median of three lines of therapy, and 53% of patients were in remission at the time of transplantation. Reduced-intensity conditioning was used in 89% of patients. At the time of this report, 19 patients were alive at a median observation time of 39 months (range: 18–101 months). Three-year overall survival and PFS rates were 44% and 37%, respectively. The cumulative incidence of progressive disease at 4 years was 34%. No late relapses were observed in nine patients, with a follow-up longer than 4 years. The authors concluded that allogeneic HSCT has the potential to induce long-term disease-free survival in CLL patients with 17p deletion.

These data are highly encouraging for patients with high-risk disease, but as they are all retrospective relative to the timing of transplantation, there is an argument that timing of transplant may be based upon response to initial therapy. It is recommended that transplantation be discussed as a consolidation option in newly diagnosed patients with these high-risk features.

- **What is the upper age limit for allogeneic HSCT in CLL patients?**

Considering that the average age of CLL patients at diagnosis is older than 60 years, the question of upper-age eligibility for allogeneic transplantation is highly relevant. The utilization of reduced-intensity and nonmyeloablative conditioning regimens has broadened the applicability of allogeneic HSCT to older patients. Additionally, the development of comorbidities indices has aided our ability to assess who are appropriate transplant candidates. Sorror and collaborators within the Seattle Transplantation Consortium (2011) reported on the outcomes of 372 patients, 60 years or older, who underwent nonmyeloablative allogeneic HSCT while enrolled in prospective clinical HSCT trials. The median patient age was 64.1 years (range: 60.1–75.1 years). The overall, 5-year cumulative incidences of nonrelapse mortality and relapse were 27% (95% CI: 22–32%) and 41% (95% CI: 36–46%), respectively. The 5-year overall survival and PFS rates were 35% (95% CI: 30–40%) and 32% (95% CI: 27–37%), respectively. These outcomes were not statistically significantly different ($P = 0.18$) when stratified by age groups (60–64 vs. 65–69 vs. 70 or older). Furthermore, increasing age was not associated with increases in acute or chronic GVHD or organ toxicities. In multivariate models, HCT-specific comorbidity index scores of 1 to 2 (hazard ratio = 1.58; 95% CI: 1.08–2.31) and 3 or greater (hazard ratio = 1.97; 95% CI: 1.38–2.80) were associated with worse survival compared with an HCT-specific comorbidity index score of 0 ($P = 0.003$ overall).

In most transplant centers and clinical trials, the upper age limit is 75 years. This is a relatively arbitrary upper limit, and there are several anecdotal reports of transplantation being performed for even older adults. The most important determination of transplant eligibility involves the assessment of several parameters related to comorbidities, performance status, disease status, and, ultimately, the decision by a well-informed patient relative to risks and benefits.

Our patient achieved a partial remission in his clinical trial and went on a second clinical trial resulting in a less than partial response. He then underwent a nonmyeloablative allogeneic HSCT from a 10-of-10 HLA-matched unrelated donor. He developed late-onset grade II acute GVHD with tapering of his immunosuppression and subsequent limited chronic GVHD of the skin. He achieved a morphologic CR but had persistent evidence of minimal residual disease by polymerase chain reaction monitoring. He eventually had clinical evidence of relapse 27 months after transplant, and he is currently being evaluated for a clinical trial with chimeric antigen receptor–modified lymphocytes.

Selected reading

Cwynarski K, van Biezen A, de Wreede L, *et al.* Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): a retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2012;30:2211–7.

Dreger P, European Group for Blood and Marrow Transplantation (EBMT). The evolving role of stem cell transplantation in chronic lymphocytic leukemia. Hematol Oncol Clin North Am. 2013;27:355–69.

Dreger P, Döhner H, Ritgen M, *et al.* Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood. 2010; 116:2438–47. Schetelig J, van Biezen A, Brand R, *et al.* Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol. 2008;26:5094–100.

Sorror ML, Storer BE, Sandmaier BM, *et al.* Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol. 2008; 26: 4912–20.

CHAPTER 33

Prolymphocytic leukemia

Claire Dearden

The Royal Marsden NHS Foundation Trust, Sutton *and* Institute of Cancer Research, London, UK

Case study 33.1

A 65-year-old man presented with a 2-month history of sweats and abdominal discomfort. He has massive splenomegaly, a white blood cell count (WBC) of 250 $\times$ 10^9/l, and a peripheral blood film showing a homogeneous population of medium-sized lymphoid cells with a prominent nucleolus and basophilic cytoplasm. Twelve months earlier, he had been noted to have a mild lymphocytosis of 20 $\times$ 10^9/l, which was unchanged when rechecked 6 months later.

The clinical picture and appearance of the abnormal cells in the peripheral blood suggest the possibility of prolymphocytic leukemia (PLL), either B- or T-cell, but further specialist diagnostic investigations are essential in order to clearly establish the diagnosis. An accurate diagnosis requires a systematic approach and careful integration of the results of morphology (particularly of peripheral blood) with specialist diagnostic tests, including immunophenotyping, cytogenetics, and molecular genetics.

1. What are the characteristic clinical features of PLL?

PLL usually presents in the sixth decade or older and occurs more frequently in males. Characteristically, patients have rapidly increasing lymphocyte counts and splenomegaly. Low-volume lymphadenopathy, skin rashes, peripheral edema, and pleuro-peritoneal effusions are seen relatively frequently in T-cell PLL (T-PLL) but not in B-cell PLL (B-PLL). Central nervous system (CNS) involvement has been described in both, but is rare. A minority of patients may be asymptomatic at diagnosis, and this "'indolent" phase can persist for a variable length of time. However, progression can be very rapid when it occurs, and patients should therefore be monitored closely (every 1–3 months depending on the rate of change). Clinical characteristics of PLL are summarized in Table 33.1.

2. Are there any predisposing conditions?

Rarely, the diagnosis of T-PLL is made in a patient with a preceding history of an inherited genetic disorder such as ataxia telangiectasia (AT) or Nijmegen breakage syndrome. There are no other familial or geographical predisposing features.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 33.1 Clinical and laboratory characteristics of B- and T-cell prolymphocytic leukemias.

Characteristic findings	B-PLL	T-PLL
Clinical features	Median age: 69 M:F ratio: 1.6:1 B-symptoms Splenomegaly Minimal lymphadenopathy High WBC	Median age: 61 M:F ratio: 2:1 Splenomegaly, lymphadenopathy, skin rash, edema, and pleuro-peritoneal effusions Very high WBC
Morphology	>55% prolymphocytes (usually >90%) Prolymphocyte is 2× size of CLL lymphocyte	Basophilic prolymphocytes with cytoplasmic blebs Small-cell (20%) and SS (5%) variants
Immunophenotype	SmIG strong, CD19+, CD20+, CD22+, CD79a+, CD23−, CD5−/+ FMC7+ (CLL score 0–1)	CD2+, CD3+, CD5+, CD7++ CD4/8 variable CD1a−, TdT−, CD25−/+
Cytogenetics	13q del, 11q del, 17p del, 6qdel *No* t(11;14)	t(14;14); inversion 14; t(X;14); iso8q; complex
Oncogenes	*TP53*, *C-MYC*	*TCL1*, *MTCP1*, *ATM*
Differential diagnosis	T-PLL, CLL/PL, MCL (leukemic phase), SMZL, HCL-v	B-PLL, T-LGL leukemia, A-TLL, SS
Prognosis	Median survival: 3 years	Median survival: 7 months with conventional therapy; 20 months with alemtuzumab; 37 months with alemtuzumab + HSCT

A-TLL, Adult T-cell leukemia lymphoma; B-PLL, B-cell prolymphocytic leukemia; CLL/PL, chronic lymphocytic leukemia with increased prolymphocytes (<55%); HCL-v, hairy cell leukemia variant; HSCT, hematopoietic stem cell transplant; MCL, mantle cell lymphoma; SMZL, splenic marginal zone lymphoma; SS, Sézary syndrome; T-LGL, T large granular lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia; WBC, white blood cell count.

Case study 33.2

A 37-year-old male had been investigated by a pediatrician in childhood for ataxia, dysarthria, intermittent skin erythema, and conjunctival hemorrhages. Genetic studies revealed bi-allelic inactivation of the ATM gene at the 11q23 locus, and AT was diagnosed. At the age of 35, he was first noted to have a peripheral blood lymphocytosis (18×10^9/l) on a routine clinic visit and was referred to hematology. He was clinically well with no lymphadenopathy or hepatosplenomegaly. He had a faint erythematous rash across his chest. His peripheral blood film showed a population of small, pleomorphic lymphocytes with hyperchromatic nuclei and basophilic cytoplasm with blebs. His LDH was slightly raised, and other liver function tests were mildly abnormal (ALT: 91; ALP: 117; GGT: 127; Bili: 27). Immunophenotyping of peripheral blood confirmed a clonal T-cell population, CD4 CD7 CD25 CD2 CD5 positive, with TCR αβ 99%. Cytogenetics showed a complex karyotype, including inversion (14) (q11q32). A diagnosis of T-PLL was made. He remained well for 18 months without treatment and with stable disease. He then progressed with B-symptoms, worsening rash, periorbital edema, and rising WBC (150) and ALT. The bone marrow (BM) showed heavy infiltration with small, mature T-lymphocytes with cytoplasmic blebbing. CT confirmed widespread small-volume lymphadenopathy in the axillary, mediastinal, retroperitoneal, and inguinal regions.

He achieved a complete remission (CR) following alemtuzumab treatment, was not considered a candidate for transplant, and remained in remission for 2 ½ years. At relapse, he had a short-lived response to alemtuzumab retreatment before losing CD52 expression on T-PLL cells. He failed to respond to other treatment and died 4 ½ years after the initial diagnosis.

3. What does the peripheral blood look like?

Prolymphocytes are medium-sized cells (twice the size of a chronic lymphocytic leukemia (CLL) lymphocyte) with a high nuclear-to-cytoplasmic ratio, a single prominent nucleolus, and basophilic agranular cytoplasm. In B-PLL, prolymphocytes should account for more than 55% of peripheral blood lymphoid cells, and the proportion usually exceeds 90% (Figure 33.1A). No cytoplasmic hairy projections or "villi" are seen in B-PLL in contrast to hairy cell leukemia variant (HCL-v) and splenic marginal zone lymphoma (SMZL). In B-PLL and in 50% of T-PLL cases, the cells have a round to oval nucleus. In the remainder of T-PLL cases, the nuclei are irregular, often with convolutions, although they are less pronounced than those seen in Sézary or adult T-cell leukemia/lymphoma (ATLL) cells. In typical T-prolymphocytes, the cytoplasm is more intensely basophilic and has an irregular outline with "blebs" (Figure 33.1B). Two variants, small cell (previously known as T-CLL, a term no longer used) and cerebriform, are seen in approximately 20% of cases. Both these variants have immunophenotypic, cytogenetic, and clinical features that are similar to those of typical T-PLL.

4. Is examination of the BM or other histology helpful?

In B-PLL, BM, lymph node, and spleen histology may all be important in confirming the diagnosis and distinguishing this from other B-cell disorders, whilst in T-PLL these are rarely needed.

5. How can B- and T-cell PLL be distinguished?

Despite the clinical and morphological similarities, the B- and T-cell subtypes of PLL can be distinguished readily by immunological markers. The laboratory features of PLL are summarized in Table 33.1. In B-PLL, the monoclonal B-cell proliferation is confirmed by establishing light-chain restriction, and the B-cells are further characterized by use of a panel of immunophenotypic reagents. Importantly, this will rule out the presence of typical CLL (CD5+, CD23+, weak surface immunoglobulin, and CD79b) or CLL with an increase in prolymphocytes (CLL/PL), which has the same phenotype. In contrast, in B-PLL there is strong Ig and CD79b expression, and most cases are CD23− and CD5− negative. T-prolymphocytes have a postthymic (TdT− and CD1a−) T-cell phenotype (CD5+, CD2+, and CD7+) (Figure 33.2), with variable expression of CD4 and CD8. Not all cases will express membrane CD3, although this is invariably present in the cytoplasm, and CD7 expression is strong in contrast to other mature T-cell leukemias, where this marker is often weakly positive or negative. CD25, CD38, and class II HLA-DR may be variably expressed, but markers identifying cytotoxic T-cells such as TIA-1 are negative, even in cases with a CD8+ phenotype.

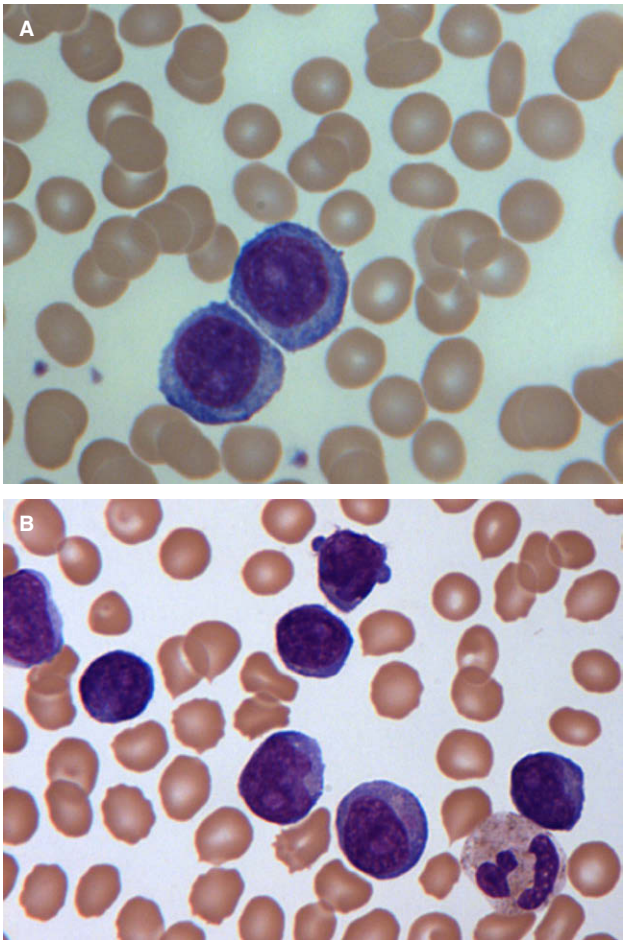


Figure 33.1 Peripheral blood morphology of PLL. (A) B-PLL, showing monomorphic prolymphocytes (PL) with condensed chromatin, prominent nucleolus, and scanty basophilic cytoplasm. (B) T-PLL showing medium-sized lymphoid cells with a regular nuclear outline, single nucleolus, and intense basophilic cytoplasm. An occasional cell shows a cytoplasmic protrusion. (Color plate 33.1A and 33.1B)

6. What other specialist tests are useful?

Cytogenetics, and in some cases molecular tests, can be helpful in confirming the diagnosis. The commonest cytogenetic abnormality seen in B-PLL is del 17p involving loss of *TP53*. Importantly, t(11,14), which is the hallmark translocation for mantle cell lymphoma (MCL), is not seen. Rarely there are translocations involving *C-MYC*. The majority of T-PLL cases will have complex karyotypes, typically with abnormalities involving chromosome 14 (Figure 33.3), and frequently also chromosomes 8 and 11. These changes result in the activation of oncogenes (*TCL-1*, *MTCP-1*, and *ATM*) that are involved in the pathogenesis of this disorder.

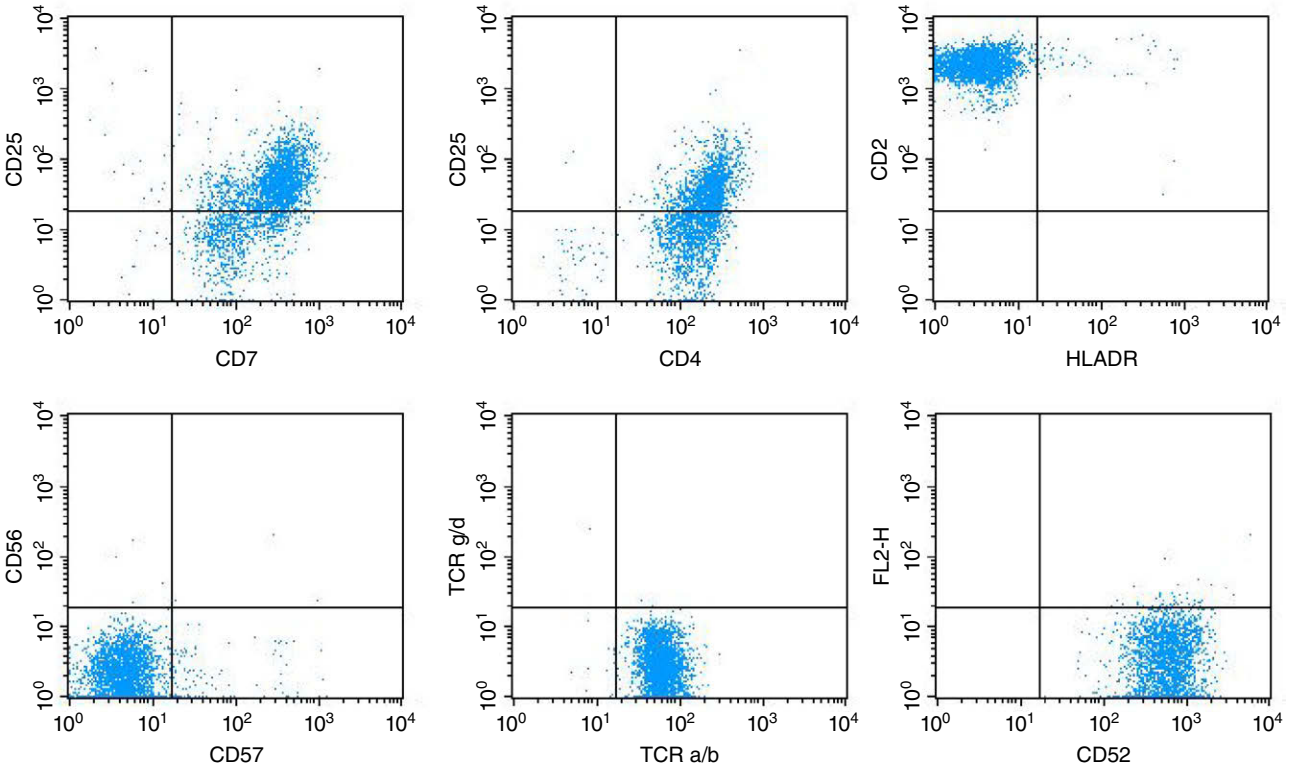


Figure 33.2 Flow cytometry in T-cell prolymphocytic leukemia (T-PLL) showing strong expression of CD2, CD7, CD4, and CD52. Natural killer (NK)-cell markers are negative (Source: Ricardo Morilla, The Royal Marsden Hospital, Surrey, UK. Reproduced with permission of Ricardo Morilla).

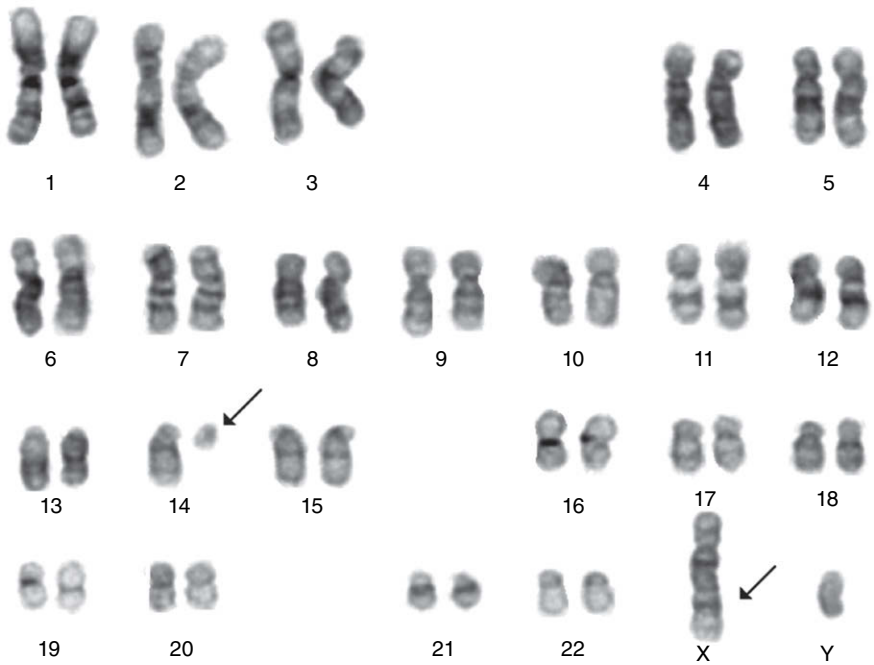


Figure 33.3 Cytogenetics in T-cell prolymphocytic leukemia (T-PLL): complex karyotype from a case of T-PLL showing the characteristic abnormality of t(X,14) (q28,q11), involving the oncogene *MTCP1* (Source: John Swansbury, The Royal Marsden Hospital, Surrey, UK. Reproduced with permission of John Swansbury).

Case study 33.3

A 73-year-old man was referred with a diagnosis of refractory peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). He had initially presented with a lymphocytosis detected on a routine full blood count (FBC). Mild splenomegaly was detected on computed tomography (CT). Lymphocytes had a CD3, CD4, and CD5 positive (CD7 not done) and CD8 and CD25 negative phenotype, and cytogenetics showed a complex karyotype with inversion 14. However, the BM trephine biopsy was reported as PTCL-NOS. On the basis of this diagnosis, he was treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), on which he progressed.

- **What mistake was made here?**

The mistake was to rely on the BM histology, which is nonspecific, rather than a careful examination of the peripheral blood morphology and a failure to integrate the results from all of the other investigations, particularly the cytogenetics, which was characteristic for T-PLL.

- **What treatment should he have received?**

After referral, we confirmed a diagnosis of T-PLL, and he commenced treatment with alemtuzumab. He remains in complete remission 4 years later.

7. What is the prognosis for patients with PLL?

There is little information regarding prognostic factors in PLL. Patients will often be aware from their reading of the literature that this is an aggressive leukemia with poor overall survival. However, this information is largely based on retrospective data, and the outlook has improved with the introduction of newer treatment approaches.

In B-PLL, retrospective data suggest a median survival of only 3 years. The presence of *TP53* deletions or mutations predicts for poor response to conventional treatment and shorter survival. Very little information is available from prospective series in the era of antibody therapy that, as in CLL, may have resulted in significant improvement in survival.

In our data set for T-PLL, biological parameters such as immunophenotype, cytogenetics, and molecular genetics do not influence survival or response to therapy. The most important predictor of outcome is response to alemtuzumab therapy. In this regard, patients with extramedullary disease (e.g., liver, CNS, and pleuro-peritoneal effusions) have lower response rates (RR) to alemtuzumab. In our series of 86 patients treated with alemtuzumab, nonresponders had a median survival of only 4 months. However, even in some older patients (over 80 years), survival has exceeded 5 years following single-agent alemtuzumab, and in some younger patients who have undergone hematopoietic stem cell transplantation (HSCT), remissions have exceeded 10 years. In the only other large series reported from the MD Anderson Cancer Center (MDACC), 5-year survival from diagnosis was 21% and poorer outcome was associated with high WBC, short lymphocyte doubling time, older age, and high expression of TCL-1 protein measured by flow cytometry and immunohistochemistry.

In the future, there is some hope that survival will improve further in both B- and T-cell PLL with the availability of additional effective therapies.

8. When should treatment for PLL be started?

The majority of patients with PLL will require treatment immediately for symptomatic disease. In those patients presenting with an asymptomatic lymphocytosis that is relatively stable or only slowly progressive, it is possible to monitor until evidence of disease progression. However, the progression may occur rapidly, and therefore closer monitoring is required than would be the case for patients with early-stage CLL. This will often allow time to identify a suitable donor if allogeneic transplant is planned, so that there will be no delays once treatment is initiated. The duration of an indolent phase is variable, but it is unusual for it to persist for more than 1–2 years.

9. What is the best first-line therapy for PLL?

The rarity of PLL has meant that there have been no prospective randomized controlled studies to compare the efficacy of different therapies. Nonrandomized studies are mostly retrospective, with small patient numbers accrued over prolonged periods of time. Many of the reports, especially for B-PLL, are of only one or two patients. There are a number of problems with this type of data, including the bias in reporting and the difficulty of comparing small studies. Entering patients into clinical trials is therefore to be encouraged.

Typically patients with PLL present with an aggressive clinical picture; the disease is often resistant to conventional chemotherapy, such as alkylator-based therapies, and can be rapidly fatal. Improvements in outcome have arisen following the introduction of monoclonal antibody approaches, including the anti-CD20 antibody rituximab in B-PLL and the anti-CD52 antibody alemtuzumab in both B- and T-cell PLL. Neither of these antibodies is licensed for these specific treatment indications.

The use of high-density genomic mapping and whole-genome sequencing is likely to identify further candidate

genes, leading to a better understanding of pathogenesis in PLL and a more directed approach to therapy in the future.

10. What is the evidence for rituximab-based therapy in B-PLL?

B-PLL is not only difficult to diagnose but also often difficult to treat. Despite the differences in biology and clinical features, it is reasonable to adopt a similar treatment approach as to a patient with CLL. Alkylating agents such as chlorambucil are of little value in the management of B-PLL. Combination regimens such as CHOP have recorded responses (partial responses and rare CRs) in up to one-third of cases. Single-agent purine analogs such as fludarabine, cladribine, and pentostatin may achieve responses in 50% of patients, including a minority of complete remissions, but with few lasting more than 12 months. There are little data on the use of purine analog combinations in B-PLL. A phase II trial using fludarabine and cyclophosphomide (FC) showed an overall response rate of 50% with a median survival of 32 months.

Rituximab is a chimeric anti-CD20 monoclonal antibody widely used in B-cell malignancies. However, supporting data for any specific therapeutic recommendations in B-PLL are very limited, and it is necessary to draw on the experience gained in other related B-cell disorders. There are case reports documenting the successful treatment of B-PLL with rituximab monotherapy, although the durability of these responses appeared short. Combinations of rituximab with fludarabine or bendamustine together with an anthracycline (mitoxantrone or epirubicin) (FMR, FER, and BMR) have also been reported to have activity in B-PLL (Table 33.2). Given the excellent responses seen in CLL and MCL with the combination of fludarabine, cyclophosphamide, and rituximab (FCR), this is a suitable first-line therapy for fit patients without *TP53* abnormalities. In our experience this has induced durable CRs in two out of four patients lasting for more than 5 years. Since bendamustine plus rituximab has been shown to have efficacy in CLL and other B-cell malignancies, this could also be an appropriate therapy, and it may be associated with less hematological toxicity.

11. What is the evidence for alemtuzumab-based therapy in T-PLL?

Currently the best first-line treatment for T-PLL is alemtuzumab, followed by consolidation with a stem cell transplant where possible. This approach has led to an extension of the median survival from 7 months in our historic series of over 70 patients treated with conventional chemotherapy to over 3 years for those patients receiving alemtuzumab followed by HSCT.

Historically, patients were treated with alkylating agents such as chlorambucil or combinations such as CHOP, with only a minority (<30%) of short-lived responses (3 months) and a dismal median survival of only 7 months. These treatments are therefore not recommended.

The advent of purine analogs such as pentostatin, fludarabine, and cladribine (2CDA) improved response rates and in some cases induced a durable remission, enabling the patient to undergo a stem cell transplant. In our Royal Marsden Hospital (RMH) series of 56 predominately relapsed and refractory T-PLL patients treated with pentostatin, the overall response rate (ORR) was 45%, with 9% achieving complete remission (CR). Median duration of response was only 6 months, but survival was improved for responders compared to historical controls.

Alemtuzumab (campath-1H) is a humanized IgG1 antibody, which targets the CD52 antigen that is highly expressed on normal and malignant T- and B-lymphocytes and monocytes but not on hematopoietic stem cells. The CD52 antigen is expressed at particularly high density on T-PLL cells. The mechanism of action of alemtuzumab in

Table 33.2 Summary of treatment trials in B-PLL.

Treatment	Patients	ORR/CR	Median PFS
Rituximab 375 mg/m^2 weekly ×4	2	Stable disease	5, 8 months
	1	1 CR	8 months at time of report
R + fludarabine + mitoxantrone	2	100% CR	—
R + fludarabine + epirubucin + R maintenance every 2 months ×6	4	100% CR	61 months
R + bendamustine + mitoxantrone	1	CR	17 months
R + fludarabine + cyclophosphamide	4	2 CR, 1 PR	60 months+*
Alemtuzumab	1 (first-line)	CR	10+ months
Alemtuzumab	3	2 CR, 1 PR	Up to 36 months*

CR, complete remission; ORR, overall response rate; PR, partial remission; R, rituximab.
*Royal Marsden Hospital experience, unpublished data.

vivo is not fully elucidated, but in vitro the antibody can induce cell death by antibody-dependent cellular cytotoxicity (ADCC), complement activation, and possibly also direct apoptosis. We have previously reported the results of a study using intravenous alemtuzumab at the standard dose of 30 mg 3 times a week until maximal response in 39 previously treated relapsed or refractory patients, which showed 60% complete remission (CR) and 16% partial remission (PR). Median disease-free interval (DFI) post therapy was 7 months (range 4–45 months). Longer follow-up of this series shows a median survival of 2 years for those patients achieving a CR and 9 months for those in PR. We have now treated a total of 88 T-PLL patients with single-agent alemtuzumab (Table 33.3): 45 previously treated patients and 43 who were therapy naïve. Nine of the patients who were treated first-line were enrolled in a pilot study to evaluate the subcutaneous (SC) route of administration of alemtuzumab. Although data from CLL suggest that SC alemtuzumab has equal efficacy compared to intravenous (IV) administration, we found that this was not the case in T-PLL. The pilot study was terminated early because of the dramatic fall in response rates associated with the change to SC administration. IV alemtuzumab results in ORRs in excess of 90% with 81% CRs when given to previously untreated patients with T-PLL (Table 33.3). The ORR fell to only 33% when the antibody was administered SC. It was possible to rescue a proportion of these patients by switching to IV administration and/or adding pentostatin, but two out of nine patients died in treatment. The likely reason for this poor result is the longer delay in achieving peak antibody levels via the subcutaneous route, which may be critical in this rapidly progressive leukemia. Alternatively, the poor result may be because SC administration in a previously untreated patient could be sufficiently immunogenic to induce neutralizing antibodies. This is the only study that has examined the use of SC alemtuzumab, but the effects were so striking that on the basis of these results, I always use IV administration of alemtuzumab in patients with T-PLL.

Thus, alemtuzumab administered intravenously as a single agent will induce remissions in the majority of patients treated first-line with minimal toxicity. Remarkably, these responses occur regardless of the apparent bulk of the disease at presentation (i.e., high WBC, LDH, and splenomegaly). It is not advisable to use a debulking strategy with steroids or multi-agent regimens such as CHOP since this is usually ineffective, delays starting more effective antibody therapy, and adds substantially to toxicity.

Skin disease responds very well to alemtuzumab therapy, and there is also experience of good efficacy of single-agent alemtuzumab in Sézary syndrome. However, for patients with CNS disease, it is necessary to administer CNS-directed therapy, either triple (methotrexate 12.5 mg, cytarabine 50 mg, and hydrocortisone 12.5 mg) intrathecal (IT) or high-dose systemic methotrexate (3 g IV) depending on the distribution of disease. We do not use routine CNS prophylaxis.

12. How should CNS involvement in T-PLL be diagnosed and treated?

See Case study 33.4.

Case study 33.4

A 77-year-old man was first noted to have a mild lymphocytosis when under the urology team for treatment of a benign bladder tumor. The film was reported as "probable CLL," but no further tests were done. At his postop follow-up, the lymphocyte count was noted to have risen, immunophenotyping was undertaken and reported as "T-CLL," and 6-monthly follow-up was recommended. Within a month, he presented with an acute onset of third, fourth, and sixth cranial nerve palsies. He was referred to neurology, where he underwent a number of investigations including lumbar puncture (LP) (but without immunophenotyping) and brain magnetic resonance imaging (MRI), which were inconclusive. He was treated with steroids for assumed vasculitis without symptomatic improvement. No connection was made between his hematological and neurological conditions. His WBC had also increased significantly, and he was referred for an urgent second opinion.

- **What investigations should be done or repeated?**

We were able to make a diagnosis of T-PLL with CNS involvement with careful examination of the MRI and cerebrospinal fluid (CSF). The MRI showed clear evidence of meningeal enhancement, and the CSF contained T-lymphocytes with the same aberrant phenotype as those in the peripheral blood.

- **What treatment should he receive?**

He commenced treatment with IV alemtuzumab and intrathecal therapy (methotrexate, cytarabine, and hydrocortisone ×6), achieving CR with complete resolution of his neurological impairment. He remains well and in remission 6 years later.

Table 33.3 Treatment of T-PLL comparing patients treated first-line with either IV or SC alemtuzumab, with those treated with relapsed or refractory disease ($N = 86$).

	First-line IV	First-line SC	Relapsed or refractory IV
Number of patients	32	9	45
ORR (%)	91	33 *	74
CR (%)	81	33 *	60
PFS at 12 months (%)	67	67	26
HSCT (%)	50	55	30
OS at 48 months (%)	37	33	18

CR, complete remission; HSCT, hematopoietic stem cell transplant; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial remission; SC, subcutaneous.
*Increased to 67% when changed to IV and/or pentostatin added, but 2/9 patients died while on treatment.

13. What are the side effects of alemtuzumab, and how can they be managed?

We have found alemtuzumab to be well tolerated in patients with PLL, especially when given as first-line therapy, with fewer infectious complications than when it is used in the relapsed CLL patient group (approximately 10% in T-PLL vs. 40% in CLL in our institution). Careful attention to infection prophylaxis for *Pneumocystis jerovicci* and herpes viruses and regular monitoring for CMV reactivation have minimized serious infections. Infusion reactions are common on initiating IV therapy but can be readily controlled with the use of premedication and rarely last beyond the first week of treatment. None of our patients has developed tumor lysis.

14. How should patients with T-PLL who have an initial slow or poor response to alemtuzumab be managed?

In T-PLL, treatment failures with alemtuzumab are in a minority. In those patients where there is a high tumor bulk and the WBC remains elevated 3 weeks or more after initiating treatment, it is reasonable to increase the frequency of alemtuzumab administration to daily (in order to more quickly saturate the binding sites) and/or to add pentostatin at a dose of $4\,mg/m^2$ once a week for 4 weeks, followed by every 2 weeks in responding patients until best response or a maximum of 12 weeks. Administration of this dose of pentostatin is dependent on adequate renal function. Pentostatin causes more myelosuppresssion than alemtuzumab used alone and is also associated with nausea that may last up to 72 hours after administration of the dose. The choice of pentostatin is based on our prior experience with this as a single agent. The addition of an alternative purine analog or a novel therapy may provide equivalent or superior disease control, but currently the data on combination regimens are limited. Extramedullary disease such as serous effusions and liver involvement more often predict resistance to alemtuzumab monotherapy, but this can frequently be overcome by the addition of a purine analog such as pentostatin.

15. Is combination chemo-immunotherapy better than single-agent alemtuzumab for T-PLL?

The successful use of chemo-immunotherapy in B-cell malignancies prompted similar studies in T-PLL. The German CLL Study Group (GCLLSG) have conducted a prospective phase II trial in 25 patients with previously treated (9) and treatment-naïve (16) T-PLL. The sequential therapy comprised up to four cycles of FMC (fludarabine, mitoxantrone, and cyclophosphamide) given every 4 weeks followed by consolidation with IV alemtuzumab three times a week in responding patients, 1–3 months after completion of chemotherapy. ORR was 68% post FMC (6CR) and 92% after both therapies. Alemtuzumab consolidation in 21 patients increased the ORR to 95% in these patients (80% of all the trial patients) with a doubling of the CR rate (12 CR). Median overall survival (OS) and progression-free survival (PFS) were 17 and 12 months, respectively. The MDACC has explored the use of alemtuzumab in combination with pentostatin in a range of PTCL, including T-PLL, and found activity (ORR 69%) similar to that seen with alemtuzumab alone. These treatment trials are summarized in Table 33.4. However, given the comparable results with single-agent alemtuzumab, these combination strategies may not offer convincing additional benefit while adding substantially to toxicity, and combination therapy can be reserved for slow or poor responders, as stated here.

16. What treatment should be used for patients with relapsed or refractory PLL?

In B-PLL patients who relapse following a good prolonged remission (>3 years) achieved with a chemo-immunotherapy regimen, this treatment can be repeated. For those with early relapse or who have acquired a *TP53* abnormality, alemtuzumab-based treatment is more suitable. The advent of newer treatments, particularly the B-cell receptor (BCR) inhibitors, is likely to change the way we manage relapsed and refractory disease in the future.

17. Which is the most important cytogenetic test in B-PLL?

In B-PLL, up to 50% of patients will harbor abnormalities of *TP53*, which are usually detected by fluorescent in situ hybridization (FISH) (deletion) (Figure 33.4) but are also present as mutations. As in CLL, this genetic abnormality is associated with inherent chemo-resistance and probably explains, in part, the poor outcome seen.

Case study 33.5

A 48-year-old man presented in July 2005 with a 1-month history of fatigue, night sweats, and upper-left-quadrant abdominal pain. He had no relevant past medical history. His spleen was palpable 11 cm below the costal margin, but he had no lymphadenopathy. FBC showed Hb 10.7 g/dl, WBC 83 $\times$ 10^9/l, and platelets 215 10^9/l. Peripheral blood morphology is shown in Figure 33.1. His LDH was raised at 259. Immunophenotype confirmed a mature B-cell malignancy: clonal B-cells with strong SmIG, CD79b, and CD20+. He was t(11,14) negative.

1. What is the diagnosis?

A. CLL
B. Mantle cell lymphoma
C. B-PLL
D. Hairy cell variant
E. Splenic marginal zone lymphoma

The clinical presentation, peripheral blood morphology, and immunophenotyping are consistent with a diagnosis of B-PLL. MCL is very unlikely in the absence of a t(11,14) translocation.

2. What treatment should he receive?

A. Alemtuzumab
B. Rituximab
C. Rituximab-based chemo-immunotherapy (e.g., FCR or BR)

He was treated with FCMR $\times$3 to September 2005, achieving only a minor response with reduction in WBC but progressing massive splenomegaly.

3. Which one of the following is NOT a management option now?

A. Continue with rituximab-based treatment
B. Refer to surgeons for splenectomy
C. Repeat cytogenetics or FISH
D. Switch to alemtuzumab
E. Treat with novel agents or a clinical trial

4. Is there still a role for splenectomy in B-PLL?

Patients who present with massive splenomegaly but are not considered fit for systemic treatment or are refractory to chemotherapy may be effectively palliated with splenectomy or splenic irradiation. Not only does splenectomy remove a major proliferative focus and considerable tumor bulk in this disease, but also it can relieve hypersplenism and facilitate further treatment. In frail patients, splenectomy may not be feasible, and splenic irradiation may be a suitable alternative.

He actually underwent splenectomy in October 2005, the histology of which showed infiltration of white and red pulp by prolymphocytes in a typical pattern for B-PLL. Repeat FISH revealed a *TP53* deletion. He had a persistent low-level lymphocytosis and BM involvement.

5. Would you give any further treatment at this point, and with what?

Splenectomy helped to debulk his disease, but progression would be rapid without further treatment to clear the BM.

Given that he was young and fit, he went on to receive alemtuzumab from November 2005 to January 2006, achieving a CR. He underwent a reduced-intensity conditioning (RIC) sibling allograft in February 2006 (carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning). He remains well in continued remission 7 years later.

Alemtuzumab is important in the therapy of B-PLL patients who have deletions and/or mutations of *TP53*, whether this is detected at diagnosis or subsequently. Alemtuzumab is also most active in the blood, bone marrow, and spleen, which are the main sites involved in B-PLL, while bulky lymphadenopathy is almost never seen. Alemtuzumab can also be an effective salvage therapy for patients who are refractory to purine analog-based treatment. There have been some single case reports. We have seen a complete remission in two patients with B-PLL following alemtuzumab. In both cases, a *TP53* deletion was detected following failure to respond to FCR. One of these patients is described here. The other declined an allograft in first CR and remained in remission for 36 months. He subsequently relapsed with a high-grade transformation to diffuse large B-cell lymphoma. He obtained a CR following R-CHOP (CHOP plus rituximab), went on to receive an unrelated reduced-intensity allograft, and died a year later from transplant-related complications.

Table 33.4 Summary of treatment trials in T-PLL.

Study	Regimen	No	CR	ORR	MPFS months	MS months
Mercieca (1994)	Pentostatin*	55 pretreated	9%	45%	6	9
Dearden (2001)	Alemtuzumab (IV)	39 pretreated	60%	76%	7	10
Keating (2002)	Alemtuzumab (IV)*†	76 pretreated	38%	50%	4.5	7.5
Dearden (2011)	Alemtuzumab (IV)	32 previously untreated	81%	91%	67% at 1 years	37% at 4 years
Hopfinger (2011)	FMC, then alemtuzumab (IV)	9 pretreated 16 previously untreated	24% (FMC) 48% (alemtuzumab)	Total 92% 17/25 = 68% after FMC 20/21 = 95% after alemtuzumab	11.5	17.1
Ravandi (2009)	Pentostatin + alemtuzumab (IV)	13 (treated + untreated)	62%	69%	7.8	10.2

CR, complete remission; MPFS, median progression-free survival; MS, median overall survival; ORR, overall response rate.
*Retrospective analysis.
*†Compassionate-use trial.

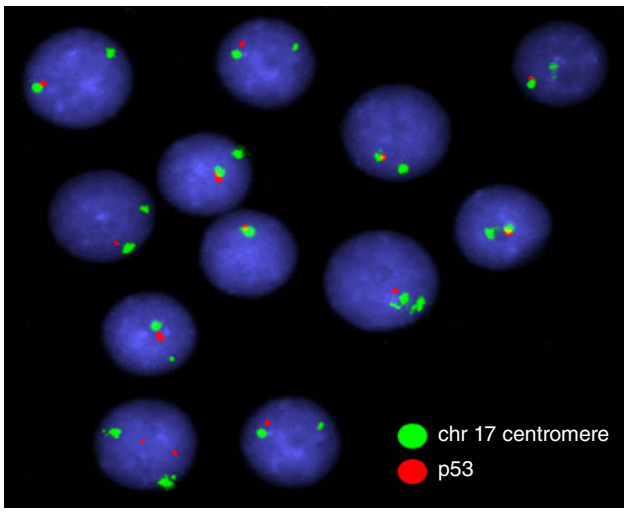


Figure 33.4 Fluorescent in situ hybridization (FISH) in B-cell prolymphocytic leukemia (B-PLL) showing del17p: the green dot shows the centromere for chromosome 17, and the red dot is the probe for *TP53* (Source: John Swansbury, The Royal Marsden Hospital, Surrey, UK. Reproduced with permission of John Swansbury). (Color plate 33.2)

18. Are there any new therapies for B-PLL?

New anti-CD20 monoclonal antibodies (e.g., ofatumumab and GA101) have not been evaluated in B-PLL, although it is likely that activity will be similar to that seen in CLL. In addition, the new BCR antagonists targeting molecules such as Bruton's tyrosine kinase and PI3 kinase delta may also have activity in B-PLL, including in those cases with *TP*53 abnormalities.

19. Can patients with T-PLL be retreated with alemtuzumab at relapse?

For those patients who have not previously received alemtuzumab, this is the treatment of choice at relapse, and good RRs have been documented in the relapsed and refractory (and alemtuzumab-naïve) patient group. For those patients who received induction therapy with alemtuzumab, with a response duration of at least 6 months, retreatment can be successful in achieving a second, or even third, remission (>50% of patients will respond a second time), but this is usually of much shorter duration. Occasionally the T-PLL cells lose expression of the CD52 antigen, precluding further use of alemtuzumab. It is important to always retest for this at relapse. Maintenance alemtuzumab has not been formally evaluated and is likely to encourage early loss of CD52 expression.

Despite the very high RR with alemtuzumab, relapse is inevitable for all but the minority of patients who appear "cured" following allogeneic HSCT. Although improved, median survival remains only 20 months (Figure 35.5A).

20. What treatment is available for T-PLL patients who are refractory to alemtuzumab?

For those patients who fail or are unsuitable for alemtuzumab retreatment, a purine analog–based therapy (e.g.,

FCM) may be used, but response rates are not high. Nelarabine, with or without fludarabine, is an alternative for which there is some evidence of activity in T-PLL. In a phase I study in 11 T-PLL patients, ORR was 20% for nelarabine alone, rising to 63% (13% CR) when given in combination with fludarabine. If the patient is a suitable candidate for an allogeneic transplant, then it is sometimes possible to induce a remission with an intensive combination regimen and proceed directly to HSCT. With current treatment options, very few patients will have a successful outcome after relapse. Most patients with PLL will still die from their disease, and new therapies are badly needed. The advent of novel small-molecule inhibitors targeting dysregulated growth and survival pathways in T-PLL may improve the outlook in the future and may eventually supersede current treatment options. Potential targets include ATM, AKT, TCL1, and telomerase. Epigenetic modification (e.g., with HDAC inhibitors) may be able to overcome resistance to alemtuzumab caused by downregulation of CD52.

21. Who should have a transplant?

The main challenge as a clinician treating PLL is to deliver long-term disease-free survival. Stem cell transplantation can be considered in younger, fit patients who have responded to their initial therapy, as disease progression is inevitable. Allogeneic HSCT gives patients the possibility of a long-term cure by potentially harnessing a graft-versus-leukemia effect. However, the morbidity and mortality associated with this procedure are significant, and often it is not a feasible option due to patient age or comorbidities. However, the introduction of nonmyeloablative approaches has widened the eligibility, making this available as a treatment option in a larger cohort of patients.

In B-PLL, published experience of HSCT is confined to a few successful case reports and one registry study. The latter was a retrospective review of the Center for International Blood and Bone Marrow Research database from 1995 to 2005, which identified 11 patients with B-PLL (median age 54 years) who had undergone an allo-HSCT. With relatively short follow-up, the median PFS was only 3.5 months, with less than one-third of patients alive and disease-free at 1 year. Given that B-PLL generally affects an older patient population than T-PLL (median age 69 years vs. 61 years), fewer will be suitable candidates for allogeneic HSCT, even with the extended eligibility associated with RIC regimens. However, we would use the same criteria for selection as for CLL, namely, the presence of a *TP53* deletion and/or mutation or failure to achieve a durable remission (>2 years) following chemo-immunotherapy.

Although some responses with alemtuzumab are very prolonged (more than 5 years), longer-term follow-up on patients treated with alemtuzumab in our series suggests that all patients do eventually relapse (Figure 33.5A). Experience with both autologous and allogeneic HSCT, although limited, is encouraging. Single case reports and small series are often misleading because of patient selection bias, and there are only three larger reports of HSCT in the literature. Nevertheless, our experience suggests that consolidation with an HSCT in first or subsequent remission offers potential advantages to patients. We have recently published data on 28 T-PLL patients, and update that here with a further eight patients (total = 36) treated on a common protocol with alemtuzumab followed by either autologous (16) or allogeneic (20) transplantation (Table 33.5). We compared clinical outcomes to 25 retrospectively selected patients who had achieved a CR following alemtuzumab treatment and survived at least 6 months, but who had not undergone a transplant (non-HSCT group). Apart from age (median 66 years in the non-HSCT group versus 59 for auto-HSCT and 53 for allo-HSCT), the clinical and disease characteristics of the retrospective cohort were the same as those of the patients undergoing HSCT. Overall survival was similar in the auto-HSCT and allo-HSCT groups at a median of 37 months, compared with a median survival for the non-HSCT group of 20 months (Figure 33.5B), with higher TRM for allo-HSCT patients (35%) but a higher relapse rate in the auto-HSCT group (81%) (Table 33.5). There was no association between age and survival in either group. We have not seen any failure of engraftment despite the prior use of alemtuzumab, although we usually ensure at least a 3-month period between completing induction treatment and the allo-HSCT. There has been a retrospective review of the European Bone Marrow Transplantation Registry (EBMT) database with 41 T-PLL patients identified who have undergone an allogeneic HSCT. Three-year PFS and OS were 19% and 21%, respectively. The 3-year nonrelapse mortality and relapse rates were each 41%, with the majority of relapses occurring in the first year. The main difference between this group of patients and our own allo-HSCT series was the proportion of patients in CR at the time of transplant (11/41 for the EBMT series vs. 10/13 for the RMH series). In multivariate analysis, factors associated with longer PFS were the use of total body irradiation in the conditioning regimen and a shorter interval between diagnosis and HSCT.

We therefore believe that HSCT after alemtuzumab may provide benefit over alemtuzumab alone and is associated with long-term survival (>5 years) for some patients. The introduction of RIC has reduced but not eliminated the transplant-related mortality (TRM), which remains significant. However, it is hoped that, after longer follow-up, the reduced relapse rate will translate into improved survival for the allo-HSCT group. Nevertheless, allo-HSCT patients do still have a risk of relapse, and, so far, outcome after

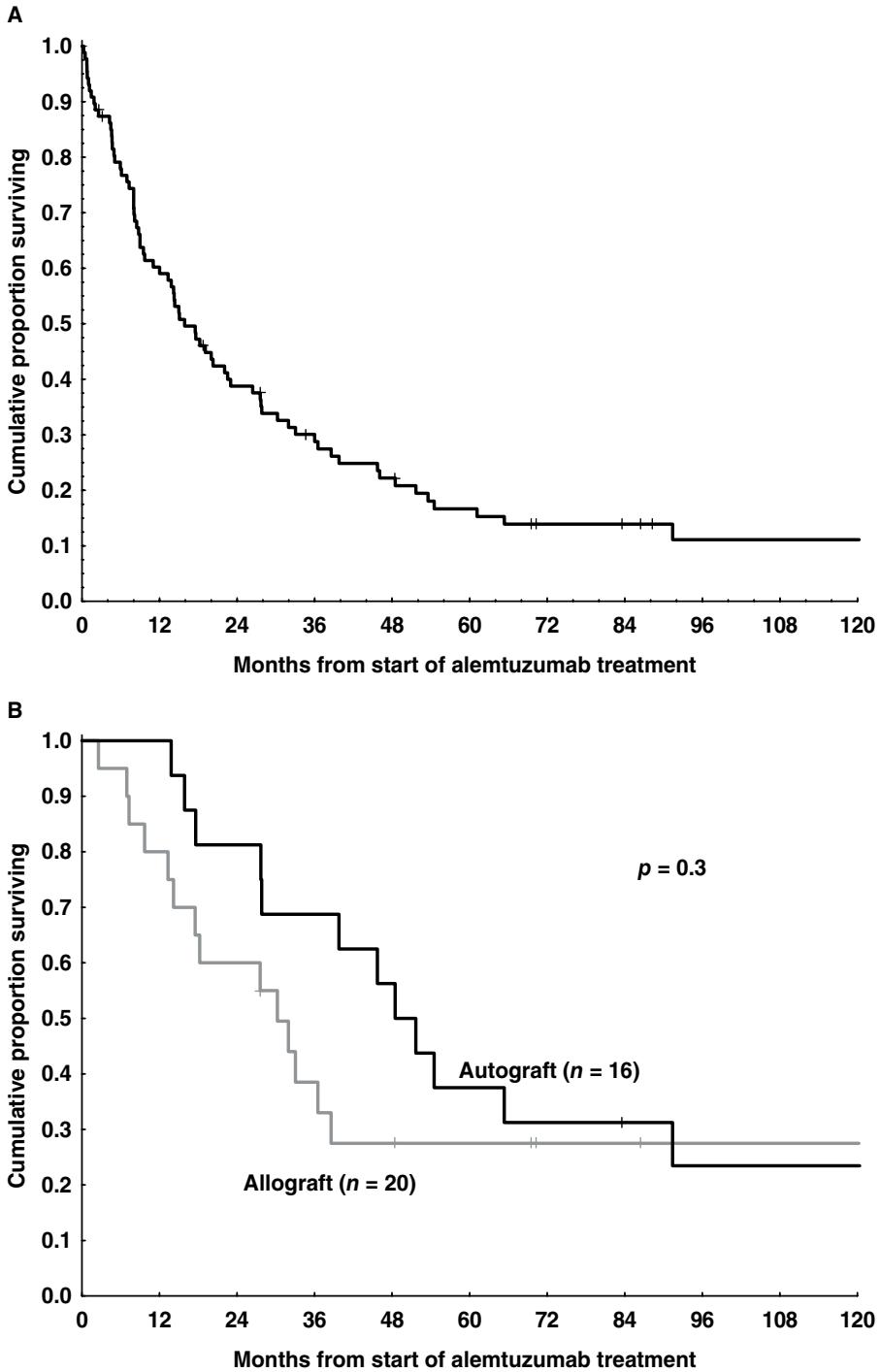


Figure 33.5 (A) Survival curve for 88 T-cell prolymphocytic leukemia (T-PLL) patients treated with alemtuzumab. Survivors beyond 72 months are those who received consolidation with a hematopoietic stem cell transplant. (B) Survival curves for 36 T-PLL patients treated with alemtuzumab followed by an autologous or allogeneic hematopoietic stem cell transplant (see Table 33.5).

Table 33.5 Outcomes for patients with T-PLL treated with alemtuzumab alone or followed by autologous or allogeneic HSCT (RMH series 2013).

	Auto-HSCT	Allo-HSCT	All HSCT	Controls*
Number of cases	16	20	36	25
Median age (range), years	59 (43–68)	52 (39–71)	56 (39–71)	66 (36–85)
Males : females	9 : 7	16 : 4	25 : 11	18 : 7
TRM rate	6%	35%	22%	n/a
Relapse rate	81%	35%	56%	96%
Median DFS (months)	17	21	19	13 †
Median OS † (months)	49	31	37	20
2 year OS rate †	81%	60%	70%	30%
5 year OS rate †	37%	27%	31%	10%

DFS, disease-free survival; HSCT, hematopoietic stem cell transplant; OS, overall survival; TRM, transplant-related mortality.
*Control group: patients who achieved complete remission and survived at least 6 months.
†Measured from start of alemtuzumab treatment.

relapse in our experience has been very poor with no clarity regarding the best relapse treatment or the benefit of donor lymphocyte infusions (DLIs). At 3 years, a plateau does seem to appear on the survival curve for allo-HSCT patients (Figure 33.5B). Out of our series of over 80 patients, almost one-half of those achieving remission have proceeded to either auto-HSCT or allo-HSCT (Table 33.3). One of our patients who achieved only a PR following alemtuzumab received a RIC unrelated donor transplant and remains in CR more than 10 years later, suggesting that this approach has curative potential. There remains some uncertainty about the optimal strategy for allo-HSCT, which would be best addressed by conducting prospective clinical trials that are currently not available. In the absence of such robust data, but in the knowledge that allo-HSCT may currently provide the only possibility of cure in this disease, it is reasonable to continue to offer this to all suitable patients in first remission. Allografts, however, are an option in only a proportion (30–50%) of patients with T-PLL. Auto-HSCT is also a benefit for patients, prolonging remissions with much less treatment-related toxicity than allo-HSCT but not resulting in cure. For those patients who are also ineligible for auto-HSCT, other strategies need to be explored.

Summary

B-PLL and T-PLL are two rare, clinically aggressive, but distinct disease entities with characteristic morphological, immunophenotypic, and molecular features. Rituximab-based chemo-immunotherapy combinations should be considered as first-line therapy for B-PLL, with alemtuzumab used for those presenting with abnormalities of *TP53*. Splenectomy or splenic irradiation may still have a role, especially as palliation. Therapeutic options for T-PLL have improved with the use of alemtuzumab monoclonal antibody therapy, delivered intravenously, with the majority of patients now achieving durable remissions. However, this treatment is not curative, and remission should be consolidated with stem cell transplant in suitable patients. Eligible patients with high-risk B-PLL should also be considered for HSCT procedures. It is possible that HSCT may provide benefit for selected patients with PLL, with some achieving long-term survival (>5 years). The advent of new targeted therapies may change the treatment landscape in the future.

Case study answers

Case study 33.5

Question 1: Answer C
Question 2: Answer C
Question 3: Answer A

Selected reading

Dearden CE, Khot A, Else M, *et al.* Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood. 2011;118:5799–802.

De Lavallade H, Faucher C, Furst S, *et al.* Allogeneic stem cell transplantation after reduced intensity conditioning in a patient with T-cell prolymphocytic leukaemia: graft versus tumour effect and long-term remission. Bone Marrow Transpl. 2006;37:709–10.

Dreger P, Corradini P, Kimby E, *et al.* Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia. 2007;21(1):12–17.

Dürig J, Bug S, Klein-Hitpass L, *et al.* Combined single nucleotide polymorphism-based genomic mapping and global gene expression profiling identifies novel chromosomal imbalances, mechanisms and candidate genes important in the pathogenesis of T-cell prolymphocytic leukemia with inv(14)(q11q23). Leukemia. 2007;21:2153–63.

Swerdlow SH, Campo E, Harris N, *et al.* World Health Organization classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.

CHAPTER 34

Hairy cell leukemia

Justin M. Watts and Martin S. Tallman
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Case study 34.1

A 52-year-old Caucasian man is referred to you with abnormal blood counts. The white blood cell (WBC) count is 3000/μl, absolute neutrophil count (ANC) 1800/μl, hemoglobin 11 g/dl, and platelet count 130,000/μl. Further work-up reveals an enlarged spleen of 14.5 cm. The patient continues to work full-time as a bank manager. He denies B-symptoms or recurrent infections.

1. All of the following statements with regard to the diagnosis of hairy cell leukemia (HCL) are true EXCEPT:

A. Bone marrow examination usually shows a hypercellular marrow with increased reticulin fibrosis, mast cells, and absence of blasts
B. Monocytopenia is seen in almost all cases
C. Flow cytometry is negative for CD25 and CD22
D. There is absolutely no specific immunophenotypic marker for the diagnosis of HCL
E. Immunohistochemistry (IHC) is positive for DBA.44, TRAP, and ANXA1

HCL is a rare B-cell lymphoproliferative neoplasm that represents approximately 2% of all leukemias and affects 600–800 individuals annually in the United States. HCL is more common in Caucasians than African Americans and is more common in males by a ratio of 4:1. The median age at disease onset is 52 years. HCL is characterized by clonal proliferation of small, mature lymphocytes with classic "hair-like" cytoplasmic projections that accumulate in the peripheral blood, bone marrow, and spleen (Figure 34.1). This leads to decreased production of normal hematopoietic elements, causing anemia, thrombocytopenia, and neutropenia and monocytopenia. Splenomegaly is usually present and may be massive; however, lymphadenopathy is rare except in relapsed disease. Patients typically present with either incidental or symptomatic cytopenias or abdominal symptoms from splenomegaly. Leukocytosis is unusual, and most patients (60–80%) are pancytopenic at diagnosis. On bone marrow examination, the marrow is typically hypercellular with diffusely infiltrating hairy cells, and abundant cytoplasm surrounding nuclei may give cells a "fried-egg" appearance. There is often increased reticulin fibrosis (due to hairy cell infiltration), and there may also be an increased number of bone marrow mast cells. Blasts are not increased. Immunophenotyping by flow cytometry is an important, confirmatory test for the diagnosis of HCL, which has a characteristic immunophenotypic profile consisting of both mature B cell markers (CD19, CD20, and CD22) and aberrant expression of non-B-cell markers (CD11c, CD25, CD103, and CD123). However, there is no one marker or combination of markers that is 100% specific for the disease. Immunohistochemical stains for DBA.44, TRAP, and ANXA1 are typically positive in HCL but have been largely replaced by flow cytometry.

2. All of the following neoplasms are considered in the differential diagnosis of patients presenting with splenomegaly and B-cell lymphoid aggregates in the bone marrow EXCEPT:

A. Splenic marginal zone lymphoma (SMZL)
B. Prolymphocytic leukemia (PLL)
C. Chronic lymphocytic leukemia (CLL)
D. HCL variant (HCL-v)
E. Primary myelofibrosis (PMF)

Primary myelofibrosis is a myeloid malignancy, and while it may cause splenomegaly it would not result in lymphoid aggregates in the bone marrow. See Table 34.1 for characteristics of A–D in relation to HCL.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

3. The bone marrow biopsy of the patient presented in Question 1 shows a hypercellular marrow, but the marrow was inaspirable (a "dry tap"). Reticulin stain shows 2+ fibrosis surrounding hairy cells. Both flow cytometry on the peripheral blood and IHC on the marrow are consistent with the diagnosis of HCL. Should this patient be treated or observed?

This patient should be observed. Many patients with HCL are asymptomatic and can be observed for months to years before requiring treatment. HCL is typically idolent and slowly progressive, and there is no clear benefit to early treatment. Patients should be treated only when they become symptomatic or develop significant cytopenias. Typical indications for the treatment of HCL include an ANC <1000/μl, symptomatic anemia with hemoglobin <11 g/dl, and platelet count <100,000/μl. Symptomatic splenomegaly—early satiety, abdominal fullness and discomfort, and weight loss—is also an indication for treatment. Bulky lymphadenopathy at initial presentation is rare, and other diagnostic possibilities should be considered if present. Constitutional symptoms, such as fever and night sweats, should also prompt consideration of treatment after infection is ruled out. Infection should always be suspected and treated appropriately in a febrile patient with HCL; bacterial infections are most common, but opportunistic infections can occur as well.

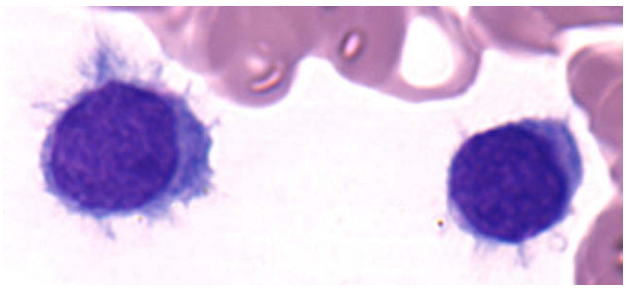


Figure 34.1 Hairy cells with classic circumferential, hairlike cytoplasmic projections. (Color plate 34.1)

Table 34.1 Characteristics of various neoplasms in relation to hairy cell leukemia (HCL).

Disease	Total white blood cell (WBC) count	Bone marrow involvement	Morphology	Flow cytometry	Splenic involvement
HCL	Typically low or normal	Diffuse	Small cells; long cytoplasmic projections	(+) CD19, 20, 22, 25, 11c, 103, 123; (−) CD5, 23	Yes; red pulp
Splenic marginal zone lymphoma (SMZL)	Usually normal	Nodular	Small cells; short, polar villi	(+) CD19, 20, 22; (−) CD5, 23, 25, 103	Yes; red and white pulp
B-prolymphocytic leukemia (PLL)	High	Variable (nodular, interstitial pattern)	Medium cells; prominent nucleoli	(+) CD19, bright 20, 22, bright surface Ig; (−) CD5, 23, 25, 103	Yes; red and white pulp
Chronic lymphocytic leukemia (CLL)	Variable, can be normal to very high	Varies, in late stages may be diffuse	Small cells; smooth cytoplasmic outline	(+) CD5, 23, 19, weak 20; (−) CD25, 103	Yes; red and white pulp
HCL variant (HCL-v)	High	Variable	Medium cells; cytoplasmic projections and prominent nucleoli	(+) CD20, 22, 11c, 103; (−) CD25, 123	Yes; red pulp

Case study 34.2

A 35-year-old woman with HCL presents for routine evaluation. She has been observed without therapy since diagnosis about 18 months ago. Now, she reports new onset of fatigue and early satiety. The most recent complete blood count shows a WBC of 1300/μl, ANC of 800/μl, hemoglobin of 9 g/dl, and platelet count of 80,000/μl. Further work-up reveals an enlarged spleen of 18.0 cm. The diagnostic bone marrow biopsy, performed 18 months ago, was consistent with HCL.

1. Should the bone marrow examination be repeated prior to the initiation of therapy?

No. This patient's clinical course is consistent with the natural history of HCL, and the bone marrow biopsy does

(*Continued*)

not need to be repeated prior to treatment unless the initial diagnosis was in question or there is suspicion of another hematologic problem.

2. What is the best therapeutic strategy for this patient with symptomatic HCL?

A. Cladribine or pentostatin
B. Cladribine plus rituximab
C. Pentostatin plus rituximab
D. Cladribine plus granulocyte colony-stimulating factor (G-CSF)
E. Interferon-alpha
F. Splenectomy and transfusion support

Single-agent therapy with a purine analog, either cladribine (2-CdA) or pentostatin, is standard front-line therapy in patients with symptomatic HCL. Cladribine and pentostatin are purine analogs that interfere with normal purine metabolism. Mechanistically, cladribine is resistant to adenosine deaminase (ADA), and pentostatin directly inhibits ADA. The end result of both agents is the accumulation of toxic deoxynucleotides in lymphoid cells, which can cause DNA double-strand breaks and disrupt successful DNA synthesis and repair mechanisms. Both agents are highly effective in HCL, but cladribine is usually preferred given its safety profile and tolerability as well as the convenience of administration (given over a single cycle) compared to pentostatin (which is given repeatedly over several cycles). Both agents induce a *durable* complete remission (CR) in almost all patients with classical HCL, regardless of the extent or bulk of disease, and have similar long-term survival rates (approaching 90% or higher). Clinical trials showing the remarkable effectiveness of a single cycle of cladribine were first reported in the early 1990s. Several large studies have shown CR rates of at least 80–90% (with most other patients achieving a partial response) and 4-year progression-free survival (PFS) and overall survival (OS) of approximately 70–80% and 85–95%, respectively. Furthermore, some of these studies had very long follow-up and demonstrated 12-year OS rates of 80–90% (Figure 34.2). Pentostatin has similar response rates and is an acceptable alternative to cladribine. The dosing schedule of pentostatin has varied across clinical trials, but it is commonly given at 4 mg/kg intravenously every 2 weeks until maximal response (usually around six to eight cycles of treatment). Rituximab has been successfully combined with cladribine in clinical trials, and it may play an important role in relapsed disease. However, it is not currently indicated as part of front-line therapy. A phase II study by Ravandi and coworkers evaluated cladribine followed one month later by eight weekly doses of rituximab in newly diagnosed patients, and while the regimen was well tolerated, remission rates with cladribine alone were excellent and it is not known if the sequential addition of rituximab improves OS (endpoint not yet reached). Coadministration of G-CSF with cladribine decreases the length of neutropenia but does not affect the incidence or duration of febrile neutropenia or rates of hospitalization, and thus is not routinely recommended. Interferon-alpha (IFNα) is active in HCL and can improve the peripheral blood counts, although achievement of CR is uncommon and there is usually residual splenic and marrow involvement even if it is continued indefinitely. IFNα is rarely used in the upfront setting given the side effects (e.g., flulike symptoms and depression) and the superiority of purine analog therapy. While splenectomy was the first known treatment for HCL and can temporarily improve the peripheral blood counts in most patients for about 1–2 years, it is no longer indicated except for splenic rupture or as salvage in patients with multiply relapsed or refractory disease and no other treatment options.

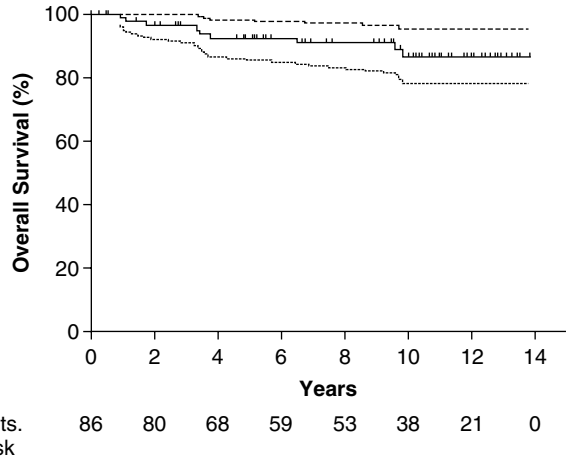


Figure 34.2 Overall survival curve for 86 patients treated with cladribine (26 patients were previously treated). Dotted lines represent the 95% confidence interval. (Source: Chadha P, Rademaker AW, Mendiratta P, *et al.* Blood 2005;106:241–246. Reproduced with permission of the American Society of Hematology).

3. A decision to initiate therapy with cladribine is made for this patient. What is the optimal route and schedule for the administration of cladribine? How do you manage the fever that commonly occurs after cladribine?

Cladribine is administered intravenously (IV) when treating symptomatic HCL, although there are oral and subcutaneous formulations available. Two recommended dosing schedules exist that are probably equivalent: (i) cladribine 0.1 mg/kg per day for 7 days by continuous IV infusion, and (ii) cladribine 0.14 mg/kg by 2 h IV infusion daily for 5 days ("bolus dosing"). The 7-day infusional program was the first to be studied and was the regimen used in many of the large

clinical trials leading to the drug's approval. It is generally considered the standard regimen, and it may be more convenient for the patient as there are less outpatient visits required. However, if there are logistical issues with an outpatient 7-day continuous infusion, which requires a peripherally inserted venous catheter (PICC) and portable pump, then the 5-day bolus schedule is an acceptable alternative regimen.

Approximately 40% of patients will become febrile during treatment with cladribine. This fever is usually noninfectious and coincides with decreasing peripheral neutrophil and hairy cell counts, and it may be related to cytokine release from apoptotic hairy cells. However, given that these patients are often neutropenic, blood cultures should be obtained and a broad-spectrum oral antibiotic initiated. Usually, patients do not need to be admitted to the hospital for a cladribine-associated fever unless they are systemically ill. If blood cultures are negative at 24 h, naproxen can be effective for persistent fever. Both cladribine and pentostatin can cause prolonged immunosuppression, and prophylaxis with acyclovir is indicated to prevent herpes zoster. Opportunistic infections are rare, but *Pneumocystis jiroveci* prophylaxis is advisable if the patient is otherwise immunosuppressed (e.g., on corticosteroids).

In terms of long-term side effects, cladribine has been associated with hypocellularity and foci of aplasia on posttreatment bone marrow biopsies. These findings can be seen in patients with durable remissions and normal blood counts, and they are of uncertain significance.

4. The patient is discharged home after a single cycle of cladribine (0.1 mg/kg per day by continuous infusion for 7 days). What would be the best time for restaging scans and bone marrow examination? How are partial and complete responses defined in hairy cell leukemia?

Approximately 80–90% of patients with newly diagnosed HCL achieve CR after one cycle of cladribine. CR is defined as normalization of peripheral blood counts, resolution of organomegaly, and morphologic remission (absent hairy cells) in the blood and bone marrow (although minimal residual disease (MRD) may still be detectable). A partial response, achieved in 10–15% of patients after cladribine, is defined as normalization of the peripheral blood counts, $\geq$50% reduction in organomegaly and bone marrow hairy cells, and $<$5% circulating hairy cells. Computed tomography (CT) or other scans are usually not necessary either at initial diagnosis or after treatment. Splenomegaly, which occurs in approximately 80% of patients with HCL, is the most common and often only physical and radiographic finding, and it can be followed by physical examination. In fact, massive splenomegaly (extending into the pelvis) should always prompt consideration of the following limited differential diagnosis: HCL, chronic myeloid leukemia, myelofibrosis, non-Hodgkin's lymphoma, Gaucher disease, and Kala-Azar infection. In the past, restaging bone marrow examinations were typically performed 3 to 6 months after treatment. However, our current practice in the purine analog era, when we know that the vast majority of patients will achieve CR, is to observe patients expectantly without restaging if the blood counts return to normal and splenomegaly resolves. Patients with MRD on posttreatment bone marrow examinations often have durable hematologic remissions, and the detection of MRD in these patients is of unclear significance and would not currently change management (see Question 1).

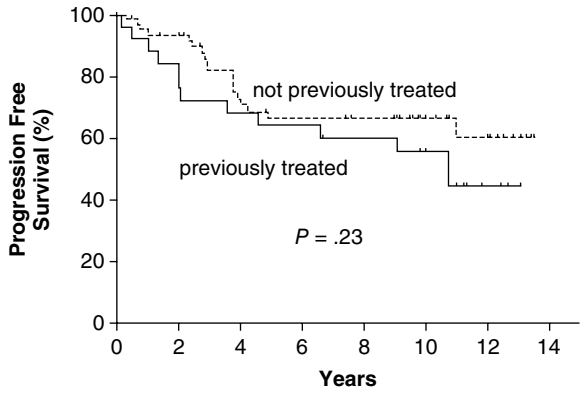
Multiple choice and discussion questions

1. How is MRD defined, and does it portend relapse in HCL?

Minimal residual disease (MRD) can be detected by IHC for markers such as CD20 or DBA.44. Depending on the criteria used, anywhere from 15% to 50% of patients in morphologic CR will have evidence of MRD after one cycle of cladribine; however, it has not been proven that MRD positivity correlates with early relapse. Immunophenotyping by flow cytometry is another useful, and perhaps more sensitive, method for evaluating MRD. Additionally, polymerase chain reaction (PCR) testing for clonal IGH may identify some residual disease even in patients who are MRD negative by flow cytometry. Postremission rituximab therapy has been used to successfully eradicate MRD (as detectable by PCR and flow cytometry) in patients with MRD after initial treatment with cladribine, but there is no current evidence that this strategy improves DFS or OS, and it is generally not recommended. Moreover, one study by Sigal and colleagues, which examined 19 patients in continuous hematologic CR for a median of 16 years after a single cycle of cladribine, showed that nine patients had no detectable MRD, seven were MRD positive, and three had morphologically overt disease (despite having normal blood counts). This highlights the fact that *very* long-term CRs can occur with a single cycle of cladribine, and that even in the case of MRD or overt bone marrow relapse, patients may have clinically quiescent disease for many years. The clinical significance of MRD in HCL and the role of rituximab to eradicate MRD remain unclear, and we do not recommended routine testing for MRD post cladribine if complete hematologic remission is achieved.

2. If a patient relapses after a single cycle of cladribine, what is the best therapeutic approach?

Repeat a single cycle of cladribine (or a course of pentostatin). Relapse of HCL is common but responds very well to



No. Pts. At Risk

Not Prev. Tx.	60	53	33	25	23	16	10	0
Prev. Tx	26	21	17	16	14	11	4	0

Figure 34.3 Demonstrates the similar progression-free survival (PFS) curves for newly diagnosed patients and those previously treated with one cycle of cladribine. (Source: Chadha P, Rademaker AW, Mendiratta P, *et al.* Blood 2005;106:241–246. Reproduced with permission of the American Society of Hematology).

retreatment. One series showed that at 10 years, 48% of patients treated with cladribine and 42% of those treated with pentostatin had relapsed. However, multiple studies have shown that retreatment with a purine analog leads to a second CR in as many as 70% of patients, and there appears to be no difference in outcome if retreatment is with the same purine analog used for first-line therapy (e.g., cladribine). Moreover, once a second CR (CR2) is achieved, the CR2 duration may be as long or nearly as long as the duration of first CR (CR1) (Figure 34.3). However, DFS does appear to shorten after multiply repeated courses of purine analog therapy (i.e., after third- or fourth-line treatment). One small retrospective study examining second-line purine analog therapy plus rituximab (given concurrently or sequentially) showed that eight out of nine patients achieved CR2, and only one patient relapsed at a median follow-up of 29 months. However, the use of rituximab in the first relapse setting has not been definitively shown to provide additional benefit and is not considered standard practice.

3. What is the best treatment for patients with multiply relapsed HCL, and is there a role for hematopoietic cell transplantation (HCT)?

There are multiple effective treatment options in patients with multiply relapsed or refractory HCL, including many encouraging new clinical trials. Given the typically indolent progression of disease in HCL, the advent of highly effective new therapies, and existing palliative treatment options such as splenectomy and IFNα, allogeneic HCT is rarely, if ever, indicated. If patients relapse after a second course of purine analog therapy, then it is reasonable to try a new strategy such as rituximab (with or without a purine analog). Several smaller studies have shown that rituximab monotherapy for relapsed HCL after treatment with cladribine can have high response rates, but a larger phase II study showed an overall response rate of only about 25%. Multiply repeated courses of cladribine or pentostatin are generally not advised due to decreasing effectiveness, increased risk of infection, and possibly bone marrow hypoplasia. In the rare case (<5%) that a patient is refractory to upfront treatment with cladribine or pentostatin, then another purine analog should be tried. Perhaps the best treatment option for multiply relapsed HCL is a clinical trial with an investigational agent (see Question 4), such as an antibody–drug conjugate (ADC). Lastly, splenectomy and IFNα can be effective for maintaining adequate blood counts in some patients with refractory HCL, although the response to splenectomy wanes with time and IFNα usually has to be given continuously for an ongoing response. For early relapsed or primary refractory disease, one should consider a different diagnosis, such as HCL variant, which is classically resistant to both purine analogs and splenectomy. Antibody-directed therapies, such as rituximab or an ADC, may be more effective in patients with HCL-v.

4. Are all of the following potential therapeutic targets in HCL?

A. CD20
B. CD22
C. CD25
D. CD52
E. BRAF mutation
F. All of the above

In general, the only clear role for anti-CD20 therapy with rituximab is in multiply relapsed patients who have failed at least two courses of cladribine or other purine analog therapy. Rituximab is relatively nontoxic, and multiple clinical trials have shown efficacy in relapsed or refractory disease, although response rates have varied considerably. The investigational agent BL-22, a recombinant anti-CD22 antibody conjugated with a pseudomonas exotoxin, has shown highly promising early results in clinical trials. For example, a phase II study (Kreitman *et al.* 2009) of 36 patients with relapsed or refractory HCL demonstrated complete and overall response rates of 47% and 72%, respectively, after two courses of treatment with BL-22. Patients without massive splenomegaly or prior splenectomy appeared to have better response rates. Neutralizing antibodies developed in some patients that prevented retreatment, and significant side effects included a reversible hemolytic uremic syndrome. A newer anti-CD22 antibody–immunotoxin conjugate, CAT-8015 or HA-22, which uses a modified pseudomonas exotoxin, appears to

have greater binding affinity to CD22 and is also being studied in clinical trials. LMB-2, another ADC employing a truncated pseudomonas exotoxin linked to a recombinant anti-CD25 antibody, has also shown significant activity in relapsed or refractory HCL in phase I studies. Alemtuzumab (Campath), an unconjugated anti-CD52 antibody that is highly immunosuppressive, is used more commonly for PLL and HCL-v. Given the availability of other effective agents, it is rarely used for classical HCL. Vemurafenib is a US Food and Drug Administration–approved small-molecule BRAF inhibitor for the treatment of stage IV melanoma. The *BRAF* V600E mutation leads to constitutive activation of the MEK–ERK pathway, thereby driving cellular proliferation; has been implicated in almost all cases of classical HCL; and appears to be a driver mutation. Studies have shown that 79–100% of patients with HCL have an activating *BRAF* V600E mutation, and patients with HCL-v appear to be universally wild-type *BRAF*. A recent case report from Dietrich and coworkers (2012) has described a patient with *BRAF*-mutant refractory HCL who had a remarkable response to vemurafenib, achieving CR, and this drug is being actively investigated in early-phase clinical trials for multiply relapsed and refractory disease. As in melanoma, mechanisms of resistance to BRAF inhibition may arise, requiring successive interventions.

5. What is the best front-line therapy in a symptomatic pregnant patient with HCL?

Interferon-alpha. Purine analogs are contraindicated in pregnancy. If treatment is required, then IFNα can be effective, especially for improving the blood counts, and it has been shown to be safe in pregnancy. If IFNα is ineffective and cytopenias or symptoms from splenomegaly are severe, then the relative risk and benefits of splenectomy should be carefully considered.

Selected reading

Chadha P, Rademaker AW, Mendiratta P, *et al.* Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. Blood. 2005;106:241–6.

Else M, Dearden CE, Matutes E, *et al.* Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. Br J Haematol. 2009;145:733–40.

Grever MR. How I treat hairy cell leukemia. Blood. 2010;115:21–38.

Ravandi F, O'Brien S, Jorgensen J, *et al.* Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. Blood. 2011;118:3818–23.

Tallman MS. Implications of minimal residual disease in hairy cell leukemia after cladribine using immunohistochemistry and immunophenotyping. Leuk Lymphoma. 2011;52:65–68.

Case study answers

Case study 34.1

Question 1: Answer C
Question 2: Answer E

Case study 34.2

Question 2: Answer A

Multiple choice answer

Question 4: Answer F

PART 6

Hodgkin Lymphoma

CHAPTER 35

Management of classical Hodgkin lymphoma

Kristen Sanfilippo and Nancy L. Bartlett
Washington University School of Medicine, St. Louis, MO, USA

Case study 35.1

A 19-year-old man presents with a 6-week history of intractable cough. A chest X-ray (CXR) shows an anterior mediastinal mass confirmed by computed tomography (CT) to measure 6.1 × 3.4 cm. A mediastinoscopy with biopsy shows classical Hodgkin lymphoma (cHL).

1. What additional study would be most reasonable to complete the staging work-up?

A. Whole-body positron emission tomography–computed tomography (PET–CT)
B. Bilateral bone marrow biopsy with aspirate
C. CT of the abdomen and pelvis

PET–CT is the preferred imaging modality for initial staging of cHL given its improved sensitivity of 94% compared to 77% with CT. PET–CT upstages approximately 10–20% of patients, resulting in a change in treatment recommendations. While limited data exist regarding the specificity of PET–CT in the upfront setting, a meta-analysis found a specificity of 87.7%, suggesting that there may be a small number of false positives that can potentially lead to inappropriate upstaging. If a PET–CT is performed at initial staging, the utility of a bone marrow biopsy (BMBx) appears limited. In a series of 454 HL patients staged with both PET and BMBx, no patient with stage I or II disease by PET had bone marrow involvement. Of those with stage III disease, 5 of 106 patients were upstaged by BMBx, but none had a change in treatment plan. A negative PET–CT for focal skeletal lesions has a 99% negative predictive value for marrow involvement.

Case study 35.2

A 26-year-old woman presents with left supraclavicular swelling. CT confirms a conglomerate of enlarged nodes measuring 3.0 × 2.9 cm and a 4.3 × 2.3 cm anterior mediastinal mass. An excisional lymph node biopsy reveals cHL. A PET–CT scan shows no other sites of disease. Initial labs were unremarkable, including an erythrocyte sedimentation rate (ESR) of 10 mm/h.

1. What is the best course of management for this patient?

A. Four cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), followed by 30 Gy of involved field radiation therapy (IFRT)
B. Two cycles of ABVD followed by 20 Gy IFRT
C. 4–6 cycles of ABVD
D. 2–3 cycles of ABVD followed by an interim PET. If PET negative, one additional cycle of ABVD; if PET positive, one additional cycle of ABVD followed by IFRT

This patient has nonbulky, stage II HL with favorable features. In contrast to advanced-stage HL, there is no uniform risk stratification system for early-stage HL, which limits the comparison and generalizability of study results and can occasionally lead to mismanagement of patients. In North America, early-stage patients are stratified based only on bulky disease, which is defined as a mediastinal mass

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

ratio (MMR) of more than one-third the maximum thoracic diameter or a single 10 cm mass. The German Hodgkin Study Group (GHSG) defines unfavorable disease as an MMR greater than one-third, ESR $\geq$50 mm/h in the absence of B-symptoms or $\geq$30 mm/h with B-symptoms, extranodal disease, or $\geq$3 involved lymph node sites. Although therapy for early-stage HL continues to evolve, current evidence-based options include combined modality therapy (CMT) versus chemotherapy alone with cure rates >90% with either approach. For the most favorable subset of patients, as defined by GHSG criteria, two cycles of ABVD + 20 Gy IFRT is equivalent to four cycles of ABVD + 30 Gy IFRT. Unfortunately, this approach is occasionally being applied outside the setting of a clinical trial to early-stage patients who do not meet the GHSG definition of "favorable," most commonly in the setting of more than two nodal sites of involvement where limited chemotherapy and low-dose radiation therapy (RT) have not been tested. The long-term complications of 20 Gy IFRT are unknown, and concerns remain regarding potential late effects.

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and Eastern Cooperative Oncology Group (ECOG) conducted the HD.6 trial comparing 4–6 cycles of ABVD alone versus subtotal lymph node irradiation (STNI) in patients with nonbulky, stage IA–IIA HL. Patients with a complete response (CR) on CT after two cycles of ABVD received two additional cycles, while those achieving a PR received an additional four cycles. The 12-year failure-free progression and overall survival (OS) for the most favorable subset treated with ABVD alone were 89% and 98%, respectively. Based on these results, ABVD alone for 4–6 cycles is also a reasonable option for early-stage, favorable HL.

More recently, several trials were conducted to evaluate the use of interim PET to direct therapy, specifically to guide the use of consolidative IFRT. The United Kingdom National Cancer Research Institute RAPID trial treated nonbulky, stage I–IIA HL patients with three cycles of ABVD followed by interim PET. Those with a negative interim PET (PET−), defined as a London Deauville score of $\leq$2, were randomized to observation versus IFRT, whereas those with a positive interim PET (PET+) received one additional cycle of ABVD followed by IFRT. At a median follow-up of 48.6 months, the PET− patients on observation had a 3-year PFS of 90.7% compared to 94.5% with IFRT (95% CI: −10.7% to 1.4%), while PET+ patients had an 85.9% 3-year PFS. There was no difference in 3-year OS.

In summary, both CMT and chemotherapy alone are effective strategies for managing patients with early-stage, favorable HL. While CMT results in a small improvement in PFS even in interim PET− patients, there is no survival advantage. The potential long-term complications of IFRT influence my recommendation of chemotherapy alone as the preferred treatment in early-stage nonbulky HL, particularly in young patients.

Case study 35.3

A 32-year-old woman presents with generalized pruritis and bilateral cervical lymphadenopathy. A cervical lymph node biopsy shows cHL. A PET–CT reveals a 10 cm anterior mediastinal mass and bilateral cervical adenopathy.

1. What is the most appropriate therapy?

A. 4–6 cycles of ABVD followed by 30 Gy of IFRT
B. 4–6 cycles of ABVD
C. Two cycles of ABVD followed by 20 Gy of IFRT
D. Two cycles of ABVD followed by an interim PET. If PET negative, one additional cycle of ABVD; if PET positive, one additional cycle of ABVD followed by IFRT
E. Stanford V + IFRT

This patient presents with bulky, early-stage HL. Patients with bulky, early-stage disease have been included in both advanced-stage and early-stage, unfavorable trials. Similar to the HD10 trial, the GHSG conducted a parallel HD11 trial for patients with early-stage, unfavorable HL based on the GHSG criteria. Patients treated with four cycles of ABVD + 30 Gy IFRT had a superior 5-year freedom from treatment failure (FFTF) (87.2 vs 82.1%) compared to those treated with four cycles of ABVD + 20 Gy IFRT. While no subgroup analysis was done, approximately 20% of patients had bulky mediastinal disease.

The ECOG E2496 trial included patients with bulky, early-stage disease, defined as an MMR greater than one-third, in addition to patients with advanced-stage disease and compared CMT with 6–8 cycles of ABVD versus Stanford V. All patients with bulky disease received 36 Gy modified IFRT. In the bulky subgroup, there was no appreciable difference between ABVD + IFRT and Stanford V + IFRT, with 5-year failure-free survival (FFS) and OS rates of 82% and 94%, respectively. More Grade 3 and 4 neuropathy and hematologic toxicity were seen with Stanford V. The trial was not designed as a noninferiority study, and ABVD remains the standard of care. Clinical trials are ongoing to assess the use of interim PET to guide the use of RT in patients with bulky HL. The UK RAPID and NCIC trials did not include patients with bulky disease. There are no prospective data on the outcome of early-stage, bulky patients treated with chemotherapy alone. Therefore, CMT remains the standard of care outside the setting of a clinical trial.

Case study 35.4

A 45-year-old man presents with cervical and supraclavicular lymphadenopathy. Biopsy of a cervical node reveals cHL. Routine blood tests show a white blood cell (WBC) count of 17,000/mm^3, an absolute lymphocyte count (ALC) of 300/mm^3, hemoglobin (Hgb) 9.8 mg/dL, albumin 3.2 mg/dL, and an ESR of 52 mm/h. A PET–CT reveals multiple enlarged supraclavicular, cervical, mediastinal, and retroperitoneal lymph nodes and splenomegaly. BMBx is positive, for cHL

1. What is this patient's 5-year PFS with ABVD chemotherapy?

A. 25%
B. 42%
C. 66%
D. 50%

This patient presents with high-risk disease based on the Hasenclever International Prognostic Score (IPS) for advanced HL, which assigns one point to each of the following adverse features: age ≥45 years, albumin <4.0 mg/dL, Hgb <10.5 g/dL, stage IV disease, WBC ≥15,000/mm^3, ALC <600/mm^3, and male gender. The initial publication of the IPS predicted the following 5-year freedom from disease progression rates based on the number of risk factors: 0 = 84%, 1 = 77%, 2 = 67%, 3 = 60%, 4 = 51%, and ≥5 = 42%. More modern series have shown improved cure rates with standard ABVD, with 5-year PFS rates of 66% for IPS ≥5, which are perhaps related to better supportive care and greater efforts to administer chemotherapy at full dose on schedule.

2. What is the best treatment option for this patient?

A. Escalated BEACOPP ×6 cycles
B. ABVD ×6 cycles
C. Stanford V regimen
D. Participation in a phase III clinical trial comparing ABVD to AVD + brentuximab vedotin

The optimal treatment for stage III–IV HL varies by country. ABVD remains the standard of care in North America regardless of IPS. The Germans have adopted the escalated BEACOPP (escBEACOPP) regimen based on the results of a randomized trial showing an improved FFTF when compared to COPP and ABVD. Toxicity was significantly higher in the escBEACOPP group, including hematologic toxicity, secondary leukemias, and nearly universal infertility. Follow-up studies of escBEACOPP compared to ABVD confirmed the advantage of escBEACOPP in terms of PFS, but showed no difference in OS. Based on these additional studies and the significant toxicity of escBEACOPP compared to ABVD, most oncologists outside of Germany continue to use ABVD as first-line therapy, understanding that more patients will relapse and require stem cell transplantation. The Stanford V regimen has also been compared with ABVD with no difference in OS, but it is a less attractive option secondary to the potential long-term complications associated with RT.

Although outcomes for advanced-stage HL have dramatically improved over the past 30 years, there is still a 35% relapse risk. Given a 75% single-agent response rate in multiply relapsed cHL treated with brentuximab vedotin (an antibody drug conjugate directed against CD30), an ongoing 1000 patient phase III international trial is assessing the efficacy of adriamycin, vinblastine, dacarbazine, and brentuximab versus ABVD as front-line therapy in advanced-stage HL. In conclusion, ABVD remains the standard of care for treatment of advanced-stage HL in North America. Escalated BEACOPP is a reasonable option for high-risk patients, and patients should be encouraged to participate in the phase III trial of ABVD versus AVD and brentuximab vedotin if available.

This patient receives two cycles of ABVD and has an interim PET–CT done to evaluate response. He has had marked improvement in disease but has residual fluorodeoxyglucose (FDG) avidity in a residual mediastinal node with uptake slightly greater than the liver.

3. Should you change treatment?

A. Yes
B. No
C. Either answer is acceptable

The study needed to answer this question, a randomized trial of interim PET+ patients, is not feasible due to small patient numbers and the concern by many investigators that such a study is unethical based on current retrospective data. A prospective study by Gallamini *et al.* (2007) showed a 12.8% 2-year PFS for interim PET+ patients after two cycles of ABVD compared to 95% for those who had a negative interim PET. Consequently, future trials were designed to change therapy in all interim PET+ patients, most commonly to escBEACOPP, the results of which are pending. While a positive interim PET likely portends a worse prognosis, the precise prognosis depends on the method used to interpret the PET (e.g., absolute SUV, delta SUV, and comparison to blood pool or liver). There is some evidence that a positive PET following cycle 4 of ABVD may be more predictive of outcome. In my practice, outside the setting of a clinical trial, for responding patients with a positive PET following cycle 2, I administer two additional cycles of ABVD and repeat the PET. If it is still positive after cycle 4, I change to salvage ICE (ifosfamide, carboplatin, and etoposide) chemotherapy and refer the patient for autologous stem cell transplantation.

Case study 35.5

A 26-year-old man presents with newly diagnosed favorable, stage IIA HL for treatment recommendations. The pathology report describes 3+ staining for CD68.

1. Does this finding change your management?

A. Yes
B. No

Recently, there has been interest in the prognostic significance of the immune microenvironment in cHL, including CD68, a macrophage marker. In the first published study of CD68 expression in cHL, high levels of CD68 staining correlated with a poor prognosis. Several additional small retrospective studies have tried to confirm these findings with mixed results. Until these results are confirmed in a prospective trial, CD68 staining should not be done routinely and should not be used to guide therapy. Hopefully, CD68 and other biologic markers will eventually lead to improved prognostic models in cHL.

Case study 35.6

A 23-year-old woman with bulky stage II HL is currently receiving ABVD. She presents for cycle 2 of treatment and has an absolute neutrophil count (ANC) of 300. She is afebrile and feels well.

1. How should you manage her?

A. Administer full-dose ABVD chemotherapy today
B. Hold treatment and recheck counts in a week
C. Administer ABVD with a 35% dose reduction today
D. Administer full-dose ABVD and start prophylactic pegfilgrastim

Several retrospective studies have shown the safety of continued full-dose ABVD despite significant neutropenia on the day of treatment. In several large series, the incidence of febrile neutropenia with ABVD was <5%. Prophylactic growth factors are not indicated with ABVD and should not be instituted for asymptomatic neutropenia. Retrospective studies have shown a possible increase in serious bleomycin lung toxicity in patients receiving granulocyte colony-stimulating factor with ABVD, providing another reason to avoid growth factors with this regimen.

Case study 35.7

A 36-year-old man has received three cycles of ABVD for stage III HL. He presents for cycle 4 of treatment and mentions a 2-week history of a persistent dry cough. He denies shortness of breath, fever, or other associated symptoms. His oxygen saturation is 95% on room air. He has a history of tobacco use but has not smoked since starting ABVD. A chest X-ray shows no pulmonary infiltrates.

1. Should you discontinue bleomycin and complete three cycles of AVD?

A. No
B. Yes

Bleomycin lung toxicity (BLT) commonly presents as a dry cough without associated symptoms. In a large retrospective study of patients receiving bleomycin for treatment of cHL, BLT occurred in 18% of patients and was fatal in 24% of patients diagnosed with BLT. Thus, BLT should be considered in all patients on ABVD presenting with unexplained cough, as cough is the earliest sign of toxicity. Once fevers, pulmonary infiltrates, shortness of breath, or hypoxia develop, the prognosis is more guarded. Physicians should have a low threshold for withholding bleomycin if lung toxicity is suspected. Retrospective data show no difference in outcome when bleomycin is discontinued prematurely. A randomized trial eliminating bleomycin following cycle 2 of ABVD in patients with a negative interim PET is near completion.

Case study 35.8

A 26-year-old woman completed six cycles of ABVD chemotherapy 4 weeks ago for stage IIIB cHL. Her posttreatment PET–CT reveals a complete metabolic response to therapy with no FDG avid disease. She has a 2 cm residual mediastinal mass that has decreased by 75% compared to pretreatment.

1. What follow-up imaging should she receive?

A. No surveillance imaging
B. PET–CT every 6–12 months for 5 years
C. PET–CT every 6–12 months for 2 years
D. CT chest–abdomen–pelvis every 6–12 months for 5 years
E. CT chest–abdomen–pelvis every 6–12 months for 2 years

In a prospective surveillance trial in which cHL patients in remission underwent a PET–CT scan every 6 months for 4 years, 85% of relapses occurred in the first 18 months following treatment. Despite lacking supportive data, the National Comprehensive Cancer Network (NCCN) guidelines recommend obtaining imaging studies of the chest (X-ray or CT) and abdomen and pelvis (CT) every 6–12 months for the first 2–3 years following completion of therapy. Importantly, there is no evidence that routine surveillance scans improve the outcome of patients with relapsed HL. In retrospective studies, 65–80% of relapses are detected by patient symptoms or physical exam findings, not by surveillance imaging, and these studies show no difference in patient outcomes based on method of relapse detection. In addition, there is a risk of false-positive results when obtaining surveillance PET–CT and CT scans. The largest trial looking at the predictive value of surveillance scans was published by the Dana-Farber Cancer Institute and revealed a positive predictive value for detecting recurrent HL of 22.9% and 28.6% in PET–CT and CT, respectively.

Case study 35.9

A 38-year-old woman presents to establish care with a new primary care physician. Her past medical history is significant only for HL diagnosed at the age of 15, which was treated with MOPP–ABV (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine) followed by IFRT to the mediastinum. Her physician calls you to discuss screening and preventative care. She has not been followed by a physician for the past 10 years.

1. Which of the following tests should you recommend?

A. Screening colonoscopy
B. Pneumococcal and meningococcal vaccination
C. Screening mammogram and breast magnetic resonance imaging (MRI)

Successful improvements in treatment of patients with HL have led to an increasing number of long-term survivors of the disease. Long-term follow-up studies have noted a marked increased risk for competing causes of death from treatment-related complications, including secondary malignancies, heart and lung disease, in addition to thyroid dysfunction and infertility. The most common second cancers following treatment of HL are breast and lung cancer. This patient's risk of developing breast cancer is fivefold that of the normal population, with an absolute risk approaching 25% at 30 years of age and 35% at 40 years. Annual mammograms and breast MRIs are recommended for all women treated for HL with mediastinal or axillary RT between ages 10 and 30. In women diagnosed with breast cancer, the incidence of a subsequent contralateral breast cancer is high, and bilateral mastectomy should be considered at the time of initial breast cancer diagnosis.

Case study 35.10

A 40-year-old man was treated with ABVD and mediastinal RT 10 years ago. He has a family history of coronary artery disease and was recently found to have a low-density lipoprotein (LDL) level of 130 and a high-density lipoprotein (HDL) level of 35.

1. What would you recommend to the patient's internist?

A. Dietary consult and recheck in 12 months
B. Start a statin
C. Start a statin and obtain a cardiac stress test

Patients treated with mediastinal RT are at high risk of developing cardiovascular disease following treatment, and this includes a threefold increased risk of fatal myocardial infarction. By 10 years, 4.5% of patients have evidence of clinically significant cardiac disease, a number that increases to 23.2% by 25 years following completion of therapy. Given this elevated risk, all patients who have had mediastinal RT should be considered high risk for cardiovascular disease. Thus, the most appropriate management strategy would be to treat the LDL with a statin and obtain a screening cardiac stress test.

Case study answers

Case study 35.1

Question 1: Answer A

Case study 35.2

Question 1: Answer B, C, or D

Case study 35.3

Question 1: Answer A

Case study 35.4

Question 1: Answer C
Question 2: Answer A, B, or D
Question 3: Answer C

Case study 35.5

Question 1: Answer B ("No")

Case study 35.6

Question 1: Answer A

Case study 35.7

Question 1: Answer B

Case study 35.8

Question 1: Answer A or E

Case study 35.9

Question 1: Answer C

Case study 35.10

Question 1: Answer C

Selected reading

Eich HT, Diehl V, Gorgen H, *et al.* Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol. 2010; 28:4199–206.

Engert A, Plutschow A, Eich HT, *et al.* Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010;363:640–52.

Gallamini A, Hutchings M, Rigacci L, *et al.* Early interim 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;25:3746–52.

Meyer RM, Gospodarowicz MK, Connors JM, *et al.* ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012;366:399–408.

Swerdlow AJ, Cooke R, Bates A, *et al.* Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012;30:2745–52.

CHAPTER 36

Nodular lymphocyte-predominant Hodgkin lymphoma

Dennis A. Eichenauer

University Hospital Cologne, Cologne, Germany *and* German Hodgkin Study Group (GHSG), Cologne, Germany

Multiple choice questions

1. Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL) are usually treated similarly. However, there are significant differences. With respect to which features do NLPHL and cHL differ?

A. Immunohistology
B. Clinical presentation
C. Course of disease
D. All of them

NLPHL is a rare entity accounting for about 5% of all Hodgkin lymphoma (HL) cases. It substantially differs from the histological subtypes of cHL in terms of immunohistology, clinical presentation, and course. The consistent expression of the B-cell marker CD20 represents a hallmark of the disease-defining lymphocyte predominant (LP) cells in NLPHL. In contrast, it is only infrequently found on Hodgkin and Reed–Sternberg (H-RS) cells in cHL. Further immunohistological differences between the malignant cells in NLPHL and cHL include the lack of the antigens CD15 and CD30 on LP cells; these surface antigens are typically expressed on H-RS cells. In addition, LP cells do not harbor Epstein–Barr virus (EBV) DNA, which can be found in a relevant proportion of H-RS cells. These and other markers that can be used to distinguish LP cells from H-RS cells are summarized in Table 36.1.

The most comprehensive data addressing the differences between NLPHL and cHL in terms of clinical presentation and course came from the German Hodgkin Study Group (GHSG). In a retrospective analysis, Nogova and coworkers compared the characteristics and clinical outcomes of 394 NLPHL and 7904 cHL patients treated within GHSG trials. NLPHL was more often diagnosed in early favorable stages. Whereas 63% of patients with NLPHL were diagnosed with early favorable stages, 16% had early unfavorable and 21% had advanced stages. In contrast, 22%, 39%, and 39% of patients with cHL were diagnosed with early favorable, early unfavorable, and advanced stages, respectively. Furthermore, fewer patients with NLPHL had B symptoms (9% in NLPHL vs. 40% in cHL; $P < 0.0001$). The presence of clinical risk factors such as elevated erythrocyte sedimentation rate (ESR) (4% in NLPHL vs. 45% in cHL; $P < 0.0001$), the involvement of three or more nodal areas (28% in NLPHL vs. 55% in cHL; $P < 0.0001$), extranodal disease (6% in NLPHL vs. 14% in cHL; $P < 0.0001$), mediastinal bulk of more than one-third of the maximum thoracic width (31% in NLPHL vs. 55% in cHL; $P < 0.0001$), and elevated lactate dehydrogenase (LDH) (16% in NLPHL vs. 32 in cHL; $P < 0.0001$) was also less common (Table 36.2).

After adequate stage-adapted chemotherapy and/or radiotherapy (RT), NLPHL patients included in the GHSG analysis had an excellent clinical outcome. Freedom from treatment failure (FFTF) and overall survival (OS) rates after a median observation of 50 months were 88% and 96%, respectively. However, especially patients with more advanced disease at initial diagnosis showed a tendency to develop late relapses. As compared with 8.6% of cHL patients, 23.5% of NLPHL patients initially treated for early unfavorable and advanced stages relapsed more than one year after completion of first-line treatment. In contrast, NLPHL patients treated for early favorable stages had no increased rate of late relapses (4.8% in NLPHL vs. 6.4% in cHL; $P = 0.3991$). The frequency of early relapses did also not significantly differ between NLPHL and cHL.

In summary, NLPHL is characterized by pathological and clinical features that differ significantly from those of cHL. However, the outcome is excellent with standard HL treatment approaches.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 36.1 Staining characteristics of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL) (Source: Adapted and modified from Smith LB. Arch Pathol Lab Med. 2010;134(10):1434–9).

	NLPHL	cHL
CD20	+	−/+
CD30	−	+
CD15	−	+
CD45	+	−
CD79A	+	−/+
EBER	−	−/+
EMA	+/−	−
OCT-2	+	−/+
BOB.1	+	−/+
PU.1	+	−

EBER, in situ hybridization for EBV; EMA, epithelial membrane antigen; +, positive; −, negative; +/−, usually positive, may be negative; −/+, usually negative, may be positive.

Table 36.2 Characteristics of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL) patients (Source: Adapted and modified from Nogova L, *et al.* J Clin Oncol. 2008;26(3):434–9. Reproduced with permission of the American Society of Clinical Oncology.).

	NLPHL ($n = 394$)	cHL ($n = 7904$)
Age (median)	37	33
Male gender (%)	75	56
B symptoms (%)	9	40
Elevated ESR (%)	4	45
3 or more nodal areas involved (%)	28	55
Extranodal disease (%)	6	14
Large mediastinal mass (>1/3 of the maximum thoracic width) (%)	31	55
Elevated LDH (%)	16	32
Early favorable stages (%)	63	22
Early unfavorable stages (%)	16	39
Advanced stages (%)	21	39

ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

2. In cHL, combined-modality treatment (CMT) was shown to result in a superior clinical outcome as compared with RT alone and is thus considered the standard of care for early favorable stages. In NLPHL, RT alone still represents the widely accepted standard of care for stage IA disease without clinical risk factors. Is this recommendation based on randomized clinical trials?

A. Yes
B. No

Randomized clinical trials exclusively including patients with NLPHL have not been conducted to date due to the low overall incidence. Thus, recommendations in NLPHL are based on results from smaller prospective phase II studies and retrospective analyses.

The Australasian Radiation Oncology Lymphoma Group retrospectively evaluated 202 patients with stage I/II NLPHL treated with RT alone between 1969 and 1995. Radiation fields included the full mantle field, the modified mantle field, the inverted-Y field, the modified inverted-Y field, and total lymph node irradiation. The median RT dose applied was 36 Gy. At a median follow-up of 15 years, the estimated 15-year rates for freedom from progression (FFP) and OS were 82% and 83%, respectively. Among the 17% of patients who had died within 15 years, only 3% died from NLPHL, whereas 2% died from secondary non-Hodgkin's lymphoma (NHL), 2% from in-field secondary solid tumors, 4% from cardiac and respiratory reasons, and 6% from other causes.

With the aim to decrease the risk for the development of RT-related late sequelae, RT fields were continuously reduced in recent years. At present, most patients with early favorable NLPHL receive involved-field (IF)-RT either alone or as part of CMT approaches. This is based on results from some larger retrospective studies conducted by different groups.

The GHSG retrospectively analyzed 131 NLPHL patients diagnosed with stage IA disease without clinical risk factors. Patients received extended-field (EF)-RT ($n = 45$), IF-RT ($n = 45$), or CMT ($n = 41$). Complete remission (CR) was achieved in 99% of cases (98% after EF-RT, 98% after IF-RT, and 100% after CMT). FFTF rates at 24 months were 100% for EF-RT, 92% for IF-RT, and 97% for CMT, with no significant differences between the treatment approaches; OS rates at a median follow-up of 78 months for EF-RT, 17 months for IF-RT, and 40 months for CMT were 94%, 100%, and 96%, respectively. Treatment-related toxicity was more common among patients who had CMT (48.8% grade III/IV toxicity) in comparison with EF-RT (2.2% grade III/IV toxicity) and IF-RT (2.2% grade III/IV toxicity).

Chen and colleagues conducted a retrospective analysis on the long-term course of 113 stage I/II NLPHL patients treated with RT alone ($n = 93$), CMT ($n = 13$), or chemotherapy alone ($n = 6$). After a median observation of 136

months among survivors, patients treated with RT alone had an excellent outcome, with 10-year progression-free survival (PFS) and OS rates of 89% and 96%, respectively, for stage I patients and 72% and 100%, respectively, for stage II patients. Results could not be improved by the addition of chemotherapy. Chemotherapy alone was associated with an increased relapse rate. The extent of RT could be safely reduced from EF-RT to IF-RT without compromising treatment results. Secondary malignancies and cardiovascular disease were less frequent after IF-RT when compared with EF-RT. In contrast to PFS ($P < 0.006$), no differences in OS were seen between stage I and stage II patients ($P = 0.53$).

Given the inferior PFS rates for stage II patients in comparison with stage I patients, RT alone may not represent the appropriate approach in stage II NLPHL. This impression is supported by a retrospective Canadian study. The outcome of 32 patients treated with RT alone between 1966 and 1993 was compared with the outcome of 56 patients treated with CMT approaches between 1993 and 2009. As a major finding, the analysis revealed a significantly better PFS for patients treated with CMT approaches ($P = 0.0024$). Although this analysis has some limitations and results have to be interpreted with caution because patients were treated over a period of more than four decades, the improved tumor control with CMT approaches should be kept in mind when choosing treatment for patients with NLPHL in early favorable stages other than stage IA.

In summary, IF-RT alone is widely considered the standard of care for newly diagnosed stage IA NLPHL without clinical risk factors. The question of whether patients with stage II NLPHL without risk factors are also sufficiently treated with RT alone is not definitely answered, and recommendations are not consistent. Whereas CMT approaches represent the standard within the GHSG and other European groups, the National Comprehensive Cancer Network (NCCN) also recommends RT alone for patients with stage IIA NLPHL.

3. The minority of NLPHL patients are diagnosed in early unfavorable or advanced stages. Are there treatment differences between NLPHL and cHL in these stages?

A. Yes
B. No

According to a large retrospective analysis performed by the GHSG, early unfavorable and advanced stages account for 37% of NLPHL cases (16% early unfavorable stages and 21% advanced stages). Treatment is very similar to that for cHL; it mostly consists of CMT approaches for early unfavorable stages, and six to eight cycles of chemotherapy followed by localized RT to larger residual disease for advanced stages. Chemotherapy mostly consists of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) or ABVD-like protocols and escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone). According to the GHSG analysis, FFTF rates at a median follow-up of 50 months were 87% for early unfavorable stages and 77% for advanced stages, and thus were comparable with rates for cHL. It is a matter of debate whether patients with more advanced NLPHL may benefit more from alkylator-based chemotherapy protocols than from ABVD or ABVD-like protocols. The Cancer and Leukemia Group B (CALGB) retrospectively evaluated 37 patients with advanced NLPHL who were treated with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), MOPP–ABVD, or ABVD–EVA (etoposide, vinblastine, and adriamycin). As a result, the relapse rate after ABVD–EVA was 75% compared to only 32% after MOPP or MOPP–ABVD, indicating a superior tumor control after alkylator-based chemotherapy. However, a recent matched-pair analysis comprising 42 patients with advanced NLPHL and 82 patients with cHL mainly treated with ABVD or ABVD-like protocols did not show significant outcome differences between both histologies. FFTF ($P = 0.930$) and OS ($P = 0.5808$) estimates at 15 years were comparable. Thus, further analyses are required to define the optimal treatment for patients with more advanced NLPHL.

4. In NLPHL, the consistent expression of the B-cell marker CD20 represents a hallmark of the disease-defining LP cells. Therefore, it is tempting to treat NLPHL with approaches including anti-CD20 antibodies. Are there prospective data on the value of anti-CD20 antibodies in this entity?

A. Yes, for all stages
B. Yes, but only for some stages
C. No, there are no data at all

Groups from the United States and Europe conducted several phase II trials evaluating the chimeric anti-CD20 antibody rituximab in NLPHL (Table 36.3).

A study by the Stanford group included a total of 22 patients; 12 patients had newly diagnosed NLPHL, while 10 patients had relapsed disease. After four doses of rituximab at 375 mg/m^2, the response rate was 100%. However, at a median follow-up of 13 months, 9 patients had relapsed. The median FFP was 10.2 months. Subsequently, the study was continued with a modified design. After the initial four weekly doses of rituximab at 375 mg/m^2, the patients received rituximab maintenance every 6 months for 2 years. After a median observation of 30 months for the 16 patients receiving this extended rituximab schedule, the median FFP was not reached; the estimated 30-month FFP rate was 88%.

Two prospective phase II studies came from the GHSG. One study included 28 patients with newly diagnosed

Table 36.3 Rituximab for the treatment of NLPHL

Disease status	Stages included	Schedule	*N*	Response rate	PFS	References[a]
Untreated	Stage IA without RFs	Rituximab standard	28	100%	81.4% at 36 m	Eichenauer *et al.* (2011)
Untreated	All stages	Rituximab standard or extended	S = 10; E = 9	100%	Median PFS: S = 50 m; E = 67 m	Advani *et al.* (2011)
Untreated or relapsed	All stages	Rituximab standard	U = 12; R = 10	100%	Median PFS: 10.2 m	Horning *et al.* (2007)
Relapsed	All stages	Rituximab standard	15	94%	Median PFS: 33 m	Schulz *et al.* (2008)

The standard rituximab schedule is 375 mg/m^2 for 4 consecutive weeks; the extended rituximab schedule is the standard schedule plus four rituximab doses every 6 months for 2 years. E, extended; m, months; PFS, progression-free survival; R, relapsed; RF, risk factor; S, standard; U, untreated.

[a]Eichenauer DA, *et al.* Blood. 2011;118(16):4363–5; Advani RH, *et al.* ASH Ann Meeting Abstracts. 2011;118(21):2686; Horning SJ, *et al.* ASH Ann Meeting Abstracts. 2007;110(11):644; Schulz H, *et al.* Blood. 2008;111(1):109–11.

stage IA NLPHL without clinical risk factors. Treatment consisted of four weekly standard doses of rituximab. The response rate was 100%. However, at a median follow-up of 43 months, 7 patients had relapsed, so this approach appeared to be associated with inferior tumor control as compared with IF-RT alone. Thus, single-agent rituximab was not adopted as the novel standard of care for patients with stage IA NLPHL without clinical risk factors.

The second GHSG study included 15 patients with relapsed NLPHL. Four weekly standard doses of rituximab were given. The response rate was 94%. At a median follow-up of 63 months, the median time to progression was 33 months and the median OS was not reached. Thus, on the basis of the impressive response rates, the relevant proportion of patients with lasting remissions, and the excellent tolerability, treatment with rituximab or follow-up products appears justified in the majority of patients with relapsed NLPHL. This is particularly true for patients with low tumor burden and slow disease progression.

Some retrospective data on the use of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone) in newly diagnosed NLPHL are available in abstract form. The response rate among 20 patients (8 stage I/II and 12 stage III/IV) treated with this protocol optionally followed by IF-RT was 100%. No relapses occurred at a median follow-up of 42 months. However, the results of prospective studies confirming these promising results are pending. The same is true for the combination of anti-CD20 antibodies with other chemotherapy protocols.

In summary, there are prospective data from clinical trials evaluating the anti-CD20 antibody rituximab as a single agent in newly diagnosed NLPHL. In stage IA NLPHL, treatment with rituximab appears to result in inferior tumor control as compared with IF-RT alone. In contrast, single-agent rituximab may represent the most suitable treatment in the majority of patients with relapsed NLPHL. This is due to the excellent response rates and the relevant proportion of long-term remissions observed with rituximab, on the one hand, and the reduced toxicity in comparison with the standard treatment for relapsed cHL [consisting of high-dose chemotherapy followed by autologous stem cell transplantation (auto-SCT)], on the other hand. The question of whether the prognosis of patients with newly diagnosed NLPHL is improved by adding rituximab to standard chemotherapy protocols has not been answered to date because results from prospective studies are not available.

5. A 45-year-old male patient was diagnosed with stage IIIA NLPHL 8 years ago. He achieved continuous remission after six cycles of escalated BEACOPP. The patient now presents with cervical and mediastinal lymphadenopathy, B-symptoms are not reported, and the LDH is slightly elevated. What is the next diagnostic or therapeutic step?

A. Start treatment with rituximab
B. Plan high-dose chemotherapy and auto-SCT after salvage treatment and stem cell harvest
C. Obtain a lymph node biopsy
D. Start treatment with steroids

In NLPHL patients presenting with clinical signs of relapse, a lymph biopsy should be obtained whenever possible. This is due to an increased risk of transformation from NLPHL into aggressive B-cell NHL (B-NHL), in particular T-cell-rich B-NHL (TCRBNHL). Some analyses addressing this issue were recently performed. The transformation rates reported exceeded previous estimations. A

registry-based analysis comprising 164 patients initially diagnosed with NLPHL between 1973 and 2003 came from France. At a median follow-up of 9.5 years for survivors, 66 patients had recurrence of lymphoma, of which 19 presented with histological transformation into aggressive B-NHL. The median time from the initial NLPHL diagnosis to the occurrence of transformation was 4.7 years; the cumulative 10-year transformation rate was 12%. Patients with transformation were treated with either conventional chemotherapy (10/19) or high-dose chemotherapy followed by auto-SCT (9/19) and thus received more aggressive treatment than patients who relapse with NLPHL histology. However, despite this more aggressive treatment, patients with transformed lymphoma had an impaired prognosis as compared with patients presenting with NLPHL at relapse.

A second report from Canada using the British Columbia Cancer Agency (BCCA) database included a total of 95 patients initially diagnosed with NLPHL. Transformation into aggressive B-NHL occurred in 13 of them; the median time to transformation was 8.1 years. The actuarial risks for the development of transformed lymphoma after initial diagnosis of NLPHL were 5%, 7%, 15%, 31%, and 36% after 5, 10, 15, 20, and 25 years, respectively. Interestingly, two clusters of transformation were seen. One cluster of early transformation occurred less than 3 years after the initial lymphoma diagnosis (5/13), while a cluster of late transformation occurred 10 to 25 years (7/13) after the initial lymphoma diagnosis. Transformation was more likely in patients with initial splenic involvement ($P = 0.006$). Similar to the French report, prognosis after diagnosis of aggressive B-NHL was worse than expected after NLPHL relapse. Although patients with transformed lymphoma were being treated with multi-agent chemotherapy mostly followed by high-dose chemotherapy and auto-SCT, 10-year estimates for PFS and OS were only 52% and 62%, respectively.

According to these data, a rebiopsy should be obtained whenever possible if clinical signs of relapse occur in patients initially treated for NLPHL. The most appropriate treatment can be chosen only on the basis of a correct histological diagnosis. Treatment options range from anti-CD20 antibody treatment for patients with NLPHL histology and low tumor burden to aggressive treatment approaches including high-dose chemotherapy and auto-SCT for patients relapsing with transformation into aggressive lymphoma.

Multiple choice answers

Question 1: Answer D
Question 2: Answer B ("No")
Question 3: Answer B ("No")
Question 4: Answer B
Question 5: Answer C

Seleced reading

Al-Mansour M, Connors JM, Gascoyne RD, *et al*. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol. 2010 10;28(5):793–9.

Chen RC, Chin MS, Ng AK, *et al*. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. J Clin Oncol. 2010 1;28(1):136–41.

Nogová L, Reineke T, Eich HT, *et al*. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol. 2005;16(10):1683–7.

Nogová L, Reineke T, Brillant C, *et al*. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J Clin Oncol. 2008 20;26(3):434–9.

Schulz H, Rehwald U, Morschhauser F, *et al*. M. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood. 2008 1;111(1): 109–11.

CHAPTER 37

Hematopoietic cell transplantation in Hodgkin lymphoma

Tsiporah Shore and Koen van Besien

Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

Autologous transplantation is the standard treatment for patients with recurrent Hodgkin lymphoma (HL). It is an overall well-tolerated treatment that can result in durable remissions, and it cures a large proportion of patients with chemosensitive disease and some with chemotherapy-refractory disease. Its role has been extensively reviewed. Here, we address some management questions that remain or that have arisen as a consequence of novel developments in the field.

1. Does residual marrow involvement affect the results of autologous transplantation?

There is considerable evidence that occult marrow or stem cell involvement as determined by a variety of methods (polymerase chain reaction, clonogenic assays, etc.) contributes to disease recurrence in patients with lymphoma undergoing autologous transplantation. Further evidence of the detrimental effect of occult marrow involvement comes from a comparative study showing that patients with lymphoma undergoing syngeneic transplantations have a lower risk of disease recurrence than those undergoing autologous transplantation. Such studies provide compelling evidence that submicroscopic marrow or stem cell involvement is common in lymphoid malignancies and constitutes an adverse prognostic feature. Whether circulating clonogenic lymphoma cells exist or can be mobilized in HL remains to be determined. Tantalizing but preliminary data suggest that they might.

Only a minority of patients with HL present with overt marrow involvement at the time of initial diagnosis or at the time of disease recurrence, and such patients pose a peculiar challenge. In an apparent paradox, such overt marrow involvement does not constitute an absolute contraindication for autologous transplantation. Several cases have been reported of patients with overt marrow involvement who underwent bone marrow harvest followed by autologous transplantation and who achieved durable complete remissions.

Cells from HL collected during marrow harvest therefore do not always lead to disease recurrence, and marrow involvement should thus be considered in the context of the overall patient assessment and only as a relative contraindication. By itself, it is not sufficient reason to recommend a change in treatment strategy or to recommend an allogeneic transplant with its attendant risk for serious complications. The likelihood of durable response after autologous transplantation should take into account other, better-established risk factors such as disease response assessed by radiological or functional testing.

2. What is the best conditioning regimen?

Early studies of autologous transplants for Hodgkin lymphoma used total body irradiation (TBI)-based regimens, which were also widely used at the time in allogeneic transplantation. TBI-based regimens have not, however, been shown to be superior to chemotherapy-based regimens; are logistically more difficult to organize; cannot be utilized in patients with prior dose-limiting radiation; and probably are associated with higher rates of late therapy-related acute myeloid leukemia and myelodysplastic syndrome (t-AML–MDS). Most centers have therefore abandoned their routine use in HL.

The most commonly used chemotherapy-based regimens include high doses of the nitrosourea BCNU (bischloroethylnitrosourea) combined with another alkylating agent such as cyclophosphamide or melphalan, and it often also incorporates etoposide and sometimes high-dose cytarabine [e.g., carmustine, etoposide, cytarabine, and melphalan (BEAM); carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC); and cyclophosphamide, car-

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

mustine, and etoposide (CBV)]. The reported treatment-related mortalities associated with the use of these regimens have declined over the years thanks to improvements in stem cell support and infection prophylaxis and treatment. Toxicity also depends somewhat on the doses of BCNU utilized, which range from 300 mg/m^2 to 800 mg/m^2. At the higher end of this dose range, there is a considerable incidence of pulmonary toxicity and also of sinusoidal obstructive syndrome (also known as veno-occlusive disease). Doses of BCNU exceeding 450 mg/m^2 should be avoided.

Regimens incorporating busulfan instead of BCNU are also increasingly being used and may have less risk for pulmonary toxicity. Other regimens incorporating active agents such as gemcitabine, bendamustine, and thiotepa have been developed in attempts to improve efficacy. Early results are promising but ideally should be compared in a randomized trial against older regimens.

3. What is the role of positron emission tomography (PET) scanning before transplantation?

Patients with HL who have received curative therapy often remain with enlarged fibrotic masses. Functional imaging is necessary to assess response and prognosis. Older methods based on gallium scanning have been superseded by PET, which is less time consuming, has better resolution, and can be combined with computed tomography (CT) scanning. In a retrospective study by Jabbour *et al.* (2007), functional imaging of Hodgkin patients before transplantation using both PET scans and gallium scans was superior to radiologic imaging alone in predicting both relapse and overall survival (OS) post-transplantation.[26] Patients with a positive functional image before transplantation had progression-free survival (PFS) of 23% and an OS of 58%, compared with 69% and 87%, respectively, in those with negative functional imaging. Similarly, patients in partial remission with a positive functional image had a 3-year PFS of only 27% versus 51% if the functional imaging was negative. In a multivariate model, positive functional imaging was found to be independently prognostic of PFS. Several other studies also suggested that a pretransplantation positive PET in HL confers a worse prognosis. And a meta-analysis of 16 studies confirmed the prognostic value of a pretransplantation PET scan in predicting both relapse and OS in patients with lymphoid malignancies.

But the interpretation of PET scan results has its own challenges with ongoing debates over threshold values and ever-changing technologies. It is not uncommon to encounter false-positive PET scan results due to a variety of causes (brown fat, thymic rebound, bleomycin-induced inflammation, etc.). Sometimes, biopsy is required. But even in cases where there is consensus that PET positivity represents residual disease, this does not constitute an absolute contraindication for transplantation. For example, in a study from the University of Washington, patients with positive PET scans prior to transplantation had a 3-year expected event-free survival (EFS) of 42%, which was considerably worse than that of PET-negative patients but still respectable. Other prognostic factors may aid in assessing prognosis in such patients and to identify those with a dismal prognosis. A prospective study sheds some light on this complex quandary. It confirmed that patients with a negative PET had an EFS of >80% versus only 28.6% in those patients whose PET was still positive pretransplantation. But in a multivariate analysis, PET scan and extranodal disease were both significant such that patients with a negative PET scan but a history of extranodal disease truly had a dismal prognosis (Figure 37.1).

Recently, a British group developed an algorithm to utilize PET scan in treatment assignments to autologous versus allogeneic transplantation. Patients who are PET negative after salvage therapy undergo autologous transplants, but those with positive scans are referred for allogeneic transplants. They report approximately 90% long-term survival for those undergoing autologous transplantation. Of interest, long-term survival for those undergoing allogeneic transplantation, all of whom had positive PET prior to transplantation, is also in the 90% range. Only two of 25 patients died of treatment-related causes after

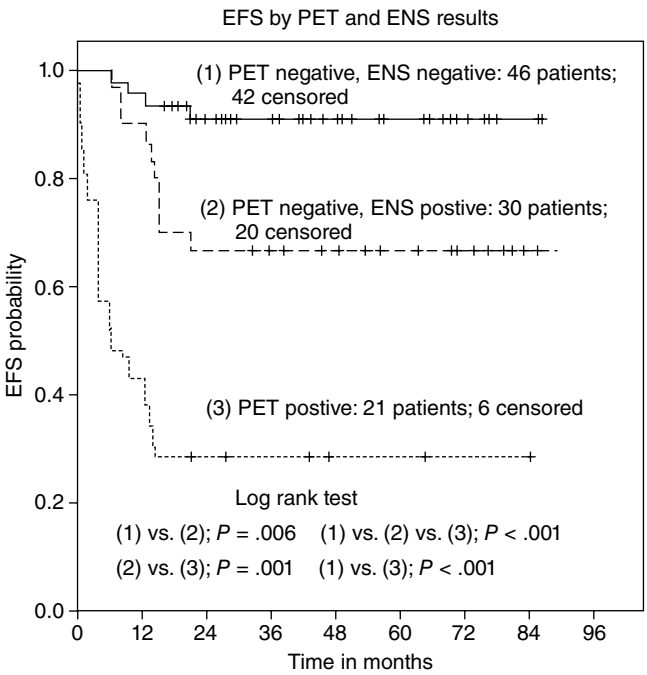


Figure 37.1 Event-free survival (EFS) after autologous transplantation for Hodgkin lymphoma based on pretransplantation positron emission tomography (PET) scan results and the presence or absence of extranodal disease. ENS, extranodal sites of disease (Source: Moskowitz CH, Matasar MJ, Zelenetz AD *et al.* Blood 2012;119:1665–1670. Reproduced with permission of American Society of Hematology).

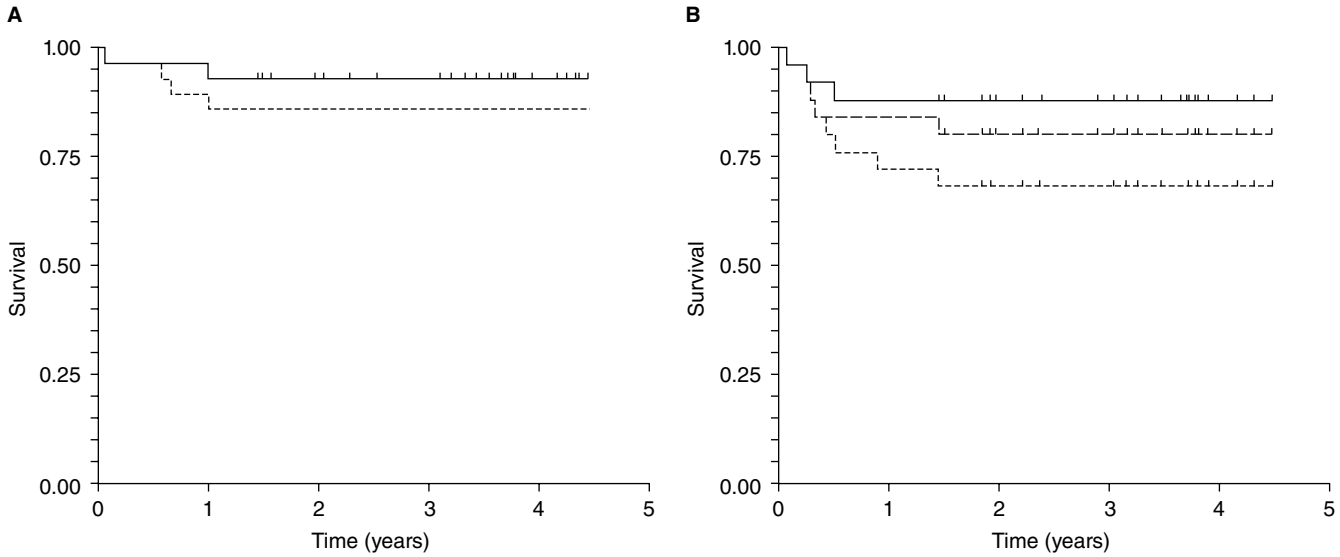


Figure 37.2 (A) Overall survival and progression-free survival after autologous transplantation for patients with negative positron emission tomography (PET) scan before stem cell transplantation (SCT). (B) Overall survival, event-free survival, and current progression-free survival (PFS; after immune manipulations) after allogeneic transplantation for patients with positive PET scan pre-SCT (Source: Thomson KJ *et al.* Leukemia. 2013;27(6):1419–22. Reproduced with permission of Nature Publishing Group.).

allogeneic transplantation. This low treatment-related mortality can be explained best by the relatively young age of the patients, their rather limited exposure to prior chemotherapies, and consequently their good performance score and limited comorbidities. Allogeneic transplantation was quite effective at controlling Hodgkin lymphoma. Although some patients relapsed after allogeneic transplantation, many responded to immune manipulations such as donor lymphocyte infusion and/or withdrawal of immune suppression (Figure 37.2).

4. What is the role of autologous transplantation in the era of escalated BEACOPP?

Escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone) is a more intensive chemotherapy regimen than ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and results in superior outcomes with initial treatment. It may therefore be expected that patients who relapse or are refractory to BEACOPP may be more difficult to salvage using autologous stem cell transplantation or that stem cell collection may be more difficult. Recent data compiled by a Swiss collaboration suggest, however, that autologous transplantation is feasible and effective. They described 22 patients with chemosensitive recurrences of HL after initial treatment with escalated BEACOPP. Two- and 5-year survival were 72% and 65%, respectively, which was not significantly different from that of patients who had received ABVD as initial treatment.

Escalated BEACOPP, although more effective than ABVD, also has more acute toxicity, effects on fertility, and risk for t-AML–MDS. Many patients and oncologists, particularly in the United States, are reluctant to use it. An Italian group compared patients receiving escalated BEACOPP to those receiving ABVD. Patients who did not achieve a complete remission went on to autologous stem cell transplantation after radiation. More patients in the ABVD arm required salvage therapy than those in the BEACOPP arm. However, as expected, the salvage was more effective in the ABVD arm (51% versus 35% in the BEACOPP arm). Ultimately, the OS of the two groups was similar because more patients could be salvaged after ABVD.

5. Should involved-field radiation therapy (IFRT) play a role either pre- or post-transplantation?

High-energy radiation therapy was the first curative therapy for Hodgkin lymphoma and continues to be a part of many successful treatment strategies. Occasional patients with late localized relapse can be cured with involved-field radiation and can avoid autologous transplantation. But what about the patient who presents with extensive recurrent disease and is to undergo autologous transplantation? Does he or she benefit from additional radiation treatment to the involved area? This is one of the most enduring unresolved questions in this area. Most studies of involved-field radiation as a component of high-dose therapy and stem cell transplantation in Hodgkin lymphoma have been

retrospective, small studies, and the results are controversial. Most studies show an improvement in local disease control, but none have convincingly demonstrated a benefit in overall long-term survival. The most recent study, from the University of Rochester, reported on 62 patients with Hodgkin disease who underwent autologous stem cell transplantation. Thirty-two with residual disease after salvage chemotherapy or bulky disease at relapse had IFRT after transplantation recovery but within the first 6 months post-transplantation. The median dose was 30.6 Gy (range: 6.0–44.2 Gy). A multivariate analysis failed to show an advantage for those receiving IFRT. The debate on the role of IFRT is likely to change in the near future as treatment decisions are increasingly affected by the results of PET scans.

6. Is there a role for allogeneic transplantation, and if so, when?

Early studies from Seattle and from Johns Hopkins in lymphoma patients showed that relapse rates after allogeneic transplantation were lower than those after autologous transplantation. Two studies with "genetic randomization" (i.e., based on donor vs. no donor comparison) confirmed this. There are several explanations for the decreased relapse rates after allo-transplantation. Graft-versus-lymphoma effects can contribute to lymphoma control as demonstrated by reports of lymphoma regression upon donor lymphocyte infusions (DLIs) or other immunologic manipulations. However, occult tumor contamination of the autologous graft could be responsible for some of the increased relapse rate after autologous transplantation, although this has not been formally demonstrated in Hodgkin lymphoma transplants. Allogeneic transplantation invariably has higher rates of treatment-related mortality than autologous transplantation. In some of the older studies, such toxicities were prohibitive, and allogeneic transplantation is therefore not routinely recommended.

Over the past decade, however, a body of literature has established a role for allogeneic transplantation, particularly for those who relapse after a prior autologous transplantation. Treatment-related mortality in this situation remains in the 20% range, but anywhere between 25% and 50% of patients obtain prolonged remissions. The most compelling evidence for the benefit of allogeneic transplantation in patients relapsing after autologous transplantation comes from an Italian study. They studied patients relapsing after autologous transplantation and for whom human leukocyte antigen (HLA) typing was performed. Of 185 patients, 122 had a donor and 63 did not. Clinical features of the two groups did not differ. Two-year PFS and OS were better in the donor group (39.3% vs. 14.2%, and 66% vs. 42%, respectively; $P < .001$) with a median follow-up of 48 months. In multivariable analysis, having a donor was significant for better PFS and OS ($P < .001$). The improvements in outcome of allogeneic transplantation over the past decade are usually attributed to the use of reduced-intensity conditioning (RIC), but it has been difficult to identify any specific conditioning regimen that is superior. It is likely that other factors such as patient selection, better donor selection, improved supportive care, and infection prophylaxis all have played a role in the steady improvement in results of allogeneic transplantation.

Although allogeneic transplantation is relatively more effective than autologous transplantation, patients with chemorefractory disease who do not exhibit any response to salvage therapy have still done consistently poorly, as do patients who relapse very early after autologous transplantation. In a study by the European Bone Marrow Transplantation Registry, patients with chemorefractory disease had a PFS of only 8% and an overall survival of only 25% compared with 42% and 56% for those patients who were still chemotherapy sensitive. Because of the high recurrence rates in such situations, there is an ongoing interest in developing more effective conditioning regimens. One such regimen consists of the addition of gemcitabine to fludarabine and melphalan, reported to have an 89% overall survival and 49% PFS at 2 years.

Graft-versus-host disease (GVHD), particularly extensive chronic GVHD, is a major cause of severe chronic morbidity, detriments in quality of life, and long-term survival. In an interesting approach, a British study attempted to decrease GVHD in RIC allo-transplants for HL using alemtuzumab as a method for T-cell depletion. Sixty-six patients underwent RIC transplants using fludarabine, melphalan, and alemtuzumab conditioning. Subsequently, 22 patients underwent DLI for mixed chimerism and 24 patients for relapse. Relapse was significantly higher in those patients who did not develop any GVHD (53% vs. 22% for those with no GVHD). Patients who received DLI often developed GVHD requiring immunosuppressive therapy (23% in those receiving DLI for mixed chimerism and 54% for those getting DLI for relapse). This strategy produced gratifying results. In those patients who underwent DLI for relapse, there was a 4-year OS of 59%, and even in those relapsed patients who did not receive DLI the OS at 4 years was 47%, better than many of the published studies, suggesting that the initial T-cell depletion was of benefit. The entire group of 76 patients had a 4-year OS of 64%. The 4-year current PFS was 59%, reflecting the salvage rate of DLI. This study confirms the concepts of T-cell depletion in decreasing transplantation-related mortality and of DLI to improve PFS and OS via a graft-versus-malignancy effect.

Because of these promising results, the same group has extended the use of allogeneic transplantation to patients who had partial responses to salvage therapy but residual

PET positivity. Earlier implementation of allogeneic transplantation, with minimal tumor burden and before the illness has affected the patient's health, resulted in excellent outcomes. In summary, allogeneic transplantation definitively has a role in the treatment of HL, particularly in those patients failing autologous transplantation, but also those with partial responses to salvage therapy. In that particular circumstance, treatment-related morbidity and mortality associated with allogeneic transplantation are much more modest than what is commonly reported in patients failing autologous transplantation.

We also favor stringent GVHD prophylaxis to avoid the detrimental effects of extensive chronic GVHD. Judicious use of DLI or targeted post-transplantation interventions with less risk for GVHD may further improve results.

7. What is changed with brentuximab? What is its role in maintenance? Is transplantation still necessary?

Brentuximab vedotin is a CD30-directed antibody chemotherapy conjugate that has been shown to be effective in treating relapsed and refractory Hodgkin lymphoma, even in those patients deemed too ill and refractory to undergo transplantation. The pivotal study in HL was conducted in patients who had progressed or relapsed after autologous transplantation. In that situation it has a 75% response rate, with a CR rate of 34% and a median duration of response of 6.7 months. For those who achieved CR, the median response duration was 20.5 months. Only about one-third of patients were subsequently consolidated with transplantation. Most relapsed again, but those with a CR confirmed by PET scan often had very prolonged responses, even if they did not get another transplant. As a matter of fact, the investigators were unable to show any difference in long-term outcome between those who did and those who did not undergo a subsequent transplant.

Does complete PET response to brentuximab then obviate the need for transplant consolidation? We believe not. Transplant consolidation for PET-negative patients is an established treatment with demonstrated cure rates and large numbers of patients who have been followed for decades. Prolonged remissions with brentuximab pertain to a very small number of patients who have been followed for relatively limited periods of time. As more experience accumulates, our recommendations may change, but currently we recommend transplant consolidation for patients who achieve CR to brentuximab.

The use of maintenance brentuximab post autologous transplantation in HL has been studied in a randomized study (the AETHERA study) that recently completed accrual, but the data have not been reported. If this study shows a benefit from maintenance brentuximab, it may further change the field.

Brentuximab may have additional roles in rendering patients candidates for autologous or allogeneic transplantation. Currently, patients with partial response to front-line therapy receive a variety of salvage regimens in order to induce remissions prior to transplantation. Achievement of complete response is associated with better outcome, and this leads to the adoption of complex and sometimes quite intensive chemotherapy regimens for poorly responsive patients. Brentuximab likely offers a better-tolerated and more effective alternative. A retrospective review of 17 patients who received brentuximab as a bridge to RIC allogeneic transplants showed that indeed it allowed patients the opportunity to have an allogeneic transplant with good results and that it did not interfere with engraftment or GVHD.

Last, for those patients who relapse after RIC allogeneic transplants, brentuximab has been used in combination with DLI in four patients with tumor response. Another study utilized brentuximab vedotin in 25 patients relapsing after allogeneic RIC transplant, with a 50% overall response rate and a 38% complete response rate, again durable. The median PFS was 7.8 months, and the median survival was not reached.

Brentuximab is probably the most effective single agent in HL and therefore is likely to be incorporated in front-line regimens in the near future. Patients referred for transplantation will likely already have been exposed to it. How this will affect our management of patients with recurrent HL and the role of transplantation is difficult to foresee.

Selected reading

Castagna L, Sarina B, Todisco E, *et al.* Allogeneic stem cell transplantation compared with chemotherapy for poor-risk Hodgkin lymphoma. Biol Blood Marrow Transplant. 2009;15: 432–8.

Holmberg L, Maloney DG. The role of autologous and allogeneic hematopoietic stem cell transplantation for Hodgkin lymphoma. J Natl Compr Canc Netw. 2011;9:1060–71.

Moskowitz CH, Matasar MJ, Zelenetz AD, *et al.* Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. Blood. 2012;119: 1665–70.

Sarina B, Castagna L, Farina L, *et al.* Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. Blood. 2010;115:3671–7.

Viviani S, Zinzani PL, Rambaldi A, *et al.* ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med. 2011;365:203–12.

PART 7

Non-Hodgkin's Lymphomas

CHAPTER 38

Pitfalls in the diagnosis of non-Hodgkin's lymphomas

Carmen Barcena and Laurence de Leval
University Hospital of Lausanne, Lausanne, Switzerland

Case study 38.1

A 57-year-old woman presented with acute abdominal pain and a 15 cm retroperitoneal mass. A needle biopsy (Figure 38.1) showed a dense diffuse proliferation of pleomorphic medium to large lymphoid cells with prominent nucleoli and irregular nuclei. Mitotic figures and apoptotic bodies were frequent, focally imparting a "starry sky" appearance. The cells were positive for CD20, PAX5, CD10, BCL2, BCL6, c-MYC, and MUM1, with a Ki67 labeling index up to 80%, and they were negative for cyclin D1 and CD138. Fluorescence in situ hybridization (FISH) analysis using break-apart (BA) revealed ***MYC*** and ***BCL2*** rearrangements.

1. What is the diagnosis?

A. Burkitt lymphoma (BL)
B. Diffuse large B-cell lymphoma (DLBCL)
C. B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLU-DLBCL/BL)
D. Mantle cell lymphoma, blastoid

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL

A subset of aggressive and high grade B-cell lymphomas that feature characteristics intermediate between those of DLBCL and BL are grouped together under the designation BCLU-DLBCL/BL, a category that was introduced in the 2008 World Health Organization (WHO) classification.

It is a highly aggressive disease that usually presents at high stage, and patients do poorly whether they are treated with intensive regimens used for BL or with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like regimens. Some cases morphologically resemble DLBCL, whereas others are reminiscent of BL or have an aberrant immunophenotype or genetic profile. In cases morphologically resembling BL (monotonous population of medium-sized lymphoid cells, with round nuclei, multiple nucleoli, and a scant amount of deeply basophilic vacuolized cytoplasm, numerous mitoses, apoptotic bodies, and tingible body macrophages conferring a starry-sky appearance), strong BCL2 staining and/or a Ki67 proliferation index of less than 90% are an absolute contraindication to the diagnosis of BL, and such cases should be placed in the BCLU-DLBCL/BL category.

Cases resembling DLBCL with a cell size smaller than expected and an immunophenotype resembling that of BL, with *C-MYC* translocation, should be classified as BCLU-DLBCL/BL. *MYC* translocation is common in BCLU-DLBCL/BL, occurring in approximately 35% to 50% of cases. In contrast to BL, it is often associated with a complex karyotype. Many, but not all, of the so-called double-hit B-cell lymphomas carrying both *MYC* and *BCL2* translocations fall within the BCLU-DLBCL/BL category. In contrast to BL, double-hit DLBCL/BL is BCL2+ and the proliferation index is high but usually lower than 95%. The aggressive and refractory nature of these tumors likely relates to their simultaneous expression of both pro-proliferative (MYC) and anti-apoptotic (BCL2) oncoproteins. Most cases with *MYC* translocations have high levels of nuclear staining for c-MYC by immunohistochemistry (greater than 70–80% of

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

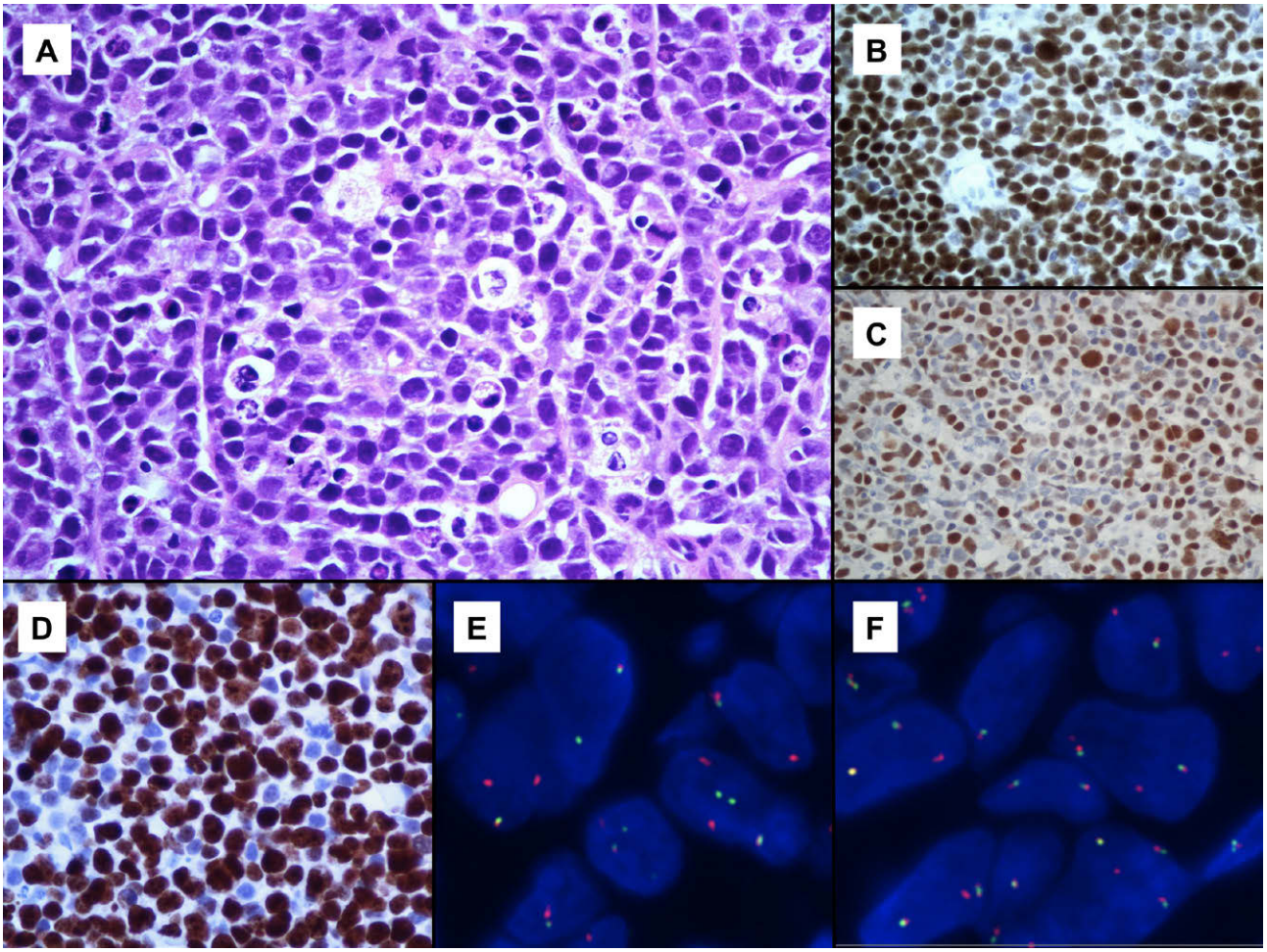


Figure 38.1 B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. Diffuse proliferation of medium- to large-sized cells with few associated small lymphocytes with starry sky macrophages, numerous mitoses, and prominent apoptosis (A). The lymphoma cells are PAX5+ (B), and most express c-MYC protein (C). The Ki67 proliferation index is estimated to be >90% (D). FISH with break-apart probes for *BCL2* (E) and *MYC* (F) show numerous split signals indicative of rearrangement of both genes. (Color plate 38.1)

the malignant cells positive), and this may be used as a screening test to determine which cases may require further genetic testing. The BCLU-DLBCL/BL group is not associated with Epstein–Barr virus (EBV) infection.

Burkitt lymphoma

BL comprises endemic, sporadic, and immunodeficiency-associated clinical variants, more commonly seen in children and young adults. BL has typical morphology (see above) and immunophenotypic features (BCL2− CD10+ BCL6+ Ki67 proliferation index close to 100%). Cytogenetically, nearly all cases harbor a translocation involving the *MYC* gene at the 8q24 locus, most commonly with the immunoglobulin heavy-chain (*IGH*) gene on 14q32 or, less frequently with *IGK* (2p12), *IGL* (22q11), which is often the only genetic aberration detected in the karyotype. The association with EBV is variable, in approximately 90% of endemic BL cases, 30% of sporadic BL, and 25–40% of immunodeficiency-associated cases. Accurate diagnosis and distinction from other aggressive B-cell lymphomas are crucial for proper clinical management, as BL requires more intensive chemotherapy.

Diffuse large B-cell lymphoma

DLBCL, defined as a diffuse proliferation of large lymphoid cells (centroblastic, immunoblastic, and/or anaplastic), is morphologically distinct from BL. The neoplastic cells express B-cell markers; are variably positive for BCL2, CD10, BCL6, MUM1, and c-MYC; and may co-express CD5; EBV infection may be present.

Importantly, *MYC* rearrangement is found in 7 to 14% of de novo DLBCLs, and it has been recently identified as a worse prognostic factor, predicting for a more aggressive disease, poorer response to therapy, and worse overall sur-

vival. DLBCL with *MYC* rearrangement does not have BL's genetic profile; instead, it is molecularly similar to DLBCL without *MYC* rearrangement. DLBCLs that are morphologically (large cells with frank pleomorphism) and immunophenotypically consistent with DLBCL but with *MYC* rearrangement should be diagnosed as such and not as BCLU-DLBCL/BL or BL.

Mantle cell lymphoma, blastoid variant

The blastoid variant of mantle cell lymphoma (MCL) enters in the differential diagnosis of high grade B-cell neoplasms. It is both immunophenotypically and genetically similar to classic MCL and is composed of a monotonous population of medium-sized lymphocytes with finely dispersed chromatin and absent or indistinct nucleoli, resembling lymphoblasts. Numerous mitoses and a "starry-sky pattern" may be seen. The immunophenotype is similar to that of classic MCL: expression of CD20, CD79a, and PAX5, usually with coexpression of CD5, SOX11, and CD43 and negativity for CD10, BCL6, and CD23. Most cases show overexpression of cyclin D1. However, aberrant phenotypes and genetics in MCL have been recently reported, including expression of BCL6 and/or CD10, negativity for CD5, and coexistence of *CCND1* and *MYC* rearrangements.

Case study 38.2

A 36-year-old female presented with shortness of breath, and imaging revealed a bulky anterior mediastinal mass. The biopsy (Figure 38.2) showed a diffuse infiltrate of large cells with round or lobulated nuclei and abundant clear cytoplasm, in a background of compartmentalizing sclerosis. Occasional cells had Hodgkin/Reed-Sternberg (HRS)-like features. The tumor cells were diffusely and intensely positive for CD20, PAX-5, and CD79a, with diffuse weak expression of CD30; strong expression of MUM1, BCL6, OCT2, and BOB1; and heterogeneous positivity for CD23. CD15 was negative. The Ki67 index was around 40%. In situ hybridization (ISH) with EBER (Epstein-Barr Early RNA) probes produced no staining. By staging, the disease was localized to the mediastinum (stage I).

1. What is the diagnosis?

A. Nodular sclerosis Hodgkin lymphoma
B. Diffuse large B-cell lymphoma
C. Primary mediastinal (thymic) large B-cell lymphoma
D. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Primary mediastinal (thymic) large B-cell lymphoma

The clinical, morphological, and immunohistochemical features are consistent with primary mediastinal large B-cell lymphoma (PMBCL), a distinct DLBCL entity arising in the mediastinum, thought to be derived from thymic B cells. PMLBCL tends to occur in young patients (median age about 35 years), and it affects women more commonly.

Patients often present with a bulky anterior mediastinal mass and symptoms related to impingement of local anatomic structures. The disease is usually localized at presentation, but progression can be characterized by dissemination to other extranodal sites, including lung, liver, kidneys, adrenals, ovaries, brain, and the gastrointestinal tract.

Histologically, PMBCL is a diffuse proliferation of medium to large cells. Particular (but not entirely specific) morphologic features include the presence of fine compartmentalizing sclerosis, the presence of cells with abundant clear cytoplasm and/or multilobated nuclei, and the presence of large cells with Reed-Sternberg-like morphology. The tumor cells express the B-cell-associated antigens CD19, CD20, and CD79a, but often lack surface immunoglobulin (Ig), despite expression of the IG-associated transcription factors BOB.1, Oct-2, and PU.1. Most cases express BCL6, MUM1/IRF4, BCL2, and CD23, and a variable proportion of cases also express CD30.

By gene expression profiling, PMLBCL has a molecular signature distinct from that of both germinal center-like (GCB) and activated (ABC) DLBCL, NOS, characterized by low levels of expression of multiple B-cell signaling components and co-receptors and high expression of cytokine pathway components, tumor necrosis factor (TNF) family members, and extracellular matrix elements. The PMBCL signature partly overlaps with that of Hodgkin lymphoma cell lines. Altered JAK–STAT signaling, manifested by constitutive activation of STAT5 and STAT6, represents another alteration common to both PMLBCL and cHL and may cause a defective suppressor of cytokine signaling.

The most frequent genetic abnormalities are gains in chromosomes 9p24 (including the *JAK2* locus) in up to 75% of cases, and gain of *REL* on chromosome 2p (50% of cases). Recently the MHC class II transactivator CIITA has been implicated in the pathogenesis of PMLBCL, as *CIITA* translocations, associated with the downregulation of surface human leukocyte antigen class II expression, are highly recurrent in PMLBCL (occurring in about 40% of the cases).

PBMCL versus classical Hodgkin lymphoma

PMBCL and classical Hodgkin lymphoma (cHL), especially nodular sclerosis type (NSHL), have overlapping features.

(*Continued*)

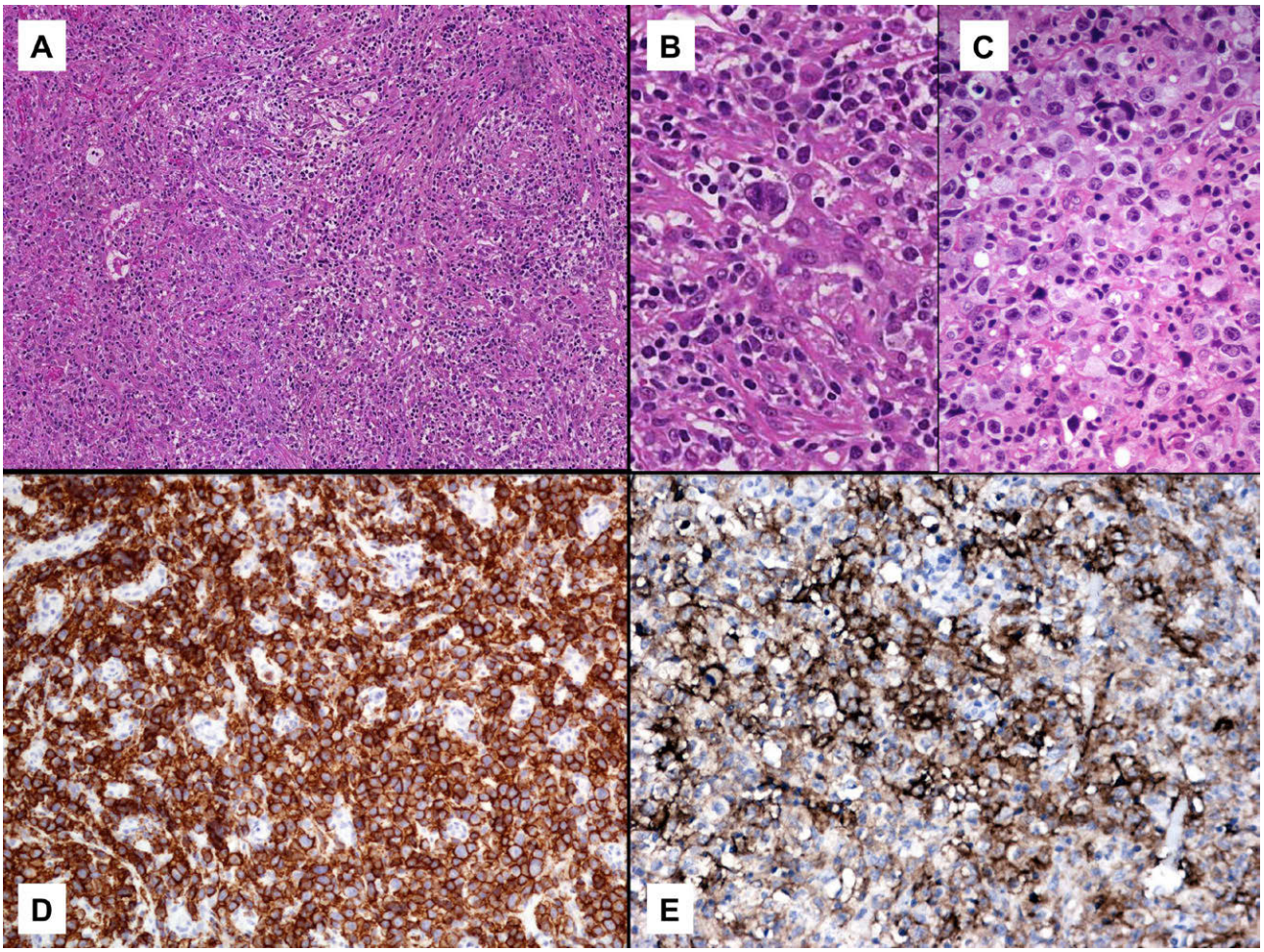


Figure 38.2 Primary mediastinal large B-cell lymphoma. Diffuse sheets of medium to large cells with abundant eosinophilic or pale cytoplasm admixed with cells with Reed-Sternberg-like appearance in a background of "compartmentalizing" sclerosis (A–C). The lymphoma cells are positive for CD20 (D) and show strong membrane staining for CD23 (E). (Color plate 38.2)

Both frequently present in young patients as mediastinal neoplasms with prominent fibrosis, HRS, or HRS-like cells. Making a correct diagnosis is important due to differences in management and prognosis. In PMBCL, large cells are often positive for CD30, but more weakly and heterogeneous than in NSHL. CD20 and PAX5 are strongly expressed in PMBL and are generally negative or weak in NSHL. In situ hybridization for EBV, when positive, strongly favors the diagnosis of cHL. There remain cases of B-cell mediastinal lymphomas that have features intermediate between those of PMBCL and cHL, and that cannot be classified despite thorough phenotyping and molecular studies. It is important to recognize these cases designed as "B-cell lymphoma unclassifiable with features intermediate between PMBCL and cHL" as they carry a more aggressive clinical course and a worse prognosis than both cHL and PMBCL. Cases categorized as such include those morphologically resembling NSHL but immunohistochemically consistent with PMBCL, and those morphologically suggestive of PMBCL but with an immunophenotype typical of cHL. Both strong expression of CD15 in a case otherwise interpreted as large B-cell lymphoma and, conversely, strong and diffuse expression of CD20 and other B-cell factors in a case morphologically suggestive of cHL (especially if rich in large neoplastic cells) qualify for categorization as unclassifiable lymphomas with intermediate features.

PBMCL versus DLBCL, NOS involving the mediastinum

This distinction cannot be made based on histopathological grounds only. Although PMBCL features distinct morphologic and immunohistochemical characteristics, none is entirely specific and clinical correlation is mandatory. Staging procedures must rule out secondary mediastinal involvement by a systemic DLBCL; extrathoracic lymph node or bone marrow involvement would favor the latter diagnosis. A molecular signature defined by gene expression profiling is able to distinguish between these entities, but this technique is not performed routinely.

Case study 38.3

Acute lymphoblastic leukemia and lymphoblastic lymphoma

A 14-year-old boy presented to the emergency room. Laboratory studies revealed anemia, thrombocytopenia, leukocytosis, and elevated lactate dehydrogenase. Imaging demonstrated a large anterior mediastinal mass. An excisional biopsy (Figure 38.3) showed a diffuse infiltrate of medium-sized lymphoid cells, with a high nuclear–cytoplasmic ratio, basophilic cytoplasm, and small nucleoli. The cells were positive for TdT, CD10, CD3, and CD5, and negative for CD20. Ki67 showed a high proliferation index (>80%).

1. What is the most likely diagnosis?

A. Thymoma
B. Thymic hyperplasia
C. Burkitt lymphoma
D. T-lymphoblastic leukemia/lymphoma

T-lymphoblastic leukemia/lymphoma

T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) frequently manifests with a large anterior mediastinal mass (50–75%) or with lymphadenopathy (50%). Bone marrow involvement is seen in approximately 60% of cases. Morphologically, T-ALL/LBL is characterized by a diffuse proliferation of lymphoblasts that are small to medium-sized cells with round, oval, or convoluted nuclei; dispersed chromatin; inconspicuous or small nucleoli; and scanty cytoplasm. Frequent mitoses, a starry-sky pattern, or necrosis may be seen.

Immunohistochemically, lymphoblasts are usually TdT+ (most specific marker) with a variable expression of CD1a and T-cell markers. CD4 and CD8 are usually coexpressed. CD10 may also be positive. In addition to TdT, other markers of immaturity are represented by CD99, CD34, and CD1a. Myeloid markers, such as CD13, CD33, may be expressed and do not exclude the diagnosis. CD117 may be positive. T-LBL almost always shows clonal rearrangements of the T-cell receptor (*TCR*) genes, but there may be concomitant clonal *IGH* gene rearrangement.

T-ALL and LBL versus lymphocytic-rich thymoma (type B1: thymoma)

Thymomas are the most common tumors of the anterior mediastinum. They typically consist of an encapsulated mass composed of a mixture of neoplastic epithelial cells and non-neoplastic immature thymocytes. B1 thymomas (lymphocyte-rich thymoma) can be difficult to differentiate from T-ALL/LBL. B1 thymomas mostly manifest in the adult life, whereas T-ALL/LBL occurs in adolescents and young adults. With adequate sampling and immunohistochemistry, the differential diagnosis is straightforward. However, thymocytes and malignant lymphoblasts are morphologically and immunohistochemically essentially indistinguishable owing to their early stage of differentiation.

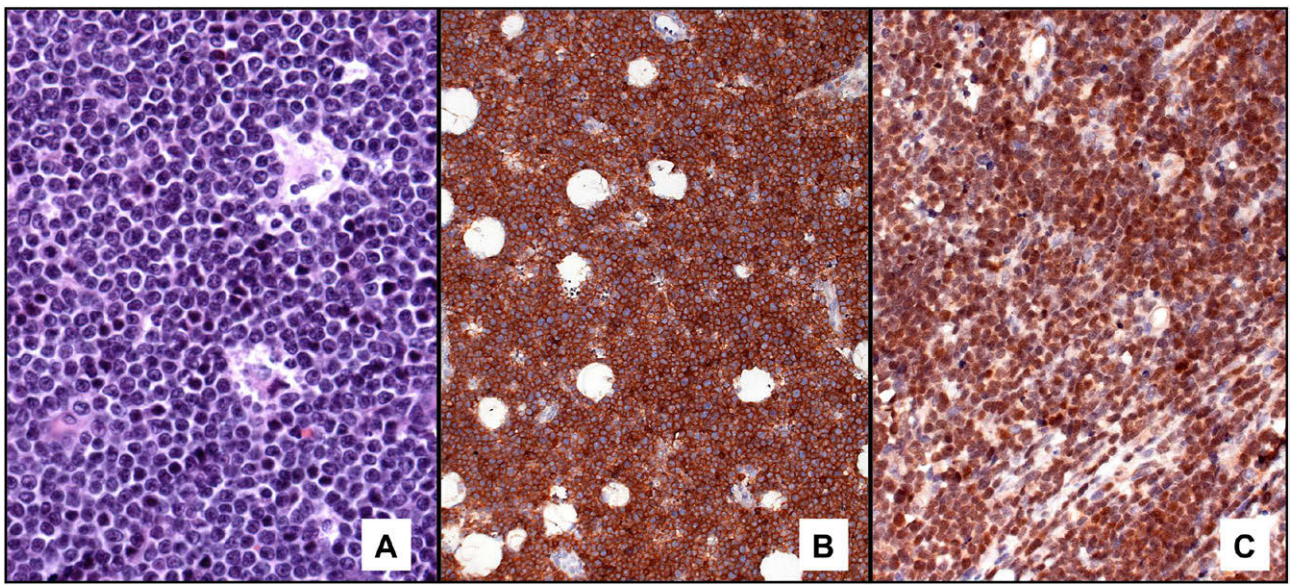


Figure 38.3 T lymphoblastic leukemia/lymphoma. Diffuse proliferation of medium-sized lymphoid blasts with macrophages imparting a starry-sky pattern (A). The lymphocytes are strongly and diffusely positive for CD5 (B) and TdT (C). (Color plate 38.3)

(*Continued*)

The infiltration of the thymic septa and capsule by lymphoblasts would favor a diagnosis of T-ALL/LBL. Conversely, an expansion of the epithelial meshwork is a feature of thymoma, not seen in T-ALL/LBL. Therefore, cytokeratins staining may help in the diagnosis highlighting the epithelial proliferation in B1-thymomas.

T-ALL and LBL versus thymic hyperplasia
Microscopically, thymic hyperplasia reveals lobulated normal-looking thymic tissue with a good demarcation between cortex and medulla and Hassall corpuscles.

T-ALL and LBL versus Burkitt lymphoma
Despite some morphologic overlap, the distinction of those entities is usually straightforward as BL comprises TdT-negative mature B cells, while T-ALL/LBL comprises TdT+ immature T-lymphoblasts.

Case study 38.4

A 16-year-old boy underwent excision of a persistent 2 cm submandibular adenopathy. Histologically (Figure 38.4), the architecture was partially effaced by numerous large, expansile, coalescent follicles composed of medium-sized centroblasts surrounded by a preserved or focally attenuated mantle zone. The follicular centers showed numerous mitosis, macrophages with apoptotic debris, and a starry sky pattern. CD20 and PAX5 stained the follicles and an interfollicular component of B cells. CD3, CD5, and CD43 stained the small T-cells in the background. No coexpression of CD5 or CD43 was detected in the B-cells. B-cells in the follicle centers were BCL2–BCL6+ CD10+ BCL2 with monotypic IgM+D+kappa expression and a high Ki67 proliferation index (close to 100%). CD21 stained a follicular dendritic meshwork in association with the follicles.

1. What is the diagnosis?

A. Pediatric follicular lymphoma
B. Marginal zonal lymphoma
C. Follicular lymphoma, conventional type
D. Reactive follicular hyperplasia

Pediatric follicular lymphoma
Pediatric follicular lymphoma (PFL) is a variant of follicular lymphoma (FL) that occurs in children, adolescents, and young adults and typically presents as a clonal follicular proliferation resulting in a localized adenopathy in the head and neck region or extranodal lesions such as the tonsil or the testis. The features that are distinct from those of conventional FL are large expansile or coalescent follicles, frequent medium-sized centroblasts within the neoplastic follicles, high Ki67 proliferation index, and lack of BCL2 protein expression or *IGH–BCL2* rearrangement. Similar to conventional FL, PFL usually expresses BCL6 and CD10 and may coexpress CD43. PFLs are also clinically distinct from adult-type follicular lymphoma in that they remain localized and are curable, even after excision alone in some cases. A subset of these cases, particularly those affecting Waldeyer's ring, express MUM1 protein and bear *IRF4* translocations; these cases are often associated with higher grade histology (grade 3B) and areas of diffuse large B-cell lymphoma, but are usually localized and also have excellent prognosis.

Pediatric follicular lymphoma versus "classical" follicular lymphoma
The distinction between "classical" follicular lymphoma (FL) and PFL is important because FL is considered an indolent but incurable disease, usually associated with recurrence after systemic chemotherapy. In contrast, although PFLs are usually of grade 3, they usually remain localized and curable. BCL2 immunostaining is often helpful in the differential diagnosis of PFL and FL, since the neoplastic follicles are typically BCL2-negative in PFL, and usually BCL2+ in FL. However, a subset of classical FL, especially of grade 3, lacks *BCL2* rearrangement and BCL2 expression.

Pediatric follicular lymphoma versus reactive follicular hyperplasia
More problematic is the differential diagnosis between PFL and reactive follicular hyperplasia (RFH) as both are more common in children and young adults and in both entities the follicular centers lack BCL2 expression. Morphologically, in RLH there is no architectural effacement as seen in PFL; the lymphoid follicles are large and irregularly shaped, often coalescent, but generally restricted to the cortex. The germinal centers are prominent and polarized, and the periphery is sharply demarcated by a mantle of small, mature lymphocytes. The cell population is not homogeneous and contains macrophages engulfing nuclear debris. Immunophenotyping is helpful in demonstrating polytypic B-cells and plasma cells in benign hyperplasia, and Ki67. Sometimes, the distinction between PFL and florid follicular hyperplasia with monotypic light-chain expression and clonal *IGH* gene rearrangement by polymerase chain reaction (PCR) can be extremely difficult. The starry-

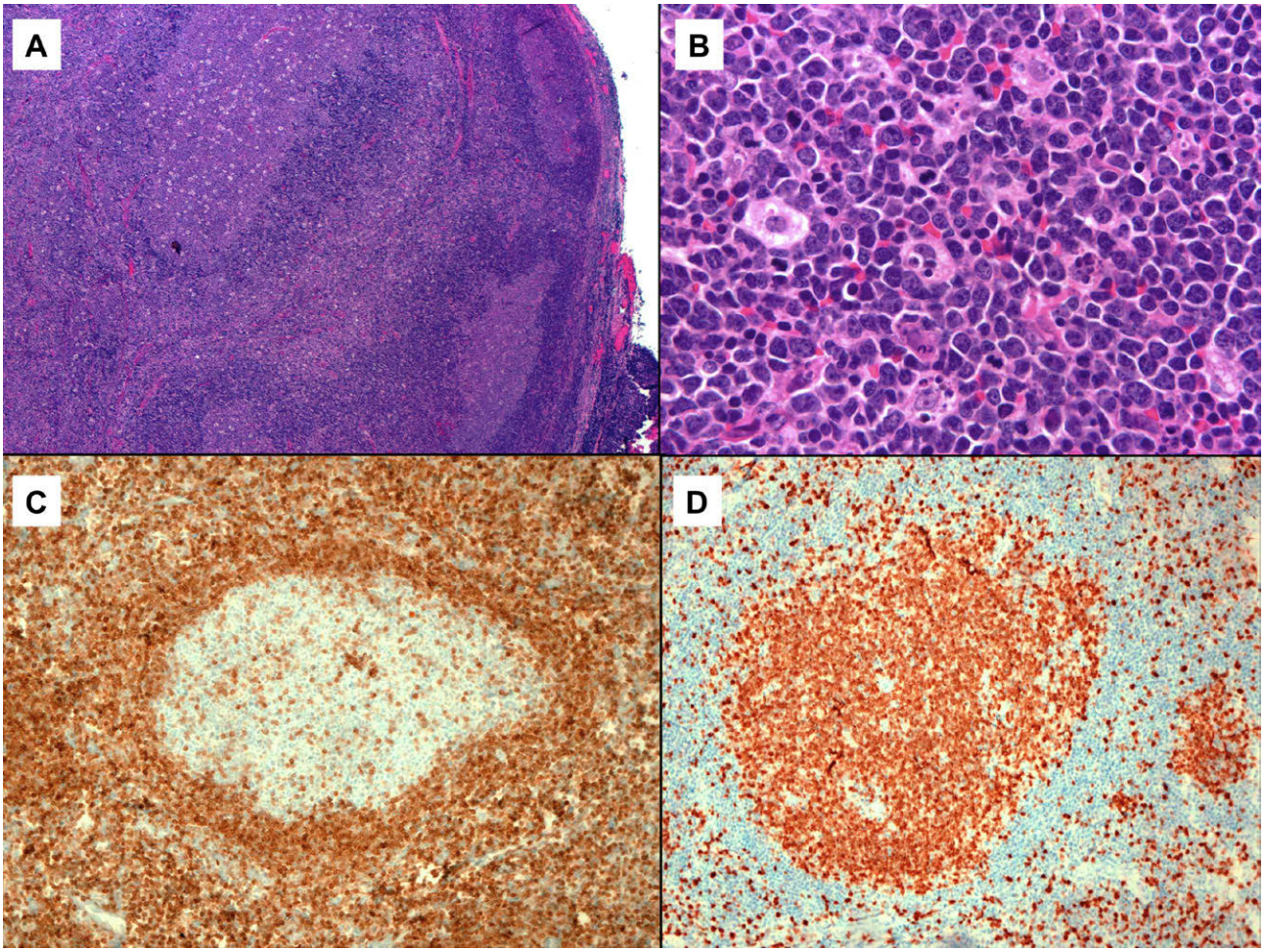


Figure 38.4 Pediatric follicular lymphoma. The lymph node comprises large, expansile, coalescent follicles (A) composed of medium-sized centroblasts and displaying a "starry-sky" pattern (B). The follicular B-cells are negative for BCL2 (C) and show a high Ki67 proliferation index (D). (Color plate 38.4)

sky appearance characteristically seen in nodal PFL cases further complicates the matter. In these situations, recognition of a monotonous, blastoid cytologic composition without polarization or typical centroblasts and centrocytes is helpful. PCR for detection of a clonal B-cell population appears to be a very sensitive test in PFL.

Pediatric follicular lymphoma versus pediatric nodal marginal zone lymphoma (PNMZL)

The distinction between PFL and PNMZL also can be problematic, owing to the overlapping features, as both are more frequent in young male patients, who present with localized disease with predilection of the head and neck region. However, characteristics seen in pediatric nodal MZL, such as expanded interfollicular areas by B-cells and progressive transformation of GCB changes, are usually absent in PFL. Immunophenotype and genetics in PNMZL are similar to those of its adult nodal counterpart.

Case study 38.5

A 79-year-old female presented with a right tonsillar mass. The biopsy (Figure 38.5) showed a lymphoepithelial tissue infiltrated by a vaguely nodular and partially diffuse monomorphic lymphoid proliferation composed of medium-sized cells with slightly irregular nuclear contours, fine chromatin, and inconspicuous nucleolus. The tumor cells were strongly and positive for CD20, CD5, SOX11, BCL2, CD30, p53, and p27, and weakly expressed CD43. The cells showed monotypic IgM kappa expression. They were negative for CD10, BCL6, CD23, and cyclin D1.

- **What is the diagnosis?**

Cyclin D1-negative mantle cell lymphoma (MCL).

Cyclin D1-negative mantle cell lymphoma

The general view of MCL is that of a genetically homogeneous B-cell lymphoma entity characterized by *CCND1* rearrangement, usually by the t (11;14) translocation, resulting in cyclin D1 overexpression. In recent years, several cases of "cyclin D1-negative MCL" have been documented. These cases show morphologic and molecular features indistinguishable from cyclin D1+ MCL, but they lack *CCND1* rearrangement and cyclin D1 expression and are otherwise similar to cyclin D1+ MCL in their genomic profile. The most frequent alternative genetic event in cyclin D1-negative MCL is the occurrence of *CCND2* translocations (55% cases) with consequent cyclin D2 overexpression. The diagnosis of cyclin D1-negative MCL has to be made with caution as many small B-cell lymphomas, such as marginal zone lymphomas, follicular lymphomas, and small lymphocytic lymphomas, may co-express CD5 and/or to some extent mimic MCL. The transcription factor SOX11 has been recently identified as a specific and highly reliable biomarker for MCL, including cyclin D1-negative MCL, as it is negative in other types of mature B-cell lymphomas. Clinically, it has been reported that cyclin D1-negative MCL patients presented extranodal disease more frequently than patients with cyclin D1+ MCL.

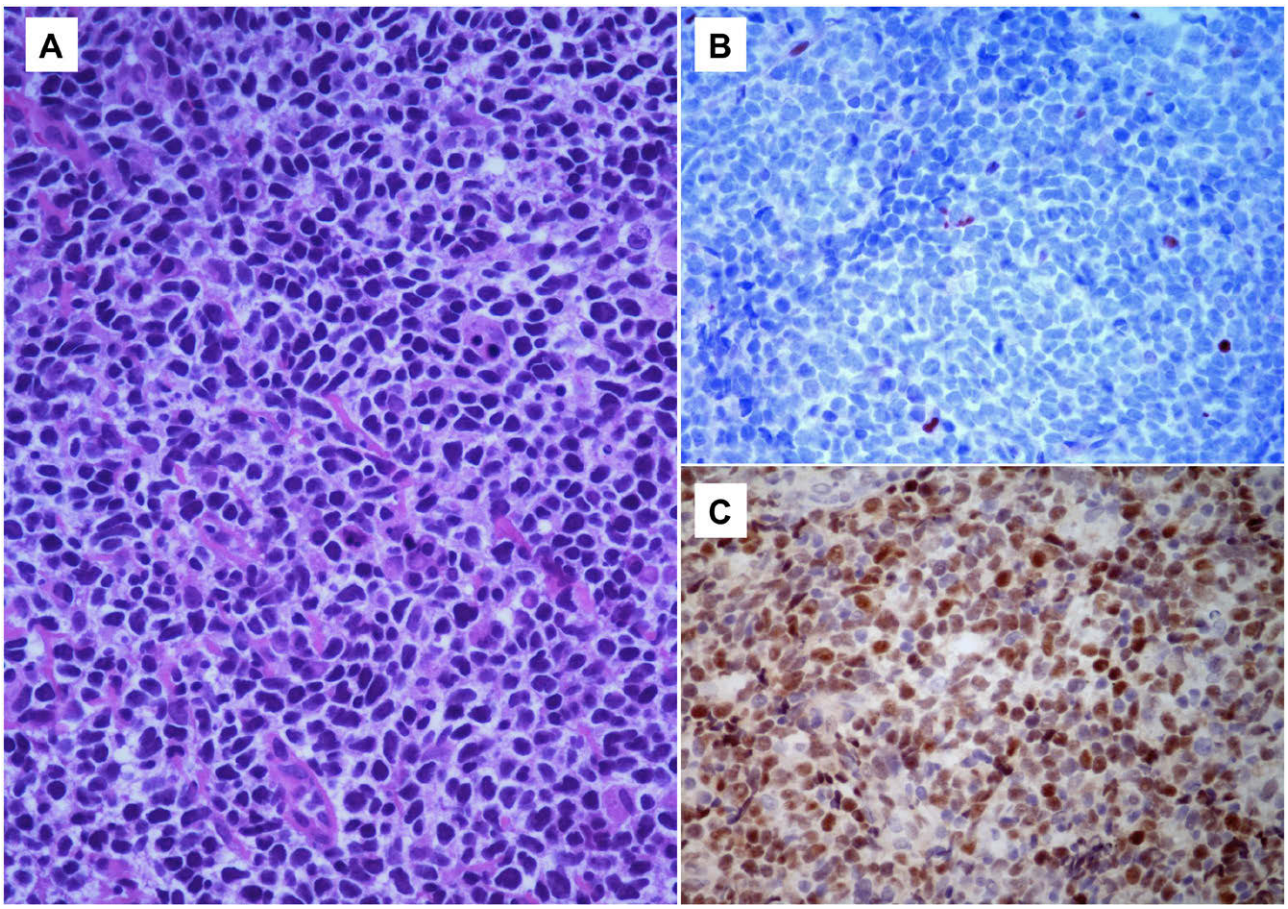


Figure 38.5 Cyclin D1 mantle cell lymphoma. Diffuse proliferation of small to medium-sized lymphoid cells with centrocytic-like morphology (A), which were positive for CD20 and PAX5 (not shown), negative for cyclin D1 (B), and positive for SOX11 (C). (Color plate 38.5)

Case study 38.6

A 33-year-old man with a previous history of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) underwent biopsy of a 2 cm right axillar lymphadenopathy (Figure 38.6). The lymph node showed complete architectural effacement with a mixed vaguely nodular and diffuse pattern. The lymphoproliferation mainly comprised small lymphocytes and histiocytes, admixed with scattered large atypical cells, with irregular contours, multilobated nuclei, pale chromatin, and prominent nucleoli. Confluent sheets of large atypical cells were not seen. No significant infiltrate of eosinophils or plasma cells observed. No follicular dendritic cell proliferation was demonstrated by immunohistochemistry. The large atypical cells were CD20+, BCL6+, CD10+, CD15−, CD30−, MUM1−, and EMA−; the small lymphocytes were mostly (CD3+ and CD5+) T-cells including numerous PD1+ cells, with a small subset of CD20 B cells. In situ hybridization for EBV was negative.

1. What is the diagnosis?

A. Classical Hodgkin lymphoma
B. T-cell histiocytic rich diffuse large B-cell lymphoma
C. Peripheral T-cell lymphoma
D. Nodular lymphocytic predominant Hodgkin lymphoma, diffuse

Nodular lymphocytic predominant Hodgkin lymphoma (NLPHL)

NLPHL accounts for approximately 5% of Hodgkin lymphomas and commonly presents with localized lymphadenopathy. The lymph node architecture is altered

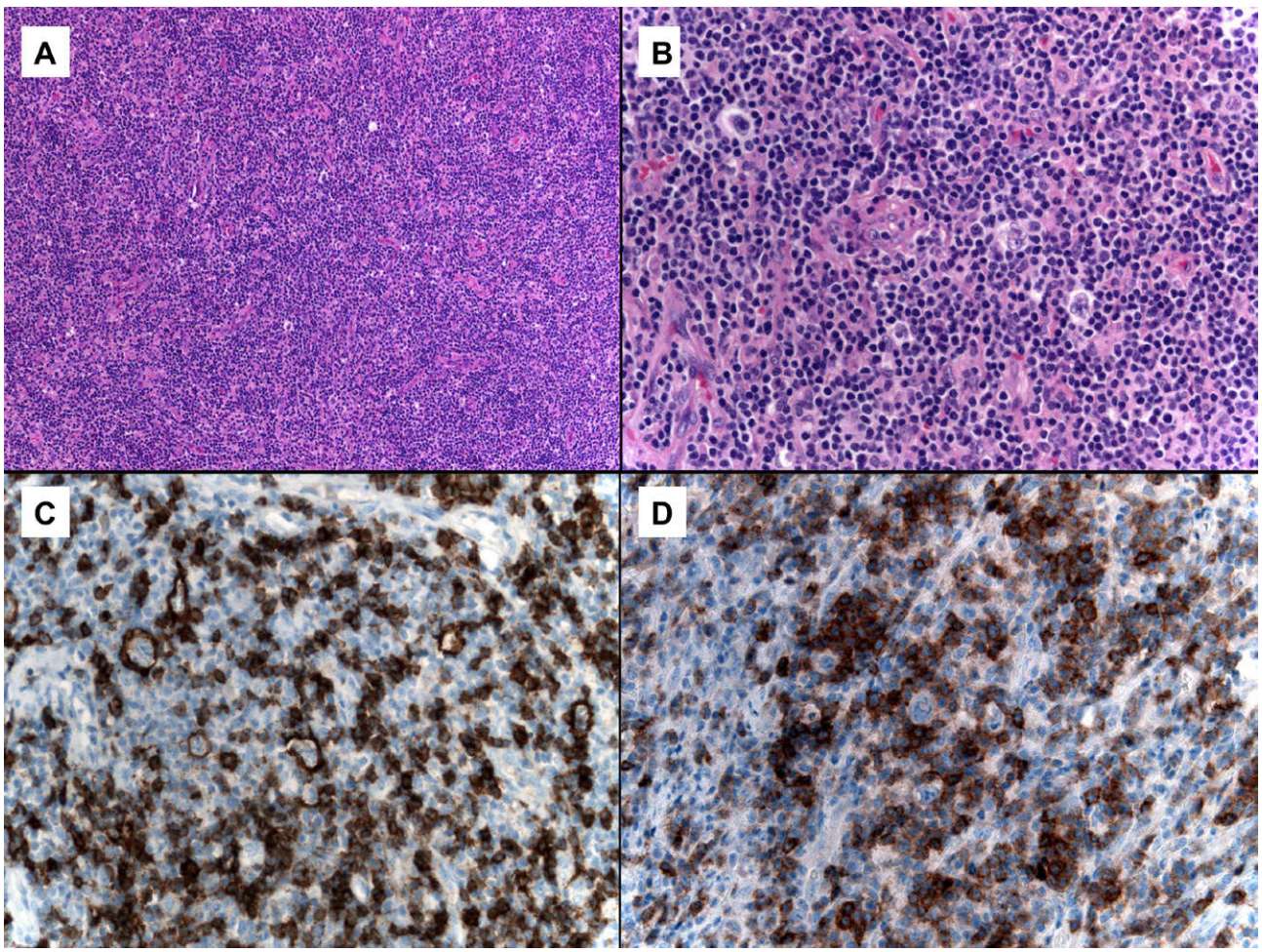


Figure 38.6 Nodular lymphocyte predominant Hodgkin lymphoma, diffuse pattern. At low magnification, there is a diffuse pattern with a predominance of lymphocytes (A). Diffuse lymphoid infiltrate comprising mostly small lymphocytes with scattered large lymphoid cells with lobated nuclei and moderately abundant cytoplasm (B). CD20 stains the large lymphoid cells and a subset of the small reactive lymphoid cells (C) Numerous PD1+ cells form rosettes around the large CD20+ lymphoid cells (D). (Color plate 38.6)

(*Continued*)

by a nodular or nodular +/− diffuse proliferation of a few large neoplastic cells called lymphocyte-predominant (LP) cells or "popcorn" cells embedded in a background of numerous small lymphocytes, histiocytes, and follicular dendritic cells. LP cells are positive for CD20, PAX5, CD79a, CD45, BCL6, OCT2, BOB1, CD45, BCL6, MUM1, and EMA, and are generally negative for both CD30 and CD15. At recurrence or with progression, there is often transition toward a more diffuse pattern.

NLPHL with large diffuse areas versus T-cell and histiocytic-rich DLBCL (THRLBCL)

The distinction between those two entities can be very problematic, but is crucial as they have distinctive clinical courses—THRLBCL is an aggressive neoplasm, while NLPHL is usually relatively indolent—and require different therapies.

In both diseases, the neoplastic cells are large B cells that exhibit overlapping morphologic, immunophenotypic, and molecular genetic features. The main distinctive features are (i) the architecture of the lymphoid proliferation and (ii) the nature of the associated background. THRLBCL is diffuse and lacks a follicular dendritic cell meshwork by CD21 or CD35 staining, whereas NLPHL manifests at least partially a nodular pattern in association with follicular dendritic cells. The difficulty lies in the recognition of those rare cases of NLPHL that are predominantly diffuse, in which case deeper sections will often reveal typical nodular structures comprising large tumor cells. Regarding the reactive cellular background, morphology alone is not discriminant as in both entities it comprises mostly small lymphocytes and a variable proportion of histiocytes that may form clusters or microgranulomas. Immunohistochemistry shows a T-cell-rich background with few CD57-positive cells and scant B cells in THRLBCL, versus a B-cell-rich background with many CD57-positive cells in NLPHL. Rosetting of T-cells expressing follicular T-cell markers (CD57+ or PD1+) around neoplastic cells is not seen in THRLBCL and is common in NLPHL. Importantly, although the presence of reactive small B-cells is a defining feature of NLPHL, the small B-cell population may be obscured by abundant reactive T-cells.

Although it has been suggested that NLPHL may transform into the more aggressive THRLBCL, currently it is recommended that the diagnosis of THRLBCL should be restricted to de novo cases only, and not applied in patients with a previous history of NLPHL.

NLPHL versus classical Hodgkin's lymphoma

NLPHL must be distinguished from classical Hodgkin lymphoma (cHL), especially the lymphocyte-rich types. By immunohistochemistry, the neoplastic cells of NLPHL are typically CD45+, CD20+, and CD79a+; although they may express CD30, they are negative for CD15. Conversely, the RS cells of cHL are always CD30+, often CD15+, negative for CD45, and, when CD20+, usually express the antigen heterogeneously and fail to express CD79a. EMA is often detected in the neoplastic cells of THRLBCL and is never present in cHL. EBV may be detected in the neoplastic cells of cHL, whereas it is generally negative in NLPHL.

Case study answers

Case study 38.1

Question 1: Answer: C

Case study 38.2

Question 1: Answer: C

Case study 38.3

Question 1: Answer: D

Case study 38.4

Question 1: Answer: A

Case study 38.6

Question 1: Answer: D

Selected reading

Campo E, Swerdlow SH, Harris NL, *et al.* The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117:5019–32.

Harris NL. Shades of gray between large B-cell lymphomas and Hodgkin lymphomas: differential diagnosis and biological implications. Modern Pathol. 2013;26:S57–70.

Jaffe ES, Harris NL, Stein H, *et al.* Classification of lymphoid neoplasms: the microscope as a discovery tool. Blood. 2008;112:4384–99.

Isaacson PG. Haematopathology practice: the commonest problems encountered in a consultation practice. Histopathology. 2007;50:821–34.

Slack GW, Gascoyne RD. MYC and aggressive B-cell lymphomas. Adv Anat Pathol. 2011;18:219–26.

CHAPTER 39

Follicular lymphoma

Myron S. Czuczman
Roswell Park Cancer Institute, Buffalo, NY, USA

Case study 39.1

A 75-year-old retired schoolteacher notes an increase in some nontender bilateral neck lymph nodes (LNs) (the largest are now in the 3 cm range), which he first recalls noticing ~1 year ago. Otherwise, he feels well overall. During an annual visit to his primary care physician, he describes the neck adenopathy. When his preferred medical doctor (PMD) notes no change in adenopathy after a 10-day course of oral antibiotics, he is suspicious that his patient may have low-grade lymphoma (note: the patient is a nonsmoker and denies alcohol use), and he is referred for surgical consultation.

1. Which of the following choices regarding LN biopsy techniques is the best in order to make a definitive diagnosis for suspected indolent lymphoma?

A. Fine needle aspiration
B. Core biopsy
C. Excisional or incisional biopsy
D. Any of the above biopsy techniques—they are all equivalent

Optimally, excision of an enlarged LN is necessary to make a histologic diagnosis of indolent lymphoma (i.e., follicular histology (FL) being the most common histology) by a hematopathologist. A fine needle aspirate is *not* adequate and does not permit the pathologist to "grade" the FL (e.g., grade 1, 2, 3a, or 3b) because that requires an evaluation of LN architecture. A needle core biopsy may consist predominately of the diffuse or the interfollicular component of FL and result in an inaccurate diagnosis. An excisional or incisional biopsy provides adequate material for flow cytometry, immunohistochemistry, and molecular studies, but it also can rule out the possibility of large-cell transformation in the biopsy material. An accurate histopathologic diagnosis of lymphoma subtype by a hematopathologist on an adequate tumor biopsy strongly contributes to the therapy prescribed by the oncologist.

Case study 39.2

A 69-year-old woman has had an excisional biopsy of an enlarged axillary node that was performed to evaluate extensive nonbulky LA, and the pathology reveals FL, grade 2.

1. Which of the following tests is not part of the current recommendations for the initial work-up of a patient with FL (following a full history and physical)?

A. Routine bloodwork, which includes a complete blood count (CBC), a full comprehensive metabolic profile (plus uric acid and lactate dehydrogenase (LDH)), and beta-2 microglobulin
B. Virological testing for hepatitis B and C
C. Unilateral bone marrow aspiration and biopsy
D. Computed tomography (CT) scans of neck, chest, abdomen, and pelvis (with oral and IV contrast, unless contraindicated)
E. Whole-body fluoro-deoxyglucose positron emission tomography (FDG-PET) scan

All of the above, except whole-body FDG-PET scan, should be part of the "current" routine assessment of FL based on review of the literature. FL is an FDG-avid disease (i.e., ~90% of FL patients have PET-positive disease, and the sensitivity of PET scans is in the 95%+ range). Two recently

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

published studies (i.e., Trotman (retrospective) and Dupuis (prospective)) show that posttreatment FDG-PET scans in high-tumor-burden FL patients treated with primarily rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improve the accuracy of response assessment and appear to be better than conventional methods in predicting progression-free survival (PFS) and possibly overall survival (OS). The effect of different induction therapies and/or maintenance therapy on posttreatment PET scans is unknown. Although very promising, the routine use of FDG-PET needs further validation before it will be added to the routine staging of FL as part of the revised international working criteria (IWC).

2. True or false? FL patients (grade 1, 2, or 3a) with stage I or II disease receiving involved-field radiation therapy (IFRT) may achieve excellent outcomes and maybe even be cured.

A. True
B. False

FL is a highly radiosensitive disease. Up to 25% of FL patients present with clinical stage I or II disease. Most of the data on the impact of IFRT in early-stage FL come from retrospective analyses and demonstrate 10-year OS rates in the range of 60–80% and a median survival of ~20 years. Relapse after 10 years is uncommon. Risk factors associated with relapse in these patients include elevated LDH, age >60, and size of lymph nodes (>3 cm and >5 cm). Relapse following IFRT is usually outside of the radiation field. In an attempt to identify "true" early-stage FL patients who would theoretically be optimal candidates for IFRT, the clinician should fully stage the patient, including consideration of molecular testing (e.g., polymerase chain reaction (PCR) assay for t(14:18) chromosomal rearrangement and/or immunoglobulin gene rearrangement) of blood and bone marrow for occult disease and also a whole-body FDG-PET scan to assess for additional disease not identified by CT scans. The last two tests would be able to identify patients with more extensive disease who either would not be optimal candidates for IFRT alone and/or could theoretically benefit from the addition of systemic therapy (e.g., rituximab +/− chemotherapy). In these patients with disease localized to abdominal and pelvic areas at risk for significant post-RT morbidity, then observation or systemic therapy is reasonable alternatives.

Case study 39.3

A 62-year-old policeman was referred to a local hematologist-oncologist for work-up of FL, grade 1, which was found on biopsy of one of several 1–2 cm enlarged left cervical nodes. Staging work-up was consistent with asymptomatic stage IIIA (low-tumor-burden) disease.

1. Which of the following therapeutic approaches would you choose at this time?

A. Watchful waiting (WW)
B. Rituximab induction
C. Rituximab induction + 2 years of maintenance rituximab (MR)
D. Rituximab-chemotherapy combination immunochemotherapy
E. Either A or B

In general, "low"-tumor-burden patients are those who do *not* meet the definitions of patients who "require therapy" that have been previously published in the pre-rituximab era by various lymphoma study groups (i.e., the British National Lymphoma Investigation and Group d'Etude des Lymphomes Folliculaires (GELF); see Table 39.1). In addition, low-tumor-burden patients should have serum LDH and serum beta-2 microglobulin levels below the upper normal values and no significant impairment of performance status associated with their lymphoma diagnosis.

In the pre-rituximab era, randomized controlled trials evaluated WW to initial therapy with oral alkylating agent, interferon alpha 2b (IFNα-2b), or ProMACE-MOPP (prednisone (oral), methotrexate, adriamycin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine). There was no evidence of improved OS in the immediate treatment arms compared to WW.

In addition, deferring initial toxic chemotherapy could be supported by the following: systemic therapy-associated side effects would negatively impact the patient's quality of life (QOL) and/or early intervention with toxic chemotherapy might impact negatively on bone marrow reserve and the ability to tolerate future treatment at relapse or transformation.

In the rituximab era, WW versus single-agent rituximab in asymptomatic nonbulky FL patients was studied by Ardeshna *et al.* (2012) in 463 patients randomized to one of three arms: A, watch and wait ($n = 187$); B, rituximab (four weekly infusions) induction ($n = 84$; closed early); and C, rituximab induction + 2-year maintenance ($n = 192$). Primary endpoint was time to initiation of new therapy. Three years after randomization, ~50% of WW patients had

Table 39.1 Criteria consistent with high tumor burden requiring therapy.

British National Lymphoma Investigation criteria
• Presence of B-symptoms or pruritis
• Rapid generalized disease progression (within 3 months)
• Significant bone marrow (BM) involvement with BM compromise
• Localized bone lesions
• Renal infiltration (even with normal renal function)
• Macroscopic liver involvement
Group d'Etude des Lymphomes Folliculaires criteria
• Presence of B-symptoms
• Involvement of >3 nodal sites, each with a diameter >3 cm
• Nodal or extranodal mass >7 cm diameter
• Risk of vital organ compression
• Cytopenias (Hgb <10 g/dL, ANC <1.5 × 10^9/L, and platelets <100 × 10^9/L)
• Serous effusions (pleural effusion or peritoneal ascites)
• Splenomegaly (>16 cm on CT scan) or symptomatic splenic enlargement
• Leukemic phase (>5.0 × 10^9/L malignant cells)

ANC, absolute neutrophil count; CT, computed tomography; Hgb, hemoglobin.

not received further therapy, whereas 80% of patients in the rituximab induction arm and 91% of patients in the rituximab induction + maintenance arm had not initiated new therapy. No difference in OS was seen between the three arms (i.e., 95% of patients alive at 3 years). There were some benefits associated with immediate rituximab therapy (i.e., improved DFS, longer time to first chemotherapy, and less anxiety in a subset of patients) compared to WW. The RESORT (E4402) trial should also be mentioned here. Of the 384 low-tumor-bulk FL patients enrolled on the RESORT trial, 274 (71%) responded to rituximab (R) induction (i.e., four weekly infusions) and were then randomized to rituximab retreatment (RR: $n = 134$) versus maintenance rituximab (MR: $n = 140$). With a median follow-up of 3.8 years: (i) RR was as effective as MR for "time to treatment failure," (ii) MR was slightly better than RR for "time to first chemotherapy," and (iii) MR patients received (on average) 3.5 times more rituximab than RR patients. Thus, it could be concluded that RR is preferable to MR if single-agent rituximab is used to treat low-tumor-burden FL patients. Currently, no information is available on whether there exists any difference in sensitivity to subsequent "R-chemotherapy" between the RR versus MR arms. It should be noted that single-agent rituximab given weekly 4× in previously untreated FL patients can result in long-term remission durations in a significant subset of patients.

Based on the above discussion, E would be the best answer. With the advent of a number of targeted therapeutic agents with excellent therapeutic indices, it will be very interesting to see how the incorporation of these novel agents will change treatment paradigms and the future treatment approach of FL (including asymptomatic, low-tumor-burden patients).

Case study 39.4

A 58-year-old businessman sees his PMD to evaluate increasing easy fatiguing for the past 5 months, along with decreased appetite, a 20-lb weight loss (baseline weight is 185 lbs) and abdominal bloating. His past medical history is unremarkable. He is found to have abdominal distension, palpable splenomegaly, and slightly enlarged bilateral inguinal lymphadenopathy (LA). Body CT scans were obtained and demonstrate diffuse LA (at least five nodes are >4 cm) and splenomegaly (i.e., 18 cm in cranio-caudal measurement). CBC with differential is within normal limits, and chemistry labs show that both LDH and uric acid are within the normal range. The patient undergoes a laparoscopic excisional biopsy of a 4 cm mesenteric LN, which comes back as FL, grade 1–2. He is referred to a local oncologist for definitive therapy; bone marrow studies demonstrate 10% lymphomatous involvement, and his beta-2 microglobulin level is above normal.

1. Which induction therapy choice would you choose from the list below (choose the "best" answer)?

A. R-CHOP
B. Rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP)
C. R-fludarabine + mitoxantrone (R-FM)
D. R-bendamustine (BR)
E. Either A or D

This patient has symptomatic, high-tumor-burden (see Table 39.1, Question 4) FL, grade 1–2, on presentation and has "intermediate"-risk disease on both the FLIPI and FLIPI2 prognostic scoring systems. Federico *et al.* (2012) presented the final results of the FOLL05 Italian trial at ASCO 2012. This trial randomized a homogenous FL population into one of three induction R-chemotherapy arms: (i) R-CVP, (ii) R-CHOP, or (iii) R-FM. Conclusions from this trial were as

(*Continued*)

follows: (i) R-CVP was associated with an inferior 3-year time-to-treatment failure (TTF) and PFS compared to R-CHOP and R-FM, (ii) R-FM was associated with a higher rate of adverse events (including secondary tumors) compared with the other two regimens, and (iii) OS was similar among study arms. Indirect data from the nonrandomized PRIMA study or North American Lymphocare study have demonstrated that the R-CHOP regimen may be associated with prolonged survival in patients with adverse features (e.g., high-risk FLIPI scores).

Rummel *et al*. (2009) have presented data from a phase III German Stil NHL1 multicenter study comparing induction R-CHOP to R-bendamustine in abstract form (the final update was at the ASCO 2012 annual meeting); $n = 513$ patients: ~1/2 had FL (*only* grade 1 or 2 histology!), and the remaining patients had non-FL indolent lymphoma or mantle cell lymphoma. Final conclusions were that BR demonstrates a PFS benefit (no OS benefit) and improved tolerability compared with R-CHOP. Some investigators have pointed out that the results obtained with R-CHOP in this trial appear inferior to R-CHOP data from other studies. At the ASH 2012 annual meeting, results from the Bright study (an international randomized study of BR versus R-CVP or R-CHOP (determined by the investigator prior to randomization), with the primary objective to demonstrate a non-inferiority of the CR rate by BR to R-CVP and R-CHOP) were presented. Overall, BR produces a CR rate that is non-inferior to R-CHOP and R-CVP in indolent lymphoma (note: data from the FL subset are not presented separately); adverse events, including dose delays in 35% of BR-treated patients, appear to be significantly higher for BR patients in this trial as compared to those described in the StiL trial.

Thus, although it appears that current data suggest that BR is non-inferior to R-CHOP and "less" toxic, I feel that longer follow-up, peer-reviewed publication of the Bright study, and additional confirmative studies are needed before BR should be the preferred choice over R-CHOP in FL (grades 1 and 2) patients in all cases. One last point: the healthy 58-year-old patient above may demonstrate refractory disease and need to be considered for autologous stem cell transplant; in general, R-CHOP is not associated with prolonged marrow suppression, but a comprehensive evaluation of the risk of BR-associated marrow suppression in a large number of patients has not yet been evaluated or published in peer-reviewed format.

2. For this same case, change the biopsy results to FL, grade 3. Which of the following induction therapy choices would you select?

A. R-CHOP
B. R-CVP
C. FCR
D. BR
E. Either A or D

FL, grade 3 histologies (i.e., 3a or 3b), have historically been designated as follicular large-cell lymphoma. FL, grade 3b, should be considered an aggressive histology with presentation, behavior, and outcomes resembling those of diffuse large B-cell lymphoma. As such, FL, grade 3b, should be treated with anthracycline-based R-chemotherapy (e.g., R-CHOP). Unless reviewed by an experienced hematopathologist, the clear designation between FL, grade 3a, versus 3b may be difficult for several reasons: the histological identification of centroblasts may not be clear, counting the number of centroblasts in a high-power field in 10 follicles is not easily reproducible, and small specimens (e.g., core biopsy) may not be completely representative of the FL subtype. Therefore, remembering that the StiL trial only included FL, grade 1 and 2 patients, those patients with FL, grade 3 (unless 3a is confirmed by an expert hematopathologist), should receive an anthracycline-containing R-chemo regimen (e.g., R-CHOP).

3. Should every FL patient receive maintenance rituximab (MR) following R-chemotherapy induction?

A. Yes
B. No

FL is a very heterogeneous disease in which treatment options range from prolonged WW up to allogeneic stem cell transplantation. Significant variability is seen in tumor and host characteristics, and therefore it is somewhat naïve to believe that one approach (i.e., MR) should be incorporated for all FL patients following R-chemotherapy. The Primary Rituximab and Maintenance (PRIMA) phase III study in 1018 previously untreated "high-tumor-burden" FL patients evaluated the impact of 2 years of MR compared to observation following a response to R-chemotherapy (i.e., R-CHOP, R-CVP, or R-FCM). Although it is clear that 2 years of MR after an objective response to R-chemotherapy induction improves PFS, it is not clear that this should be the "gold" standard practice that should be utilized by all oncologists treating FL. Why is this the case?

i. No OS difference between both groups.
ii. Although there was a higher "progression" rate seen in the observation group, it is unclear what percentage was only picked up radiographically (CT scans every 6 months ×5 years) and was clinically insignificant (i.e., not requiring therapy).
iii. PFS curves in both arms have dropped at approximately the same rate between 2 years and 3 years post induction: there were no plateau and a continuous relapse rate in both arms.
iv. A significantly higher percentage of patients had grade 3 and 4 adverse events and infections in the MR group.
v. Current results do not inform us about possible differences on "responsiveness" to subsequent therapy between the two arms.

vi. Must balance the benefits and risks (e.g., rituximab resistance or prolonged B-cell depletion) and financial "costs" between arms.
vii. Extrapolated from RESORT trial results (discussed earlier), it may be speculated that 2 years of obligatory RM may be excessive and that rituximab retreatment at the time of documented progression may give similar "time to next chemotherapy treatment" results.
viii. It is likely that the incorporation of novel targeted agents (e.g., different antibodies, antibody-drug conjugates, immunomodulatory drugs (IMiDs), BTK inhibitors, PI3K inhibitors, radioimmunotherapy, bcl-2 inhibitors, etc.) into current therapy as part of induction therapy or as a short course of "consolidation" utilizing non-cross-resistant agents not used in the induction regimen may see MR becoming obsolete in the near future.

The EORTC 20981 phase III trial described a PFS benefit of MR in relapsed and resistant FL patients following either CHOP or R-CHOP. However, this FL patient population had a "maximum of two non-anthracycline-containing chemotherapy regimens" as part of the inclusion criteria, and they were excluded if they had received prior rituximab. This population is significantly different from the current "rituximab era" FL population (i.e., upfront R-chemotherapy + MR in a significant percentage of patients), and there are no data demonstrating that the use of MR after each R-chemotherapy induction and re-induction course is beneficial.

Case study 39.5

A 62-year-old hospital administrator was diagnosed with stage IIIA FL, grade 2, 4 years ago, and he achieved a CR following six cycles of R-CHOP. One month ago, he noticed enlarged (~2 cm) lymph nodes in his cervical and axillary regions and some easy fatiguing. Following full staging evaluation and excisional lymph node biopsy, the patient was found to have stage IVA FL, grade 1, and anemia (hemoglobin: 9.7), along with a poor-risk FLIPI score.

1. Which of the following factors should be considered before choosing second-line therapy?

A. Age and comorbidities
B Disease-associated symptoms
C. Stage and grade of FL
D. Prognostic factors
E. Prior therapy and duration of response
F. All of the above

When patients present with relapsed FL that requires therapy, they have a relatively long list of options, ranging from rituximab alone to R-chemotherapy (usually a different regimen than that used as initial induction), radioimmunotherapy, autologous or allogeneic stem cell transplantation, or participation in an ever-growing list of clinical trials. Whatever second-line therapy is chosen, it will require an assessment of all the above-mentioned factors in order to preserve quality of life while attempting to optimize OS.

2. Several novel "targeted" therapies are demonstrating exciting early activity in FL and include (oral) small molecules that inhibit and moderate which of the following? (Choose all that apply.)

A. B-cell receptor (BCR) signaling pathway
B. BCL-2
C. Tumor microenvironment
D. All of the above
E. None of the above

Although it is beyond the scope of this chapter to describe the increasingly growing list of exciting antilymphoma agents in preclinical and clinical trials, oral agents targeting the BCR signaling pathway, BCL-2 anti-apoptotic protein, and the tumor microenvironment are among the most exciting newcomers on the lymphoma therapeutic scene. Inhibitors of kinases active in the B-cell receptor signaling pathway include the following: idelalisib (GS-1101, CAL-101), ibrutinib (PCI-32765), and fostamatinib (R788) target the phosphatidylinostol 3 kinase (PI3K) delta isoform, Bruton's tyrosine kinase, and spleen tyrosine kinase (SyK), respectively. Early single-agent studies in relapsed and refractory FL patients demonstrated response rates between 10% (fostamatinib) and 54% (idelalisib).

Currently, phase III trials evaluating R-monotherapy or R-chemotherapy (e.g., B + R) +/− idelalisib are being initiated in relapsed and refractory B-cell lymphoma and will likely demonstrate augmented antitumor activity in the treatment arms utilizing the B-cell kinase inhibitors. ABT-199 is a highly potent, orally bioavailable, and BCL-2-selective inhibitor that inhibits growth of BCL-2-dependent tumors while sparing human platelets. Interim results from a phase I study of ABT-199 in patients with relapsed NHL were presented at the ASH 2012 annual meeting; four out of five FL patients demonstrated nodal disease reductions. Immunomodulatory drugs (IMiDs) have several proposed mechanisms of action (e.g., targeting the tumor microenvironment, inducing T-cell immunity and NK-cell activation, antiangiogenic activity, downregulation of nuclear factor kappa B, and direct antitumor effects). Results

(*Continued*)

from CALGB 50401, "A randomized trial of lenalidomide (L) alone versus L + R in patients with recurrent FL," was presented at the ASCO 2012 annual meeting; a 49% overall response rate (ORR) (13% CR) was seen with L alone, and a 75% ORR (32% CR) was seen with L + R with similar toxicity profiles.

As could have been predicted, the combination of L + R in previously untreated indolent lymphoma is proving to be a very effective initial therapy. The final results of a phase II L + R study in untreated indolent lymphoma were presented at the ASH 2012 annual meeting. A 98% ORR, including an incredible 87% CR–CRu rate, was seen in the 46 evaluable FL patients on this study; high response rates were seen regardless of tumor bulk, GELF criteria, or FLIPI score. The estimated 2-year PFS is 89% in patients with FL. A recently launched randomized phase III study to compare L + R versus R + chemotherapy followed by maintenance therapy in patients with previously untreated FL (the RELEVANCE trial) is enrolling at multiple sites around the world. If the L + R arm demonstrates noninferiority with less toxicity (or better) compared to the R-chemotherapy arm, then a major therapeutic paradigm shift away from the routine use of standard chemotherapy agents in the upfront therapy of FL may occur in the near future.

Case study answers

Case study 39.1

Question 1: Answer C

Case study 39.2

Question 1: Answer E
Question 2: Answer A ("True")

Case study 39.3

Question 1: Answer E

Case study 39.4

Question 1: Answer E
Question 2: Answer A
Question 3: Answer B ("No")

Case study 39.5

Question 1: Answer F
Question 2: Answer D

Selected reading

Barrington SF, Mikhaeel NG. Imaging follicular lymphoma using positron emission tomography with [(18)F]fluorodeoxyglucose: to what purpose? J Clin Oncol. 2012;30:4285–7.

Cabanillas F. Curability of advanced indolent or low-grade follicular lymphomas: time for a new paradigm? J Clin Oncol. 2013;31:14–6.

Czuczman M. Controversies in follicular lymphoma: "who, what, when, where, and why?" (not necessarily in that order!). Blood. 2006;303–10.

Jacobson CA, Freedman AS. Early stage follicular lymphoma, current management and controversies. Curr Opin Oncol. 2012;24:475–9.

Zinzani PL, Marchetti M, Billio A, *et al.* SIE, SIES, GITMO revised guidelines for the management of follicular lymphoma. Am J Hematol. 2012;88:185–92.

CHAPTER 40

Diffuse large B-cell lymphoma

Andrew D. Zelenetz

Memorial Sloan Kettering Cancer Center, *and* Weill-Cornell Medical Center, New York, NY, USA

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma encountered throughout the world with significant geographical variation. There were an estimated 69,740 cases of non-Hodgkin's lymphoma (NHL) in the United States in 2013, of which approximately 25,000 cases were some form of DLBCL. Pathologically, DLBCL is a heterogeneous disorder composed of several entities within the World Health Organization (WHO) classification (Table 40.1). This chapter reviews the pathobiology of DLBCL as well as consideration regarding staging, management, and prognosis.

Multiple choice and discussion questions

1. All of the following are correct statements regarding the epidemiology of DLBCL EXCEPT:

A. The incidence of DLBCL has steadily declined over the course of the last 10 years.
B. Systemic lupus erythematosus (SLE) can be associated with an increased risk of DLBCL.
C. Familial history of NHL increases the risk for the development of NHL of any histology by 1.8-fold.

The incidence of NHL doubled in the United States and other developed countries between 1975–1977 and 2004–2006 (SEER Cancer Statistics Review, 1975–2006). Multiple factors have contributed to the rise in incidence, including the rise in AIDS-related lymphoma, improved diagnosis, and an aging population; however, these factors do not fully account for the rise in incidence. Factors associated with an increased risk of NHL include occupation exposure to agricultural chemicals, immunodeficiency associated with HIV infection, immune suppression associated with solid-organ and allogeneic bone marrow transplantation, and prior chemotherapy. Viral agents associated with the development of lymphoma include the herpes viruses Epstein–Barr virus (EBV) and human herpes virus 8 (HHV8), the retrovirus human T-lymphotropic virus (HTLV1), and hepatitis B virus (HBV) and hepatitis C virus (HPC) infections. Autoimmune diseases, particularly Sjögren syndrome and SLE, are associated with increased risk of NHL, including DLBCL. A familial history of NHL increases the risk for the development of NHL of any histology by 1.8-fold and increases the risk of DLBCL specifically by 2.3-fold.

2. How important is the expertise of a hematopathologist in the diagnosis of NHL?

The foundation for optimal management of DLBCL lies in establishing an accurate histopathologic diagnosis. In the absence of specialized hematopathology expertise, pathologic consultation is often necessary. Classification of malignant lymphoma has evolved as pathologists and clinicians have gained greater insight into the immunobiology and, more recently, molecular pathology of individual entities. The current standard for classification is the 2008 WHO classification of lymphoid neoplasms; however, it is recognized that classification of lymphoma remains a work in progress. Recent series have demonstrated that 6% (in a series restricted to DLBCL and follicular lymphoma) to 18% (in a series of all lymphomas) of diagnoses are changed on review at comprehensive cancer centers in a way that would likely impact clinical management. Fine-needle aspirate is not acceptable for an initial diagnosis of DLBCL. Ideally, the patient should undergo an excisional or incisional lymph node biopsy. Laparoscopic-guided intra-abdominal biopsies have been shown to be more effective and minimally more difficult than computed tomography (CT)-guided core needle biopsy.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 40.1 Heterogeneity of diffuse large B-cell lymphoma (DLBCL).

Entity (World Health Organization (WHO))	Frequency in the United States (Armitage 1998)
DLBCL-NOS	31%
Primary mediastinal B-cell lymphoma	2%
Variants	3%
T-cell/histocyte-rich large B-cell lymphoma	
Primary cutaneous DLBCL, leg type	
EBV-positive DLBCL of the elderly[1]	
Lymphomatoid granulomatosis (EBV)	
Intravascular large B-cell lymphoma	
ALK positive large B-cell lymphoma	
Primary CNS large B-cell lymphoma	

[1]Provisional entity in 2008 WHO classification.

3. True or false? Gene expression profiling (GEP) in DLBCL-NOS has identified subtypes with distinct oncogenic pathways.

A. True
B. False

DLBCL is a heterogeneous disorder; even the most common subtype, DLBCL-NOS, is itself heterogeneous. GEP has demonstrated that DLBCL-NOS represents at least two different diseases based on the cell of origin (COO): germinal center DLBCL (GC-DLBCL) and activated B-cell DLBCL (ABC-DLBCL). GC-DLBCL and ABC-DLBCL have distinct oncogenic pathways. GC-DLBCL is characterized by genomic instability caused by *PTEN* deletion, *ING1* deletion, *MDM2* gain or amplification, *TP53* mutation, mTOR activation as a consequence of *miR-17-92* amplification, and *BCL2* activation by translocation. ABC-DLBCL is characterized by recurrent mutations in MYOM2, TNFAIP3, CD79B, PRDM1, and CARD11; deletion of INK4A-ARF; trisomy 3; and 19p gain or amplification, resulting in activation of nuclear factor kappa B (NF-kB). Recurrent mutations seen in more than 10% of cases of both GC-DLBCL and ABC-DLBCL include *MLL2*, *CREBBP*, *TP53*, *CD36*, *B2M*, and *MEF2B*. Both progression-free survival (PFS) and overall survival (OS) are superior for GC-DLBCL compared to ABC-DLBCL following treatment with standard R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); at 4 years, the PFS and OS differences are approximately 40% and 30%, respectively (also reviewed in Chapter 52). Though COO has clear prognostic implications, routine clinical application has proven to be difficult. The gold standard for determination of COO is GEP. New technologies, including quantitative nuclease protection (High Throughput Genomics, Tucson, AZ), microfluidics quantitative polymerase chain reaction (Fluidigm, South San Francisco, CA) and direct assay of RNA with capture and detection probes (Nanostring, Seattle, WA), have made it possible to perform GEP on formalin-fixed paraffin-embedded (FFPE) tissue; however, they are not in routine clinical use for determination of COO.

4. Is the identification of COO by immunohistochemistry (IHC) algorithms as good as GEP analysis?

A. Yes
B. No

There have been attempts to determine COO by IHC. The most widely used algorithm includes three antigens: CD10, IRF4–MUM1, and BCL6. In this algorithm, CD10 expression is associated with GC-DLBCL, regardless of expression of other antigens. In the absence of CD10 expression, IRF4–MUM1 expression is associated with non-GC-DLBCL. In cases negative for both CD10 and IFR4–MUM1, BCL6 expression correlates with GC-DLBCL and lack of expression with non-GC-DLBCL. This has been the most commonly used algorithm; however, the ability to predict outcome in different patient cohorts has been variable. The alternative IHC-based algorithms Colomo (IRF4–MUM1, CD10, and BCL6), Muris (BCL2, CD10, and IRF4–MUM1), Choi (GCET1, IRF4–MUM1, CD10, FOXP1, and BCL6), and Tally (CD10, GCET1, IRF4–MUM1, FOXP1, and LMO2) have been reported to predict the outcome of patients. Both Choi and Tally have reported greater specificity than the Hans algorithm in classification of GC- and non-GC-DLBCL. The ability of these newer algorithms to predict outcome by COO has also been called into question. It appears that IHC algorithms can enrich for patients with either GC- or ABC-COO but are not highly reproducible in predicting for PFS and OS.

5. What are double-hit (DH), triple-hit (TH), and immunohistochemistry double-hit (IHC DH) lymphoma?

Another increasingly recognized challenge has been the management of cases of DH or TH lymphoma. DH cases were originally described as having translocation t(14;18)(q32 q21.3) involving both *IGH–BCL2* and *MYC*–8q24, and TH cases have additional translocation of *BCL6*–3q27. Some authors have included cases with MYC and BCL6 rearrangements in the definition of DH lymphoma. *BCL2–MYC* DH lymphomas account for 1–8% of cases, and TH lymphomas are rare, occurring in 0–3% of cases is various series. DH and TH lymphomas have a poor prognosis when treated with conventional R-CHOP chemotherapy (discussed in Chapters 45 and 46). DH and TH lymphomas as defined above are restricted to patients with GC-DLBCL. More recently, concurrent overexpression of MYC (≥40% of cells) and BCL2 (≥70% of cells) proteins (IHC DH) has

been reported to be associated with a poor prognosis with a similar magnitude of impact as the genetic DH lymphomas; IHC DH lymphomas are independent of COO. Optimal treatment regimens for DH, TH, and IHC DH lymphomas have not yet been defined.

6. When should cerebrospinal fluid (CSF) be evaluated in DLBCL?

Lumbar puncture with examination of CSF by flow cytometry is indicated in patients with $\geq$2 extranodal sites, elevated lactate dehydrogenase (LDH), and involvement of paranasal sinus, testes, or epidural sites, or bone marrow involvement with large cell.

7. What should be the approach in patients with HBV infection and DLBCL?

Patient planned to receive rituximab should have a hepatitis B surface antigen assessment given the risk of viral reactivation. Universal screening for hepatitis B surface antigen was found to be cost-effective in patients receiving R-CHOP chemotherapy. There is some controversy about the added benefit of hepatitis B core antibody testing. Approximately 10% of patients will be hepatitis B core antibody positive, and the risk of reactivation is approximately 4%. In patients at risk for hepatitis B reactivation, prophylaxis with an antiviral is superior to treatment upon activation. Recent data suggest that entecavir is superior to lamivudine for prophylaxis. The risk of reactivation persists for at least 6 months beyond the completion of chemotherapy, and prophylaxis should be continued during this period.

8. What is the role of the International Prognostic Index (IPI) model in the rituximab era?

A large number of clinical prognostic models have been proposed for DLBCL. However, the IPI, originally published in the pre-rituximab era, has proven to be very robust. The IPI includes five simple clinical factors (adverse in parentheses): age (>60), performance status $\leq$2, LDH > upper limit of normal, $\geq$2 extranodal sites, and stage III–IV disease. Patients are assigned to a risk group based on the number of risk factors (RFs): low risk (LR), 0–1 factors; low-intermediate risk (LIR), two factors; high-intermediate risk (HIR), three factors; and high-risk disease (HR), 4–5 factors. An age-adjusted IPI (aaIPI) appropriate for the analysis of patients uniformly $\leq$60 years of age or >60 years of age includes three factors: performance status $\leq$2, LDH > upper limit of normal, and stage III–IV disease. The risk groups for the aaIPI are as follows: LR, 0; LIR, 1; HIR, 2; and HR, 3. In the rituximab era, the IPI has continued to be of value. However, as a result of improving outcomes with rituximab in combination with chemotherapy, the standard IPI resulted in two major risk groups: 0–2 RFs (IPI LR and LIR) with 4-year PFS 80–85% and OS 81–82%; and 3–5 RFs (IPI HIR and HR) with 4-year PFS 51–57% and OS 49–59%. A revision of the IPI was suggested, dividing patient into three risk groups: 0 RFs (very good) with 4-year PFS 94% and 4-year OS 94%; 1–2 RFs (good) with 4-year PFS 80% and OS 79%; and 3–5 RFs (poor) with 4-year PFS 53% and OS 55%. Another proposed variant of the IPI is the elderly IPI (E-IPI), which uses age $\geq$70 in place of age $\geq$60 as the adverse factor. This index has the clear advantage in that the age cutoff is near the median age for patients with DLBCL. Furthermore, in the United States patients between 60 and 69 years old are often treated similarly. Estimated 3-year failure-free survival (FFS) and OS for the E-IPI were LR 77% and 86% (27% of patients), LIR 62% and 74% (28% of patients), HIR 47% and 58% (29% of patients), and HR 28% and 36% (16% of patients). The E-IPI identified a high-risk group of patients expected to have poor outcome, but for the purposes of clinical trials this population is relatively small.

9. What is the utility of IPI in early-stage DLBCL?

In patients with early-stage disease, the IPI is suboptimal because all patients would be favorable for both staged and extranodal sites. This is appropriate for analysis of a mixed population of limited (stages I and II) and advanced-stage patients (stages IIB, III, and IV) but of less utility in the analysis of outcome in patients with early-stage disease. A stage-modified IPI was proposed for patients with stage I and II disease, which includes the same factors save for extranodal sites ($\geq$2). The stage-modified IPI has been applied in two ways: by number of risk factors (0–1, 2, and $\geq$3) as well as by none versus any, both of which proved to have prognostic value.

10. What are the data behind R-CHOP in DLBCL?

The national high-priority study (South-West Oncology Group (SWOG) 8516, US Intergroup 0067) compared the first-generation CHOP regimen to second- and third-generation regimens, including m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, and methotrexate), and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), for the treatment of advanced-stage aggressive non-Hodgkin's lymphoma. This study included patients with intermediate-grade lymphoma according to the International Working Formulation (IWF) groups D through H and group J. The IWF is an antiquated classification system that sought to act as a "Rosetta stone" between disparate lymphoma classification schemas that were wildly in use at the time. The IWF used morphological and clinical characteristics to classify

tumors and did not employ immunohistochemistry to classify lymphomas as derived from B- or T-cells. However, most patients with IWF F–H have aggressive B-cell lymphoma, and these groups represented approximately 82% of the patients on the study. Thus, the results are applicable to patients classified as DLBCL according to the modern WHO classification. The study found that CHOP provided similar FFS and OS at lower cost and lower severe toxicity than the comparative regimens and emerged as the standard of care for the treatment of advanced-stage DLBCL.

No clinically meaningful improvement to CHOP as the standard of care occurred until the introduction of rituximab. Rituximab is a chimeric anti-CD20 monoclonal antibody originally demonstrated to have activity in the treatment of relapsed and refractory follicular lymphoma. Two studies, one in follicular lymphoma and a second in DLBCL, demonstrated the safety of combining rituximab with standard CHOP chemotherapy. This prompted the Group d'Etude des Lymphomes de l'Adulte (GELA) to compare standard CHOP chemotherapy with rituximab plus CHOP (R-CHOP-21) for patients aged 60–80 with DLBCL. This study demonstrated significant improvements in event-free survival (EFS) and OS for the addition of rituximab to eight cycles of standard CHOP chemotherapy. This study has been updated several times with persistence in the clinical benefit. At a median follow-up of 10 years, the PFS for was 36.5% versus 20% and the OS was 43.5% versus 27.6% for patients treated with R-CHOP-21 and CHOP, respectively. Relapses after 5 years represented 7% of all disease progressions; however, few of the cases underwent a repeat biopsy, and some of the late relapses may have represented indolent lymphoma. At 10 years, the median age of the surviving patient is 80 years. The most common cause of death was from cardiovascular disease and second malignancies at rates expected for the age group. There was no difference between the two treatment arms with respect to these deaths. The results of the GELA study have been confirmed in a US Intergroup trial, ECOG 4494–CALGB 9793. This trial had a 2×2 factorial design. The first randomization compared CHOP-21 to R-CHOP-21, and the second randomization asked if maintenance rituximab (RM) was beneficial. There was significant interaction between the two randomizations because a significant difference in the effect of maintenance therapy was observed by induction therapy. Therefore, result of the first randomization was performed using a weighted analysis. The addition of rituximab to CHOP improved 3-year FFS 53% versus 46% but did not impact OS. MR significantly prolonged FFS after CHOP but not R-CHOP; the 2-year FFS was 77%, 79%, 74%, and 54% after R-CHOP-21, R-CHOP-21 + MR, CHOP-21 + MR, and CHOP-21 alone, respectively. The most important finding from this study was that MR has no additional benefit after treatment with R-CHOP-21.

The GELA study established R-CHOP-21 as the standard of care for patients aged 60–80. There remained questions regarding the appropriate standard for younger patients. The MInT trial addressed the addition of rituximab to CHOP-like chemotherapy. Regimen use was dependent on country. In addition to standard CHOP-21 (used in Argentina, Australia, Austria, Brazil, Canada, Czech Republic, Denmark, Finland, France, Israel, Norway, Poland, Spain, Switzerland, and the United Kingdom), CHOP-like regimens included CHOEP (CHOP with the addition etoposide; used in Germany and Sweden), MACOP-B (Italy), and PMitCEBO (mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, prednisone (United Kingdom)). The study included patients 18–60 years of age with stage IB or II–IV disease, but was limited to patients with 0 or 1 RF according to the aaIPI. The results were somewhat confounded by the addition of radiation therapy to treatment of patients with extranodal disease at the discretion of the investigator; radiation (30–40 Gy) was included for patients with initially bulky disease according to national standards. This trial demonstrated that addition of rituximab to CHOP-like chemotherapy resulted in significant improvement in 3-year EFS 79% versus 59% and OS 93% versus 84% at a median follow-up of 34 months. The major limitation of this study is that it was restricted to patients with good-prognosis DLBCL. There is a relative dearth of prospective clinical trial data examining the outcome of younger poor-risk patients with advanced-stage DLBCL with R-CHOP-21. A population-based evaluation of the addition of rituximab to CHOP-21 was conducted in British Columbia. The outcome of patients with DLBCL treated for the 18 months prior and subsequent to a province-wide recommendation that rituximab be added to CHOP-21 was analyzed. In this analysis, patients under the age of 60 had a statistically superior 2-year OS (85% vs 67%) after the introduction of rituximab. Furthermore, they found no significant difference in the relative benefits of treatment in the post-rituximab era between age groups.

11. Can we improve on R-CHOP-21 in DLBCL?

There have been a number of approaches to improving on R-CHOP-21, including increasing dose density (R-CHOP-14), altering drug delivery (DA-EPOCH-R), using alternative drugs (R-ACVBP), or administering sequential therapy (R-CHOP→ibritumomab or R-CHOP→ICE).

About the same time that GELA was evaluating the value of adding rituximab to CHOP-21, the German High Grade Lymphoma Study Group (DHGLSG) evaluated standard CHOP-21 versus CHOP-14, CHOEP-21, and CHOEP-14 in patients aged 61–75 (NHL-B2) and younger patients aged 18–60 with good prognosis (normal LDH) (NHL-B1). Patients with sites of bulky disease received

IFRT (36 Gy). There was a significant benefit for the administration of the dose-dense regimens in both younger and older patients. However, in older patients CHOEP-21 and particularly CHOEP-14 were poorly tolerated. In the older patients, CHOP-14 was superior to CHOP-21 in EFS (44% versus 33%) and OS (40.6% versus 53.3%). In the younger patients, CHOEP was superior to CHOP for 5-year EFS (69% versus 58%); however, the dose-dense 14-day regimens were associated with a 6% statistically significant 5-year OS advantage over the 21-day regimens (85% vs. 79%). RICOVER-60 examined if rituximab added additional benefit to dose density. In this 2 × 2 trial, CHOP-14 was examined with and without rituximab, and the second question examined cycle number (6 vs. 8) in patients aged 61–80. Addition of rituximab improved 3-year PFS for both 6 (73%) and 8 (69%) cycles compared to CHOP-14 ×6 (57%). However, only R-CHOP-14 ×6 improved OS (78% vs. 68%) because of nonlymphoma deaths seen in the patients who were treated with R-CHOP ×8. These are the best data to support the use of six cycles of R-CHOP rather than eight cycles of R-CHOP. R-CHOP-14 has been associated with a higher risk of *Pneumocystis jirovecii* pneumonia (PJP, previously called PCP) and should be given with appropriate prophylaxis.

The DHGLSG and GELA trials established two standards of care: R-CHOP-14 ×6 and R-CHOP-21 ×8, respectively. However, it was not clear if dose density added to R-CHOP. Two prospective randomized trials compared R-CHOP-21 to R-CHOP-14. In the UK trial, patients were treated either with R-CHOP-21 ×8 according to the original GELA trial or with R-CHOP-14 with two doses of additional rituximab according to the RICOVER-60 trial. R-CHOP-14 was not superior to R-CHOP-21. As a consequence of prophylactic administration of hematopoietic growth factors (GFs) with R-CHOP-14, the incidence of grade 3 or 4 neutropenia and febrile neutropenia was significantly less than with R-CHOP-21 given without prophylactic GF support; however, grade 3 or 4 thrombocytopenia was greater with R-CHOP-14. In the GELA study, prophylactic GF was not given to the R-CHOP-14 arm; therefore, that arm did not achieve the planned dose intensity, and there was more grade 3 or 4 neutropenia compared to the R-CHOP-21 arm. In this study, there was no improvement in outcome with the dose-dense regimen. Based on these findings, R-CHOP-21 remains the standard for patients aged 61–80, although, based on the UK study, prophylactic GF should be given. However, there may be clinical situations where the shorter R-CHOP-14 regimen would be preferred, and these data support this as an acceptable alternative.

Investigators at the National Cancer Institute (NCI) developed the dose-adjusted EPOCH regimen (DA-EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) based on modeling that demonstrated that continuous low-dose drug exposure enhances cell kill of rapidly proliferating cells. DA-EPOCH was tested in patients with untreated DLBCL and had promising activity. Rituximab was subsequently added to the regimen and found to have benefit in patients with BCL2-positive tumors. Based on these preliminary results, a multicenter phase II study of DA-EPOCH-R was conducted by the Cancer and Leukemia Group B (CAGLB). This study demonstrated a very high complete response rate, and the 5-year PFS and OS were 81% and 84%, respectively. PFS was particularly favorable (100%) in patients with GC-phenotype DLBCL compared to 67% in non-GC DLBCL. In contrast to the hypothesis underlying the regimen, a tumor with a proliferation fraction of >60% had an inferior outcome compared to a tumor with lower proliferation. In contrast to the NCI study, outcome was not influenced by BCL2 expression. These results were favorable compared to historical controls to R-CHOP-21 chemotherapy, prompting CALGB 50303, a prospective randomized comparison of R-CHOP-21 and DA-EPOCH-R; enrollment has completed, and the results should be available in 2014.

Following the development of CHOP, numerous regimens were developed adding additional drugs to this backbone. Ultimately, the National High Priority Study comparing CHOP, m-BACOD, MACOP-B, and ProMACE-CytaBOM demonstrated that this strategy was largely unsuccessful. The exception to this was the ACVBP (doxorubin, cyclophosphamide, vindesine, bleomycin, and prednisone with sequential consolidation) regimen developed by GELA, which demonstrated superiority in EFS (39% versus 29%) and OS (46% versus 38%) for the dose-intensive regimen compared to CHOP in patients aged 61–69 with poor-prognosis (at least on IPI RF) aggressive NHL. A subsequent trial evaluated the rituximab added to ACVBP compared to R-CHOP-21 in patients aged 18–59 with at least one aaIPI RF. The 3-year EFS (81% versus 67%) and OS (92% versus 84%) were superior for R-ACVBP compared to R-CHOP. The lack of vindesine in the United States has prevented the adoption of this regimen.

The ICE (ifosfamide, carboplatin, and etoposide) chemotherapy regimen was developed at Memorial Sloan Kettering Cancer Center for the treatment of relapsed and refractory DLBCL. The regimen was highly effective for cytoreduction prior to HDT–ASCR. Building on the concept of sequential non-cross-resistant chemotherapy, ICE ×3 was integrated into front-line therapy after induction with R-CHOP-14 ×4. Patients 18–65 years of age with at least one aaIPI RF were included; 79% of the 98 patients had HIR and HR disease according to the aaIPI. Radiation was excluded save for testicular involvement. At the median follow-up of 44 months, the PFS and OS were 79% and 90%, respectively. In this study, the treatment overcame the adverse impact of COO by the Hans algorithm and pre-

treatment IPI. Only the proliferation index of >80% was associate with an inferior PFS of 69% versus 89%. The study also examined the role of interim fluoro-deoxyglucose positron emission tomography (FDG-PET) and found that FDG avidity after R-CHOP-14 ×4 induction did not predict outcome.

Consolidation with radioimmunotherapy following R-CHOP chemotherapy has been explored in phase II trials. Both trials accrued high-risk elderly patients with DLBCL. Following R-CHOP-21 ×4–6, patients were treated with ^{90}Y-ibrituimab tixuetan at a standard dose of 0.3 or 0.4 Ci/kg (depending on platelet count). Compared to historical R-CHOP-21 controls, both studies demonstrated improvements in PFS and OS. This strategy is currently being explored in ZEAL, a prospective randomized trial; patients with CR after R-CHOP-like therapy are randomized to ^{90}Y-ibritumomab tixuetan or observation (discussed further in Chapter 62).

12. What is the treatment of early-stage DLBCL?

The management of early-stage disease has been controversial. The SWOG 8736 study evaluated CHOP-21 for eight cycles alone compared to CHOP-21 for three cycles followed by involved-field radiation (IFRT, 40–55 Gy). At the time of the initial publication with a median follow-up of 4.4 years, there was a statistically significant advantage in 5-year OS for the combined modality therapy (82% versus 72%). With long-term follow-up, there is evidence of late relapse in both arms with the FFS curves crossing at 8 years, and there is no longer an OS advantage for combined modality. In the updated analysis, when the patients from both arms were pooled, patients with no RFs according to the stage-modified IPI had an excellent 5-year OS (94%) compared to those with one or more RFs (71%). This identified a patient population with relatively poor prognosis that was amenable to evaluation of new approaches. SWOG 0014 subsequently evaluated R-CHOP-21 for three cycles followed by IFRT (40–46 Gy) for patients with DLBCL and at least one RF according to the stage-modified IPI. The results were compared to historical controls drawn from SWOG 8736 who had DLBCL and at least one RF. The 4-year PFS and OS rates were 88% and 92%, respectively. This compared favorably to the historical control (4-year PFS 78% and OS 88%), and the study met its prespecified endpoint of a 2-year PFS of at least 84%. However, again there was a pattern of continuing late relapse that limited the improvement in OS. R-CHOP-21 for three cycles followed by IFRT remains an appropriate treatment choice, although alternative approaches are clearly necessary to reduce the risk of late relapses.

The role of radiation therapy in the management of early-stage DLBCL has been questioned. ACVBP for three cycles followed by sequential consolidation was compared to CHOP-21 for three cycles and IFRT (40 Gy) in patients ≤60 years of age with localized CS I or II aggressive lymphoma and no RFs according to the IPI. At a median follow-up of 7.7 years, 5-year EFS (82% versus 74%) and OS (90% versus 81%) were significantly higher for the chemotherapy-only arm. A subsequent study evaluated ACVBP with or without rituximab in patients ≤65 years with early-stage disease and one RF according to the IPI. The addition of rituximab improved the 3-year EFS (93% versus 82%) but did not affect OS. In older patients, GELA LNH 93-4 examined treatment with CHOP-21 for four cycles compared to the same treatment with IFRT (40 Gy). The patient population was >60 years but had no aaIPI adverse risk factors. Two-thirds of the patients had stage I disease and 8% had bulky disease. At a median follow-up of 7 years, there was no difference in EFS (61% vs. 64% for RT) or OS (72% vs. 68% for RT). Thus, for low-risk patients with localized disease, there was no advantage for the addition of radiation; the addition of rituximab to chemotherapy improved EFS and PFS without improvement in OS.

Another approach to limit the role of radiation therapy has been to direct therapy based on interim FDG-PET. The lymphoma group at the British Columbia Cancer Agency has adopted an approach of treating patients with three cycles of R-CHOP-21 and performing an interim FDG-PET scan. Patients with no residual FDG avidity (103/234) were given one additional cycle of R-CHOP-21. The 3-year time to progression (TTP) was 92%. The 30 patients (one was not evaluable) with residual FDG-avid disease were given IFRT; the 3-year TTP was 60%. Thus, resolution of FDG-avid disease after three cycles of R-CHOP predicts for an excellent outcome in early-stage disease. This program needs to be more fully evaluated in a prospective trial to determine its widespread applicability.

In summary, the optimal approach to early-stage DLBCL remains controversial, although treatment with R-CHOP-21 for three cycles followed by IFRT for patients with at least one stage-modified RF is appropriate. For patients with no RF, treatment with R-CHOP-21 for four cycles alone may be sufficient, particularly if the interim FDG-PET is negative.

Conclusion

DLBCL is the most common lymphoma worldwide. The tumor is pathologically and clinically heterogeneous. Rituximab in combination with chemotherapy has improved the survival of patients. Though R-CHOP-21 remains the standard of care, several approaches have resulted in *apparent* improvement in outcome. However, we learned from the National High Priority Study that reliance on phase II results can be very misleading. A number of prospective randomized trials are ongoing or have been

completed that will evaluate these new strategies compared to R-CHOP-21. Our increased understanding of the disrupted pathways in DBCL has led to the testable hypothesis that targeted therapy may be another path to improved outcomes. The coming challenge in targeted therapy of DLBCL will be to reliable identify the actionable mutations in DLBCL and evaluate new agents in populations preselected for increased likelihood of success. Proving that this approach is valuable and not a Roy Rogers effect is a major challenge to innovative clinical trial design.

Multiple choice answers

Question 1: Answer A
Question 3: Answer A ("True")
Question 4: Answer B ("No")

Selected reading

Alizadeh AA, Eisen MB, Davis RE, *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503–11.

Coiffier B, Lepage E, Briere J, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. New Engl J Med. 2002;346(4): 235–42.

Fisher R, Gaynor E, Dahlberg S, *et al.* Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. New Engl J Med. 1993;328(14):1002–6.

Swerdlow SH, International Agency for Research on Cancer, World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues (4th ed.). Lyon, France: International Agency for Research on Cancer; 2008.

CHAPTER 41

Mantle cell lymphoma

Stephen Smith[1] and John Sweetenham[2]

[1]University of Washington, Seattle, WA, USA
[2]Huntsman Cancer Institute *and* University of Utah, Salt Lake City, UT, USA

Case study 41.1

A 64-year-old male presents to his primary care physician with weight loss and anemia. Physical exam reveals splenomegaly. A colonoscopy reveals grossly nodular mucosa, and biopsy shows an extensive infiltrate of medium-sized lymphocytes, lambda-restricted and positive for CD5, CD20, and cyclin D1, but negative for CD23 by immunohistochemistry. Fluorescence in situ hybridization shows translocation 11;14. The patient is referred for evaluation and management.

1. What additional studies are required for evaluation and disease staging?

A. No further workup, as diagnosis and stage have been established
B. Splenectomy, bone marrow aspirate, and biopsy
C. Physical exam, contrast-enhanced computed tomography (CT) scan, bone marrow aspirate, and biopsy
D. Upper endoscopy and positron emission tomography (PET)–CT scan

This patient's sex, age, and presentation are typical of MCL, and the combination of immunophenotype and genetic findings is diagnostic. MCL has a unique predilection for leukemic involvement and infiltration of bone marrow and the gastrointestinal (GI) tract, and it may present with splenomegaly without nodal involvement. On endoscopy, polyps, nodules, or ulcers may be seen in the upper or lower GI tract (including a minority with diffuse "multiple lymphomatous polyposis")—but grossly normal colonic mucosa is common. Even in such patients, MCL is commonly found on immunohistochemical analysis. In series of newly diagnosed MCL patients (mostly without GI symptoms), about 90% will have GI involvement by lymphoma on biopsy. Such patients appear not to face higher risk of complications during therapy (e.g., bleeding), and management or surveillance is not affected by endoscopic data. Therefore, routine endoscopic staging evaluation for all MCL patients—or performing an upper endoscopy in this case—is unwarranted. Endoscopy may be useful when other staging studies are equivocal, or to investigate diarrhea, GI bleeding, or iron deficiency anemia in newly diagnosed MCL patients.

As with other non-Hodgkin's lymphomas, radiographic imaging is useful for identifying the extent and size of nodal masses, splenomegaly, or organ involvement by lymphoma. PET is sensitive in pretreatment staging of MCL, but it adds little to standard staging including bone marrow aspirate and biopsy, and any role in guiding therapy remains investigational. Based on available data, CT scan remains the reasonable standard imaging test in the modern era.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 41.2

A 54-year-old male presents with adenopathy and night sweats, and he has become fatigued to the point of spending most of the time resting at home. Lymph node biopsy reveals MCL with a classical growth pattern and a Ki-67 proliferation index of 40%, and he is found to have leukemic involvement of the peripheral blood. Total white blood cell (WBC) count is 20 × 106/μL, and serum lactate dehydrogenase is 320 IU/L (normal 100–220).

1. What *favorable* prognostic feature does this patient have?

A. LDH level
B. Stage
C. Performance status
D. Ki-67 proliferation index
E. Age

MCL has been historically marked by a poor long-term prognosis, with standard regimens offering remissions lasting 1–2 years and a median survival of under 5 years—although survival appears to be improving. This patient's only favorable prognostic feature is his age. A number of studies have demonstrated age over 60 (or 70) to be an adverse prognostic feature in MCL, affecting relapse risk and survival.

This patient falls into the high-risk category using the Mantle Cell International Prognostic Index (MIPI) score, which is calculated using age, LDH level, performance status, and total WBC count. The MIPI has been validated in several data sets and has been proven superior to the International Prognostic Index in some series.

A further refinement to the MIPI incorporates the Ki-67 proliferation index, the so-called biologic MIPI. Mitotic index has long been identified as an adverse prognostic factor in mantle cell lymphoma, supplanted by Ki-67 as the standard marker of tumor cell proliferation. The median Ki-67 index in mantle cell lymphoma is about 20–30%, with values above the median range adversely prognostic. Efforts to harmonize measurement of Ki-67 have been proposed, given challenges in its reproducibility. The role and prognostic impact of the SOX11 transcription factor, expressed in most MCL but reported absent in some MCL with nonnodal presentation, are under study. Absent nuclear sox11 staining may predict an indolent clinical course, particularly among MCL cases with hypermutated IGHV genes, and may be useful as a diagnostic marker for the uncommon, cyclin-negative MCL cases. The evolution of prognostication in MCL is outlined in Figure 41.1.

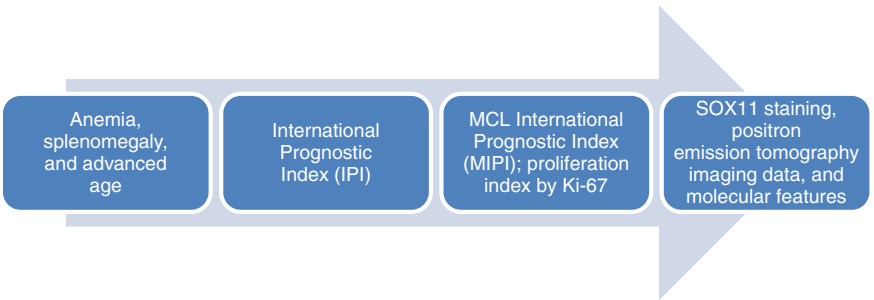


Figure 41.1 Evolution of prognosis in MCL.

Case study 41.3

A 68-year-old schoolteacher presents in the autumn with a history of two episodes of bronchitis, a peripheral lymphocytosis without anemia, and total WBC 9 × 10^6/μL. He has a palpable spleen 2 cm below the left costal margin, and bone marrow biopsy shows involvement by mantle cell lymphoma in an interstitial pattern. He has no other symptoms related to his lymphoma, and asks about the role of observation so that he may complete his scheduled year of teaching.

1. Is observation an appropriate option in newly diagnosed mantle cell lymphoma?

A. Yes
B. No

Although mantle cell generally behaves in an aggressive manner, cases of indolent mantle cell lymphoma are well described. Such cases may present with leukemic blood involvement and no (or low-level) lymphadenopathy, with or without splenomegaly; some show unique features, including kappa light-chain restriction (as opposed to lambda, which is more typical for MCL), hypermutated immunoglobulin heavy-chain genes (seen in a minority of MCL cases), and absent nuclear staining for the transcription factor SOX11.

Clinical data suggest that observation is acceptable for a proportion of MCL patients. Some data show no survival decrement for those initially observed with mantle cell lymphoma. In this case, there is certainly a concern that his episodes of bronchitis are a disease-related phenomenon, but lacking other MCL-specific high-risk features or symptoms, one may opt to observe this patient while evaluating (by measuring his immunoglobulin G level) and treating his pulmonary infection as needed.

Case study 41.4

A 53-year-old male is diagnosed with mantle cell lymphoma, intermediate risk by the MIPI score, and with a Ki67 of 50%. He has a 6 cm adenopathy in the retroperitoneum, has low back pain, and has lost 15% of his weight in the last 6 months. He has no renal, cardiac, or hepatic comorbidities.

1. Among the choices listed below, what induction regimen would you recommend for this patient, assuming good overall health and organ function?

A. Single-agent rituximab therapy, followed by rituximab maintenance
B. Bortezomib and dexamethasone
C. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) alone, followed by rituximab maintenance
D. Augmented R-CHOP alternating with high-dose cytarabine, followed by autologous stem cell transplantation (auto-SCT)

Among the choices listed, an intensive chemoimmunotherapy regimen using augmented R-CHOP and cytarabine as a backbone followed by high-dose chemotherapy with autologous stem cell transplantation (auto-SCT) is best supported by available evidence. This regimen was developed by the Nordic lymphoma group, and long-term follow-up data have been reported. When feasible, enrollment in a clinical trial would be the first priority for this patient. Although several regimens appear superior to standard R-CHOP induction, randomized trials are lacking and the optimal approach for younger patients has not yet been defined.

Intensive chemotherapy approaches—in particular, those incorporating auto-SCT, high-dose cytarabine, or both into rituximab- and anthracyline-based induction therapy—have emerged as the modern standard of care for younger MCL patients based on an array of data. Auto-SCT was shown superior to interferon maintenance after CHOP-like induction therapy in a randomized clinical trial in adults younger than 65 years. This study established the role of auto-SCT for improving disease control in MCL for eligible, young patients after CHOP therapy. Whether auto-SCT provides the same benefit after more intensive induction regimens is not well studied. One intensive regimen studied in the United States, rituximab + hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) (alternating with high-dose methotrexate and cytarabine), showed promising outcomes without auto-SCT in a single-institution study, with 87% achieving complete response and a 3-year failure-free survival rate of 64% (73% for patients under the age of 65). With 8 years of follow-up, the median time to treatment failure was 4.6 years, and median overall survival was not reached. The hematologic toxicity of full-course rituximab + hyperCVAD is substantial, restricting its use to young patients, and frequent dose reductions are required; and a multicenter study failed to yield similarly good outcomes. The role of rituximab–hyper-CVAD with regard to auto-SCT is not well defined, although some data suggest poor stem cell mobilization after hyper-CVAD induction is used.

The incorporation of cytarabine into first-line therapy for younger MCL patients has also been extensively studied in Europe. DHAP (dexamethasone, cytarabine, and cisplatin) has been shown to improve response rates after CHOP induction, allowing most patients to undergo auto-SCT during first remission. The European Mantle Cell Lymphoma Network conducted a randomized trial comparing alternating courses of R-CHOP and R-DHAP to standard R-CHOP induction, among patients younger than 65 years. Responders in both groups underwent auto-SCT. Results showed higher complete responses, longer disease control, and superior overall survival for the group receiving R-DHAP during induction. The Nordic group has reported long-term outcomes of an augmented CHOP, rituximab, and high-dose cytarabine (as a single agent), followed by auto-SCT in 160 patients under the age of 66 (the MCL2 study). This study also employed minimal residual disease (MRD) monitoring and "preemptive" therapy using rituximab in MRD-positive patients. Results with 6.5 years of follow-up suggest an overall survival of over 10 years, and median event-free survival of 7.4 years. Long-term toxicity included only one case of myelodysplasia. However, a continual pattern of relapses was observed, particularly in high-risk MIPI patients. In light of phase II rituximab + hyperCVAD data from the United States, and randomized data from the European MCL Network, it appears that cytarabine is an important element of induction for younger, fit patients with MCL.

The other answers do not describe optimal first-line therapy for a young, symptomatic MCL patient. Single-agent rituximab has a low response rate in MCL, and extended (maintenance) therapy after single-agent induction has not been shown to be beneficial. Bortezomib is approved for relapsed and refractory mantle cell lymphoma based on a study showing a 33% response rate as a single agent, with a median response duration of 9 months. However, its role as induction in younger patients remains to be defined. While a study of bortezomib with hyperCVAD (and a reduced vincristine dose to mitigate neuropathy) showed promise, this approach has not been subject to randomized comparison and is not being pursued further. Last, R-CHOP followed by rituximab maintenance is a reasonable option for the older patient, in whom this approach was recent compared to FCR (fludarabine, cyclophosphamide, and rituximab) in a randomized trial. When possible, consideration of referring the patient for a clinical trial is important. The US Intergroup study, for example, is a 4-arm study comparing induction bendamustine + rituximab with or without velcade, followed by 2 years of consolidation using rituximab with or without lenalidomide.

Case study 41.5

A 71-year-old man diagnosed with MCL by axillary lymph node biopsy 6 months ago has been managed expectantly. He has mild hypertension and chronic renal insufficiency. However, he has now developed uncomfortable enlarging, right-sided cervical adenopathy, and CT shows numerous sites of enlarging nodes measuring 5–6 cm and an enlarging spleen to 17 cm. LDH is elevated to 312 U/L (normal up to 220 U/L), and he has a normal complete blood count; creatinine clearance is 65 cc/min.

1. What treatment would you recommend?

A. Rituximab + hyperCVAD regimen, without high-dose methotrexate
B. Lenalidomide and rituximab
C. Temsirolimus and rituximab
D. R-CHOP followed by rituximab maintenance
E. FCR

This 71-year-old requires therapy, based on symptomatic nodal progression. Regimens including auto-SCT and rituximab + hyperCVAD are not well studied in this age group, although the latter was shown to be less effective and more prone to dose reductions in patients over the age of 65. As life expectancy increases, an impetus to treat based on so-called physiologic age has emerged—although there are currently little data to inform this strategy. The age range of 60–70 years old is best regarded as a gray zone, in which individualized attention to comorbidities, patient preference, and disease characteristics may allow selection of intensive regimens for suitable patients.

In this patient, with comorbidities including chronic renal insufficiency, R-CHOP with maintenance rituximab is the optimal choice among those presented. In recognition of the German STiL study, which found that bendamustine rituximab improved median progression-free survival compared to R-CHOP in a subgroup of MCL patients (33 months for BR compared to 23 for R-CHOP), BR is also feasible. In that study, alopecia, neutropenia, neuropathy, and growth factor utilization were less frequent with BR; only skin rash and lymphopenia were more common than in R-CHOP. However, the STiL results have yet to be confirmed. A preliminary report of the BRIGHT study, comparing BR to R-CHOP or RCVP (rituximab, cyclophosphamide, vincristine, and prednisolone) in follicular and mantle cell lymphoma, showed higher rates of infusion reactions, nausea, vomiting, and respiratory complications with BR. At present, R-CHOP and RCVP remain reasonable choices for first-line chemotherapy for elderly patients with MCL.

Extended rituximab therapy, or rituximab maintenance, is supported by a recent study that compared R-CHOP to FCR, and 2 years of rituximab to interferon maintenance, in MCL patients using a two-step randomization. This study enrolled 560 patients, with a median age of 70 years, and found superior survival with R-CHOP, with less hematologic toxicity; and maintenance rituximab decreased the risk of progression or death by 45%. Based on these data, 2 years of rituximab maintenance has emerged as a reasonable strategy in this population.

Lenalidomide clearly has activity in mantle cell lymphoma, and it is currently being compared to R-CHOP and follicular lymphoma, but a paucity of data exist for first-line lenalidomide in MCL. Temsirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), has efficacy in relapsed or refractory mantle cell lymphoma, but it is not currently approved for this indication in the United States. Further studies to better define its role and that of other mTOR inhibitors are underway.

Case study 41.6

A 56-year-old with MCL who underwent R-CHOP for six courses, followed by auto-SCT and rituximab maintenance for 2 years, is seen for evaluation. Now 5 years after auto-SCT, he has developed progressive pancytopenia. Bone marrow biopsy shows 40% involvement with MCL in a hypocellular marrow and reduced trilineage hematopoiesis, and imaging reveals 3 cm retroperitoneal adenopathy. Absolute neutrophil count is 600/μL, and hemoglobin is 8.6 g/dL without evidence of hemolysis.

1. What is the next best therapy?

A. Fludarabine, cyclophoshamide, and rituximab
B. Bortezomib
C. Lenalidomide
D. Rituximab + hyperCVAD
E. Radioimmunotherapy with Y-90 Ibrituimomab tiuxetan

Treatment of relapsed or refractory mantle cell lymphoma requires consideration of an individual's prior therapy, comorbidities, and the nature of their relapse. In this patient with a hypocellular marrow after auto-SCT, the option most likely to offer an acceptable hematologic toxicity profile is bortezomib. Bortezomib gained US Food and Drug Administration approval based on a phase II study showing a 33% response rate and a median response duration of 9.2 months, with acceptable toxicity with the exception of neuropathy and reactivation of herpes zoster necessitating

(*Continued*)

antiviral prophylaxis. Subcutaneous administration of bortezomib is associated with less neuropathy with preserved pharmacodynamic properties and efficacy in multiple myeloma; despite a lack of data specific to mantle cell lymphoma, subcutaneous dosing is a reasonable consideration. Lenalidomide is under ongoing study in mantle cell lymphoma, with data showing a response rate of 53% with a median response duration of over a year in mantle cell lymphoma. However, its principal toxicities are hematologic, including grade 3 neutropenia in 40% of patients, making it a potentially unsafe option in this patient.

Fludarabine is also likely to pose excessive risk of hematologic toxicity if given at standard doses with cyclophosphamide. HyperCVAD is not an optimal choice based on risk of anthracycline cardiotoxicity, because this patient was presumably exposed to a 300 mg/m^2 cumulative dose of doxorubicin with six courses of R-CHOP. Finally, radioimmunotherapy is not feasible in patients with significant marrow involvement due to lymphoma; it is an exclusion criterion for clinical trials of reduced-intensity transplant (RIT) and carries concern for excess hematologic toxicity in that setting. Although not an option listed, reduced-intensity allogeneic stem cell transplantation should be considered in this patient if his disease is sensitive to second-line therapy, and concurrent myelodysplasia investigated in light of his marrow findings. For young patients with chemosensitive disease, this approach offers the chance of cure, albeit in a minority of patients. Referral to a hematopoietic transplantation center, ideally for consideration of allogeneic transplantation in the context of a prospective clinical trial, should be entertained early in the course of relapse.

Of particular interest are novel agents targeting dyregulated intracellular signaling pathways related to MCL tumor growth, differentiation, and survival. The orally administered inhibitor of Bruton's tyrosine kinase, PCI32765 (Ibrutinib), was recently shown to produce a high response rate in relapsed and refractory mantle cell lymphoma, irrespective of prior exposure to bortezomib. Novel therapies addressing the specific pathobiology of mantle cell lymphoma, particularly cell cycle dysregulation and genetic instability, hold potential to reverse the pattern of continual relapse and shortening remissions that continues to characterize MCL in the present era.

Case study answers

Case study 41.1

Question 1: Answer C

Case study 41.2

Question 1: Answer E

Case study 41.3

Question 1: Answer A ("Yes")

Case study 41.4

Question 1: Answer D

Case study 41.5

Question 1: Answer D

Case study 41.6

Question 1: Answer B

Selected reading

Geisler C, Kolstad A, Laurell A, *et al*. Mantle cell lymphoma—does primary intensive immunochemotherapy improve overall survival for younger patients? Leuk Lymphoma. 2009;50:1249–56.

Herrmann A, Hoster E, Zwingers T, *et al*. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol. 2009;27:511–8.

Romaguera JE, Fayad LE, Feng L, *et al*. Ten-year follow-up after intense chemoimmunotherapy with rituximab-hyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010;150:200–8.

Shah BD, Martin P, Sotomayor EM. Mantle cell lymphoma: a clinically heterogeneous disease in need of tailored approaches. Cancer Control. 2012;19(3):227–35.

Vose JM. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. Am J Hematol. 2012;87(6):604–9.

CHAPTER 42

Marginal zone lymphoma

Sarah Rutherford, Wayne Tam, and Peter Martin
Weill Cornell Medical College, New York, NY, USA

1. How is marginal zone lymphoma (MZL) distinguished from other non-Hodgkin's lymphomas (NHLs)?

MZLs originate in the marginal zone B-cells of lymph nodes, spleen, or mucosa-associated lymphoid tissue. The marginal zone is particularly prominent in areas of chronic exposure to antigenic stimulation, from either infectious or inflammatory sources. Exactly how chronic inflammation results in tumorigenesis is unclear and may vary among the different MZL subtypes. It is likely that there is a stepwise progression from reactive B-cell, to localized antigen-dependent tumor, to antigen independence and more aggressive phenotypes. Ultimately, abnormal B-cell clones arise, then proliferate and replace the normal B-cell population.

Cytological features of MZLs are quite variable. They can resemble germinal center centrocytes, with small to medium size, slightly irregular nuclei, moderately clumped chromatin, and inconspicuous nucleoli. Sometimes they have a monocytoid appearance with round or irregular nuclei, more abundant pale cytoplasm, and distinct cytoplasmic membranes. In some cases, they resemble closely small lymphocytes. Plasmacytoid or plasmacytic differentiation can be seen in up to 30 to 50% of cases. Scattered larger transformed cells resembling centroblasts or immunoblasts are usually present. These large cells should not constitute the majority of the cells present, become confluent, or form diffuse sheets, which would signify disease progression and transformation to large-cell lymphoma. The growth pattern of the lymphoma cells is frequently parafollicular with a marginal zone distribution. Interfollicular and diffuse areas of involvement may also be seen. In nodal MZL and mucosa-associated lymphoid tissue (MALT) lymphomas, residual reactive follicles are frequently present, which can be hyperplastic, regressed, or sometimes colonized by neoplastic cells. The typical immunophenotype of MZL is CD20+, CD79a+, CD5−, CD10−, and CD23−. CD21 can be positive. Most nodal MZLs and MALT lymphomas are sIgM+ and IgD−, while sIgG+ and sIgA+ are less common. Splenic MZL (SMZL) is typically sIgMD+. Rare cases of MZL are CD5+ and may carry a worse prognosis. Neoplastic B-cells in cases with plasmacytoid or plasmacytic differentiation express MUM1–IRF4 and monocytypic cytoplasmic immunoglobulins. Extranodal MZLs are commonly associated with chromosomal abnormalities, including t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), t(3;14)(p12;q32), and trisomy 3 or 18. Many of the genetic changes found in MZLs result in upregulation and constitutive activation of the nuclear factor kappa B (NF-kB) pathway, suggesting a vital role in its pathogenesis as well as a target for future therapies.

Due to limitations in available pathologic material, it can be challenging to differentiate MZL from other subtypes of indolent B-cell lymphomas, and "small B-cell lymphoma" is frequently reported as the diagnosis. The following subquestions discuss diagnoses that can be confused with MZL and tips to differentiate between them. A collaborative effort between clinicians and pathologists is often required to arrive at the correct diagnosis.

• **How is MZL distinguished from chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL)?**
CLL and SLL are characterized by small lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes. The typical immunophenotype is CD5+ and CD23+. Rare cases of CD5+ MZL can be difficult to distinguish from CLL and SLL. For those cases, dim CD20 and surface immunoglobulin expressions, as well as lack of FMC7, favor CLL or SLL. A nodal or extranodal clinical presentation with minimal marrow involvement favors a diagnosis of MZL but should not be used as the sole criterion for differentiation. Morphologically, CLL and SLL tend to

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

exhibit more monotony and have a diffuse growth pattern. Proliferation centers (pseudo-follicles) are frequently seen, particularly in the lymph nodes. MZL is characterized by small to medium-sized lymphocytes surrounding a reactive follicle. In addition, plasmacytic and plasmacytoid differentiation is common in MZL but not CLL or SLL. Except for unusual cases, these diseases do not share common cytogenetic abnormalities, and fluorescent in situ hybridization (FISH) for common genetic anomalies associated with CLL, SLL, and MZL can be helpful in differentiating MZL from the others.

• How is follicular lymphoma (FL) distinguished from MZL?

FL is the most common indolent non-Hodgkin's lymphoma and can present similarly to MZL. However, the vast majority of FL cases are primary nodal FL, although extranodal dissemination can occur. FL is characterized by a follicular growth pattern, consisting of neoplastic germinal centers with markedly attenuated or absent mantle zones. Nodal MZL and MALT occasionally have a follicular growth pattern mimicking FL when follicular colonization is extensive. Staining for germinal center–associated markers like BCL6 and CD10, as well as BCL2 and Ki67, may also help to distinguish between FL and MZL with prominent follicular colonization. The residual germinal center B-cells are BCL6 and CD10 positive and BCL2 negative, with a very high proliferation rate highlighted by Ki67; the neoplastic MZL cells infiltrating the follicles are BCL6 and CD10 negative and BCL2 positive, with a low proliferation rate. FL with marginal zone differentiation may mimic nodal NZL. In those cases, immunostains with BCL6 and CD10 will help in the diagnostic evaluation. SMZLs usually have a micronodular growth pattern that may be mistaken for FL with splenic infiltration. However, the biphasic appearance of SMZL, coupled with the lack of BCL6 and CD10, differentiates it from FL. CD21 staining to highlight the distribution of follicular dendritic cell (FDC) meshwork is also useful in differentiating between FL and MZL (nodal and MALT types). In FL, FDC meshworks are often expanded and relatively more regular. In MZLs, the FDC meshworks can be expanded and fragmented when follicles are run over or colonized by the neoplastic MZL cells, or they can be small and tight, as seen in regressed follicles. While the majority (about 80%) of FL harbor t(14;18)(q32; 21) involving the BCL2 gene, t(14;18)(q32; 21) can also be found in a small percentage of MALT lymphomas. However, the MALT1 gene, not BCL2, is rearranged in t(14:18) in MALT lymphoma.

• How is mantle cell lymphoma (MCL) distinguished from MZL?

MCL typically presents with lymphadenopathy, but bone marrow and gastrointestinal tract involvement are very common. Morphologically, lymph nodes involved by MCL have a nodular or diffuse growth of monotonous small to medium-sized lymphocytes with irregular nuclear contours. MCL is CD5+, CD23 −/dim+, FMC7+, and CD43+, and is characterized by overexpression of cyclin D1 and the presence of t(11;14). FISH for t(11;14) is almost always positive, even in CD5− cases, making it relatively easy to distinguish from other types of lymphoma, including MZL. Cyclin D1–negative MCL may be difficult to distinguish from CD5-positive MZL. SOX11 is a useful ancillary stain in those circumstances. SOX11 is consistently positive in MCL, while it is negative in MZL.

• How is lymphoplasmacytic lymphoma (LPL) distinguished from MZL?

LPL is an indolent lymphoma of small B lymphocytes with plasmacytic differentiation (i.e., plasmacytoid lymphocytes and plasma cells are also present); it tends to involve the bone marrow but can be found in lymph nodes or spleen in 15–30% of cases. A paraprotein, usually immunoglobulin M (IgM), is common but is not diagnostic of LPL and can also occur in cases of MZL with plasmacytoid differentiation. There is considerable morphologic and immunophenotypic overlap between MZL and LPL. Centrocyte-like and monocytoid cells, which can be seen in MZL, are absent in LPL. However, in bone marrow biopsies, neoplastic MZL cells appear often as small lymphocytes, and MZL with plasmacytoid and plasmacytic differentiation can be difficult to distinguish from LPL, especially when the involvement by the former is extensive. Immunohistochemistry is rarely helpful in differentiating between LPL and MZL. CD25 is more commonly positive in LPL, and CD11c is more commonly positive in MZL. Comparative genomic hybridization may help to differentiate MZL from LPL. While the two entities share deletions of 6q23 and 13q14 and gains of 3q13–q28, 6p, and 18q, gains of 4q and 8q are associated with LPL but not MZL. Recently, the L256P mutation of the MYD88 gene was reported to be present in almost all cases of LPL but was uncommon in MZL. A polymerase chain reaction (PCR) assay designed to detect and quantify this mutation identified it in 97/104 patients with Waldenström's macroglobulinemia and 2/20 patients with SMZL. This finding, however, needs to be verified in additional patient populations before being adopted into routine clinical use.

• How are other indolent splenic B-cell lymphomas distinguished from SMZLs?

The differential diagnoses for SMZLs include a number of small B-cell lymphomas involving the spleen that are recognized by the World Health Organization (WHO) as splenic B-cell lymphoma, unclassifiable, and hairy cell leukemia (HCL). The two best-defined provisional entities of these categories are splenic diffuse red pulp small B-cell

lymphoma and hairy cell leukemia variant (HCL-v). Differentiation of these entities by peripheral blood cytology can be difficult, since they share similarities including the presence of villi. Morphologic features are more distinct among these entities. In the spleen, SMZL involves the white pulp and also the red pulp in a follicular or micronodular pattern. A biphasic cytological pattern typically observed is characterized by small round lymphocytes in the interior of the follicles surrounded by an outer zone of marginal zone cells with more abundant pale cytoplasm, admixed with scattered larger transformed cells. Splenic diffuse red pulp small B-cell lymphoma involves the red pulp with both cord and sinusoidal patterns. The neoplastic cell population is monotonous with scattered blasts, and it does not show follicular replacement, biphasic cytology, or marginal zone infiltration. An intrasinusoidal infiltration pattern is consistently seen in the bone marrow. HCL and HCL-v diffusely involve the red pulp, and the white pulp is atrophic. Immunophenotypically, SMZL cells express IgM and almost always IgD, while splenic diffuse red pulp small B-cell lymphoma, HCL, and HCL-v tend to be IgG positive. CD103 and CD11c are more frequently positive in HCL and HCL-v. Contrary to SMZL, HCL is also positive for Annexin A1, TRAP, and CD25. About 40% of SMZLs show allelic loss of chromosome 7q22–36, which is not found in splenic diffuse red pulp small B-cell lymphoma. HCL has been found to harbor a V600E mutation in the BRAF gene. This may serve as a molecular marker for HCL that could potentially distinguish it from SMZL, although it has not yet been adopted into diagnostic criteria. Although analysis of both bone marrow and peripheral blood lymphocytes is the primary means of diagnosis, occasionally the only way to acquire sufficient material for pathologic diagnosis is to perform a splenectomy. Under these circumstances, the clinician must weigh the benefits of having a precise diagnosis against the risks of the procedure.

2. How are the types of MZL distinguished?

• How is SMZL different from nodal MZL and MALT lymphoma?

Although considered an MZL like nodal MZL and MALT lymphoma, SMZL actually is quite distinct from the other two entities in terms of clinical, immunophenotypic, and genetic features. The putative origin of SMZL is a splenic B-cell of unknown differentiation stage with variable somatic mutations (present in about 50% of cases) in the Ig heavy-chain variable (IGHV) region. Its relationship to normal marginal zone B-cells is controversial, but it is thought that SMZL might develop from a B-cell that has been exposed to chronic antigenic stimulation in the germinal center and has the capacity for marginal zone differentiation supported by the splenic environment. Analysis of the B-cell receptors of SMZL revealed stereotypical antigen-binding regions and selective usage of specific immunoglobulin heavy variable alleles, for example VH1-2, implying that stimulation of the B-cell clones is driven by a common antigen. SMZL is frequently associated with hepatitis C infection. The mechanism may involve an interaction between the HCV E2 glycoprotein, with CD81 resulting in B-cell receptor activation and proliferation of B cells. Common cytogenetic abnormalities include deletions in 7q and gains in 3q. Although the t(11;18) and t(14;18) seen in MALT lymphomas are not seen in SMZL, activation of NF-kB is common, suggesting a similar pathobiology. Recent genomic evaluation of SMZL revealed activating mutations in NOTCH2 as the most frequent lesions.

Patients with SMZL typically present with splenomegaly and associated cytopenias. Lactate dehydrogenase is typically within normal limits, but beta 2-microglobulin is frequently elevated. A monoclonal paraprotein is seen in 10–40% of cases. These patients often have splenomegaly but are not always symptomatic. Autoimmune hemolytic anemia, immune thrombocytopenic purpura, cold agglutinin, acquired von Willebrand disease, lupus anticoagulant, and other autoimmune phenomena are found in 10–15% of SMZL patients. SMZL commonly involves the bone marrow as well as peripheral blood and splenic hilar lymph nodes. Dissemination to other extranodal sites is uncommon, making clinical presentation one of the more important diagnostic factors. The diagnosis of SMZL is typically made from morphologic and immunophenotypic examination of peripheral blood or bone marrow; examination of the spleen pathology is not usually required. SMZLs frequently have peripheral blood involvement, which is rare in nodal MZL and MALT lymphoma. The immunophenotype of SMZL is similar to that of other MZLs, except that IgD is almost always present in SMZL but absent in MALT lymphoma.

• How is nodal MZL (NMZL) different from SMZL and MALT lymphoma?

NMZL was categorized as a distinct type of lymphoma in the 2008 WHO classification. It develops in lymph nodes and is often disseminated at presentation (stage III–IV). Reported 5-year OS in NMZL ranges from 55–75% as compared to 50–85% in SMZL and 85% in MALT lymphoma. For a primitive diagnosis of NMZL, primary involvement of extranodal sites must be excluded, as one-third of cases with nodal involvement are secondary to extranodal disease. NMZL may be difficult to distinguish from nodal dissemination of a MALT lymphoma or SMZL in lymph node biopsies. A thorough clinical history is very important for making this distinction. SMZL often involves splenic hilar lymph nodes and, infrequently, other peripheral lymph nodes. Unlike nodal MZL and MALT lymphoma

with nodal involvement, a marginal zone growth or marginal zone differentiation of the neoplastic B-cells is rarely seen. Instead, the neoplastic SMZL cells resemble small round lymphocytes and have a micronodular growth pattern with sparing of the sinuses. NMZL often has a greater proportion of large cells and an elevated mitotic index compared to the other types of MZL. The presence of IgD makes a nodal involvement by MALT highly unlikely. Dissemination to bone marrow is found more frequently in SMZL than NMZL but occurs in about one-half of patients with NMZL. Trisomy 12 may be more common in NMZL than in the other types of MZL. NMZL is less likely to be associated with autoimmune disease than MALT lymphoma, although cases of hemolytic anemia have been reported.

Treatment controversies

1. What is the role of splenectomy in SMZL?

Splenectomy may serve both diagnostic and therapeutic roles in SMZL. Although the gold standard for diagnosis is evaluation of spleen histology, splenectomy is infrequently worthwhile as a purely diagnostic procedure. The morphology, immunophenotype, and cytogenetics of peripheral blood and bone marrow can be used to make the diagnosis in most cases. Only when more aggressive lymphomas or histologic transformation is suspected is diagnostic splenectomy absolutely indicated. The degree of fluoro-deoxyglucose uptake seen on positron emission tomography imaging can be associated with indolent versus aggressive histologies and can be helpful in guiding management.

Many patients with SMZL can be monitored closely without treatment until cytopenias or symptoms secondary to splenomegaly necessitate therapeutic intervention. Therapeutic splenectomy is followed by a median of 8 years without treatment despite persistent bone marrow and peripheral blood involvement, and is commonly cited as the standard first-line approach. Increasing experience with rituximab suggests that it may have a role as front-line therapy. In contrast to the morbidity and mortality associated with splenectomy, single-agent rituximab is associated with minimal impact on quality of life, results in a low risk of infection, appears to result in durable remissions in the majority of patients, and may be reused successfully at the time of relapse. A recent retrospective review of 43 patients with SMZL reported that 34/43 patients treated with rituximab (either alone or in addition to chemotherapy) achieved a complete response (CR). Disease-free survival at 3 years was 79% with rituximab and 29% with splenectomy alone. In this series, only 3/10 patients treated with chemotherapy alone (fludarabine and cyclophosphamide) achieved CR. Multiple other case reports and case series have failed to show a significant response from chemotherapy. Given the lack of randomized phase III clinical trials, it is unlikely that an overall survival benefit will be demonstrated in the near future. However, rituximab has demonstrated a survival benefit in virtually every other B-cell lymphoma studied, suggesting at least a potential to improve survival in SMZL. When SMZL is associated with hepatitis C virus (HCV), antiviral treatment should be initiated, as pegylated interferon and ribavirin have been shown to result in a complete remission of SMZL in 75% of cases.

We therefore rarely recommend diagnostic or therapeutic splenectomy. We recommend watchful waiting in asymptomatic patients with SMZL, antiviral therapy for those cases associated with HCV, and a consideration of rituximab for front-line treatment in symptomatic patients who are HCV negative. The addition of chemotherapy to rituximab should be considered depending on patient factors (e.g., age and comorbid conditions) and disease factors (e.g., the extent of disease and acuity of illness).

2. What is the best treatment for localized MALT lymphoma?

Here, we review treatment of early-stage MALT lymphomas. While there is evidence to support treatment of localized MALT in particular sites, a review of 44 patients with stage I–II MALT did not find a significant difference in 5-year overall survival (OS) among those patients treated with curative intent versus those who were not treated with curative intent.

- **What is the role of surgery for pulmonary MZL (or bronchial-associated lymphoid tissue (BALT) lymphoma)?**

BALT lymphomas, like other types of MZL, are indolent and often remain solely in the lung(s) for many years. A standard treatment approach has not yet been established. The largest cohort identified was 326 patients from the SEER database. Fifty-one percent were treated with surgery. All of the patients who had surgical resection of BALT lymphoma had a CR. The second most common treatment modality was radiation (7%). Median OS was 112 months. This suggests that these patients do well regardless of treatment modality.

In addition to surgical resection, radiation, or watchful waiting, several small studies have reported outcomes following treatment with various chemotherapy regimens. Reponses related to treatment with rituximab were often reported in combination with chemotherapy regimens and rarely as a single agent. In a review of 21 patients, responses to chemotherapy regimens, including cyclophosphamide, vincristine, prednisone (CVP), or chlorambucil and prednisone, were variable: two patients had CR, two had partial response (PR), two had stable disease, and one had pro-

gressive disease. The four untreated patients remained free from progression of the disease after 40.5 months. Second-line treatment with radiation resulted in CR in all patients who were treated with that modality. A review of 22 patients suggested that surgery is optimal for unilateral, disease whereas multifocal disease could be treated with combination chemotherapy or watchful waiting. In that study, 6 patients were treated with surgery, 2 were treated with radiation therapy, and 12 were treated with chemotherapy and/or rituximab. Seven of nine patients who received a CR had unilateral disease. The two treated with single-agent rituximab had a PR. All patients, including the 2/10 patients with bilateral disease, were alive after a median follow-up time of 36 months. A recent retrospective study of 17 patients treated with fludarabine and mitoxantrone (FM), plus or minus rituximab, reported a CR in over 80% of patients. Patients were treated upfront if they had bilateral disease or if they developed progression respiratory symptoms. All patients who received FM plus rituximab achieved CR. At a median follow-up time of 5 years, 75% of patients were still in CR. The reported side effects were primarily related to myelosuppression.

Given the indolent nature of the disease, we believe that asymptomatic patients with BALT lymphoma can be followed closely without treatment. Surgical resection is a reasonable first-line option for those who have localized disease, although surgery is not without risks and often causes reduction in lung function. Radiation can be considered but may be associated with similar morbidity. No strong data support the use of rituximab monotherapy in BALT lymphoma, but given its role in other B-cell lymphomas we typically add it to other systemic therapies. In symptomatic patients, data for treatment with fludarabine and mitoxantrone are compelling, though potential side effects are serious and should be weighed when considering treatment.

• Should ocular adnexal MALT lymphoma (OAMZL) be treated with antibiotics?

MZL of the ocular adnexae (conjunctiva, lacrimal gland, or orbit soft tissue) has been associated with *Chlamydial psittaci* infection. Diagnosis of *C. psittaci* requires a labor-intensive process of PCR from DNA extracted from ocular specimens or conjunctival swabs. The detection of this infection in patients with ocular adnexal MZL varies significantly depending on geographic location even within the same country. The highest incidence has been reported in Italy, Austria, Korea, and Germany. A phase II trial in Italy investigated the use of doxycycline 100 mg daily for 3 weeks in patients with stage IE MZL of the ocular adnexae. The patients in this study received antibiotic therapy regardless of their chlamydial infection status. Eradication of *C. psittaci* was documented in 14/34 patients with objective regression of the lymphoma in 12 of those cases (6 CR and 6 PR). A study of 38 patients reported that OAMZL patients initially unresponsive to a 3-week course of doxycycline demonstrated an improved response after a second 3-week course of the antibiotic.

Chemotherapy and radiation therapy are alternate treatment options for OAMZL. Chlorambucil was studied in 33 patients with a median total dose of 600 mg over four courses of treatment; 79% had CR. Mean follow-up time was 32 months, and no major side effects occurred. A retrospective study of 24 patients treated with radiation (24–25 Gy) reported that 100% of patients achieved a CR. PFS was 90% at 2 years and 81% at 5 years. Radiation to the ocular adnexae has been associated with conjunctivitis, dry eye, keratitis, and cataracts; the amount of radiation in the current study is less than in prior studies and is asserted to have less toxicity.

Single-agent rituximab has infrequently been reported in OAMZL patients. In a study of eight patients treated with this agent, five previously untreated patients had a CR after receiving rituximab, but the median time to relapse was 4 months. Radioimmunotherapy with ^{90}Y ibritumomab tiuxetan has also been reported as an effective front-line treatment option and is worthy of further evaluation.

We do not think that antibiotics are sufficient to cure most cases of ocular adnexal MZL, particularly in North America. However, in certain populations and in asymptomatic individuals, it may be worthwhile to start with a trial of doxycycline. Radiotherapy is currently the most accepted front-line treatment for symptomatic patients, although systemic therapy is also a reasonable option. As with other indolent lymphomas, we believe that it is important to avoid overtreatment, and frequently observe asymptomatic patients or pursue trials of less aggressive treatment (single-agent rituximab) prior to initiating radiotherapy or chemotherapy.

• How should primary cutaneous MZL (PCMZL) be managed?

PCMZL is an uncommon form of MZL in which patients present with unifocal or, more commonly, multifocal cutaneous lesions. Rarely does PCMZL develop extracutaneous manifestations in the absence of aggressive transformation. Management is dependent on the extent of the disease. Solitary lesions can be treated with curative intent using surgical resection or radiotherapy, but relapse at a distant site is common. Disseminated disease can often be managed with observation alone. Treatment options include intralesional rituximab, interferon alpha, steroids, and chemotherapy. A link between PCMZL and *Borrelia burgdorferi* has been suggested, but there is little evidence to support this connection or antibiotic treatment. A retrospective analysis of 35 patients with indolent primary cutaneous lymphomas, including 18 patients with MZL treated with intralesional rituximab (often in second- or third-line settings),

reported CR of 71% with a median follow-up of 21 months. Though the CR rate is less than that observed with surgery or radiotherapy, it is a reasonable option for treatment in cases in which there are multiple lesions or lesions located in areas in which it would be difficult to surgically excise or radiate.

• Which cases of gastric MALT lymphoma are least likely to respond to eradication of *Helicobacter pylori*? Should they be treated with radiation?

Gastric MALT lymphoma is the sole subtype for which strong evidence of response to antibiotic therapy exists. However, among patients with early-stage gastric MALT lymphoma, the response to *H. pylori* eradication varies from 60% to 100%. First, those patients without evidence of *H. pylori* infection are unlikely to respond to antibiotic therapy. Second, gastric lymphomas with the t(11;18) cytogenetic aberration are unlikely to respond to *H. pylori* eradication and should probably be managed with alternative therapies such as radiation. Finally, those patients with locally advanced disease (i.e., involvement of the muscularis mucosae or local lymph nodes) have a significantly lower CR rate. Nonetheless, it may be reasonable to attempt antibiotic therapy in patients with locally advanced disease without other indications for more aggressive therapy since the disease is likely to be indolent and *H. pylori* eradication would otherwise be recommended. Patients with localized disease that does not respond to *H. pylori* eradication should be considered for radiotherapy. Despite the potential advantage of therapy with curative intent, there is no evidence that it necessarily prolongs survival, and watchful waiting can be considered in asymptomatic patients. Most of these patients will eventually require radiotherapy or chemotherapy.

3. What is the optimal first-line treatment for advanced-stage NMZL?

There is no standard front-line treatment approach for advanced NMZL. A prognostic scale has not been developed specifically for NMZL, but the International Prognostic Index (IPI) and Follicular Lymphoma International Prognostic Index (FLIPI) scales have been used to stratify patients with NMZL. Overall, patients with NMZL tend to have a poorer prognosis than those with MALT lymphoma even in stage IV disease; they also have a poorer prognosis than patients with FL or CLL. Asymptomatic patients with a low tumor burden can be monitored without treatment. We generally avoid front-line use of purine analogs due to concern over risk of myelodysplasia. Controversy exists regarding the use of regimens containing anthracyclines, with some suggesting that anthracyclines should be considered in NMZL because of a more aggressive course than other MZLs. Based on the reported efficacy of non-anthracycline regimens, we typically reserve anthracyclines for use in patients with known or suspected large cell transformation. The recent phase III study comparing bendamustine–rituximab (BR) with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with indolent or mantle cell lymphoma included a small number of patients with NMZL and SMZL. Although this study reported a significant increase in median PFS with BR in the overall study population (69.5 vs. 31.2 months; hazard ratio: 0.58; 95% CI: 0.44–0.74), this difference was not significant in patients with MZL. To date, there have been no phase III studies that have evaluated the addition of rituximab to chemotherapy in patients with NMZL. The International Extranodal Lymphoma Study Group (IELSG) 19 trial evaluated chlorambucil with or without rituximab in patients with advanced-stage MALT lymphoma and found a superior response rate and event-free survival with no difference in OS at 5 years. We recommend managing patients with advanced-stage ENMZL similarly to patients with FL. We generally observe asymptomatic cases, consider rituximab as a single agent in low-risk patients, and treat with rituximab plus chemotherapy in patients with more extensive and/or symptomatic disease.

4. What is the role of maintenance rituximab?

The RESORT trial reported on the use of maintenance rituximab in patients with previously untreated, low-tumor-burden CLL, SLL, MZL, and FL. All but one of the 137 patients with MZL, CLL, or SLL were at stage III–IV. Each patient was treated with single-agent rituximab 375 mg/m^2 weekly for 4 weeks. The 57 patients who achieved a CR or PR were randomized to receive maintenance rituximab (one treatment every 3 months) or rituximab at time of progression (four treatments). In contrast to patients with FL, fewer patients with CLL, SLL, and MZL responded to the initial rituximab, but of those who did respond, the time to treatment failure was significantly longer in those treated with maintenance rituximab (3.74 years) versus treatment at time of progression (1.07 years). This suggests that there may be a role for maintenance rituximab in those patients with low-tumor-burden MZL who respond to single-agent rituximab when given as front-line therapy. The use of rituximab maintenance following immunochemotherapy has not been adequately evaluated in MZL. We recommend caution when extrapolating data from phase III trials in other histologies and general avoid maintenance in this setting.

MZL is unique in the requirement for a multidisciplinary approach to diagnosis, staging, and treatment, especially among pathologists and clinicians. Cooperative groups like the IELSG, and collaborative relationships between academic and community physicians, will play an important

role in improving the understanding and management of these lymphomas. MZLs are an interesting group of diverse lymphomas, each one rare as a single entity, but all sharing a common pathogenesis. As we learn more about the biology of the MZLs, we are likely to discover features or therapeutic targets that are common to other B-cell lymphomas.

Selected reading

Bertoni F, Coiffier B, Salles G, *et al*. MALT lymphomas: pathogenesis can drive treatment. Oncology. 2011;25(12):1134–42.

Ferreri AJM, Govi S, Pasini E. *Chlamydophila psittaci* eradication with doxycycline as first-line targeted therapy for ocular adnexae lymphoma: final results of an international phase II trial. J Clin Onc. 2012;30(24):2988–94.

Kang HJ, Kim HJ, Kim SJ, *et al*. Phase II trial of rituximab plus CVP combination chemotherapy for advanced stage marginal zone lymphoma as a first-line therapy: consortium for improving survival of lymphoma (CISL) study. Ann Hematol. 2012;91:543–51.

Rossi D, Trifonov V, Fangazio M, *et al*. The coding genome of splenic marginal zone lymphoma: activation of NOTCH2 and other pathways regulating marginal zone development. J Exp Med. 2012;209(9):1537–51.

Thieblemont C, Davi F, Noguera M, *et al*. Non-MALT marginal zone lymphoma. Curr Opin Hematol. 2011;18:273–9.

Zinzani PL, Pellegrini C, Gandolfi L, *et al*. Extranodal marginal zone B-cell lymphoma of the lung: experience with fludarabine and mitoxantrone-containing regimens. Hematol Oncol. 2013;31:183–8.

CHAPTER 43

Primary mediastinal large B-cell lymphoma

Pier Luigi Zinzani

Institute of Hematology "Seràgnoli," University of Bologna, Bologna, Italy

Primary mediastinal large B-cell lymphoma (PMLBCL) is a subtype of diffuse large B-cell lymphoma (DLBCL) that has distinct clinical and molecular features. First recognized in the 1980s, PMLBCL was formally established as a distinct subtype of DLBCL in the revised European and American classification of lymphoid neoplasms and, more recently, the World Health Organization classification. It represents 2–3% of all non-Hodgkin's lymphoma cases and 6–10% of all DLBCL, and it has a worldwide distribution. PMLBCL occurs more often in young women, with a male-to-female ratio of 1:2 and a median age in the fourth decade.

Clinical features

PMLBCL is characterized by a locally invasive anterior mediastinal mass. The mass originates in the thymus and frequently produces compressive symptoms early on, compromising the airway or great vessels, and producing a superior vena cava syndrome. As a result, at the time of diagnosis, 80% of cases have stage I–II disease; in 70% of patients, the mediastinal tumor is larger than 10 cm, often directly infiltrating the lung, chest wall, pleura, and pericardium. Pleural or pericardial effusions are present in one-third of cases. Local invasion results in cough, chest pain, dyspnea, or complaints resulting from caval obstruction. Systemic symptoms, mainly fever or weight loss, are present in less than 20% of cases. Spread to peripheral lymph nodes is infrequent; extranodal sites, however, may be involved, particularly at the time of disease recurrence, with a propensity for involvement of the kidneys, adrenals, liver, ovaries, and central nervous system. Bone marrow infiltration at presentation is rare.

Primary management

Initial therapy is critical in treating PMLBCL patients. Salvage therapy for recurrence or progressive disease is of limited efficacy; thus, the imperative is to cure at the first attempt when possible. In PMLBCL, there are several controversial topics that warrant further study and they are matters of debate, such as the superiority of third-generation regimens over cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based regimens, the impact of rituximab, the use of involved-field radiotherapy, the assessment of clinical response by PET scan, and the utility of high-dose therapy.

- **Front-line therapy: first-generation or third-generation regimens?**

An optimum chemotherapy regimen option for patients with PMLBCL has not been clearly established, and the optimal treatment for PMLBCL patients has been a matter of debate. CHOP with or without radiotherapy (RT) is not sufficient, because cure rates do not exceed 50–60%. Some groups have suggested that more aggressive regimens, such as methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B), may be more effective. Retrospective studies have also suggested a potential benefit of high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), when used as a consolidation of response to first-line chemotherapy.

The approaches of this entity range from first-generation to third-generation chemotherapy regimens. Regarding the use of different chemotherapeutic regimens (CHOP or CHOP-like vs. third-generation regimens), a report by Fisher *et al*. showed that CHOP and intensive third-generation regimens produce equivalent results. Whereas the CHOP regimen has been used by American investigators, several European centers have suggested that the MACOP-B regimen may be superior to CHOP. However, the debate is still open because it is difficult to compare the advantages of the different types of protocols. On the basis of published phase II data by centers that have used both first-generation chemotherapy regimens like CHOP and

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

other more aggressive third-generation ones like MACOP-B, the results have clearly favored the latter. In two previous studies, we used the MACOP-B regimen in 50 patients (at our center and another Italian center) and in 89 patients (in an Italian multicenter prospective trial), in whom the CR rates were 86% and 88%, respectively, whereas the 5-year relapse-free survival (RFS) rates were 93% and 91%, respectively. In addition, two retrospective studies have reported data regarding the comparison between CHOP and CHOP-like regimens versus MACOP-B and MACOP-B-like regimens as induction chemotherapy in patients with PMLBCL. Our multinational retrospective study compared the outcomes of 426 patients with PMLBCL after first-generation (CHOP or CHOP-like regimens; 105 patients), third-generation [MACOP-B, V(etoposide) ACOP-B; 277 patients], and high-dose chemotherapy schedules (HDT and ASCT; 44 patients). In all these groups, for the most part patients underwent RT after chemotherapy. With chemotherapy, CR rates were 49%, 51%, and 53%, with the first-generation, third-generation, and high-dose chemotherapy strategies, respectively. The final CR rates, after RT on the mediastinum, became 61% for CHOP and CHOP-like regimens, 79% for MACOP-B and etoposide, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B) regimens, and 75% for high-dose regimens. Projected 10-year OS rates were 44%, 71%, and 77%, respectively; and projected 10-year progression-free survival (PFS) rates were 35%, 67%, and 78%, respectively. In addition, after RT, 81% of the patients who had already achieved a partial response obtained CR status. Todeschini *et al*. reported the long-term results from a retrospective multicenter Italian experience in 138 patients with PMLBCL treated with CHOP (43 patients) or MACOP-B or VACOP-B (95 patients). CR was 51% in the CHOP subset and 80% in the MACOP-B and VACOP-B group. The addition of RT on the mediastinum improved the outcome regardless of the type of chemotherapy. These two retrospective studies suggest the superiority of the third-generation chemotherapy strategies over first-generation ones.

A retrospective analysis of 153 patients from British Columbia reviewed outcomes from a geographical region where treatment choice was mandated by era-specific guidelines. Between 1980 and 1992, MACOP-B or VACOP-B was administered, moving to CHOP between 1992 and 2001 and then to rituximab with CHOP (R-CHOP) thereafter. The OS for the cohort was 75% at 5 years, with the OS at 5 years for those treated with MACOP-B or VACOP-B significantly higher at 87% compared with 71% for those patients treated with CHOP ($P = 0.048$).

- **What is the role of rituximab?**

Although derived from a very limited number of cases, preliminary clinical observations suggested the superiority of R-CHOP with or without RT over CHOP with or without RT, with a CR rate >80%. Those initial findings deserved confirmation in larger series, because the impressive results might have been a result of patient selection, publication bias, or merely chance. The Vassilakopoulos *et al*. study demonstrated that R-CHOP with RT, or even alone, may cure the vast majority of patients with PMLBCL, based on the analysis of 76 patients with adequate follow-up, demonstrating a 5-year failure-free progression rate of 81% and a long-term OS rate of 89%.

Anyway, the experience of R-CHOP in PMLBCL patients still remains limited, being mainly derived from small patient series. In a review of the Vancouver series, 18 patients aged <65 years were treated with R-CHOP and RT, achieving a 3-year OS rate of 82%, which is slightly (but not significantly) inferior to those seen with MACOP-B or VACOP-B.

Recently, Savage *et al.* reported an update on 59 patients treated with R-CHOP (with a PET scan at the end of the treatment). These data confirmed the superior outcome using R-CHOP compared to CHOP chemotherapy (historical data).

Results, which were similar to those of the Vancouver series, were recently published by a Korean group that reported 3-year PFS and OS rates of 79% and 83%, respectively, in 21 patients. Attempted comparison with CHOP-treated historical controls failed to show significant differences. In the context of the MabThera International Trial (MInT), 87 patients with good-prognosis PMLBCL [bulky stage I or stage II–IV, and an age-adjusted International Prognostic Index (aaIPI) score of 0 or 1] aged <60 years received six cycles of chemotherapy versus rituximab plus the same chemotherapy. More than 90% of patients received R-CHOP or R-CHOP with etoposide (R-CHOEP); etoposide (R-CHOEP) was used in 45% of these patients. RT was routinely administered to patients with bulky disease, so that 71% of the patients actually received 30–40 Gy mediastinal RT. The addition of rituximab to chemotherapy minimized the development of primary refractory disease (3% versus 24%; $P = 0.006$) and resulted in higher 3-year PFS (88% versus 64%; $P = 0.006$) and EFS (78% versus 52%; $P = 0.012$) rates, but the OS rate was only slightly greater (89% versus 78%; $P = 0.16$). Although derived from an unplanned subgroup analysis, these data provide the strongest evidence to date for the superiority of R-CHOEP over CHOEP in the treatment of PMLBCL patients.

Prior to the introduction of rituximab, several groups treated patients with PMLBCL using more intensive regimens, such as MACOP-B, dose-dense regimens, or even front-line consolidation HDT and ASCT. Most of those studies showed long-term failure-free survival (FFS) and OS rates of 65–85% and 70–88% (usually around 80% and 85%), respectively, which appear much better than the

results obtained with CHOP. However, none of these intensified approaches is now expected to provide results superior to those seen with R-CHOP.

A reasonable question arising from these observations is whether or not rituximab combined with more intensive chemotherapy would further improve the already impressive results. In our recent study, R-MACOP-B provided very good results, which, however, did not appear to be better than expected with MACOP-B alone when both were combined with RT. In our study, patients treated with a rituximab plus MACOP-B or VACOP-B regimen plus radiation therapy had a CR rate of 90%; this value is equal to the one obtained with the combination of third-generation chemotherapy regimens and radiation therapy without rituximab. In fact, literature data showed a mean CR of 83% (range: 79–88%) using MACOP-B or VACOP-B plus mediastinal radiotherapy. In addition, in our two previous studies (50 and 89 patients), the RFS rate was 93% at 96 months and 91% at 9 years, respectively; in both studies, all relapses occurred within 10 months. In a retrospective multinational study on 426 PMLBCL patients, the PFS rate was 67% at 10 years in the 277 patients treated with third-generation regimens plus mediastinal radiotherapy.

Comparing the data regarding the sole chemotherapy approach and the chemotherapy plus rituximab strategy, it is possible to extrapolate that there are no statistically significant differences in terms of RFS between third-generation regimens (MACOP-B and VACOP-B) without rituximab and first-generation regimens (CHOP and CHOP-like) plus rituximab. In addition, our study shows how the RFS rate obtained with the combination of third-generation regimens plus rituximab is absolutely the same as the one observed in the reports in which third-generation chemotherapy only was used.

On the basis of the reported nonrandomized trials, the best results in terms of CR and RFS rates seem to have come from the combination of MACOP-B and VACOP-B regimens. The role of rituximab in addition to chemotherapy is not clear. In fact, its combination with third-generation regimens does not change the final results in terms of CR and RFS rates; at the same time, the addition of rituximab to the CHOP regimen improves the CR and RFS rates in comparison to CHOP alone, but this improvement is not significantly different from the results achieved with MACOP-B and VACOP-B regimens without rituximab.

In addition, Moskowitz *et al*. reported a 78% FFS rate and 88% OS rate following four cycles of high dose R-CHOP-14 and three cycles of ifosfamide, carboplatin, and etoposide without RT. Interestingly, the National Cancer Institute group has presented very encouraging data regarding 51 patients with PMLBCL, who were treated with six to eight cycles of infusional dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) plus rituximab (DA-EPOCH-R), without consolidation RT. At a median follow-up of 5 years, the EFS and OS rates were 93% and 97%, respectively, significantly higher than in DA-EPOCH-treated historical controls without rituximab.

- **What is the role of radiotherapy as local consolidation?**

The role of mediastinal radiotherapy upon completion of chemotherapy remains unclear. The best reported outcomes in PMBL have been achieved with regimens that have incorporated radiotherapy in their planned primary treatment. Furthermore, it is clear from the IELSG series that many patients completing chemotherapy in PR may be converted to CR following radiotherapy and that radiotherapy may render active residual mediastinal masses gallium negative. Univariate and multivariate analysis in two retrospective series have suggested that receiving radiotherapy correlated to better event-free survival or OS.

However, excellent long-term results have been achieved with chemotherapy alone in some series. Following an era-specific shift in British Columbia toward the use of radiotherapy to consolidate response, there was no difference in PFS or OS by year. This observation held even with initially bulky tumors, and indeed in the whole population there was a trend toward improved PFS in the era before routine radiotherapy. From Memorial Sloan Kettering series, only 7% of patients treated with the NHL-15 regimen (comprising intensified doxoroubicin, vincristine, and cyclophosphamide) received radiotherapy. Excellent results with OS of 84% at a median follow-up of 10.9 years are reported with this chemotherapy-only approach. Similarly, the excellent results that have been reported with DA-EPOCH in combination with rituximab are purported to negate the need for radiation in this disease.

Given concerns about the long-term toxicity of radiation, a randomized study is needed to address its role (with the optimal integration of PET scan), especially now that rituximab is incorporated into therapy for PMLBCL.

- **What is the role of the PET scan?**

Owing to the prominent fibrotic component of PMLBCL, a residual mediastinal mass is often present upon completion of therapy. Distinction is needed between those that have residual disease and those that have simple fibrotic tissue. In the past, the ^{67}Gallium scan has demonstrated utility in the setting of PMLBCL and has identified patients who are likely to relapse. Recently, the PET scan has become the tool of choice in such situations, especially for evaluating residual mediastinal masses. These data clearly indicate that further evaluation is required before modifying planned therapy based upon PET evaluation alone in PMLBCL, with particular focus on the real role of radiotherapy post chemo-immunotherapy in PET-negative patients.

- **Is high-dose therapy useful?**

The low frequency of marrow involvement and the relatively young age of the PMDLBCL patient population is the basis of consideration of HDT and ASCT to consolidate first remission. Results from the GELTAMO registry have recently been reported. Thirty-five patients in first CR, but considered at "high risk" of relapse, underwent HDT with various preparative regimens. At 4 years, the OS and PFS were 84% and 81%, respectively. In the IELSG analysis, a limited number of patients ($n = 44$) underwent HDT, which resulted in an estimated OS of 77% at 10 years. In the Memorial Sloan Kettering experience, HDT with progenitor cell rescue at first remission was not superior to dose-dense sequential therapy. Based upon the results achieved with third-generation regimens and the likely benefit from the addition of rituximab, there is little at present to commend an HDT approach to consolidate first CR, even in poor-risk patients.

Selected reading

Dunleavy K, Pittaluga S, Maeda LS, *et al*. Dose adjusted EPOCH-rituximab therapy in primary mediastinal large B-cell lymphoma. New Engl J Med. 2013;368:1408–16.

Hamlin PA, Portlock CS, Straus DJ, *et al*. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. Br J Haematol. 2005;130:691–9.

Zinzani PL, Fanti S, Battista G, *et al*. Predictive role of positron emission tomography (PET) in the outcome of lymphoma patients. Br J Cancer. 2004;91:850–4.

Zinzani PL, Martelli M, Bendandi M, *et al*. Primary mediastinal large B-cell lymphoma with sclerosis: a clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy. Haematologica. 2001;86:187–91.

Zinzani PL, Martelli M, Bertini M, *et al*. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. Haematologica. 2002;87:1258–64.

CHAPTER 44

Burkitt lymphoma

Mark Roschewski and Wyndham Wilson

National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Case study 44.1

A 55-year-old man presents to the emergency department with the sudden onset of severe abdominal pain in his right lower quadrant (RLQ) over the preceding 2 days. He is afebrile with stable vital signs and slight tachycardia. He has significant point tenderness in his right lower quadrant. Complete blood count reveals a total white blood cell (WBC) count of 8.0×10^9/L, hemoglobin of 10.5 g/dL, and platelets of 110×10^9/L. Serum chemistries are notable for a lactate dehydrogenase (LDH) level of 2000 U/L and uric acid of 12.5 mg/dL with normal renal and hepatic function. A computed tomography (CT) scan of the abdomen and pelvis demonstrates a 6 × 8 cm abdominal mass arising from the cecum with a moderate amount of ascites. General surgery and medical oncology are consulted for recommendations regarding evaluation and management.

1. What are the diagnostic considerations in clinically suspected highly aggressive non-Hodgkin's lymphoma (NHL), as in this case?

In cases such as this, a highly aggressive NHL such as Burkitt lymphoma (BL) should be considered, and medical oncology consultation prior to biopsy is appropriate. Subclassification of NHLs relies on clinical, morphologic, and cytogenetic and molecular features, rendering the initial biopsy critical. In general, a fine-needle aspirate is insufficient. In the present case, BL should be suspected due to the location of the mass and the rapid onset of symptoms. BL is the fastest growing human tumor and can double in size in 24–48 h. It has a male predilection and usually occurs in children but is also seen in adults. BL presents in the abdomen in most cases and often will involve the cecum, mimicking appendicitis. Surgical resection of the tumor in BL has been associated with favorable outcomes, but it carries the potential for morbidity and can delay definitive therapy. In most cases, surgery is unnecessary with prompt institution of immunochemotherapy. Incisional biopsy via laparoscopy or adequate CT-guided core needle biopsies with tissue sent for fluorescent in situ hybridization (FISH) testing for rearrangements of the *MYC* oncogene is mandatory. Goal turnaround time from first suspecting BL to initiation of therapy is 48–72 hours, making a high initial index of suspicion critical. Morphologically, BL typically demonstrates a "starry sky" appearance of diffuse and monotonous small to medium-sized B-cells with a distinct immunophenotypic profile that is positive for surface IgM, CD20, CD10, and B-cell lymphoma-6 (BCL6), and negative for BCL2, which distinguishes it from diffuse large B-cell lymphoma (DLBCL). Still, unclassifiable cases with intermediate features exist, and hematopathologists may have difficulty distinguishing BL from DLBCL on morphologic grounds alone, further supporting the need for FISH testing.

2. What is the current understanding about the pathogenesis of BL and its relationship to DLBCL?

The normal germinal center B-cell is the suspected cell of origin for both BL and DLBCL, and these malignancies share overlapping clinical and pathologic features. While essentially all cases of BL have demonstrable *MYC* rearrangements, it is typically in the background of a few other aberrations ("MYC simple"). In contrast, up to 10% of newly diagnosed DLBCL cases will also harbor *MYC* rearrangements, but these cases are usually associated with multiple other chromosomal abnormalities ("MYC

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

complex"). Molecular classification studies readily distinguish between the two entities, demonstrating a unique gene expression profile for BL and suggesting that different oncogenic pathways are activated. *MYC* is pathognomonic of BL, but until recently, the cooperative pathways in BL were unknown. RNA-resequencing (RNA-seq) analysis on 28 biopsies of sporadic BL confirmed the molecular distinction of BL and identified many genes that were more frequently mutated in BL than DLBCL, including *TCF3*, *ID3*, and *TP53*. Another group recently reported that *ID3* mutations were seen in up to 38% of BL cases and not seen in cases of DLBCL. Components of the B-cell receptor (BCR) are upregulated by *TCF3*, similar to that seen in DLBCL but via a different mechanism. In the activated B-cell (ABC) subtype of DLBCL, BCR signaling requires the nuclear factor kappa B (NF-κB) pathway and is the "chronic active" form. In BL, however, the BCR signaling is independent of the NF-κB pathway and is more akin to "tonic" BCR signaling that engages phosphatidylinositide-3 (PI3) kinase (PI3K) signaling. RNA interference screens recently demonstrated that knockdown of the BCR subunit *CD79A* and inhibition of PI3K were toxic to BL cell lines, further supporting these as cooperative pathways in BL pathogenesis. In support of this hypothesis, Sander *et al*. (2012) demonstrated that combining constitutive c-MYC expression and PI3K activity in germinal center B-cells of the mouse led to tumors with a striking similarity to BL.

3. How do cofactors such as Epstein–Barr virus (EBV), malaria, and human immunodeficiency virus (HIV) contribute to the pathogenesis of BL?

The syndrome of rapidly enlarging tumors of the jaw in children was first described by the Irish surgeon Denis Burkitt while working in Uganda in 1958. Today, we subdivide BL into three clinical variants—endemic (African) BL, sporadic BL, and immunodeficiency (HIV)-associated B—with important differences in epidemiology, clinical presentation, and biology. Endemic BL, which is the most common subtype, occurs in developing countries such as equatorial Africa and Papua New Guinea. It frequently affects the jaw and is seen almost exclusively in children. Endemic BL is an apparent polymicrobial disease, with clonal EBV found in the neoplastic cells of virtually all patients; cases are also linked to the prevalence of malaria, and the incidence is highest in people with high titers of *Plasmodium falciparum*. In contrast, EBV occurs in 20–40% of sporadic BL and HIV-associated cases. Evidence for the oncogenic role of EBV stems from the fact that cell lines that have lost EBV do not induce tumors in mice, but re-infection with EBV reestablishes a malignant phenotype. EBV contributes to genomic instability in endemic BL. The relationship of HIV and BL was first noted in 1982; it may also increase the risk of BL, possibly via chronic stimulation of B-cells, as is suspected in malaria. Interestingly, HIV-associated BL can occur at any CD4 count, suggesting that immunosuppression itself is not the sole contributing factor. Gene expression profiles of the different subtypes reveal that cases of BL cluster separately from other lymphomas, confirming them as distinct entities but with some slight differences among the subtypes, with the endemic and immunodeficiency subtypes being almost identical.

4. What is the most effective chemotherapy regimen in BL?

Many effective regimens for BL exist, but many factors are considered during the initial treatment decision such as the patient's age and the presence of comorbidities. Patients treated with regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) have poor outcomes, and this is clearly inadequate therapy. The backbone of therapy for BL in developed countries is high-intensity, short-duration combination chemotherapy given in alternating cycles as originally developed for acute lymphoblastic leukemia (ALL) in children. BL regimens administer therapies directed at the central nervous system (CNS) in all patients without regard to tumor bulk or disease stage, although this practice may be unnecessary in patients with low tumor burden. BL regimens achieve complete remission in 80–90% of patients, but the risk of significant acute toxic effects is very high. Given the toxicity of the regimens, the age of the patient has important implications. Adult patients tolerate therapy poorly and are frequently unable to complete the therapy. The infusional regimen dose-adjusted infusional etoposide, vincristine, and doxorubicin with prednisone, cyclophosphamide, and rituximab (DA-EPOCH-R) has been used for both sporadic and HIV-associated BL, and has demonstrated a 100% complete response rate with much less toxicity. These findings are currently being validated in a multicenter phase II study utilizing a risk-adapted approach to patients with untreated BL (NCT01092182). Patients with low-risk disease, defined as Ann Arbor stage I–II disease that is negative by fluoro-deoxyglucose positron emission tomography (FDG–PET) after two cycles, are treated with three cycles of DA-EPOCH-R, whereas high-risk patients are treated with six cycles of DA-EPOCH-R. Cerebrospinal fluid (CSF) disease is determined by flow cytometry prior to therapy. Patients who have high-risk disease and are CSF negative on flow cytometry are given intrathecal (IT) therapy for CNS prophylaxis, while patients who are positive for CSF disease by flow cytometry are administered active IT therapy until the CSF is cleared. Patients with low-risk disease are not administered IT therapy. Risk-adapted approaches such as this may ultimately replace ALL-type regimens if comparable efficacy is demonstrated given the favorable toxicity profile.

5. Are subtypes of BL treated differently?

Subtypes of BL are not treated differently based on known biologic differences, but therapy depends upon the ability to administer the necessary supportive care. Because most cases of endemic BL occur in equatorial Africa, where medical resources are scarce, the use of ALL-like regimens is not possible. Dramatic responses to chemotherapy were reported in Africa with as little as a single dose of cyclophosphamide, but most patients relapsed and the survival of patients was probably no more than 10–20% until recently. In 2004, the International Network for Cancer Treatment and Research (INCTR) developed joint treatment protocols using a three-drug regimen of cyclophosphamide, methotrexate, and vincristine. These drugs were considered affordable and accessible in low-resource settings. With a uniform treatment protocol, the INCTR reported overall survival rates of 67% and 62% at years 1 and 2, respectively. Similarly, patients with HIV-associated BL are often unable to tolerate the high-intensity ALL-like regimens commonly employed for BL. In a limited number of patients, (short-course) DA-EPOCH-R has been shown to be highly effective after only 3–4 cycles of chemotherapy. These findings are currently being confirmed in a multicenter phase II study (NCT01092182). At the National Cancer Institute, we initiate therapy with DA-EPOCH-R for patients with sporadic BL regardless of risk status due to our preliminary results and relative lower toxicity compared to R-CODOX-M/IVAC or R-HyperCVAD/R. All high-risk patients are treated for six cycles, but low-risk patients who are negative by PET or CT after two cycles are treated with one more cycle of therapy. Patients with HIV-associated BL are given 3–4 cycles of immunochemotherapy, with rituximab given twice per cycle. It should be noted, however, that the NCI approach is done on a clinical trial and that choosing between available regimens varies widely across institutions based mainly on institutional experience. At this point, the presence of EBV co-infection does not have a known effect on the prognosis or treatment of BL.

6. What is the role of rituximab in BL?

Rituximab is a chimeric monoclonal antibody against CD20 that is an essential component of the treatment of both indolent and aggressive B-cell lymphomas. Until recently, the contribution of rituximab to outcomes in BL was not entirely clear because intensive chemotherapy resulted in such high remission rates. Phase II studies have reported the feasibility of rituximab use in BL, and Ribrag *et al.* (2012) recently reported the results of a randomized study of rituximab added to the backbone of the standard LMBA protocol in HIV-negative adult patients with BL. With rituximab given on days 1 and 6 of the first two courses of chemotherapy, they reported an improvement in event-free survival of 76% versus 64% at a median follow-up of 38 months without any obvious increase in toxicity. The 3-year overall survival also favored the use of rituximab (82% vs. 71%). Thus, rituximab should be included in the treatment regimen of all patients being treated for BL.

7. What is the most appropriate CNS prophylaxis method in BL?

Strategies to prevent CNS disease relapse are important considerations in the treatment of BL. Even though the incidence of CNS disease at diagnosis in sporadic BL is less than 10%, disease relapse within the CNS is a devastating clinical scenario. Ideally, all patients should have a lumbar puncture with flow cytometry to assess for CNS disease at diagnosis. Most regimens include high doses of systemic chemotherapy that crosses the blood–brain barrier (methotrexate and/or cytarabine), IT therapy, or both given to all patients. The toxicities of CNS-directed therapies, however, can be significant, and the most effective approach has not been well studied. The Cancer and Leukemia Group B (CALGB) observed that the use of prophylactic CNS irradiation led to intolerable short- and long-term complications, and it dropped its use from their protocols. Unlike DLBCL, where the risk of CNS disease is related to the presence of extranodal disease, the risk of CSF disease in BL is related to the tumor stage and total disease burden. Patients with low-risk disease and CSF that is negative by flow cytometry at diagnosis may not need CNS prophylaxis, but further research is needed to confirm these findings. High doses of cytarabine and methotrexate also contribute to myelosuppression and may not be essential in patients with low tumor burden. In endemic BL, however, patients often have CNS disease at diagnosis in the setting of localized disease involving only the jaw or sinus. In keeping with this, the outcomes are inferior in Africa in large part due to poor control of CNS disease.

8. What are the supportive care considerations in patients with newly diagnosed BL?

Aggressive supportive care with careful attention to the potential complications is essential. An improvement over the last decade in BL outcomes is likely due to modern supportive care measures. In places in which supportive care is limited, outcomes in BL are inferior. The most important consideration is prompt diagnosis and initiation of chemotherapy without delay. BL cells are rapidly proliferating, and tumor mass can double in 24–48 hours. Due to the rapid doubling, tumor cells may undergo spontaneous tumor lysis syndrome (TLS), and prevention is a major consideration when initiating therapy. Adequate hydration and allopurinol should be instituted in all cases prior to therapy. Electrolytes such as uric acid, potassium, calcium, and phosphorous should be closely monitored in order to

prevent and recognize signs of TLS. The recombinant urate oxidase, rasburicase, has been used to catalyze the uric acid already produced in cases of BL, but this is not essential in every case. Patients with glucose-6-phosphate dehydrogenase deficiencies should not be treated with rasburicase due to the risk of hemolytic anemia.

Patients treated with BL regimens are also at high risk for severe and prolonged neutropenia. The use of granulocyte colony-stimulating factors is typically employed to limit the duration of neutropenia and the incidence of treatment delay. One should pay close attention for signs of clinical infection, and prompt institution of intravenous antibiotics and antifungals in accordance with published guidelines is mandatory. Indeed, the physician and institution's familiarity with highly intense chemotherapy regimens have profound effects on individual patient outcomes.

Selected reading

Dave SS, Fu K, Wright GW, *et al*. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med. 2006;354(23):2431–42.

Dunleavy K, Pittaluga S, Shovlin M, *et al*. Low-Intensity Therapy in Adults with Burkitt's Lymphoma. New England Journal of Medicine. 2013;369:1915–25.

Dunleavy K, Wilson WH. How I treat HIV-associated lymphoma. Blood. 2012;119(14):3245–55.

Molyneux EM, Rochford R, Griffin B, *et al*. Burkitt's lymphoma. Lancet. 2012;379(9822):1234–44.

Piccaluga PP, De Falco G, Kustagi M, *et al*. Gene expression analysis uncovers similarity and differences among Burkitt lymphoma subtypes. Blood. 2011;117(13):3596–608.

Schmitz R, Young RM, Ceribelli M, *et al*. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature. 2012;490(7418):116–20.

CHAPTER 45

Gray zone lymphoma

Caron A. Jacobson[1] and Ann S. LaCasce[2]

[1]Dana-Farber Cancer Institute, Boston, MA, USA
[2]Dana-Farber/Partners CancerCare, Boston, MA, USA

Case study 45.1

A 62-year-old woman presents to the hospital with abdominal pain and leg swelling and is found to be in renal failure with bilateral hydronephrosis. Cystoscopy reveals an external mass compressing the bladder, and biopsies show bladder wall infiltration by a diffuse population of uniform and medium-sized lymphoid cells with slightly irregular nuclei, fine chromatin, small nucleoli, and small amounts of cytoplasm. Immunoperoxidase studies reveal that the neoplastic cells are CD20-positive B-cells that co-express CD10, B-cell lymphoma-6 (BCL6), and BCL2; the neoplastic cells are negative for CD5, CD30, CD34, and TdT. The Ki67 proliferation index is approximately 95% in the neoplastic cells. Staging studies reveal advanced-stage disease with extranodal involvement, including bone marrow and bladder wall involvement. Her lactate dehydrogenase (LDH) level is elevated at 764 U/L (ULN 231 U/L).

- **What is the diagnosis?**

In 2008, the WHO created a provisional diagnosis for lymphomas that shared features between, but were distinctive from, BL and DLBCL, a so-called gray zone lymphoma or B-cell lymphoma, unclassifiable, with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma (B-UNC/BL/DLBCL). These lymphomas differ morphologically from DLBCL in that the neoplastic cells are generally of intermediate to large, rather than large, size with a high proliferation rate as expressed by the Ki67 index; they are also uniformly CD10 positive by immunohistochemistry. They differ from BL in that the cells are more variable in size, are often BCL2 positive and can be BCL6 variable, and have a slightly lower Ki67 index ($\leq$90%). These lymphomas have historically been called many different things, including "non-Burkitt," "atypical Burkitt," and "Burkitt-like" lymphoma, making them difficult to study. Although this category is defined by morphologic and genetic features, gene expression profiling (GEP) has likewise identified a group of lymphomas with an expression profile between those of BL and DLBCL. This group is not synonymous with B-UNC/BL/DLBCL, but the two do overlap, suggesting that B-UNC/BL/DLBCL is not a unique entity but rather a group of distinct lymphomas, including true BL, DLBCL, and unclassifiable lymphomas, which require further characterization. Although potentially heterogeneous, these lymphomas generally carry a poor prognosis with high International Prognostic Indices (IPIs) and frequent extranodal sites; this characterization may be driven by a few particularly poorly behaving subtypes of this diagnosis.

- **What additional pathologic testing would you ask for given this diagnosis?**

Since 1993, the IPI has been the best tool to predict how patients with aggressive non-Hodgkin's lymphoma (NHL) will do following multiagent, anthracycline-containing chemotherapy, and later immunochemotherapy. It separates low-, intermediate-, and high-risk disease based on a patient's age, LDH, performance status, number of extranodal sites of disease, and disease stage, and correlates closely with response to therapy, progression-free survival (PFS), and overall survival (OS). Although we have discovered additional prognostic factors in these diseases, none have proven to be more powerful than this index. However, as we learn more about the genetic events associated with these lymphomas, we have developed new tools to identify patients with particularly high-risk aggressive NHL. Specifically, detection of multiple concurrent chromosomal

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

translocations, most often involving the *MYC*–8q24 and the *BCL2*–18q21 loci, has been shown to identify a particularly high-risk group of patients with aggressive B-cell NHL with a poor prognosis. While the partner locus for *BCL2* translocations is almost always the immunoglobulin heavy-chain (IgH) locus on chromosome 14, *MYC* translocation may involve this or other loci. This observation was first noted in pathology samples from patients with small noncleaved, non-Burkitt (Burkitt-like) lymphoma, many of whom would fall within the provisional WHO category of B-UNC/BL/DLBCL. Within this group, patients with the dual translocations of *MYC* and *BCL2* had a poor prognosis with no patients alive at one year in one series. This was in contrast to patients with an isolated *MYC* translocation or other cytogenetic abnormalities, of which 32% and 25% were alive at 2 years, respectively. Further investigation of these translocations in DLBCL found that dual translocations are present in up to 12–14% of cases, and are similarly associated with a poor prognosis. B-UNC/BL/DLBCL appears to be enriched for these dual translocations, or "double-hit" lymphomas, with approximately 30–45% of cases co-harboring *MYC* and *BCL2* translocations. While the majority of double-hit lymphomas do fall into this diagnostic category, not all B-UNC/BL/DLBCL are double-hit lymphomas. Double-hit lymphomas with this histology appear to have a particularly poor prognosis, even compared to double-hit DLBCL, with a median OS of 4 months compared to 3 years, respectively.

The overexpression of MYC and BCL2 or BCL6 can be accomplished by mechanisms other than translocations involving a gene with a constitutively active promoter like the immunoglobulin loci, and data suggest that these mechanisms are likely biologically and prognostically relevant. The development of reproducible and accurate MYC immunochemical stains has allowed for the identification of lymphomas that overexpress MYC and correlate highly with the presence of a *MYC* translocation. Furthermore, the presence of high MYC staining by immunohistochemistry was associated with inferior outcomes among DLBCL treated with R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone). More recently, a number of independent groups have investigated the use of both MYC and BCL2 immunochemical stains to identify patients with overexpression of both of these proteins. When using prespecified values to define overexpression, each group was able to identify 70–90% of patients with cytogenetically confirmed dual translocations, which were associated with an expectedly poor prognosis. Dual IHC positivity, however, identified additional patients without dual translocations but with increased staining, or overexpression, of both MYC and BCL2, and these patients likewise had a poor prognosis similar to lymphomas with dual translocations or intermediate between these lymphomas and DLBCL without *MYC* and *BCL2* translocations or protein overexpression. While fluorescent in situ hybridization (FISH) cytogenetics identifies double-hit lymphomas in 12–14% of DLBCL, dual IHC-positive lymphomas appear to account for approximately 30% of DLBCL. Immunohistochemical analysis of protein expression, then, may represent a more biologically relevant measure associated with prognosis than a specific type of genetic aberration. DLBCL with an activated B-cell (ABC) phenotype is known to be associated with a worse prognosis compared with germinal center B-cell lymphomas (GCB), and the ABC phenotype, while rarely harboring a *MYC* and/or *BCL2* translocation, is enriched for MYC and BCL2 overexpression and dual IHC positivity, and perhaps this reflects the worse prognosis in this group. Interestingly, dual IHC positivity and dual translocations in these studies appear to be prognostically significant independent of IPI, which is in opposition to what has been previously reported. Because these immunohistochemical and cytogenetic changes are associated with older age, more advanced disease with frequent extranodal involvement, and an elevated LDH, the number of patients with immunohistochemical and/or cytogenetic double-hit lymphomas and a low IPI is small, making these data difficult to interpret. It should be noted that the prognostic significance of dual IHC positivity has not been studied specifically in B-UNC/BL/DLBCL.

FISH cytogenetics for a *MYC* and *BCL2* translocation are ordered and reveal a t(8;14) and a t(14;18), consistent with a double-hit lymphoma.

- **What front-line therapy would you offer this patient?**

There has been no systematic investigation of the treatment of B-UNC/BL/DLBCL or double-hit lymphomas. Prior to the creation of the 2008 WHO provisional category and the discovery of the prognostic impact of these multiple chromosomal translocations, many of these lymphomas often were described as B-cell lymphomas with high-grade features, or Burkitt-like lymphomas, and front-line treatment consisted of a number of therapeutic regimens of varying intensities chosen at the discretion of the treating physician. These regimens included Burkitt-like therapies like modified Magrath with R-CODOX-M/IVAC (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone, methotrexate, ifosfamide, and cytarabine), R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, adriamycin, dexamethasone, methotrexate, and cytarabine), dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin), and R-CHOP. No prospective data exist to support the use of more intensive chemoimmunotherapy regimens over R-CHOP, the gold standard regimen for DLBCL. However, three groups have looked at the impact of intensified chemotherapy regimens

(*Continued*)

on outcomes specifically for B-UNC/BL/DLBCL in a retrospective fashion. These analyses are limited in that they are retrospective, involve patients diagnosed prior to the creation of this diagnostic category (and so likely included patients whose disease did not meet the criteria for this category), and are of small size. Each did show, though, that a more intensive regimen (R-hyper-CVAD, R-CODOX-M, dose-adjusted R-EPOCH, or a slightly altered modified Magrath regimen) resulted in an improvement in overall response rate (ORR) and PFS over patients who received R-CHOP +/− central nervous system (CNS) prophylaxis (ORR 86% versus 57%, 4-year PFS approximately 50–65% versus 0–30%).

Another group retrospectively examined the outcomes following intensive therapy (R-hyper-CVAD or R-CODOX-M) compared with R-CHOP in 53 patients with aggressive B-cell lymphoma with high-grade features whose *MYC* cytogenetic status was known. Interestingly, in this group only, just over half had a high-risk IPI and well under half had involvement of more than one extranodal site, suggesting this was a lower-risk group than has previously been described for B-UNC/BL/DLBCL. Among all patients, there was no difference in overall survival between R-CHOP and more intensive regimens, with approximately 50–60% of all patients alive at 4 years; this relatively good overall survival rate is widely different from what has been reported in other series and perhaps reflects that this is a better-risk group than other B-UNC/BL/DLBCL cohorts. While not significant, there was a trend toward patients with a *MYC* translocation doing worse, with approximately 40% alive at 4 years. Within the group of patients with a *MYC* translocation, those treated with higher-intensity regimens had a significantly longer PFS ($P = 0.036$) and a trend toward longer OS than those treated with R-CHOP. Finally, the *BCL2* translocation status was known for 35 of these patients, and among patients with dual translocations, there was a nonsignificant trend toward a shorter PFS and OS compared with patients with an isolated *MYC* translocation. This suggests that perhaps it is the double-hit lymphomas within the larger category of B-UNC/BL/DLBCL that drive the poor prognosis seen, and perhaps it is these patients who might benefit from more intensive upfront chemotherapy regimens like modified Magrath, R-hyper-CVAD, or dose-adjusted R-EPOCH. Data of *MYC* translocation-positive DLBCL treated with dose-adjusted R-EPOCH on the phase II studies out of the National Cancer Institute (NCI) are promising; in this study, nine patients (8%) were known to harbor a *MYC* translocation and had a 4-year event-free survival (EFS) of 83%. This regimen is currently being explored further in BL and *MYC* translocation–positive DLBCL in a multicenter US Intergroup trial.

At the present time, there is not sufficient evidence to suggest that all patients with B-UNC/BL/DLBCL should be treated with regimens more intense than R-CHOP chemotherapy. This is a heterogeneous group of patients with varied prognoses and natural histories, some of whom may do very well with standard R-CHOP chemotherapy. There is a general consensus, however, that for dual translocation, or now perhaps dual IHC, positive aggressive B-cell lymphomas, many of which are B-UNC/BL/DLBCL, chemoimmunotherapy with R-CHOP is not sufficient. The difficulty is that there is no compelling prospective evidence to show that more intensive regimens improve outcomes in this group. These patients thus should be encouraged to participate in clinical trials, like the US Intergroup trial of dose-adjusted R-EPOCH discussed here. In the absence of a clinical trial, our practice has been to treat younger (<60 years), fitter patients with dual translocation–positive aggressive B-cell lymphomas with modified Magrath and older (>60 years), more frail patients with dose-adjusted R-EPOCH in the upfront setting. Due to the documented high risk of CNS recurrence in these patients, we add CNS prophylaxis in the form of intrathecal chemotherapy to the treatment of patients being treated with dose-adjusted R-EPOCH. Agents that target BCL2 and a MYC-driven protein, aurora A kinase, are currently in development and may prove useful in these double-hit lymphomas, and these patients should be considered for clinical trials when available. How to manage the dual IHC-positive but translocation-negative patients is even less clear at this time and requires further study. We continue to treat these patients with R-CHOP chemotherapy.

This patient is treated with six cycles of dose-adjusted R-EPOCH with intrathecal chemotherapy given as CNS prophylaxis on four occasions. Mid- and posttreatment positron emission tomography–computed tomography (PET–CT_ scans confirm a complete response to chemoimmunotherapy, and a posttreatment bone marrow biopsy shows no evidence of disease.

• Is there a role for a consolidation strategy for this patient?

Just as there are no prospective studies investigating the benefit of more intensive upfront treatment regimens for the treatment of B-UNC/BL/DLBCL in general or with evidence of dual translocations, there are no data to support the use of consolidation strategies with either high-dose chemotherapy and autologous stem cell transplantation (HDC–ASCT) or allogeneic stem cell transplantation in first remission. In one retrospective series of 53 patients with dual translocation–positive lymphoma treated with either R-CHOP or R-hyper-CVAD, 11 patients had received HDC-ASCT or an allogeneic stem cell transplantation in first remission. There was no difference in PFS or OS seen in the group that received a stem cell transplant; median OS was only 18.6 months. Patients with *MYC* translocation–positive lymphoma in the CORAL (Collaborate Trial in Relapsed Aggressive Lymphoma) study did very poorly with a 4-year

PFS and OS of only 18% and 29%, respectively (compared to 42% and 62% for *MYC* translocation–negative lymphomas). Given the very high rate of early relapse in these dual translocation–positive lymphomas and the difficulty in achieving a second remission, our strategy has been to consolidate induction therapy with R-CHOP or dose-adjusted R-EPOCH chemotherapy with either HDC–ASCT alone or a tandem HDC–ASCT followed by a reduced-intensity allogeneic stem cell transplant on a clinical treatment protocol we are exploring in high-risk lymphomas. The rationale for the latter is that these patients are at high risk of early relapse before the immunologic effects of a reduced-intensity allogeneic stem cell transplant can take effect, and so the HDC–ASCT serves to improve the PFS such that the allogeneic transplant has a chance for curative potential. For patients treated with modified Magrath, we consider this to be an adequately intensive chemoimmunotherapy regimen and recommend reduced-intensity allogeneic stem cell transplantation in first remission.

This patient proceeds to stem cell collection for HDC–ASCT; her medical comorbidities and functional status preclude the upfront consideration of our tandem protocol. Unfortunately, her disease recurs just prior to her admission for her transplant. She fails to respond to further chemotherapy and passes away from her disease within a year of her initial diagnosis.

Case study 45.2

A 40-year-old man presents with 2 weeks of fevers, night sweats, malaise, and difficulty breathing. After a brief period of observation for a possible viral infection, he has a chest X-ray that shows a left-sided mediastinal mass and a chest CT that shows a 14 cm mass extending through the pericardium associated with a moderate pericardial effusion. A PET–CT shows an intensely fluoro-deoxyglucose (FDG)-avid lobulated anterior mediastinal mass measuring 11 × 7 cm with some associated hilar, supraclavicular, and pericardial lymphadenopathy as well as FDG-avid pleural and pericardial deposits. Labs are within normal limits, including an erythrocyte sedimentation rate, other than an LDH that is elevated at 422 U/L. He undergoes a mediastinoscopy with biopsy that shows a nodular infiltrate composed of lymphocytes and histiocytes separated by fibrous bands with occasional Hodgkin–Reed Sternberg (HRS) cells and intermediate to large mononuclear lymphocytes. The majority of the infiltrate is composed of small CD3+ T-cells admixed with CD68+ histiocytes. The intermediate to large lymphocytes admixed with large and pleomorphic cells (including HRS cells) are positive for CD45, BSAP, CD79a (subset), MUM1, and BCL6 (subset), and negative for CD15 and nuclear REL. CD30 (subset), fascin (subset), and CD23 are positive primarily in the HRS cells. CD20 strongly stains rare HRS forms and a small subset of the intermediate to large B-cell population that focally forms a small cluster of CD20+ intermediate- to large-sized cells.

• What is the diagnosis?

An overlap between the clinical and pathologic features of primary mediastinal large B-cell lymphoma (PMBCL) and cHL has been recognized for over a decade. Both typically occur in younger, female patients; involve contiguous as opposed to distant nodal stations; and on biopsy demonstrate a variable number of malignant B-cells within an inflammatory infiltrate with some degree of fibrosis. In 2008, the WHO created a diagnostic category to capture these gray zone lymphomas: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (B-UNC/cHL/DLBCL). The majority of these lymphomas present in the mediastinum and in men. Histopathologically one sees pleomorphic tumor cells resembling both the HRS cell and the large, atypical B-lymphocyte of cHL and DLBCL or PMBCL, respectively. These cells appear in sheets, separated by fibrotic stroma with an associated inflammatory infiltrate. Immunohistochemical profiles of the malignant cells demonstrate frequent positivity for CD45, CD20, CD79a, and CD30, but are often CD15 negative; other B-cell markers like PAX5, OCT2, and BOB1 are often positive. Methylation profiling of these tumors reveals a profile intermediate between those of PMBCL and cHL, corroborating that this entity is distinct from either diagnosis and perhaps lies on a continuum between the two. Interestingly, patients can present with composite lymphomas in which DLBCL and cHL present sequentially, in either order; whether these composite lymphomas reflect the pathogenesis of, or are related to, B-UNC/cHL/DLBCL is not known. However, the methylation profiles of both components of a single case of a composite lymphoma were most similar to that of B-UNC/cHL/DLBCL, suggesting that the two are related.

• What front-line therapy would you offer this patient?

Prognosis is notably poorer in B-UNC/cHL/DLBCL than it is in either cHL or PMBCL. This is in part due to differences in the pathobiology, but may also be the result of a lack of knowledge as to how to best treat these patients. Should they be treated with an NHL or a Hodgkin lymphoma (HL)

(*Continued*)

regimen? There have been no large prospective studies in this disease given its rarity. As a result, consensus, rather than evidence, has favored treating these lymphomas with an NHL regimen. There are several single-arm studies demonstrating the activity of CHOP in HL, with complete response rates as high as 93% with a 3-year PFS of 76%. As such, R-CHOP is an acceptable first-line therapy. More recently, the outcomes of 16 patients with B-UNC/cHL/DLBCL treated with dose-adjusted R-EPOCH have been reported. At 4 years, the EFS and OS of this group were only 45% and 75%, respectively. Given that dose-adjusted R-EPOCH has not been compared to R-CHOP chemotherapy in a randomized or systematic fashion, we currently recommend R-CHOP chemotherapy unless the patient is participating in a clinical trial.

This patient receives six cycles of R-CHOP. A PET–CT at the end of treatment demonstrates a complete metabolic remission.

• Is there a role for adjuvant radiation therapy in this disease?

The role of radiation therapy in both cHL and PMBCL is debated. In cHL, the increasing awareness of the late complications of radiation therapy, including but not limited to breast cancer, lung cancer, and premature cardiovascular disease, coupled with the very good prognosis generally seen in this disease have resulted in investigations to identify patients who do not benefit from the addition of radiation therapy to chemotherapy. This question is further reviewed in detail in other chapters of this book; however, involved-field radiation therapy is recommended for patients with early-stage disease with bulky lymphadenopathy. The role of radiation in PMBCL is likewise unclear. Many patients present with early-stage, bulky mediastinal disease; were one to extrapolate from the experience in early-stage DLBCL with bulky lymphadenopathy, one would consider the addition of adjuvant radiation therapy to the site of bulky disease. In early-stage DLBCL treated with CHOP +/− rituximab, patients with bulky disease did worse than patients with nonbulky disease, despite the uniform use of radiation therapy to the sites of bulky disease. Whether the addition of radiation therapy improved outcomes in patients with early-stage, bulky disease has not been proven in a randomized clinical trial, but it is widely recommended due to the high risk of disease recurrence in bulky sites of disease. The benefit of radiation therapy to bulky sites of disease in advanced-stage DLBCL is less compelling; these patients are nine times more likely to recur at a distant site than in an area of bulky disease, and there have been no randomized trials in the era of R-CHOP investigating the use of radiation therapy following chemotherapy for advanced-stage, bulky disease. Despite frequently presenting with bulky mediastinal disease, patients with PMBCL enjoy a favorable prognosis with a 5-year OS of over 80% following R-CHOP chemotherapy. Whether to radiate patients who achieve a complete metabolic response by PET–CT following chemoimmunotherapy is uncertain. Outcomes are similarly good among patients treated with chemoimmunotherapy who are PET negative and receive no radiation compared with those who are PET positive and treated with radiation; it is not known, though, whether the outcomes in the PET-negative group would be improved by the addition of radiation therapy. The only published randomized trial of radiation therapy for this disease was stopped early due to an interim analysis that showed an increased relapse rate in the nonradiated group; all patients on this study had achieved a complete response to R-CHOP chemotherapy. A large randomized clinical trial is ongoing in Europe to decidedly answer this question. What to do with a patient who presents with advanced-stage PMBCL with a bulky mediastinal mass is even less clear, although, given their risk of a distant relapse, radiation may be of less use akin to what we have seen in advanced-stage, bulky DLBCL.

Despite the open question as to the role of adjuvant radiation therapy for PMBCL, radiation therapy is generally incorporated into the treatment of B-UNC/cHL/DLBCL following chemoimmunotherapy due to its poor overall prognosis. In the NCI study of dose-adjusted R-EPOCH outlined in this chapter, approximately 44% percent of patients with B-UNC/cHL/DLBCL required radiation therapy, which was significantly higher than that seen in the PMBCL patients (10%). As such, we recommend adjuvant radiation therapy for these patients. The patient in this case study is currently undergoing involved-field radiation therapy.

Selected reading

Aukema SM, Siebert R, Schuuring E, *et al*. Double-hit B-cell lymphomas. Blood. 2011;117(8):2319–31.

Crockett DG, Perry AM, Armitage JO, *et al*. Lymphoma with features intermediate between DLBCL and Burkitt lymphoma: better outcome with intensive chemotherapy regimens. Blood. 2011;118:2710.

Dunleavy K, Grant C, Eberle FC, *et al*. Gray zone lymphoma: better treated like Hodgkin lymphoma or mediastinal large B-cell lymphoma? Curr Hematol Malig Rep. 2012;7:241–7.

Jaffe ES, Pittaluga S. Aggressive B-cell lymphomas: a review of new and old entitites in the WHO classification. Hematology. 2011;506–14.

Quintanilla-Martinez L, de Jong D, de Mascarel A, *et al*. Gray zones around diffuse large B cell lymphoma. Conclusions based on the workshop of the XIV meeting of the European Association for Hematopathology and the Society of Hematopathology in Bordeaux, France. J Hematopathol. 2009;2(4):211–36.

CHAPTER 46

Transformed lymphoma

Stephane Doucet[1] and Jane N. Winter[2]

[1]Centre Hospitalier de l'Université de Montréal (CHUM Hospital), Montreal, QC, Canada
[2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

Multiple choice question

1. Which of the following does *not* constitute transformation?

A. New diagnosis with areas of follicular lymphoma (FL) grade 1–2 and 5% diffuse large B-cell lymphoma (DLBCL)
B. Long-standing FL, new mass with biopsy showing DLBCL
C. Long-standing FL grade 1–2 with progression in one of the lymph nodes to FL grade 3a
D. Long-standing chronic lymphocytic leukemia (CLL) previously untreated with a rapidly increasing cervical mass with a biopsy that shows DLBCL

There is a lack of consensus regarding the definition of histologic transformation (HT). Most experts agree that grade 1–2 follicular lymphoma that progresses to DLBCL or Burkitt lymphoma represents HT (Figure 46.1). The *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* defines HT as "transformation or progression to a high-grade lymphoma usually DLBCL, but occasionally resembling Burkitt lymphoma or with features intermediate between DLBCL and Burkitt lymphoma." Progression of FL grade 1–2 to FL grade 3 (situation C) is not considered histologic transformation but rather progression. Situation A is perhaps the most controversial. Some authors have considered the presence of both FL and DLBCL in the same lymph node to represent a "composite" lymphoma, and some have referred to it as "transformation at diagnosis." Others require a defined interval between the diagnosis of FL and the more aggressive histology. The presence of both an indolent and aggressive lymphoma in the same lymph node implies but does not confirm early transformation. The WHO suggests reporting the two disease entities with their respective percentages of involvement. Composite lymphomas were rarely included in the major series of transformed lymphomas (TLs). Rarely, FL may transform to other histologies such as acute B-cell lymphoblastic leukemia or, as recently described elsewhere, to histiocytic or dendritic cell sarcoma.

Transformation to DLBCL has been described for all the major subtypes of indolent lymphomas: small lymphocytic lymphoma and chronic lymphocytic leukemia (SLL–CLL), lymphoplasmacytic lymphoma (LPL), and marginal zone lymphoma. The first description of HT in SLL–CLL was made in 1928 by Richter and constitutes situation D. SLL–CLL can rarely transform to Hodgkin lymphoma and uncommonly to B-cell prolymphocytic leukemia.

A more scientifically robust definition of "transformation" requires demonstration of a clonal relationship between the original indolent lymphoma and the subsequent aggressive counterpart. This may be best demonstrated by molecular techniques characterizing the immunoglobulin gene. In the daily clinical setting, proving that the two lymphomas have the same light-chain restriction is usually sufficient to suggest a clonal relationship. The immunophenotype of the TL may differ from the original indolent lymphoma. Loss of CD10 expression occurs in 10% of cases, and a gain of MUM1 or CD30 occurs, each in 25% of cases. A change in phenotype does not preclude a clonal relationship between the two lymphomas. Transformation was diagnosed on clinical grounds in two series because of the association between aggressive clinical behavior and transformation. This association is not absolute and, whenever possible, the diagnosis should be made pathologically.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

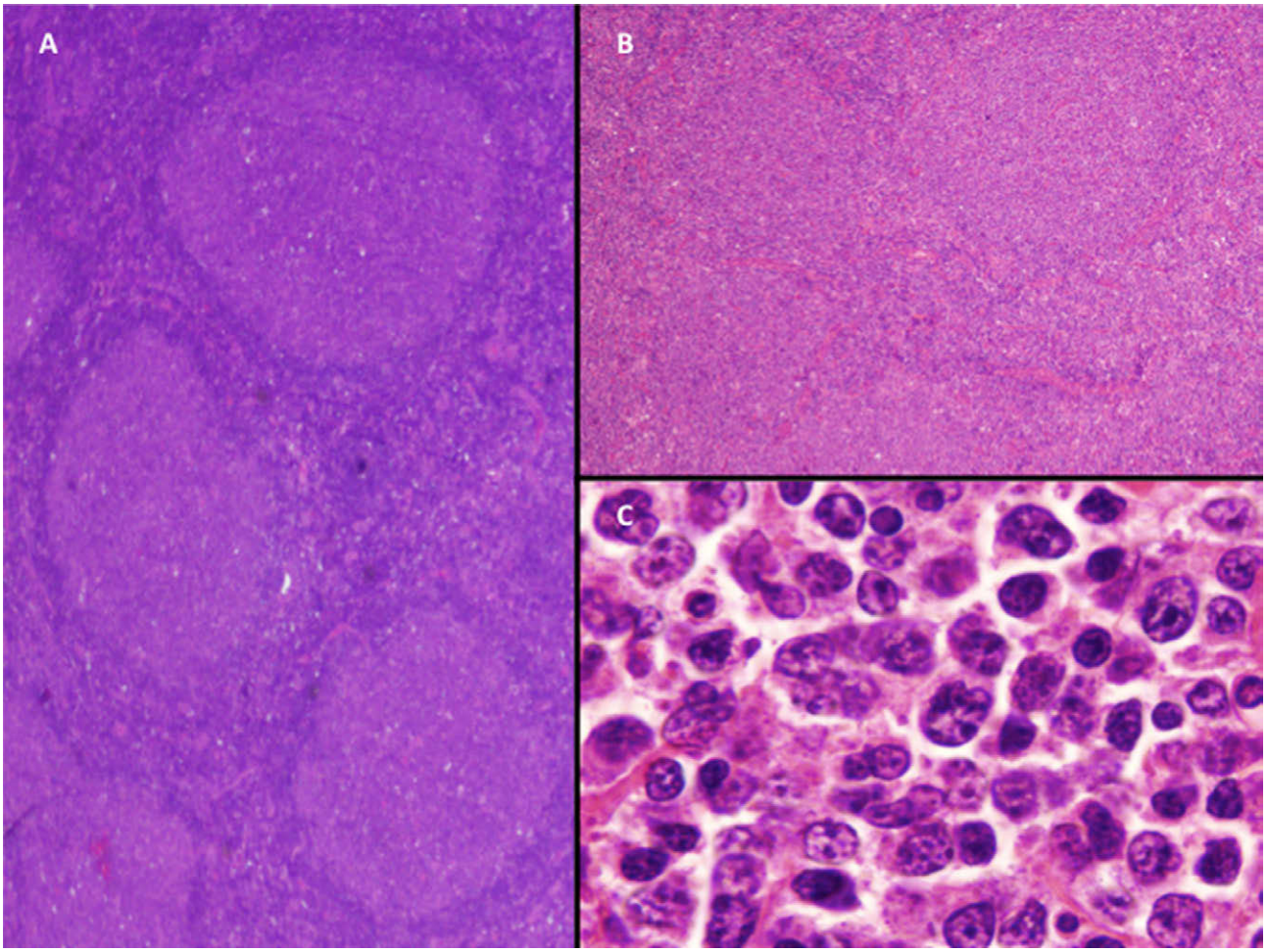


Figure 46.1 (A) Follicular lymphoma at diagnosis of an untreated patient. (B) At transformation: top area with follicles but diffuse architecture in the lower area composed of sheets of large cells. (C) High-power field of the diffuse area of Figure 1B. Large cells, prominent nucleoli, and irregular shape are noted. (Color plate 46.1)

Case study 46.1

A 45-year-old male was recently diagnosed with stage IVA FL.

1. What is his chance of histological transformation to DLBCL?

A. 1% per year
B. 2–3% per year
C. 10% per year
D. 12% per year

The rate of transformation has been estimated at approximately 3% per year. Most of the information on the incidence of transformation is derived from large series. The methodology, follow-up period, and definition of transformation vary among series, which explains the slightly different results. The largest series is from the database of the British Columbia Cancer Agency, which included 600 patients with 170 transformations. The annual risk of transformation was a continuous 3%. This series included patients with clinical transformation when biopsy was not possible. Horning also reported a continuous risk of transformation with long-term follow-up at Stanford. Investigators from the University of Iowa and Mayo Clinic recently reported a series of over 600 patients with follicular lymphoma with an overall transformation rate of 10.7% at 5 years, and an estimated rate of 2% per year. In a single institution series with a median follow-up of 15 years, Montoto *et al.* (2007) reported a risk of transformation of 28% at 10 years and, unlike the British Columbia series, this group observed a plateau after 15 years. Another single-institution retrospective study reported a probability of transformation of 31% at 10 years with a tendency to plateau after 6 years. Cases of transformation can certainly occur many years after diagnosis of indolent lymphoma. Thirty years ago, the US National Cancer Institute reported a prevalence of transformation of 70% at autopsy. We know

that rituximab (R) improves the overall survival (OS) of previously untreated patients with FL when combined with chemotherapy, but we will probably not know its real impact on the rate of transformation for another decade or more.

The incidence of transformation is lower in the nonfollicular lymphoproliferative disorders. For example, in patients with SLL–CLL, Tsimberidou *et al*. (2006) reported the MD Anderson Cancer Center experience from 1975 to 2005 with a cumulative risk of proven transformation to large-cell lymphoma (Richter's syndrome) of 3.7%, a risk of transformation to Hodgkin lymphoma of 0.4%, and a risk of transformation to prolymphocytic leukemia of 0.1%. There are less data on the annual incidence for transformation among the non-FL lymphoproliferative disorders, but the incidence is certainly less than that observed in FL.

Case study 46.2

A 56-year-old female with a 10-year history of FL grade 1–2, initially treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) and 2 years ago with R-bendamustine for symptomatic recurrence, now presents with rapidly increasing left cervical adenopathy, B-symptoms, and high lactate dehydrogenase (LDH). You suspect a histological transformation.

1. Do you need a biopsy to prove your suspicion?

The obvious answer to this question is absolutely yes, or at least whenever possible. What if you suspect transformation in a retroperitoneal lymph node that is difficult to access in a patient with risks or contraindications to biopsy? In the large series of transformed FL, biopsies were generally required, but a high clinical suspicion was considered acceptable evidence of transformation in three series. For example, in the British Columbia series, 36% of the 170 patients with transformation were diagnosed based on clinical criteria because biopsy was not feasible. The presence of at least one of the following was considered indicative of transformation: sudden rise of LDH to more than twice the upper limit of normal, rapid discordant localized nodal growth, new involvement of unusual extranodal sites (liver, bone, muscle, or brain), new B-symptoms, or new hypercalcemia. The median OS was not different in the group of patients diagnosed by biopsy compared to those diagnosed based on these clinical or laboratory findings (20 months vs. 16 months; $P = 0.2$). It should not be assumed, however, that this more aggressive behavior is the equivalent of transformation and these patients need a biopsy to confirm the diagnosis whenever possible without prohibitive risk. Indolent FL, which remains incurable, can recur after successful treatment of TL, stressing the importance of biopsy after each progression.

2. What are the molecular or genetic events that underlie the process of transformation?

A. C-myc
B. P53
C. Bcl-6 mutations or translocation
D. C-rel
E. All of the above

The process of transformation is complex and involves genomic, transcriptional, and epigenetic mechanisms. Interaction with the non-neoplastic immune cells in the tumor microenvironment likely also plays an important role. Many alternative pathways have been implicated. For an in-depth overview of this subject, the reviews by Lossos and Gascoyne (2011) and Montoto and Fitzgibbon (2011) are excellent resources. When paired samples obtained from patients both at diagnosis and at the time of transformation have been studied, a variety of mutations, including those involving proto-oncogenes, have been identified, but none consistently. Genes typically expressed in embryonic stem cells (ESCs) have been implicated in TL, and the expression of an ESC signature may predict for future transformation. It has been suggested that TL derives from a common primitive germinal center B-cell population and does not necessarily represent clonal evolution. This is currently an area of active research.

Rearrangements of *MYC* have been linked to transformation in a proportion of patients. When arising in patients with FL with t(14;18), these cases are called "double-hit lymphomas." Morphologically, they may be diagnosed as B-cell lymphoma unclassifiable with features intermediate between Burkitt lymphoma and DLBCL (67% of the cases), or as DLBCL (31%). Most cases arise de novo and cannot strictly be considered transformations, but approximately 35% of cases of double-hit lymphomas arise from a previous FL. This subgroup of TL has a particularly bad prognosis with a median OS of 6 months.

Mutation of the tumor suppressor gene *TP53* (on chromosome 17p) has been implicated in the progression of FL to TL in approximately 20–30% of cases. A small subset of patients also has amplification of the proto-oncogene *c-REL* (10%) and deletion of the tumor suppressor gene *CDKN2A* (5%) that encodes *p16*. In some cases, *BCL6* mRNA markedly increases upon transformation, but this is not required. Karyotypic abnormalities have also been implicated in the transformation process del 6q, trisomy 7, and trisomy 12. *TNFRSF14*, a newly recognized tumor

(*Continued*)

suppressor gene, is the likely candidate implicated in transformation when the frequent (35%) deletion 1p36.3 occurs.

3. What is the expected survival for this patient?

A. Less than one year
B. 1–3 years
C. 3–5 years
D. More than 5 years

The most commonly reported median OS for transformed FL is between 1 and 2 years. The British Columbia series reported a posttransformation median survival of 1.7 years, while survival was 1.2 years in the series from St Bartholomew's Hospital and only 7 months in the Lyon series. The majority of patients in these series were treated before 2000 and did not have access to rituximab and the newer therapies. Patients diagnosed between 2002 and 2009 who were included in the recently reported Iowa/Mayo series had a remarkable median overall survival of 50 months from the time of transformation. Patients who were initially observed had the worst prognosis and those treated with rituximab monotherapy, the best in this series. A series from a Swiss database that covers the period from 1979 to 2007 and included patients treated in the rituximab era reported a median survival after a transformation of 2.7 years. In this series, *FLIPI score at initial FL diagnosis*, *age more than 60 years*, and *Eastern Cooperative Oncology Group (ECOG) performance status >1 at the time of transformation* were associated with a worse prognosis. Other series reported *elevated LDH level*, *extensive disease at transformation*, and *not achieving CR after salvage therapy for TL* as poor prognostic factors. In contrast to the Iowa/Mayo experience, patients who did not receive chemotherapy prior to transformation had a better prognosis in the Stanford cohort.

Case study 46.3

A 56-year-old male who was in partial remission 2 years ago after treatment with R-bendamustine for a stage IVA FL grade 1–2 suddenly presents with drenching night sweats, unexplained fever, and an LDH level of 750 U/L. There are no palpable lymph nodes and no splenomegaly on exam.

1. How might a positron emission tomography (PET) scan be useful in this context?

A. To adequately stage the suspected TL
B. To identify a site for biopsy
C. PET scan is not useful in FL; I would not order it.
D. To confirm your clinical suspicion of transformation

The usefulness of PET or computed tomography (CT) scan in FL is usually for confirmation of newly diagnosed disease suspected to be of limited stage, when curative radiotherapy is contemplated. However, when histological transformation is suspected, a PET–CT scan may be helpful to identify a site for biopsy. Higher standardized uptake value (SUVmax) has been associated with more aggressive lymphomas. In fact, indolent lymphomas are not always detectable with fluoro-deoxyglucose (FDG) PET. Although one study showed that a SUVmax of more than 10 excludes indolent lymphoma with 84% specificity, there is also a considerable degree of overlap in the FDG uptake in lymphoproliferative diseases. For example, one of our patients with a recently diagnosed indolent lymphoma with discordant SUVmax on PET scan underwent a mediastinoscopy to biopsy the more active node (Figure 46.2). The pathology revealed FL grade 3a rather than a transformation.

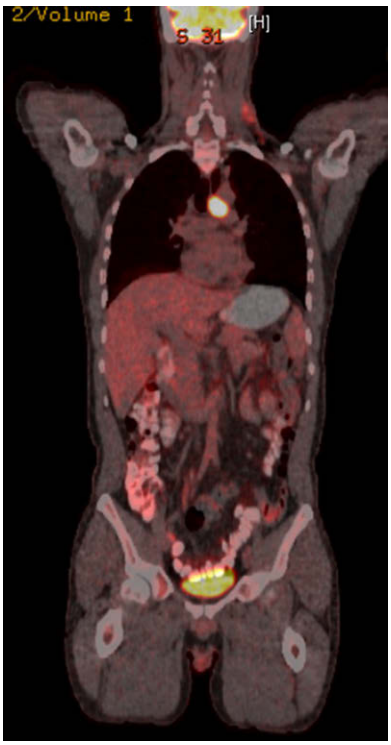


Figure 46.2 Positron emission tomography and computed tomography (PET–CT) of a newly diagnosed patient with follicular lymphoma (FL). Aorto-pulmonary node had a standardized uptake value of 21.2 compared to 5.4 for a left inferior cervical node. The pathology of the aorto-pulmonary node showed FL, grade 3a. (Color plate 46.2)

Two single-center studies examined the usefulness of PET–CT in selecting the biopsy site in suspected transformation. In patients with known indolent lymphoma, a biopsy of an accessible site with the highest SUVmax was performed when clinical features or laboratory parameters (unexplained high beta-2 (B2) microglobulin or luteinizing hormone) were suggestive of transformation. Transformation was present in only 17 of the 38 biopsies. In this study, an SUVmax of less than 11.7 was always associated with an indolent histology and a SUVmax of more than 17 was always associated with histological transformation. However, the SUV of TL is not always very high; to evaluate the SUV of TL, Noy *et al*. (2009) at Memorial Sloan Kettering Cancer Center retrospectively identified patients with TL who had baseline PET scans before starting treatment. They reported that the SUV of the biopsied site ranged between 3.0 and 38.0 with a median of 12, lower than one would have expected given other reports. Therefore, the clinical utility of PET scan in the context of transformation is probably, although not definitively so, to guide in the selection of a biopsy site. Functional imaging should not replace biopsy to diagnose transformation.

Multiple choice question

2. Which of the following are risk factors for transformation in a patient with FL grade 1–2?

A. High Follicular Lymphoma Prognostic Index (FLIPI) score
B. Advanced stage
C. Low albumin
D. High B2 microglobulin
E. Failure to achieve complete response (CR) with initial treatment
F. All of the above

As a general rule, factors that are associated with poor outcomes in FL at diagnosis are predictive for transformation. The FLIPI, which was developed specifically for prediction of outcomes of patients with FL, is also a predictor of transformation. Age more than 60 years, Ann Arbor stage III–IV, a hemoglobin level of less than 120 g/L, and four or more nodal areas are factors associated with high-risk FLIPI scores. Advanced stage (III–IV) at diagnosis is also associated with a higher risk of transformation in two large series. In the series from Lyon, France, *albumin less than 35 g/L*, *B2 microglobulin more than 3 mg/L at diagnosis*, and *a failure to achieve a complete remission with the initial treatment* were all associated with higher risks of transformation.

A more controversial and important issue is whether or not the initial management of FL changes the risk of transformation. Older data from Stanford showed a similar risk of transformation in initially untreated FL patients compared to patients with FL who were treated immediately at diagnosis. The largest population-based series from the British Columbia Cancer Agency also reported no difference in the risk of transformation among patients initially treated with chemotherapy, radiotherapy, or watchful waiting. Unlike these two series, a single-institution retrospective study noted that expectant management predicted for a higher risk of transformation. Watchful waiting was also associated with the highest risk of transformation when compared with other upfront therapies in the Iowa/Mayo series. Notably, patients who received rituximab monotherapy as initial treatment had the lowest risk of transformation. Analysis of prospectively treated patients on clinical trials such as the British randomized trial of watchful waiting compared to rituximab monotherapy will help to clarify the role of upfront therapy in transformation risk.

The use of purine analogs has also been reported to impact the risk of transformation. Two upfront regimens containing purine analogs were shown to have a higher risk of transformation than combined modality therapy with a cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like regimen. Al-Tourah *et al*. (2008) compared two cohorts of patients with FL with similar baseline characteristics treated with either BPVACOP (bleomycin, cisplatin, etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisone) and 25 Gy of radiation to involved nodal sites or cyclophosphamide and a purine analog (fludarabine or cladribine). The risk of transformation at 10 years was 18% and 30% ($P = 0.01$), respectively. In a German phase III study in elderly patients (over 65 years old), CLL patients were randomized to fludarabine or chlorambucil. Despite higher response rates in the fludarabine arm, the patients randomized to fludarabine were more likely to present with Richter's syndrome (6.5% vs. 2.0%). This was not the case in other trials of purine analogs. Whether or not purine analogs are indeed associated with higher rates of transformation in indolent lymphomas remains to be determined.

Case study 46.4

A 57-year-old women with a previous history of an untreated stage IV FL presents with transformation.

1. What is the most appropriate treatment? (Choose all that apply.)

A. CHOP plus rituximab (R-CHOP) 6×
B. CHOP 6×
C. R-CHOP 3–4× + radiation therapy (RT)
D. R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin) followed by high-dose chemotherapy and autologous transplantation

It is important to mention that there have been no randomized trials for the treatment of TL. Most of the information comes from retrospective, often single-center studies. Some of the new prospective trials for DLBCL have now included transformed lymphoma. We hope that the inclusion of TL in these trials will help define the best treatment for this population.

The goal of treatment for the patient described here is a durable remission. In a chemotherapy-naïve patient, we would favor an anthracycline-based treatment like R-CHOP. In the pre-rituximab era, 70% of the patients in the British Columbia series were treated with a CHOP-like regimen, 24% were treated with palliative chemotherapy or supportive care only, and 5% underwent either an autologous or allogeneic transplant. The median survival of the whole cohort was 1.7 years from the time of transformation, with approximately 20% long-term survivors. For patients who received R-CHOP, the addition of rituximab to CHOP for transformed cases previously untreated with rituximab improved outcomes, resulting in a 63% 5-year survival compared to 33% for CHOP-like chemotherapy ($P = 0.01$). In the St Bartholomew's series, the majority of patients (73%) were also treated with a doxorubicin-containing regimen. In the British Columbia series, patients with limited extent of disease at transformation were treated with three cycles of a CHOP-like regimen followed by involved-field radiation. Their 5-year survival was 69%, which was good in the pre-rituximab era.

If a patient with a preexisting indolent lymphoma were to present with a highly aggressive histology like B-cell lymphoma, unclassifiable, with features of BL and DLBCL or with a "double-hit" lymphoma (c-myc translocation and bcl-2 translocation), we would favor a more aggressive regimen than R-CHOP because of the poor outcome with conventional anthracycline-based treatments. At our institution, we often use hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with rituximab (R-hyper-CVAD)–MTX/Ara-C (methotrexate and cytarabine) or dose-adjusted infusional etoposide, vincristine, and doxorubicin with prednisone, cyclophosphamide, and rituximab (R-DA-EPOCH). The role of consolidative transplantation is unclear, but many centers will consider some form of transplantation in patients who achieve remission. A national trial of DA-R-EPOCH is ongoing for patients with MYC+ lymphomas, but it does not include transformations. Concerning answer D, we will discuss in more detail the usefulness of transplantation in Question 7.

Case study 46.5

A 58-year-old male with a long history of recurrent FL grade 1–2 stage IVA that has been treated with rituximab alone, R-CHOP 6×, and six cycles of fludarabine–rituximab presents with transformed lymphoma. He is stage IIIB, the histology is DLBCL, and there is no *MYC* rearrangement. He has a good performance status.

1. What treatment would you recommend?

A. Supportive or palliative therapy only
B. R-ICE or R-ESHAP or other salvage therapy followed by high-dose therapy and autologous stem cell transplant
C. Radioimmunotherapy (Y90-ibritumomab or I131-tositumomab)
D. R-bendamustine

This patient represents an example of a young heavily pretreated patient who presents with a transformed lymphoma. His prognosis is poor but a durable remission is still possible, so we would advise him against a palliative approach. His prior exposure to anthracycline precludes the use of this class of agents.

The data to support the role of high-dose therapy with autologous transplantation after salvage therapy comes from retrospective studies and case series (Table 46.1). With this strategy, approximately 25–35% of patients are alive without progression after 5 years. In the case series from British Columbia, London, and Lyon, 5%, 9%, and 13% of patients respectively were treated with high-dose therapy with autologous stem cell transplant. The largest published retrospective study contained 50 patients and is from the European Bone Marrow Transplant Registry. The 5-year survival in that series was 51% and the 5-year progression-free survival (PFS) was 30%. The conditioning regimens were variable and included cyclophosphamide + TBI (56%), carmustine, etoposide, cytarabine, and melphalan (BEAM;

Table 46.1 Results of studies of autologous and allogeneic transplantation in transformed lymphoma.

Study	*N*	Median age (range)	Main conditioning regimen used	Autologous or allogeneic	Median follow-up (y)	ORR % (CR/PR) after transplant	PFS	OS	TRM or secondary MDS
Williams *et al.* (2001)	50	45.8 (28.0–60.6)	Cy/TBI (56%), BEAM (20%)	Auto	4.9	76 (62/14)	20% at 5 years	51% at 5 years	8% at 100 days/—
Villa *et al.* (2011)	204	53 (24–72)	—	Auto	—	—	48% at 5 years	56% at 5 years	5% at 2 years/—
	66	45 (25–72)	95% myeloablative	Allo	—	—	47% at 5 years	49% at 5 years	32% at 2 years/—
Ban-Hoefen *et al.* (2012)	18	58 (40–65)	BEAM (78%), Cy/TBI (17%)	Auto	3.3	94% RR before transplant	59% at 2 years	82% at 2 yeas	0%/11%
Eide *et al.* (2011)*	47/30*	55 (31–65)	BEAM (100%)	Auto	3.9	83 (60/23)	32% at 5 years	47% at 5 years	0%/0%
Ramadan *et al.* (2008)	25	49 (29–55)	Cy/TBI (83%), Cy/VP16/TBI (10%)	Allo	2.1	—	25% at 3 years	32% at 3 years	33% at 1 year/—
Thomson *et al.* (2009)	18	46)23–64)	Fludarabine/ Alemtuzumab (100%)	Allo	4.3	—	60% at 4 years	61% at 4 years	29% at 1 year/—

CR, complete response; Cy/TBI, cyclophosphamide and total body irradiation; MDS, myelodysplastic syndrome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TRM, treatment-related mortality; VP16, etoposide.
*Only prospective study: 47 patients entered the study and 30 patients received autologous transplantation.

Table 46.2 Results of studies with newer agents that have included transformed lymphoma.

Study	*N*	Median age (range)	Treatment	Median number of prior therapies	Median follow-up (months)	ORR % (CR/PR)	PFS (months)	Major grade 3–4 toxicity (%)
Friedberg *et al.* (2008)	15	*63 (38–84)	Bendamustine 120 mg/m^2 IV every 3 weeks for six cycles	*2	*26	66 (13/53)	4.2	• Hematological: N (54), T (25), A (12) • Nausea (4), vomiting (4) • Fatigue (7)
Witzig *et al.* (2002)	9	*60 (29–80)	^{90}Y-ibritumomab tiuxetan	*2	—	56 (NR)	*11.2	• Hematological: N (55), T (60), A (1) • Asthenia (4)
Kaminski *et al.* (2001)	23	*60 (38–82)	I^{131} tositumomab	4	*47	39 (13/26)	**8.4	• Hematological (grade 4): N (18), T (22), A (0) • Fever (2), chills (2)
Czuczman *et al.* (2011)	33	66 (42–84)	Lenalidomide 25 mg days 1–21 of 28 d cycle	4	5.6	46 (21/25)	5.4	• Hematological: N (48.5), T (15.1), A (6.1) • Pneumonia (9.1) • Abdominal pain (6.1)

A, anemia; CR, complete response; N, neutropenia; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; T, thrombocytopenia.
*Results of the whole study (the specific data on TL are not reported separately in the study).
**PFS of patients who responded to I^{131}-Tositumomab in the whole study (data for TL are not reported).

(*Continued*)

20%), cyclophosphamide/etoposide + TBI (14%), and other regimens (10%). The reported transplant-related mortality at 100 days varies between studies 0–20%. There are a paucity of data regarding treatment in the rituximab era. One study from Canada showed an improvement in 5-year posttransformation PFS from 38% in patients treated with rituximab-chemotherapy only to 48% in patients who actually had an autologous transplant ($P = 0.033$). However, the 5-year OS was similar in the two groups: 54% and 56% ($P = 0.276$). A small retrospective study of 18 patients who underwent autologous transplant and who were treated at some point with rituximab demonstrated a 2-year PFS of 59% and 2-year OS of 82% after transplant. The patients who had not been exposed to rituximab prior to transformation seemed to have a better outcome similar to results from the CORAL trial for nontransformed DLBCL.

Allogeneic transplant has the advantage of the graft versus lymphoma effect and is known to be the only curative treatment for FL. Small series of patients treated with either myeloablative or reduced-intensity conditioning regimens have been published for patients with transformed lymphomas but the patient numbers are even smaller than autologous transplant series (Table 46.2). The largest published series on myeloablative allogeneic transplant reported a 3-year event-free survival (EFS) from transplant of 25% and 3-year OS of 32% for these 25 transformed lymphoma patients. At one year, the relapse rate was 35%, and the TRM 33%. To reduce the toxicity of transplant, nonmyeloablative conditioning regimens have been employed. For example, in 18 patients, Thomson *et al*. reported a 4-year PFS of 60% and 4-year OS of 61%. The TRM was 29% at one year and 43% of the patients relapsed at 4 years (2009). A single institution retrospective study from British Columbia comparing auto-transplant and myeloablative allogeneic transplant reported a better 5-year survival in the autologous group (72% vs. 33%, $P = 0.005$). In the Canadian transplant registry, the results for allo-transplant and auto-transplant were similar: 5-year posttransplant OS 46% versus 50% and PFS 46% versus 48%. The TRM at 2 years was 32% for allo and 5% for auto. For these reasons, outside a clinical trial, we would favor salvage chemotherapy and autologous transplant in the patient described above, reserving allogeneic transplantation in the event of recurrence. We will discuss the other treatments in Case study 46.6.

Case study 46.6

An 84-year-old female with FL treated previously with rituximab and R-CHOP presents with B-symptoms and transformed lymphoma.

1. What is your choice of treatment? (Choose all that apply.)

A. Supportive or palliative therapy only
B. Clinical trial
C. Radioimmunotherapy (Y-90 Ibritumomab or I131-Tositumomab)
D. R-bendamustine
E. Lenalidomide

The main objective in this patient is to improve quality of life and survival. If the patient refuses treatment or if, despite corticosteroids, the patient has a poor performance status, supportive or palliative treatment might be appropriate. Also, it is always important to consider a clinical trial; many of the new targeted agents are easily tolerated oral formulations (see http://www.clinicaltrials.gov).

Outside a clinical trial, bendamustine, radioimmunotherapy, and lenalidomide are nontransplant strategies that have been studied in patients with TL. Unfortunately, a multicenter phase II trial of bendamustine alone that included 15 patients with TL showed a response rate of 66%, but a median duration of response of only 2.3 months and a median PFS of 4.2 months for these patients. For the subset of patients with TL, the response rate to Y90-Ibritumomab was 56% (5/9 patients) compared to 75% (3/4) for monotherapy with rituximab in a comparative study published in 2002; unfortunately, the US Food and Drug Administration (FDA) has withdrawn approval for its use in TL patients because the intended follow-up trial was not completed. In the multicenter study of I131-Tositumomab, the response rate for patients with TL was 39% (9/23 patients). The median duration of response for the whole group (including mostly FL patients who are refractory to chemotherapy) was 6.5 months. More recently, a phase II study of lenalidomide in 33 patients with relapsed or refractory TL showed a response rate of 56.5% among cases of transformed FL. The median duration of response was 12.8 months and PFS was 7.7 months for transformed FL. It is important to note that bendamustine, Y90-Ibritumomab, and lenalidomide are not FDA approved for TL. Participation in a clinical trial is strongly recommended.

Case study answers

Case study 46.1

Question 1: Answer B

Case study 46.2

Question 2: Answer E
Question 3: Answer C

Case study 46.3

Question 1: Answer B

Case study 46.4

Question 1: Answer A or C, but D might also be appropriate

Case study 46.5

Question 1: Answer B

Case study 46.6

Question 1: We would consider all of the answers

Multiple choice answers

Question 1: Answer C
Question 2: Answer F

Selected reading

Ban-Hoefen M, Kelly JL, Bernstein SH, *et al*. High-dose therapy and autologous stem cell transplant for transformed non-Hodgkin lymphoma in the rituximab era. Leukemia & lymphoma. 2012;53:830–5.

Conconi A, Ponzio C, Lobetti-Bodoni C, *et al*. Incidence, risk factors and outcome of histological transformation in follicular lymphoma. British J Haemotol. 2012;157:188–96.

Czuczman MS, Vose JM, Witzig TE, *et al*. The differential effect of lenalidomide monotherapy in patients with relapsed or refractory transformed non-Hodgkin lymphoma of distinct histological origin. British J Haemotol. 2011;154:477–81.

Eide MB, Lauritzsen GF, Kvalheim G, *et al*. High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study. British J Haemotol. 2011;152:600–10.

Friedberg JW, Cohen P, Chen L, *et al*. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. Journal of the American Society of Clinical Oncology. 2008;26:204–10.

Harris N, Swerdlow S, Jaffe E, *et al*. Follicular lymphoma. In: Swerdlow SH, Harris NL, Jaffe ES, *et al*., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2008. p. 220–6.

Kaminski MS, Zelenetz AD, Press OW, *et al*. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. Journal of the American Society of Clinical Oncology. 2001;19:3918–28.

Link B, Maurer MJ, Nowakowski GS, *et al*. Rates and outcomes of follicular lymphoma in the immunotherapy era: A report from the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource. J Clin Oncol. 2013;31:3272–8.

Ramadan KM, Connors JM, Al-Tourah AJ, *et al*. Allogeneic SCT for relapsed composite and transformed lymphoma using related and unrelated donors: long-term results. Bone marrow transplantation. 2008;42:601–8.

Thomson KJ, Morris EC, Bloor A, *et al*. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. Journal of the American Society of Clinical Oncology. 2009; 27:426–32.

Williams CD, Harrison CN, Lister TA, *et al*. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. Journal of the American Society of Clinical Oncology. 2001;19:727–35.

Witzig TE, Gordon LI, Cabanillas F, *et al*. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Journal of the American Society of Clinical Oncology. 2002;20:2453–63.

Villa D, Savage K, Crump M, *et al*. Autologous and allogeneic stem cell transplantation for transformed indolent non-Hodgkin lymphoma: a report of the Canadian Blood and Marrow Transplant Group (CBMTG). Annals Oncol. 2011;22: iv115.

Wong E, Dickinson M. Transformation in follicular lymphoma: biology, prognosis, and therapeutic options. Curr Oncol Rep. 2012;14:424–32.

CHAPTER 47

HIV-associated lymphoma

Kieron Dunleavy
National Cancer Institute, Bethesda, MD, USA

1. What are the most important etiological factors for the development of HIV-associated lymphoma?

The pathogenesis of HIV-associated lymphoma is complex and involves the interplay of several biological factors, such as chronic antigen stimulation, co-infecting oncogenic viruses such as Epstein–Barr virus (EBV) and human herpes virus-8 (HHV8), genetic abnormalities, and cytokine deregulation. Most HIV-associated lymphomas are of B-cell lineage and demonstrate clonal rearrangement of immunoglobulin genes. T-cell lymphomas are uncommonly observed in the setting of HIV infection.

Chronic antigen stimulation, which is associated with HIV infection, can lead to polyclonal B-cell expansion, and this may then promote and result in the emergence of monoclonal B-cells. Recently, circulating free light chains were found to be elevated in patients at increased risk of HIV-associated lymphomas. These may represent markers of polyclonal B-cell activation and, in the future, may be useful for identifying HIV-positive individuals at increased risk for the development of lymphoma.

EBV is the most commonly found oncogenic virus in HIV-associated lymphomas and is observed in approximately 40% of cases. All cases of primary central nervous system lymphoma (PCNSL) and most cases of Hodgkin lymphoma (HL) harbor EBV, as do the majority of DLBCL cases with immunoblastic features. Primary effusion lymphoma (PEL) cases also harbor EBV in addition to HHV8. In contrast, EBV is only variably present in Burkitt lymphoma (BL) (30–50%) and plasmablastic lymphoma (50%), and it is typically absent in centroblastic lymphomas. EBV-positive HIV-associated lymphomas frequently express the EBV-encoding transforming antigen latent membrane protein-1 (LMP1), which activates cellular proliferation through the activation of the nuclear factor kappa B (NF-κB) pathway and may induce B-cell lymphoma-2 (BCL2) overexpression, promoting B-cell survival and lymphomagenesis.

2. How has the prognosis for patients with HIV-associated lymphoma changed over recent years with the advent of combination antiretroviral therapy?

It has improved significantly. Following the arrival of combination antiretroviral therapy (CART) and the development of novel therapeutic strategies, most patients with HIV-associated lymphomas are now cured of their disease, in contrast to the pre-CART era. The majority of patients with diffuse large B-cell lymphoma (DLBCL) and BL in particular have an excellent outcome, with recent studies supporting the role of rituximab in these diseases (this is further discussed in a later question in this chapter). The curability of many patients with HIV-associated lymphoma is now similar to that of their HIV-negative counterparts. New treatment frontiers need to focus on improving the outcome for patients with advanced immune suppression in particular and for those with adverse tumor biology such as the activated B-cell (ABC) type of DLBCL and the virally driven lymphomas.

3. What are the most important prognostic factors in HIV-associated lymphoma?

While the International Prognostic Index (IPI) is the standard prognostic assessment tool in HIV-negative DLBCL, its applicability to HIV-associated DLBCL lymphomas is questionable. Indeed, in a recent study of short-course EPOCH-R (infusional etoposide, vincristine, and doxorubicin with prednisone, cyclophosphamide, and rituximab) in newly diagnosed HIV-associated DLBCL, the IPI did not predict progression-free survival (PFS) or OS. The prognostic importance of CD4 cell count and immune function in HIV-associated DLBCL, neither of which are part of the IPI, are the most likely confounding variables. Patients with CD4 counts lower than 100 cells/μl are at increased risk of serious opportunistic infections and death.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Furthermore, patients with severe immune suppression have a higher incidence of immunoblastic subtypes, most of which are of postgerminal center or ABC derivation, and these patients have a poor outcome compared to patients with preserved immunity and higher CD4 counts, where the "germinal center B-cell-like" subtype is more common. There has been controversy about the prognostic role of the cell of origin in HIV-associated DLBCL. A recently report from the AIDS Malignancy Consortium (AMC) did not find an association between cell of origin and outcome, but this analysis was retrospective and included patients treated with a variety of different regimens, which may have confounded results. Involvement of the CNS, which is increased in HIV-associated aggressive B-cell lymphomas, also confers an adverse prognosis.

4. How should patients with HIV-associated lymphoma be evaluated, and what different and additional tests do they require compared to HIV-negative patients?

Patients should have a comprehensive medical history with attention paid to signs and symptoms of lymphoma, and a detailed HIV history including prior opportunistic infections, immune function, HIV viral control, and a history of all antiretroviral treatment with special attention paid to any history of antiretroviral drug resistance. Then, the physical examination should include in particular a careful assessment of all lymph node regions as well as the liver and spleen. Laboratory studies, including a complete blood count, a chemistry profile with lactate dehydrogenase (LDH) and uric acid levels, a CD4 cell count, and HIV viral load, should be performed. HIV and hepatitis B and C serologies should be assessed. Ideally, an excisional biopsy should be performed and an entire lymph node evaluated by an expert hematopathologist who is experienced in the diagnosis of lymphomas and aware of all of the pitfalls and nuances involved; sometimes, a core needle biopsy may be acceptable, but a fine-needle aspiration biopsy is usually inadequate for a definitive diagnosis. A bone marrow aspirate and biopsy should be done because involvement by lymphoma is found in up to 20% of cases. Patients with aggressive B-cell lymphomas should have a lumbar puncture for analysis of cerebrospinal fluid by both cytology and flow cytometry to check for the presence of leptomeningeal lymphoma.

Imaging studies should include computed tomography (CT) scanning of the chest, abdomen, and pelvis. Radiographic evaluation of the head should also be performed, preferably by magnetic resonance imaging (MRI). Fluoro-deoxyglucose positron emission tomography (FDG-PET) is useful in HIV-negative aggressive lymphomas, but its role in HIV-associated lymphomas is poorly studied and can be confounded by inflammation from HIV-associated nodal reactive hyperplasia, infections, and lipodystrophy. Prior experience evaluating FDG-PET in HIV-associated lymphoma is limited to small retrospective series. In one of these studies of 13 patients with HIV, although a negative scan during and following the completion of treatment was associated with a lasting complete remission (CR), most scans were positive but not predictive of remission. Similarly, in another small study of FDG-PET in HIV-associated NHL, PET positivity during and after treatment was often associated with benign findings.

5. What is the role of rituximab in HIV-associated DLBCL, and should it be standard in upfront therapy?

Although the benefit of rituximab is well established in HIV-negative DLBCL, its role in HIV-associated DLBCL has been controversial in the past. This controversy really stems from an AMC randomized phase III study of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without rituximab in HIV-associated aggressive lymphomas, where it was demonstrated that rituximab was associated with significantly more infectious deaths but only a trend in improved tumor control; based on this, the authors concluded that rituximab does not improve the clinical outcome of HIV-associated DLBCL. A retrospective analysis of three phase II trials from Italy, where patients received infusional cyclophosphamide, doxorubicin, and etoposide (CDE) with rituximab, also concluded that rituximab might increase infections. On closer evaluation of the AMC trial, however, the increased infectious deaths occurred primarily in patients with very low CD4 counts, and many patients received "maintenance" rituximab after chemotherapy, which has not been shown to be useful in HIV-negative DLBCL. Needless to say, these factors confound any interpretation that rituximab is not useful in HIV-associated DLBCL.

To further address the role of rituximab, the AMC performed a follow-up randomized phase II study of concurrent versus sequential rituximab with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin) in HIV-associated DLBCL; importantly, in that study, concurrent rituximab was not associated with an increased risk of infectious deaths. The study also examined if the CR rate with EPOCH-R was superior to that with CHOP $\pm$ rituximab, employing a predetermined retrospective analysis, and if concurrent versus sequential rituximab was more toxic and/or more effective. There was no difference in toxicity between the arms, and the authors rejected the null hypothesis of 50% (associated with CHOP $\pm$ rituximab) in favor of 75% CR for EPOCH with concurrent rituximab ($P = 0.005$; power: 0.89). Based on this study, we consider it very unwise to omit rituximab from upfront therapy in HIV-associated lymphoma.

6. What is the optimal therapy for HIV-associated DLBCL?

We recommend combined treatment with rituximab and chemotherapy. Based on our results with EPOCH-R and the experience of the AMC's various studies (CHOP ± rituximab, and EPOCH-R with concurrent or sequential rituximab), we recommend infusional EPOCH-R therapy. With abbreviated EPOCH-R (a minimum of three cycles with one cycle beyond CR), 80% of patients require just three cycles, and the disease-free survival was greater than 80%.

7. What is the role of CART during immunochemotherapy for aggressive lymphoma, and should it be suspended or continued during treatment?

The risks and benefits of continuing CART during curative chemotherapy for aggressive lymphomas have been variably interpreted, and it remains a therapeutic controversy. While many investigators rightly raise the concern that uncontrolled HIV replication during chemotherapy will worsen immune function, one must consider the potentially adverse effects of CART on lymphoma-specific outcomes. One of the first trials that assessed concurrent CART with chemotherapy was an AMC study of dose-reduced and standard-dose CHOP. Although this was not a randomized study, it highlighted a number of important issues. They reported that the clearance of cyclophosphamide was reduced 36% and of doxorubicin was increased 20% in patients who received CART, compared to historical results with CHOP alone. Thus, CART led to reduced exposure to the two most important agents in CHOP (cyclophosphamide has to be converted to an active form) and potentially reduced efficacy. Of concern was the poor lymphoma-specific survival, which may in part reflect adverse pharmacokinetic interactions. Interestingly, there was no change in baseline HIV viral loads, and the baseline CD4 cell counts actually increased. The mechanism for increased CD4 cell counts raises the concern that CART protects T-cells from chemotherapy-induced cytotoxic stress, an effect that might occur in the lymphoma cells. While other groups have suggested that CART can be safely administered with chemotherapy, it has not been prospectively well studied, and controversies abound. Our own approach has been to suspend CART during chemotherapy because we believe the risk–benefit ratio of CART is not favorable. We are particularly concerned with pharmacokinetic and pharmacodynamic interactions that could lead to lower steady-state drug concentrations, a particular problem with infusional regimens, and/or increase toxicity, which may lead to chemotherapy dose reductions. Of theoretical but no less important concern is the potential inhibitory effect of some antiretroviral drug classes on lymphoid cell apoptosis and the potential for CART noncompliance, which would increase the risk of developing new HIV mutations. To assess the risks of CART suspension, we performed two prospective studies where CART was suspended during chemotherapy [dose-adjusted EPOCH (DA-EPOCH) and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR)], we and did not observe a significant increased risk of infections during therapy. While the HIV viral loads rapidly increased and then plateaued after the first cycle and the CD4 cells decreased over the course of chemotherapy, both HIV viral loads and CD4 cells returned to levels below pretreatment levels. Furthermore, there was a loss of HIV viral mutations, which were present before treatment, following completion of EPOCH. There are certain situations in which CART should be given with chemotherapy, such as when treating patients with plasmablastic lymphoma, which is EBV associated. In addition, in patients who have HL, therapy with ABVD is typically given over 6 months, and this is another situation in which it may be reasonable to give CART. Newer antiretroviral agents are likely to have fewer drug interactions and may be less problematic in combination with chemotherapy, but this needs to be better studied.

8. What is the optimal therapy for HIV-associated HL?

In the setting of HIV infection, classical HL (cHL) occurs most frequently in patients with depressed immune function. However, a paradoxical increase in cHL has been observed in the CART era despite an overall improvement in immune function in most patients. This is likely explained by examining the incidence of the two major subtypes of cHL that occur with HIV infection. In the pre-CART era, most cHL was of the mixed-cellularity subtype, which is EBV positive and occurs mostly in immune-suppressed patients, whereas more recently there has been an increased incidence of nodular sclerosis HL, which occurs more commonly at higher CD4 counts. When considering treatment, one needs to consider that patients with the mixed-cellularity subtype typically have advanced disease, including bone marrow involvement, and require chemotherapy alone. In contrast, patients with nodular sclerosis HL will typically present with mediastinal masses, and they may benefit from combined-modality treatment in selected cases. No studies have adequately evaluated different regimens in HIV-associated HL to make definitive recommendations about regimen efficacy. Thus, we recommend ABVD chemotherapy, which is the standard for HIV-negative patients. The impact of CART suspension has not been well studied in HL, but given the relatively long treatment duration and bolus scheduling of ABVD, it is not unreasonable to continue CART.

9. How should HIV-associated BL be approached?

While there has been a significant improvement in the outcome of HIV-associated DLBCL since the advent of CART, this was not initially the case with HIV-associated BL, as reported in a retrospective series by Lim *et al*. (2005).

This lack of improvement is likely explained by the then-widespread use of CHOP-based regimens, which have poor efficacy in BL. While dose-intense regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and CODOX-M-IVAC, with or without rituximab, have shown encouraging results in HIV-associated BL, they are highly toxic, particularly in HIV-positive patients, and are not widely used in these patients.

BL highlights the necessity to balance treatment efficacy and toxicity by optimizing the therapeutic index, especially in patients who are immune suppressed and/or elderly. In this regard, we studied using EPOCH-R in untreated BL based on its excellent activity in highly proliferative DLBCL and its favorable toxicity profile. With a median follow-up of at least 73 months, the freedom from progression (FFP) and OS, respectively, are 95% and 100% for DA-EPOCH-R and 100% and 91% for SC-EPOCH-RR. Therefore, our current approach is to use SC-EPOCH-RR for newly diagnosed patients with HIV-associated BL. The treatment paradigm is the same one used for DLBCL, with the majority of patients requiring only three cycles of therapy and a short duration of CART suspension.

10. How should primary CNS lymphoma in the setting of HIV infection be approached?

PCNSL typically presents in patients with severe immune suppression. Thus, it is not unexpected that since the advent of CART, its incidence has decreased dramatically. Although the disease remains incurable in most patients, the duration of survival appears to have increased. Compared to HIV-negative patients, HIV-associated PCNSL is typically EBV positive. Patients frequently present with changes in mental status or focal neurological symptoms, and, unlike those with HIV-negative PCNSL, they tend to present with multiple brain lesions. Because these patients are severely immune suppressed, intracranial opportunistic infections should always be considered in the differential diagnosis when evaluating intracranial lesions on imaging studies.

Unlike HIV-negative PCNSL, where high-dose methotrexate and, more recently, combination chemotherapy remains the standard approach for most patients with HIV-associated PCNSL.While most studies in the pre-CART era report a median survival in the range of 3 months, survival over 1.5 years has been reported in patients who responded to CART and were treated with radiation. The roles of systemic therapy and rituximab remain undefined in this disease, although some studies are investigating these agents and novel approaches for this disease.

11. What are the best approaches for primary effusion lymphoma (PEL) and plasmablastic lymphoma?

The outcome of PEL is poor with standard treatment, and the median survival is in the range of 6 months. Unlike some other HIV-associated lymphomas, CART does not appear to have had a significant impact on survival. At this time, the optimal therapy for PEL remains to be defined, but regimens such as EPOCH and CDE may be beneficial. Other approaches such as high-dose methotrexate and parenteral zidovudine (AZT) with interferon alpha have been studied but have demonstrated limited efficacy. The prognosis of plasmablastic lymphoma in the setting of HIV has also been historically poor. The impact of CART has not been well studied, but anecdotal reports suggest its prognosis may have improved since the introduction of CART. It is reasonable to consider regimens such as EPOCH or CDE for this disease. Newer agents like bortezomib and lenalidomide have been used anecdotally, with some reports of activity and success.

12. What is the best approach for patients with relapsed or refractory HIV-associated lymphoma?

Relapsed lymphoma is associated with a poor prognosis, and median survivals tend to be shorter than 1 year. A recent Italian study prospectively evaluated high-dose therapy and stem cell transplantation in 50 patients with relapsed HIV-associated lymphoma (both HL and NHL). While the median overall survival of patients was 33 months, patients who had chemosensitive disease had a relatively favorable outcome and were disease free at 44-month follow-up. Given the significant improvements in HIV control and immune function, it is reasonable to approach relapsed HIV-associated lymphomas similarly to their HIV-negative counterparts and to pursue aggressive strategies if appropriate. Less aggressive strategies, such as ESHAP and CDE, have poor outcomes. The role of allogeneic transplantation has not been well evaluated at this time.

Selected reading

Carbone A, Gloghini A. AIDS related lymphomas: from pathogenesis to pathology. Br J Haematol. 2005;130(5):662–70.

Dunleavy K, Wilson WH. How I treat HIV-associated lymphoma. Blood. 2012;119(14):3245–55.

Montoto S, Shaw K, Okosun J, *et al*. HIV status does not influence outcome in patients with classical Hodgkin lymphoma treated with chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine in the highly active antiretroviral therapy era. J Clin Oncol. 2012;30(33):4111–6.

Shiels MS, Engels EA, Clark CA, *et al*. The epidemic of non-Hodgkin lymphoma in the United States: disentangling the effect of HIV, 1992–2009. Cancer Epidemiol Biomarkers Prev. 2013;22(6):1069–78.

Sparano JA, Lee JY, Kaplan LD, *et al*. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood. 2010;115(15):3008–16.

CHAPTER 48

Primary CNS lymphoma

Nicholas A. Blondin[1], Joachim M. Baehring[1], and Fred H. Hochberg[2]

[1]Yale University School of Medicine, New Haven, CT, USA
[2]Massachusetts General Hospital, Boston, MA, USA

Case study 48.1

Patrick is a 66-year-old man who developed progressively worsening headaches and left-sided weakness over a 2-week period. He fell at home and was taken to a local hospital. A computed tomography (CT) scan of the head demonstrated a mass lesion isodense to gray matter in the right frontal lobe, with a considerable amount of associated vasogenic cerebral edema (see Figure 48.1). After contrast administration, the lesion was noted to enhance homogeneously. A second lesion was seen in the superior right frontal lobe, which also demonstrated homogeneous contrast enhancement. Dexamethasone was administered in the emergency room upon discovery of the tumor, and he was admitted to the hospital for further evaluation.

1. When should central nervous system (CNS) lymphoma be considered most likely in the differential diagnosis of a patient with a brain tumor?

A. Presentation with a seizure
B. Patient younger than 50
C. Presence of multifocal enhancing mass lesions
D. Prominent visual impairment as a chief symptom
E. Presence of fevers

Primary CNS lymphoma (PCNSL) is rare, accounting for 2.2% of primary brain and nervous system tumors. The median age at diagnosis is between 53 and 61 years, although it can occur at any age. Patients often present with focal neurologic deficits or symptoms or signs of increased intracranial pressure, and less commonly present with neuropsychiatric symptoms, seizures, or ocular symptoms. Common imaging findings include the presence of multiple enhancing lesions with associated cerebral edema and mass effect.

Following hospital admission, CNS lymphoma was considered to be the most likely diagnosis, given the history and imaging findings. The differential diagnosis included other primary brain tumors, cerebral abscess or infection, and demyelinating diseases.

2. What is the appropriate diagnostic evaluation for a patient with suspected CNS lymphoma?

A. Imaging of the brain, followed immediately by biopsy
B. Imaging of the brain, lumbar puncture, and biopsy
C. Imaging of the brain, ophthalmologic exam, and biopsy
D. CT scan of the chest, abdomen, and pelvis; magnetic resonance imaging (MRI) of the brain and spinal cord; lumbar puncture; and biopsy
E. MRI brain; biopsy; if positive, CT scan of the chest, abdomen, and pelvis, lumbar puncture (unless already done preoperatively), ophthalmologic exam, serum lactate dehydrogenase, human immunodeficiency virus (HIV) testing, bone marrow biopsy, and aspiration

The International Primary CNS Lymphoma Collaborative Group (IPCG) has published consensus guidelines for the diagnostic evaluation of patients with suspected primary CNS lymphoma. Patients should undergo a comprehensive physical exam, with particular attention to lymph nodes in all patients and testes in older men, and a comprehensive neurologic exam, including evaluation of cognitive function. A dilated fundoscopic exam should be performed to exclude ocular involvement.

Serum tests should include lactate dehydrogenase, as an elevated level has prognostic implications, as well as the determination of adequate hepatic and renal function (in

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

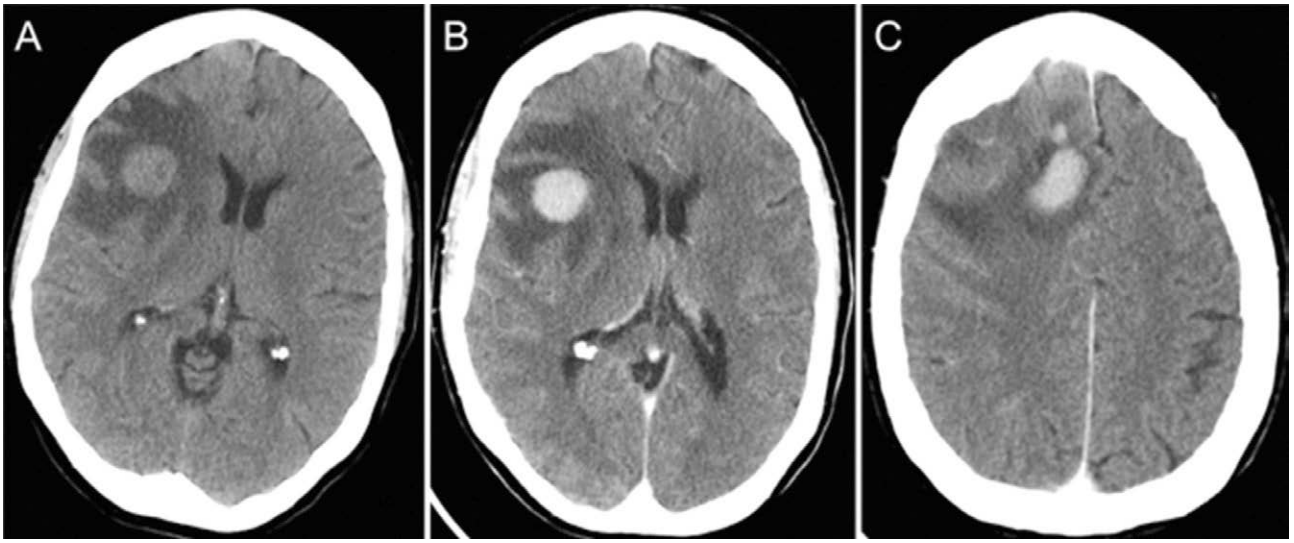


Figure 48.1 Computed tomography scan shows several right frontal mass lesions that are hyperdense prior to (A) and homogeneously enhancing after administration of contrast dye (B and C). The masses are surrounded by a hypodense area with finger-like protrusions consistent with vasogenic edema.

anticipation of treatment with high-dose methotrexate (MTX) therapy), and HIV testing, as there is an increased risk of PCNSL in this population and HIV status may have an impact on choice of therapy.

Imaging should include gadolinium-enhanced MRI of the brain parenchyma; a contrast-enhanced CT scan can be substituted in patients with a contraindication to MRI. PCNSL in the immunocompetent host typically appears as a single, homogeneously enhancing mass lesion adjacent to the ventricular system. Infiltrative growth along the course of the white matter tract is characteristic. Due to their high cellularity, the tumor masses display restriction of water diffusion, have an iso- to hypointense signal on T2-weighted sequences, and are hyperdense on CT. Premature use of corticosteroids can profoundly alter the tumor's imaging characteristics. In the immunodeficient host, PCNSL is more often multifocal and the lesions are rim enhancing. A gadolinium-enhanced MRI of the spine is only required in patients demonstrating spinal symptoms, as involvement of the spinal cord parenchyma is rare. Complete systemic staging to exclude occult systemic disease includes a CT scan of the chest, abdomen, and pelvis; a bone marrow biopsy with aspirate; and testicular ultrasound in older men to exclude an occult testicular lymphoma. An 18-fluorodeoxyglucose positron emission tomography (PET) scan increases diagnostic sensitivity but is generally not required.

A lumbar puncture should be performed unless prohibited by increased intracranial pressure and brain herniation. Cerebrospinal fluid (CSF) studies should include cell count, glucose, protein, cytomorphological examination, flow cytometry, as well as immunoglobulin heavy-chain (IgH) and T-cell receptor (TCR) gene rearrangement analysis.

Following admission to the hospital, dexamethasone was discontinued as CNS lymphoma was considered in the differential diagnosis. He underwent an MRI of the brain, which again demonstrated homogeneously enhancing mass lesions in the right frontal lobe (see Figure 48.2). There was no leptomeningeal thickening or enhancement. A CT scan of the chest, abdomen, and pelvis was unremarkable. Lumbar puncture was deferred, given the mass effect visualized on the MRI of the brain. A dilated fundoscopic exam was performed, and no retinal lesions or vitreal cells were seen. Serologic testing for HIV was negative, lactate dehydrogenase was elevated at 264 U/L, liver function tests were within normal limits, and creatinine was 1.1 mg/dL.

3. What is the role of surgery in the management of CNS lymphoma?

A. Gross total resection of mass lesions if possible
B. Diagnostic biopsy only
C. Diagnostic biopsy; debulking in the rare case of imminent herniation
D. There is no role for surgery

PCNSL is typically diagnosed via a stereotactic biopsy of a brain parenchymal lesion. Rarely, it may be diagnosed with meningeal biopsy or through CSF analysis. Gross total surgical resection does not play a therapeutic role in PCNSL, as the disease is often multifocal, is diffusely infiltrative, and may disseminate to the CSF or eyes. A large meta-analysis

(*Continued*)

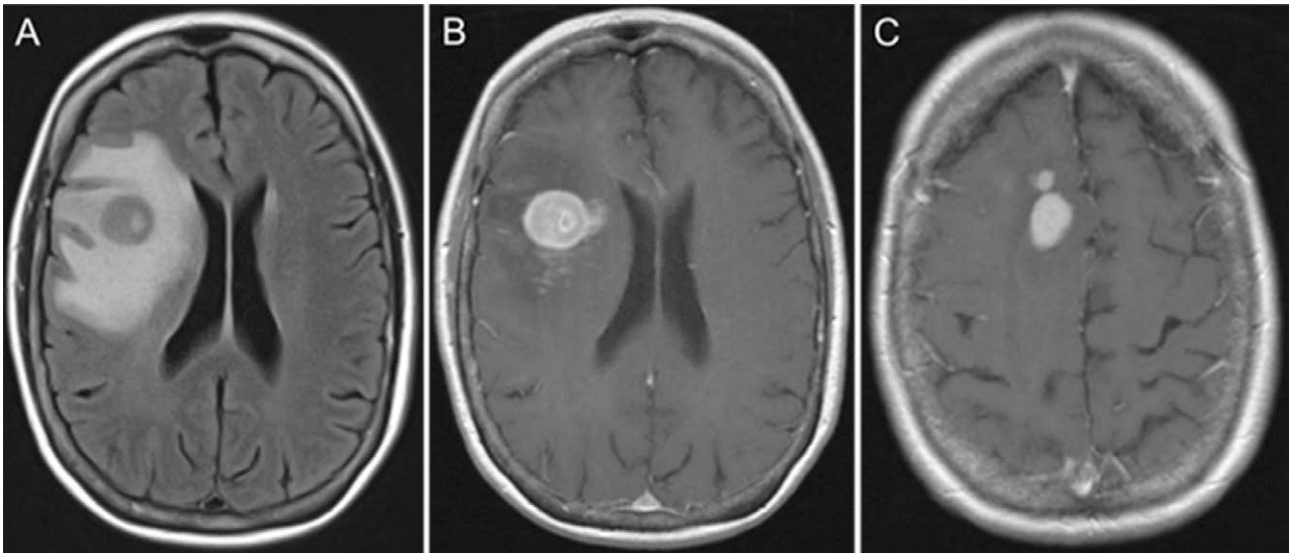


Figure 48.2 The mass lesions are hypointense on fluid attenuated inversion recovery (FLAIR) images (A) and homogeneously enhancing on T1-weighted images after administration of gadolinium (B and C). Surrounding vasogenic edema is hyperintense on FLAIR and hypointense on T1.

found no correlation between extent of resection and overall survival (OS). Furthermore, large resections may result in treatment delays and carry the risk of neurologic deficits. More extensive surgery should be reserved for cases at risk of perioperative herniation.

4. What is the sensitivity of a cerebral biopsy in a patient who has recently received corticosteroids?

A. Corticosteroids do not affect the results of a cerebral biopsy
B. There is a greater risk of a false-negative result
C. The biopsy will be nondiagnostic

Corticosteroids cause rapid apoptosis of lymphocytes, disrupting the cellular morphology of the tumor and normalizing imaging, but the tumor cannot be viewed as cured. Steroid therapy can lead to a false-negative biopsy result, as the tissue may appear diffusely necrotic or merely inflammatory with T-cell predominance. A recent retrospective analysis suggested that corticosteroid administration prior to biopsy does not have a major impact on diagnostic yield. It is currently recommended to hold corticosteroids in a patient with suspected PCNSL until after a biopsy is performed. Mannitol can be used to induce osmotic diuresis in patients with signs and symptoms of elevated intracranial pressure.

Cerebral biopsy confirmed a diagnosis of CNS lymphoma (see Figure 48.3). Pathologic findings included infiltration of numerous large CD20-positive and mitotically active lymphoid cells with prominent nucleoli, intermixed with abundant CD3+ T cells. A bone marrow biopsy was performed, without evidence of a lymphoproliferative disorder. Testicular ultrasound demonstrated no abnormalities. A 24-h urine collection was performed, and creatinine clearance was found to be 102 ml/min. A treatment plan was devised.

5. What is the current standard of care for initial treatment of primary CNS lymphoma?

A. High-dose MTX (>3.5 g/m^2 and preferably 8 g/m^2, adjusted for renal function) either alone or combined with other agents for remission induction and consolidation
B. Rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP)
C. Whole-brain radiation therapy (WBRT) alone
D. Temozolomide
E. Single-agent high-dose MTX, 8 g/m^2, administered every 14 days for eight cycles or until a complete response is achieved, in combination with intrathecal MTX given once per cycle

The current standard of care for initial treatment of PCNSL is systemic high-dose MTX-based therapy. Clinical trial data seem to suggest that polychemotherapy may be superior to monotherapy, but randomized controlled studies are lacking and a meta-analysis has revealed MTX to be the single most efficacious agent. Early administration of WBRT may increase progression-free survival (PFS) but not OS. The combination of conventional radiation doses and chemotherapy is associated with a high incidence of central neurotoxicity, especially in the elderly.

The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium conducted a multicenter phase II trial of single-agent MTX. In this trial, 25 patients with newly diagnosed PCNSL were treated with MTX in the induction,

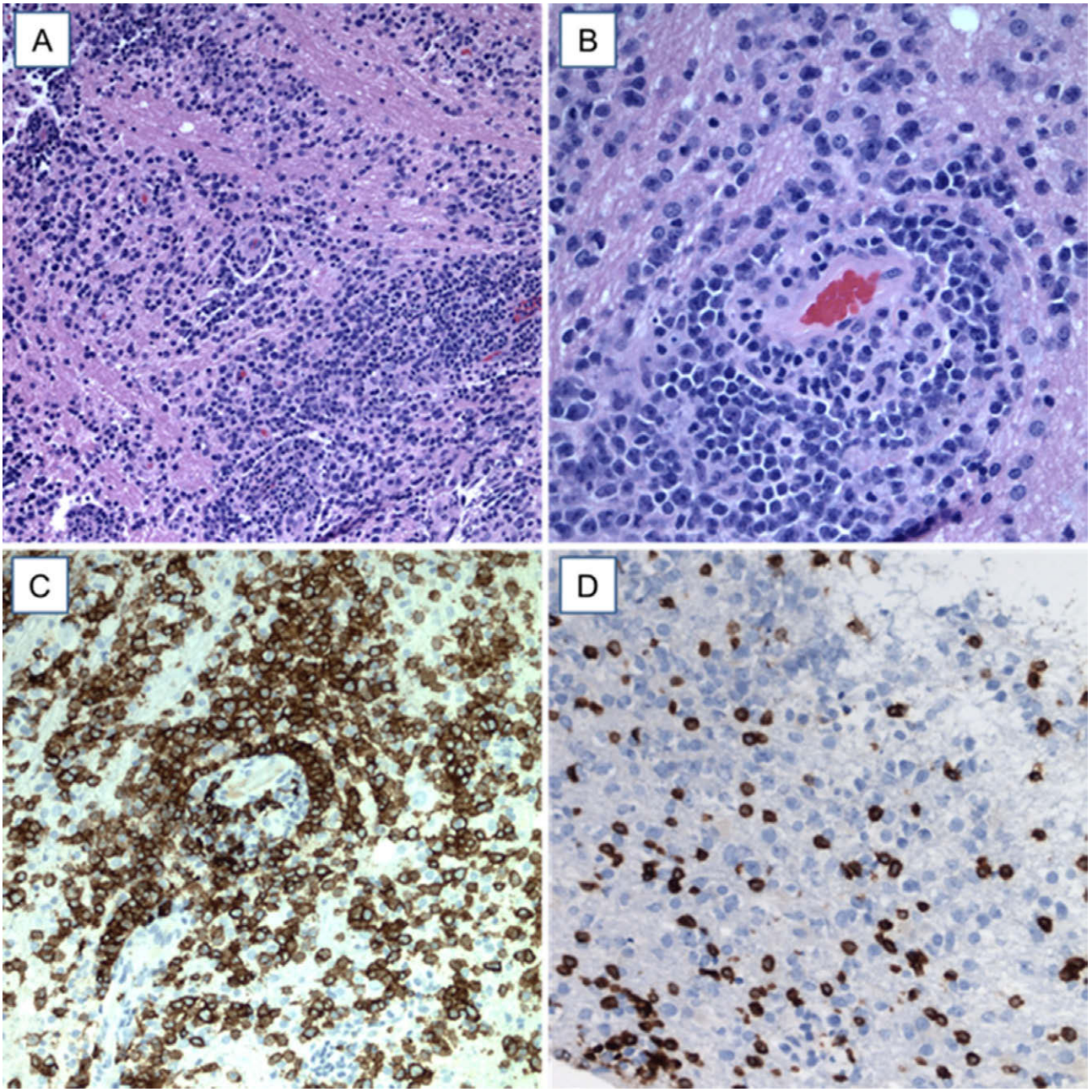


Figure 48.3 (A) Hematoxylin and eosin stain shows a mononuclear cerebral parenchymal cell infiltrate. (B) At higher-power magnification, the angiocentric arrangement of tumor cells is highlighted. (C) Immunohistochemistry using an anti-CD20 antibody identifies the large atypical cells within the infiltrate as B-cells. (D) A CD3-stain shows a reactive T-cellular infiltrate. (Color plate 48.1)

maintenance, and consolidation phases. In the induction phase, patients received MTX $8\,g/m^2$ every 14 days until a complete response (CR) was achieved or a maximum of eight cycles was administered. In patients who achieved a CR from induction chemotherapy, two consolidation cycles of MTX $8\,g/m^2$ were administered every 14 days followed by 11 maintenance cycles given every 28 days. The complete response rate was 52%, median PFS 12.8 months, and OS 55.4 months. A combination of MTX, temozolomide, and rituximab followed by intensive consolidation with etoposide and cytarabine resulted in CR in 52% of cases. Median PFS at 2 years was 78%. OS at 2 years was 93%.

Others have successfully used MTX-based polychemotherapy regimens with or without WBRT. Chemotherapy-only protocols resulted in CR of 40% to 60%. Median PFS and OS ranged from 11 to 21 months and 14 to 50 months,

(*Continued*)

respectively. In a prospective study of combination chemotherapy (five cycles of MTX 2.5 g/m^2, vincristine, procarbazine, and intraventricular methotrexate (12 mg) followed by WBRT (45 Gy) and high-dose cytarabine), the CR rate was 58%, and the partial response (PR) rate 37%. Median PFS was 24 months, and median OS 36.9 months. Twelve patients (15%) experienced severe delayed neurologic toxicity, and eight of them succumbed to it. In the International Extranodal Lymphoma Study Group (IELSG) 20 trial, a prospective randomized phase II study, 79 patients were assigned to four cycles of MTX 3.5 g/m^2 alone or in combination with cytarabine, followed by WBRT (dose and addition of a boost to the tumor depending on chemotherapy response) in both arms. The addition of cytarabine increased CR from 18% to 46%. PFS at three years was 21% in the MTX and 38% in the MTX–cytarabine arm. OS at three years was 32 versus 46%. The CHOP protocol (cyclophosphamide, doxorubicin, vincristine, and prednisone), commonly used to treat systemic B-cell lymphomas, does not have a role in the treatment of PCNSL.

MTX has also been used via intra-arterial administration following blood–brain barrier disruption with mannitol. Combined with intravenous etoposide, cyclophosphamide, or procarbazine, CR was 57.8%. Median PFS and OS were 1.8 and 3.1 years, respectively. PFS at 5 years was 31%, and at 7 years 25%. Procedure-related morbidity is considerable but largely reversible.

6. What monitoring is needed during treatment?

A. MRI every 4–8 weeks during remission induction, every 8–12 weeks during consolidation, and every 3 to 6 months during postchemotherapy follow-up. Ophthalmologic examination at least once a year. Lumbar puncture needs to be repeated at least once during therapy in patients with meningeal dissemination in order to document CR in CSF.

B. Blood counts and metabolic panel

C. MRI once monthly

D. Serum creatinine, complete blood count, and liver function tests once per cycle; and MRI every 2 months

E. Serum creatinine, complete blood count, and liver function tests once per cycle; lumbar puncture every 2 months; and MRI every 2 months

A gadolinium-enhanced MRI should be obtained every 4–8 weeks during remission induction, every 8–12 weeks during consolidation, and every 3 to 6 months during postchemotherapy follow-up. Ophthalmologic slit lamp examination has to be performed at least once a year even if patients are asymptomatic and ocular involvement was absent at initial diagnosis. A lumbar puncture needs to be repeated at least once during therapy in patients with meningeal dissemination in order to document CR in CSF. In addition, patients treated with high-dose MTX have their creatinine clearance calculated or measured prior to each cycle, which is used to adjust the MTX dose. It appears to be safe to use the calculated creatinine clearance. High-dose MTX should not be used if the creatinine clearance is less than 60 ml/min.

7. What is the role of radiation therapy?

A. WBRT) should be considered as initial treatment in all patients

B. Focal radiation therapy should be considered as initial treatment in all patients

C. WBRT should never be considered as initial treatment

D. WBRT is typically used for recurrent or refractory CNS lymphoma. There may be a role for WBRT as consolidation therapy

E. Focal radiation therapy is typically used for recurrent or refractory CNS lymphoma

Prior to the adoption of high-dose MTX, WBRT was considered to be the standard of care for initial treatment. The Radiation Therapy Oncology Group conducted a prospective study (RTOG 83-15) in which WBRT to 40 Gy was combined with a 20 Gy boost to the tumor plus a 2 cm margin. Median OS was only 11.6 months, and OS at 2 years was 28%. The addition of WBRT to chemotherapy improves PFS but not OS. Neurotoxicity is common and may be severe in the elderly (see above). Limiting the WBRT dose in polychemotherapy recipients (MTX 3.5 g/m^2, procarbazine, and vincristine, with postradiation cytarabine) achieving a CR likely reduces treatment-related morbidity, but long-term outcome results are not available. At this point, most referral centers limit the use of WBRT in newly diagnosed PCNSL to patients who cannot receive or who fail to achieve a CR to MTX-based chemotherapy.

WBRT is widely accepted as salvage therapy for recurrent or chemotherapy-refractory PCNSL. In a retrospective study of 48 patients treated with WBRT at progression or recurrence, 58% of patients had a CR, 21% had a PR, and median OS from initiation of WBRT was 16 months. Patients older than 60 and those treated with methotrexate within the prior 6 months were at increased risk for the development of neurotoxicity.

8. Are there special considerations for treatment in elderly patients?

A. WBRT should be used as first-line therapy in elderly patients

B. High-dose methotrexate can be safely used in the elderly, with dose adjustment for creatinine clearance

C. High-dose methotrexate is not an option in elderly patients

D. Temozolomide should be used as first-line treatment in elderly patients

E. Rituximab is contraindicated in elderly patients

The feasibility of MTX therapy in elderly patients has been demonstrated in numerous studies, although patient exclusion based on comorbidities or chronic renal failure is more common than in younger individuals. High-dose MTX-based therapy was associated with a lower response rate and higher mortality as well as lower PFS of patients who accomplished a CR in a large German study. The combination of MTX at $3\,g/m^2$ and temozolomide in patients with newly diagnosed PCNSL older than 60 years yielded a promising response rate (CR 55%), but the effect was short-lived (median event-free survival 8 months). The best available evidence indicates that temozolomide can be used in this patient population with reasonable efficacy and good tolerability. A study of elderly patients receiving temozolomide alone as upfront therapy found a CR of 47% and median OS of 21 months. Temozolomide may also be combined with rituximab, although this has only been formally studied as salvage therapy. WBRT is used for relapsed or chemotherapy-refractory disease.

After two cycles of high-dose methotrexate, Patrick reported the new onset of headaches that felt like a constant, dull ache in the forehead. A lumbar puncture was performed to evaluate for CNS dissemination of lymphoma. CSF analysis revealed one red blood cell, 0 nucleated cells, CSF glucose 65 mg/dL, and CSF total protein 32 mg/dL. The headaches subsequently improved with conservative management.

9. What is the role of intrathecal chemotherapy?

A. Intrathecal chemotherapy should be combined with high-dose MTX
B. Intrathecal chemotherapy is generally considered unnecessary in high-dose MTX-based treatment protocols
C. Cytarabine is superior to MTX when administered intrathecally
D. Intrathecal MTX improves PFS and OS
E. Intrathecal rituximab improves PFS and OS

With respect to the incidence of meningeal dissemination in PCNSL, a wide range of numbers has been reported (15–41%) and in most of these studies, the presence of meningeal lymphoma was of no prognostic relevance. Intrathecal chemotherapy has not been studied in a prospective, randomized fashion. In a retrospective analysis of 370 patients with PCNSL, the addition of intrathecal chemotherapy to high-dose methotrexate did not result in improved survival, and there was a higher incidence of neurotoxicity. Another retrospective analysis of 69 patients also failed to detect a significant difference in objective response rate, patterns of relapse, PFS, or OS between patients treated with or without intrathecal prophylaxis.

We and others have empirically added intrathecal to systemic therapy only in patients with primary meningeal lymphoma or those with clear clinical signs of meningeal dissemination unresponsive to systemic chemotherapy alone. MTX, cytarabine, and thiotepa are available for intrathecal use. Rituximab can be given safely via the intrathecal route, and preliminary evidence of its efficacy is available.

After six cycles of high-dose MTX, Patrick achieves a CR. No residual enhancing disease is seen on MRI of the brain. He completes consolidation therapy with MTX. One year later, he complains of "floaters" in the left eye. Dilated eye examination reveals vitreous cells. A vitrectomy confirms ocular lymphoma, and IgH gene rearrangement analysis confirms the clonal relationship between the cerebral parenchymal and the ocular tumor.

10. What is the relationship between primary CNS lymphoma and ocular lymphoma?

A. Ocular lymphoma complicates more than 50% of cases of primary CNS lymphoma
B. There is no clear correlation between primary CNS lymphoma and ocular lymphoma
C. Ocular lymphoma complicates 20–30% of cases of primary CNS lymphoma
D. Ocular lymphoma complicates less than 5% of cases of primary CNS lymphoma

Concurrent ocular lymphoma may be present in as many as 30% of PCNSL. Common symptoms are reduced visual acuity, and visual illusions ("floaters"). In as many as 50% of cases, ocular dissemination is entirely asymptomatic at diagnosis. Primary intraocular lymphoma is exceedingly rare. 80% of these cases suffer CNS dissemination. Treatment options include orbital radiation, intraocular chemotherapy (MTX and rituximab), or systemic chemotherapy. While dedicated ocular therapy can improve disease control, it has not been found to affect PFS or OS. Localized therapy is often used in patients without concurrent active CNS disease and in those in whom systemic therapy fails to clear the ocular disease component. When both eyes are affected, orbital radiation is commonly used. However, clear guidelines based on prospective randomized studies are unavailable.

An MRI of the brain is performed after his vitrectomy procedure. A small new enhancing lesion is seen, again in the right frontal lobe representing relapsed disease.

11. What options exist for salvage chemotherapy?

A. High-dose methotrexate
B. Temozolomide or rituximab, either alone or in combination

(*Continued*)

C. Temozolomide should not be considered as salvage chemotherapy
D. WBRT
E. A, B, and D

Often, relapsed disease remains sensitive to high-dose methotrexate-based regimens. Salvage therapies with activity also include temozolomide and rituximab. WBRT is commonly used as salvage treatment for relapsed or refractory CNS lymphoma, as described in Question 7. There are limited data regarding the efficacy of topotecan or combination chemotherapy regimens such as procarbazine, lomustine, and vincristine. Pemetrexed holds promise, but only preliminary data are available.

12. Is there a role for high-dose chemotherapy with autologous stem cell transplantation (HDC/ASCT)?

A. There is no role for HDC/ASCT in the treatment of CNS lymphoma
B. HDC/ASCT can be considered in patients younger than 60 years of age as consolidation therapy in first remission as well as for treatment of relapsed disease
C. HDC/ASCT should be considered in all patients
D. Strong evidence exists for HDC/ASCT as upfront treatment for CNS lymphoma

Many small studies and case series of patients treated with HDC/ASCT have been reported over the past 10 years, often with encouraging results. The treatment was first used in relapsed disease, but more recently, an increasing number of studies have focused on patients in first remission. Retrospective analysis of 105 patients treated with HDC/ASCT found a median PFS of 7 years and OS of 10 years, with low rates of toxicity. However, HDC/ASCT does carry increased mortality risk compared to conventional treatment for PCNSL, due to complications associated with this therapy, especially in the elderly.

In a study of HDC/ASCT (stem cell collection: cytarabine, etoposide, and G-CSF; HDC: thio-TEPA, busulfan, and cyclophosphamide) for patients with relapsed or refractory disease, PFS at 2 years was 43% and median OS 18.3 months. A group of German investigators used HDC/ASCT (HDC: BCNU and thio-TEPA) in patients with newly diagnosed PCNSL. Patients who failed to achieve CR were treated with WBRT in addition. Event-free survival was 81% at 2 years and 67% at 5 years. Median OS was 104 months. In a retrospective study of 13 patients with relapsed PCNSL and three individuals with newly diagnosed disease, HDC/ASCT (HDC: thio-TEPA, busulfan, and cyclophosphamide) was used, and PFS and OS at 1 year were 80% and 100%, respectively. Prospective studies for this treatment modality are ongoing.

Patrick is retreated with high-dose MTX and again achieves a complete response. Due to his age, he was not considered a good candidate for HDC–ASCT. It was decided to follow him expectantly after successful completion of MTX consolidation. He has been in remission for 15 months.

13. What is the prognosis for a patient with newly diagnosed CNS lymphoma?

A. Less than 1-year median survival
B. Less than 3-year median survival
C. Less than 1 year based on population-based statistics; 3 to 4 years based on the referral center
D. More than 10-year median survival

The prognosis of patients with newly diagnosed PCNSL has markedly improved over the past two decades. For patients treated with high-dose MTX-based regimens in prospective studies at tertiary care referral centers, the median survival is 55 months. However, population-based statistics continue to draw a less favorable picture with median OS of less than 1 year. The ten-year survival rate is 21%. Patients between 45 and 64 years of age constitute the age group with the most favorable prognosis (median OS approximately 2 years, and 10-year survival 27–28%). With survival now often exceeding years from diagnosis, treatment-related neurotoxicity must be considered when devising a treatment plan.

Case study answers

Case study 48.1

Question 1: Answer C
Question 2: Answer E
Question 3: Answer C
Question 4: Answer B
Question 5: Answer A
Question 6: Answer A
Question 7: Answer D
Question 8: Answer B
Question 9: Answer E
Question 10: Answer C
Question 11: Answer E
Question 12: Answer B
Question 13: Answer C

Selected reading

Enting RH, Demopoulos A, DeAngelis LM, *et al*. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. Neurology. 2004;63(5):901–3.

Kasenda B, Schorb E, Fritsch K, *et al*. Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma—a

long-term follow-up study. Annals Oncol. 2012;23(10): 2670–5.
Roth P, Martus P, Kiewe P, *et al*. Outcome of elderly patients with primary CNS lymphoma in the G-PCNSL-SG-1 trial. Neurology. 2012;79(9):890–6.
Schorb E, Kasenda B, Atta J, *et al*. Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. Haematologica. 2013; 98(5):765–70.
Wieduwilt MJ, Valles F, Issa S, *et al*. Immunochemotherapy with intensive consolidation for primary CNS lymphoma: a pilot study and prognostic assessment by diffusion-weighted MRI. Clin Cancer Res. 2012;18(4):1146–55.

CHAPTER 49

Primary cutaneous lymphoma

Thomas M. Habermann
Mayo Clinic, Rochester, MN, USA

Introduction

The cutaneous T-cell disorders are a complex heterogeneous group of lymphoproliferative disorders that represent the second most common extranodal site for non-Hodgkin's lymphoma. Management requires a team that includes dermatology, pathology, nurses, hematology and oncology physicians, social workers, and others. A definitive diagnosis, assessment of risk stratification, and an understanding of the multiple therapeutic interventions available aid in providing improved outcomes for patients.

1. What is the incidence of cutaneous T-cell lymphoma?

The most common cutaneous T-cell lymphomas (CTCLs) are mycosis fungoides (MF) and Sézary syndrome (SS). About 50% of cases are MF, and the second most common subtype is SS. SS more characteristically arises without a previous history of MF. If MF evolves into SS, then the diagnosis should be erythrodermic mycosis fungoides. The estimated annual incidence of these disorders in the Surveillance, Epidemiology, and End Results (SEER) database is 1 per 100,000. In a well-defined population of Rochester, Minnesota, it was 0.9 per 100,000 residents.

2. How do patients present?

The incidence increases with age, and the average age at diagnosis is 50 to 60 years, but the disorder can occur at any age, including childhood. The disorder is more likely to occur in black populations.

Patients may have a premalignant phase of several years to decades in duration with eczematous or dermatitis skin lesions before a diagnosis is firmly established. The median duration of a premalignant phase is 6 years. It is not uncommon for patients to present with a history of multiple skin biopsies. The spectrum of premalignant disorders includes large-plaque parapsoriasis, poikiloderma atropicans vasculare, follicular mucinosis, pityriasis lichenoides et varioliformis acuta (Mucha–Habermann disease), and other atypical infiltrates of the skin.

The classic malignant stages of CTCL are manifested in the skin and include patch-stage CTCL, plaque-stage CTCL, tumor-stage CTCL, and erythrodermic CTCL. Pruritis may or may not be a feature. Pigmentation may be altered. Lesions may be present for months to years before the plaque stage of CTCL develops. Plaque- and tumor-stage CTCL are sharply demarcated circular plaques that are infiltrated, elevated above the surrounding normal skin, erythematous, occasionally violaceous, and characteristically on the trunk and extremities. When patches overlap, a geographic pattern in appearance is produced. When plaques affect the face, the dermal thickening may progress to give the classic leonine facies. Infiltration of the skin of the palms and soles results in hyperkeratosis and fissuring. With disease progression, there is extracutaneous, nodal, and extranodal involvement. Tumor-stage lesions are a reflection of a more clinically aggressive course, occur at sites of previous plaque-stage involvement, and have a predilection for the body folds, including the groin, antecubital fossa, neck, axilla, and inframammary areas. At the time of the initial presentation, approximately 40% of patients have plaques on less than 10% of the body surface area, 30% have extensive plaques, 15% exhibit a tumor phase, and 10% have an erythrodermic phase.

SS is defined by the presence of Sézary cells in the peripheral blood with skin changes. Sézary cells are characterized by changes in individual nuclei, including irregularity, prominent indentations, and convolutions with a cerebriform appearance. The erythrodermic form of CTCL, SS, presents with exfoliative erythroderma, lymphadenopathy, and keratoderma or thickening of the skin of the

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

palms and soles with cracks and fissures (palmoplantar hyperkeratosis). Significant pruritis, which is characteristic, leads to excoriations, exudation, and crusting. Nail dystrophy (onychodystrophy), ectropion (eversion of the eyelids, giving the appearance of a "pulled-down" appearance of the lower lids), and alopecia are usually present.

As MF and SS progress, extracutaneous disease involves lymph nodes, bone marrow, liver, and other organs.

3. What causes cutaneous T-cell lymphomas?

The cause of the majority of CTCLs is unknown. Two case–control studies have not supported environmental factors. Prolonged exposure to contact allergens such as plants, metals, cosmetics, medications, foods, and insect bites between MF patients and controls demonstrated no associations. In selected cases, however, patients with atopy, contact sensitivity, chronic dermatitis, and immunodeficiency may develop CTCL. CTCL has been documented after B-cell lymphoma, Hodgkin lymphoma, acquired immune deficiency syndrome, and posttransplant lymphomas.

4. How are cutaneous T-cell lymphomas classified?

Cutaneous lymphomas include CTCL and cutaneous B-cell lymphomas. Cutaneous lymphomas are distinguished on the basis of their clinical, histologic, immunologic, and molecular features. The World Health Organization–European Organization for Research and Treatment of Cancer (WHO–EORTC) classification for cutaneous lymphomas is outlined in Table 49.1.

Table 49.1 World Health Organization–European Organization for Research and Treatment of Cancer classification of primary cutaneous lymphomas (Source: Willemze R, *et al*. Blood. 2005; 105:3768–85).

Cutaneous T-cell and natural killer (NK)-cell lymphomas
Mycosis fungoides (MF)
MF, variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia or lymphoma
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large-cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK- and T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous $CD4^+$ small and medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, let type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

5. How are cutaneous T-cell lymphomas diagnosed?

The diagnosis of CTCL is established by tissue biopsy, usually a punch skin biopsy with specimens 4 to 6 mm deep for histology, immunohistochemistry, and molecular genetic studies. Classic histologic manifestations include abnormal lymphocyte morphology, a band-like superficial dermal infiltrate, epidermotropism, and Pautrier's microabscesses. Significant variability exists in the expression of these pathologic characteristics.

The diagnosis is based on clinic-pathologic criteria. The diagnostic criteria for classic MF and SS are as follows. MF requires four points (histopathologic, molecular biological, and immunologic), two points for one basic criterion plus two additional criteria or one point for basic criteria and one additional criterion. The basic criteria are persistent and/or progressive patches or plaques with additional criteria of non-sun-exposed location, variation in size or shape, and poikiloderma. Histologic criteria (2 points for one basic plus one additional criterion) are as follows. The basic criterion is superficial lymphoid infiltrate, with additional criteria of epidermotropism without spongiosis and lymphoid atypia (cells with large cerebriform nuclei). Molecular biologic criteria (1 point) are clonal T-cell receptor (TCR) gene rearrangement. Clonal rearrangements of the TCR-beta gene have been documented in most patients. Immunopathologic criteria (1 point for $\geq$1 criteria) are $<$50% CD2+, CD3+, and/or CD5+ T-cells; less than 10% CD7+ cells; and erythrodermal or dermal discordance of CD2, Cd3, CD5, or CD7.

The tumor stage of MF and SS is characterized by dense dermal infiltration that often extends into the deep dermis and subcutis, becoming nonepidermotropic or less epidermotropic. A complete transformation to a large-cell variant that resembles diffuse large B-cell lymphoma or anaplastic lymphoma is typically seen in tumors.

The diagnostic criteria for SS are clonal rearrangement of the TCR (by Southern blot or polymerase chain reaction) and absolute Sézary count $\geq$1000 μl. If the Sézary count is not able to be used, then look for increased CD4+ or CD3+ T-cells with a CD4–CD8 ratio $\geq$10 or an abnormal immunophenotype as manifested by a CD4+-to-CD7− ratio $\geq$40% or a CD4+-to-CD26− ratio $\geq$30%.

6. What are the variants and subtypes of MF and SS?

The variants of MF include folliculotropic MF, which is a disorder of localized alopecia with mucin deposition in the hair follicle; pagetoid reticulosis, which is characterized by solitary slow-growing plaques (Woringer−Kolopp type) or disseminated patches on the hands and feet; and granulomatous slack skin, which is characterized by excessive redundant folds of the skin and plaques in the axilla and groin.

The differential diagnosis, variants, and subtypes of SS include different disorders. Adult T-cell leukemia or lymphoma is associated with the T-cell leukemia virus 1 (HTLV1). Primary cutaneous CD30+ lymphoproliferative disorders include anaplastic large cell lymphoma and lymphomatoid papulosis. Lymphomatoid papulosis is defined as a chronic, recurrent, erythematous, and self-healing papulonodular skin disease where the lesions spontaneously resolve in 3 to 12 weeks with an unpredictable duration of disease from months to 20 years. This disease may be associated with Hodgkin lymphoma, cutaneous anaplastic large-cell lymphoma, or mycosis fungoides.

It is essential to differentiate CTCL disorders from other T-cell lymphoproliferative disorders as defined by the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*.

7. What is the natural history of cutaneous T-cell lymphoma?

Histologic classification predicts survival. In addition, prognosis is related to the amount of skin involved and the type of skin lesion. The greater the degree of surface area involvement of the skin in CTCL, the worse the prognosis. Less than 10% involvement (stage IA) portends a better prognosis than stage IB.

The median survival in SS is 4 years. Risk factors include increased lactate dehydrogenase level at presentation, a prior diagnosis of MF, and the presence of a T-cell receptor gene rearrangement in one series.

8. Is CTCL curable?

Only limited-stage disease is potentially curable.

9. What are the initial treatment strategies for cutaneous T-cell lymphoma?

General skin care measures are the hallmark of intervention of CTCL. Nonspecific topical treatment of MF and SS includes supportive therapies that minimize skin irritation, lubricate the skin, promote hydration, limit inflammatory reactions, and limit infectious complications. Low-potency and mid-potency topical corticosteroid creams or ointments may control the symptoms of pruritus and dermatitis. Topical corticosteroids should be avoided or discontinued for several weeks before skin biopsy because these treatments can potentially mask histologic features of CTCL. Regular soaking baths and the application of lubricating creams maintain hydration and decrease symptoms. Treatment of infected areas of the skin that are colonized or purulent ulcers decreases the problem of more serious infectious complications.

10. What are the therapeutic options in cutaneous T-cell lymphoma initially and at relapse?

CTCL is characterized as a chronic disease with a natural history of recurrent relapses. Therapeutic options include topical treatments (corticosteroids, nitrogen mustard, or carmustine (BCNU)), ultraviolet B (UVB) phototherapy, photochemotherapy with psoralen plus ultraviolet A (PUVA), irradiation with electron beam or photon therapy, systemic chemotherapy with single or multiple agents, combined-modality therapy (chemotherapy, electron beam radiation therapy, and other combinations), extracorporeal photochemotherapy, interferons, monoclonal antibody therapy, retinoids, purine analogs, cyclosporine, autologous peripheral blood stem cell transplantation, allogeneic bone marrow transplantation, dentileukin difitox, alemtuzumab, gemcitabine, pegylated liposomal doxorubicin, pralatrexate, and other agents.

The treatment goal is to improve symptoms and quality of life. A randomized clinical trial of early combined-modality therapy with radiation and multiagent chemotherapy (cyclophosphamide, doxorubicin, etoposide, and vincristine) with sequential topical therapies demonstrated that combined-modality therapy did not improve disease-free or overall survival and was associated with increased toxicities. Therefore, patients with limited-stage disease are approached with skin-directed therapies.

Topical approaches

Topical corticosteroids are the mainstay of treatment for CTCL, with complete remission (CR) rates of up to

63%. Twice-daily treatment for 2 to 3 months is effective in MF plaque- and patch-stage disease with high response rates. Complications include skin atrophy and adrenal suppression.

Mechlorethamine (nitrogen mustard) can be prepared in a concentration of 10 to 20 mg/dL in water or as an alcohol extract suspended in an oil–water base such as Aquaphor. This is applied once to twice a day, avoiding the eyelids, genitalia, rectum, and intertriginous areas. The initial treatment lasts 6 to 12 months with maintenance therapy three times per week for 1 to 2 years or longer. Response rates are related to clinical stage with response rates of 80% in stage IA disease and 60% in stage III disease in one series. The major side effect of mechlorethamine is allergic contact dermatitis, which has been reported to occur in 35% to 65% of patients. The incidence is less than 10% with mechlorethamine dissolved in ointment. Other toxicities include dry skin, irritant dermatitis, hyperpigmentation, bollous reactions, urticaria, Stevens–Johnson syndrome, and telangiectasias. An increased risk of second malignancies of squamous cell carcinoma and basal cell carcinoma has been reported, although most patients were also treated with other approaches. Carmustine applied daily at doses of 10 to 20 mg per day produces similar responses with an additive toxicity of bone marrow suppression.

Topical bexarotene 1% applied twice daily is a synthetic retinoid with CR rates of 21% to 23%. Side effects include rash in 56% of patients, hypertriglyceridemia, hypercholesterolemia, pancreatitis, hypothyroidism, and headaches.

Ultraviolet B phototherapy and ultraviolet A photochemotherapy

UVB phototherapy is the treatment of choice for early patch-stage CTCL and large-plaque parapsoriasis. Treatment is three times per week. UVB penetrates only the epidermis and superficial dermis, and does not have an effect on extensive forms of CTCL. In addition, UVB may aggravate the erythroderma and purities of SS, and should be avoided in this disorder.

Treatment of CTCL with PUVA with 8-methoxypsoralen administered orally is effective in early disease. 8-methoxypsoralen inhibits DNA synthesis through the formation of monofunctional and bifunctional adducts and crosslinks of nucleic acids resulting in apoptosis, where PUVA has effects that include direct cytotoxic, anti-inflammatory, and immunomodulatory effects. 0.6 mg/kg of 8-methoxypsoralen is administered 2 hours before UVA treatment, or an encapsulated form (Oxsoralen Ultra or Uvadex) is administered orally 1 hour before treatment. The patient is exposed to UVA lamps that emit radiation in the wavelength range of 320 to 400 nm. UV-protective eyeglasses are worn for 24 hours after treatment. The therapy is usually administered 3 times per week for 3 to 6 months, followed by a taper. Contraindications to UV include systemic lupus erythematosus, skin cancer, porphyria, and genetic syndromes secondary to DNA repair defects. Response rates were 82% in plaque disease and 46% in erythrodermic CTCL. Side effects include nausea, vomiting, purities, erythema, xerosis dry skin blistering, burns, pigmented melanocytic skin macules, nail pigmentation, cataract formation, and amyloid deposition. PUVA has been combined with topical nitrogen mustard, retinoids, and interferon alpha-2a (IFNα2a). A retrospective evaluation of a study of 30 patients who were treated with low-dose IFNα2a reported a CR rate of 83% with a median remission duration of 22 months.

Total skin electron beam therapy

Total skin electron beam therapy (TSEBT) has been used for limited and extensive CTCL. Response rates of 90% have been reported. TSEBT is potentially curative in stage IA disease. Alopecia and skin cancers are associated toxicities.

Treatment of advanced-stage disease

There is no available curative therapy for advanced-stage disease. Extracorporeal photopharesis, biologic-response modifiers (bexarotene and IFNα), denileukin difitox, and histone deactetylase inhibitors (vorinostat) are generally utilized before chemotherapy agents (methotrexate, gemcitabine, pentostatin, 2-chlorodeoxadenosine, and other agents). Systemic chemotherapy is incorporated in patients with advanced-stage MF/SS who have relapsed after skin-directed therapies and biologic-response modifiers or have extensive disease with visceral organ involvement. In general, combination chemotherapy regimens (e.g., CHOP) are associated with 70–80% response rates that are of short duration and are associated with myelosuppression and infectious complications.

Extracorporeal photochemotherapy

Extracorporeal photochemotherapy (ECP), or photopharesis, is a form of PUVA therapy that combines leukapharesis with photochemotherapy. This intervention is efficacious in SS and erythrodermic MF. After the administration of oral 8-methoxypsoralen (8-MP), patients undergo leukapharesis and cell separation. Cells in the mononuclear fraction are exposed to UVA radiation from lamps housed in the apharesis device. The irradiated leukocytes, approximately 5% of the peripheral blood leukocytes, are then reinfused back into the patient. This is the treatment of choice in SS. The overall response rate (ORR) is 60% with

reported CR rates up to 20%. Current treatment protocols no longer require the oral administration of 8-MP, eliminating the nausea problem. ECP is usually performed on two consecutive days every 2–4 weeks. The median time to response is about 6 months. Patients for whom treatment is initiated promptly after diagnosis and who have circulating Sézary cells without significant nodal or visceral disease are more likely to respond. ECP is often combined with interferon or bexarotene.

Recombinant interferon

IFNα2a (Roferon-A) and IFNα2b (Intron-A) have significant activity in MF and SS. The ORR is up to 60%. The suggested doses of IFN are $1–3 \times 10^6$ IU administered subcutaneously three times per week and increasing to $9–12 \times 10^6$ IU daily or as tolerated. No dose–response data have been published. A tachyphylaxsis develops subsequent to the initial fevers and chills. Leukopenia occurs in the first 3 months of therapy but is usually of no clinical significance. Patients may experience chronic fatigue. Recombinant interferon should be considered as first-line therapy in patients with advanced disease.

Recombinant interferon may be combined with PUVA, ECP, bexarotene, and other agents. In a series of 47 patients with stage III–IV disease treated with a combination of IFNα and ECP, the ORR was greater than 80%. In a randomized study of 124 patients with early stage I and II MF, patients were treated with PUVA or PUVA plus IFNα2a at a dose of 9×106 IU three times per week. Fifty patients were evaluable in the PUVA arm, and 43 in the combined therapy arm. At a median follow-up of 101 weeks, the median PFS was 53 weeks in the PUVA arm and 113 weeks in the interferon–PUVA arm ($P = 0.039$). This combination is an initial treatment of choice for limited-stage MF disease.

Bexarotene

Bexarotene at an oral dose of 300 mg/m^2 in a series of previously treated patients resulted in a response rate of 49%. Toxicities included hyperlipidemia, hypothyroidism, and cytopenias. In clinical practice, bexarotene is frequently initiated at a dose of 150 mg/m^2 and titrated up to full doses after 2 to 4 weeks of treatment. Most responses occur by 2 to 3 months. Adjunctive PUVA therapy may be considered in combination with bexarotene.

Denileukin difitox

Denileukin difitox is a genetically engineered fusion protein containing a portion of interleukin-2 (IL2) that interacts with IL2 receptor (IL2R) truncated to a synthetic protein identical to the diphtheria toxin. The IL2 portion of this drug binds with IL2R on the MF and SS cells, the toxin is internalized, and apoptosis is induced. Denileukin diftitox is administered at a dose of 9 or 18 μg/kg/day intravenously for 5 days every 21 days for up to eight cycles. A randomized study of 71 patients with CD5 expression in 20% of lymphocytes or greater reported an ORR of 30% (10% CR and 20% partial remission) with a median time to response of 6 weeks and median duration of response of 6.7 months (range: 2.7 to 46.1 months). In a phase III study, the ORR was 44% with a median progression-free survival (PFS) of 2 years. In a meta-analysis of 307 patients, the ORR was 47.5% in CD25+ patients with a median PFS in responders of greater than 2 years, and in CD25− patients the ORR was 30.6% with a median PFS of 487 days. For 44 patients who received placebo, the ORR was 15.9%, and the median PFS was 4 months. Toxicities include flulike symptoms, acute infusion-related symptoms (episodes of hypotension, chest pain, and back pain), vascular leak syndrome, elevated liver function studies (61%), and hypoalbuminemia (79%). The vascular leak syndrome that usually occurs in the first 2 weeks of treatment with hypoalbuminemia, hypotension, and edema has been reported in approximately 25% of patients. The hypersensitivity reactions that occurred in up to two-thirds of patients within the first hour include hypotension, chest pain, angioedema, and rash.

Bexarotene upregulates the expression of high-affinity IL2R, and the OR with denileukin difitox with escalating doses of bexarotene was 57%.

Histone deacetylase (HDAC) inhibitors

Vorinostat (suberoylanilide hydroxamic acid, or SAHA) and romidepsin (depsipeptide) inhibit class I and class II HDACs. In a study of 74 previously treated advanced-stage patients, oral vorinostat at a dose of 400 mg once daily resulted in an ORR of approximately 30% with a median duration of response estimated to exceed 185 days. The responses were in ≤2 months and in tumor=stage MF and SS. Fifty percent of patients experienced gastrointestinal toxicities (nausea, vomiting, and diarrhea), and 20% of patients had anemia or thrombocytopenia. There is a risk of prolongation of the QT interval.

Romidepsin at a dose of 14 mg/m^2 on days 1, 8, and 15 every 4 weeks in patients with advanced-stage disease resulted in an ORR of 38% in patients with advanced disease with a median duration of response greater than 1 year in responding patients. The toxicity profiles were similar to those of vorinostat with no cardiotoxicity.

Purine nucleoside analogs

This class of drugs includes 2'deoxycoformycin, fludarabine, and gemcitabine. The ORR with gemcitabine is 50–70%

with CR rates of 10–20%. In one series, the ORR was 48% with a CR rate of 16% in MF patients.

Pegylated liposomal doxorubicin

One series reported an ORR of 56% with a CR rate of 20% with pegylated liposomal doxorubicin. The incidence of neutropenia was lower than with gemcitabine, but this drug is associated with infusion-related and mucocutaneous toxicities, including plamoplantar erythrodysesthesia.

Pralatrexate

Pralatrexate is an antifolate drug with a novel mechanism of resistance when compared with methotrexate. The response rate in the PROPEL study was 58% with a median PFS of 4–5 months where the majority of patients had refractory disease. This study included 12 patients with transformed MF. The optimal dose is $15\,mg/m^2$ administered weekly 3 weeks out of 4. Folic acid and vitamin B_{12} supplementation are administered to reduce the incidence of mucositis.

Monoclonal antibodies

Alemtuzumab is a humanized IgG1 monoclonal antibody directed against CD52. In one series of 22 patients with advanced MF or SS, the ORR was 56% and the CR rate was 32% with a median time to treatment failure of 1 year. The infectious complications were significant, occurring in over two-thirds of patients, and include bacterial sepsis, cytomegalovirus reactivation, and *Pneumocystis jirovecii* pneumonia. Studies targeting other T-cell antigens are ongoing and include CD2, CD4, CD25, and CCR4.

Combined-modality systemic chemotherapy

A randomized clinical trial of 105 patients compared sequential topical therapy followed by total-skin electron beam therapy followed by oral methotrexate. If extracutaneous disease developed, systemic chemotherapy was administered. The combination regimen consisted of 3000 cGy total-skin electron beam radiation therapy followed by cyclophosphamide, doxorubicin, etoposide, and vincristine administered intravenously. After a median follow-up of 75 months, the only difference in the two groups was in the CR rates: 10% in the topical group and 38% in the combined-modality group. There was no statistically significant difference in PFS or OS. Toxicity was greater in the combined-modality arm, including myelosuppression, radiodermatitis, neuropathy, and congestive heart failure. Less than 10% of patients in each arm remained disease free.

High-dose chemotherapy and hematopoietic stem cell transplantation

High-dose chemotherapy has been reported in autologous and allogeneic stem cell transplantation (SCT). The available evidence suggests that responses are transient in autologous SCT. Durable remissions have been observed following allogeneic transplantation that are likely related to a graft-versus-lymphoma effect. In a retrospective series of 60 patients, the nonrelapse mortality in patients who had received a median of four prior therapies before reduced-intensity conditioning (73%) and in myeloablative conditioning (27%) before a related (75%) or a matched-unrelated (25%) transplantation was reported. The mortality at 1 year was 14% for patients receiving reduced-intensity conditioning or HLA identical or related donor stem cells and 38–40% for those undergoing myeloablative conditioning or receiving matched-unrelated donor grafts. Twenty-six patients relapsed, 17 received donor-lymphocyte infusions, and 47% achieved a CR, supporting the principle of a graft-versus-lymphoma effect in MS and MF. The estimated 3-year PFS was 34%, and OS was 53%. Allogeneic SCT should be considered for young patients with refractory disease.

Treatment summary

Wilcox has proposed a treatment algorithm to approach the treatment of advanced-stage MF or SS (Figure 49.1). This provides a framework with which to approach patients at different manifestations of their disease.

Survivorship issues in cutaneous T-cell lymphoma

Patients treated with phototherapy may have peliosis lesions. There is a reported increased risk of lung cancer, Hodgkin lymphoma, and non-Hodgkin's lymphoma.

11. What do patients die from with cutaneous T-cell lymphoma?

Patients with erythroderma and cutaneous tumors characteristically die of complications of progressive disease. The most common cause of death is infection. The most common organisms are bacterial, including *Staphylococcus aureus*, Enterobacteriacea, and *Pseudomonas aeruginosa*, followed by disseminated herpes and fungal infections. In two series, up to 47% of deaths are caused by cardiopulmonary disease and secondary malignancies.

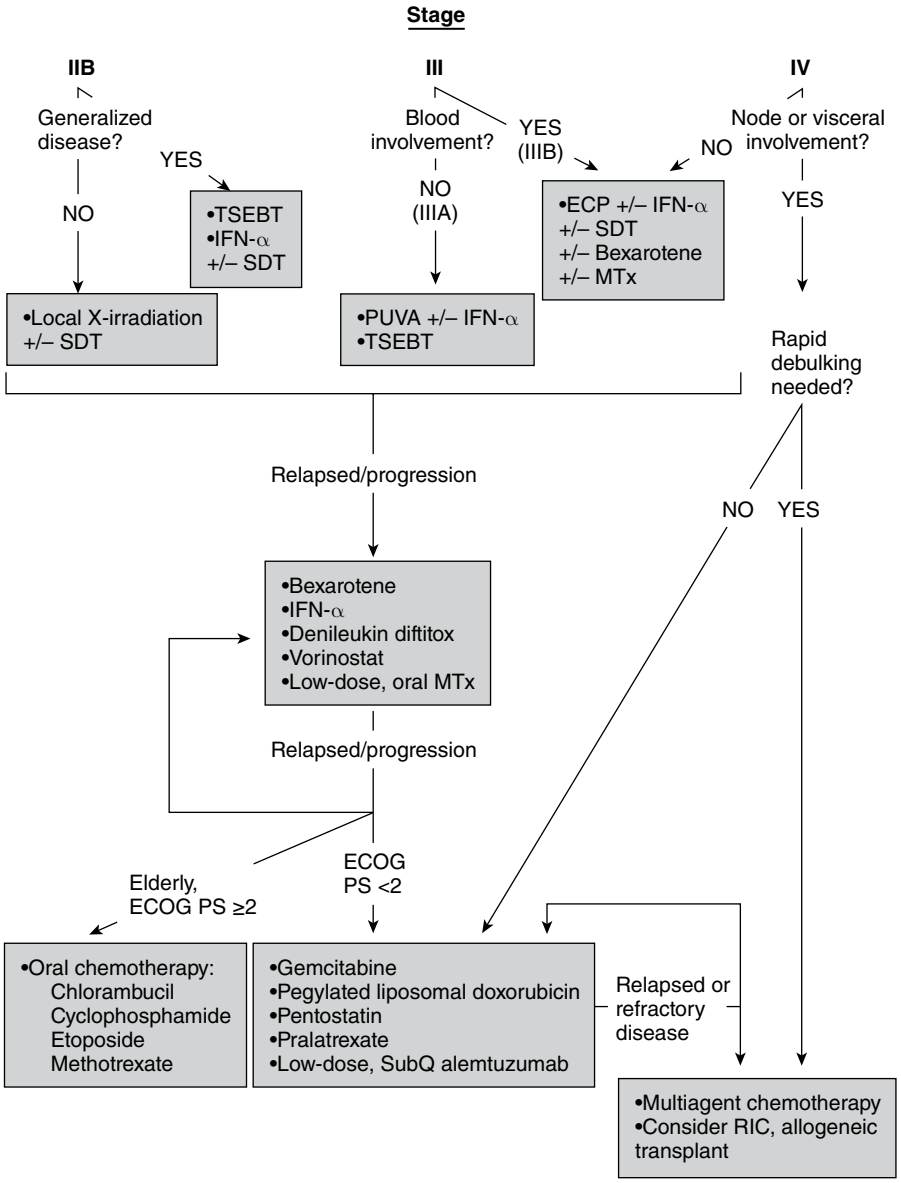


Figure 49.1 Approach to treatment of advanced-stage mycosis fungoides (MF) and Sézary syndrome (SS). MTx, methotrexate; RIC, reduced-intensity conditioning; SDT, skin-directed therapy. Clinical trial participation, whenever possible, is encouraged (Source: Wilcox RA. Am J Hematol. 2011;86:938. Reproduced with permission of John Wiley & Sons Ltd.).

Conclusion

In most cases, CTCL cannot be cured. Disease recurrence is the natural history of the disease, but long-term survival is not influenced by relapse status. Continued advances in the understanding of the biology of CTCL and new therapeutic interventions will improve outcomes in CTCL.

Suggested reading

Willemze R, Jaffe ES, Burg E, *et al*. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.

Swerdlow SH, Campo E, Harris NL, *et al*., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. IARC: Lyon; 2008.

Habermann TM, Pittelkow MR. Cutaneous T-cell lymphoma. In: Abeloff MD, *et al*., editors. Abeloff's clinical oncology. 4th ed. Philadelphia: Churchill Livingston/Elsevier; 2008. p. 2405–24.

Wilcox RA. Cutaneous T-cell lymphoma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol. 2011;86:929–48.

CHAPTER 50

Mycosis fungoides and Sézary syndrome

Stephane Dalle, Marie Perier-Muzet, Brigitte Balme, and Luc Thomas

Lyon Sud Hospital, Claude Bernard Lyon University, Pierre-Bénite, France

1. Early-stage mycosis fungoides (MF): what are the pitfalls?

The diagnosis of early MF (patch and early-plaque mycosis fungoides) is a major diagnostic challenge in dermatology and hematology. Both the dermatologic differential diagnoses and MF atypical presentations are numerous. The lack of a specific marker differentiating early MF from benign inflammatory dermatitis presents significant difficulties in the assessment and management of suspected MF patients. It cannot be overemphasized that the diagnosis of cutaneous T-cell lymphoma (CTCL) requires clinicopathologic correlation, and review by a pathologist experienced in these disorders is strongly recommended. It is also important to recognize that it is not uncommon for the diagnosis of MF to remain elusive for many years, often requiring observation and repeated biopsies. Such an approach avoids embarking on numerous investigations in a disease that is generally indolent and in which the outcome is not altered by aggressive early intervention. An algorithm has been proposed in 2005 by the International Society for Cutaneous Lymphoma to standardize the criteria for early MF (Table 50.1).

The clinical presentation of classic patch-phase MF is characterized by variability in the size, shape, and color of individual lesions. Most MF patch lesions are large (>5 cm in diameter) (Figure 50.1). Digitate lesions are uncommon in MF and would make one suspect the presence of digitiform parapsoriasis, which is a variant of small plaque parapsoriasis. Untreated lesions of MF often expand slowly to form well-demarcated lesions that vary in size with or without coalescence and may also undergo spontaneous clearing in areas. Another important clinical feature that is relatively specific for early MF is the presence of poikiloderma. Poikiloderma is defined clinically as the local juxtaposition of mottled pigmentation, telangiectasia, and epidermal atrophy (cigarette paper wrinkling) interspersed with slight infiltration (Figure 50.2).

Taking into account the possible serious effects and the limited availability of efficacy data, topical and skin-directed treatments are recommended first. As the use of early application of therapy does not affect survival, a nonaggressive approach to therapy is warranted with treatment aimed at improving symptoms while limiting toxicity. As patients with stage IA disease have a long life expectancy, an expectant policy may be a legitimate management option in selected patients, provided that it incorporates careful monitoring. Given that multiple skin sites are often involved, the initial treatment is primarily a skin-directed therapy (SDT), which aims to control skin lesions while minimizing morbidity. The key choices for SDT are topical or intralesional corticosteroids or psoralen plus ultraviolet A radiation (PUVA) or ultraviolet B (UVB). Indeed, for patients with limited patch disease, topical steroids often control the disease for many years, and often this is the only form of therapy required for such patients. Patch and thin-plaque MF can be treated with topical corticosteroids.

2. What is the relevance of transformation in mycosis fungoides?

Large-cell transformation is known to occur in patients with either Sézary syndrome or MF. Transformed mycosis fungoides (T-MF) is a well-defined histopathological condition with the presence of large cells (four times or more the size of a small lymphocyte) exceeding 25% of the cell population of the infiltrate or forming microscopic nodules (Figure 50.3). The incidence of such a transformation is diversely appreciated, but although such a transformation has been reported to occur in 8% to 55% of cases, few studies on the prognostic value of specific criteria leading

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 50.1 International Society for Cutaneous Lymphoma criteria for early MF (Source: Data from Pimpinelli N, Olsen EA, Santucci M, *et al.* J Am Acad Dermatol. 2005 Dec;53(6):1053–63).

Criteria	Scoring system
Clinical	**2 points** for basic criteria and two additional criteria
Basic	
Persistent and/or progressive patches or thin plaques	**1 point** for basic criteria and one additional criterion
Additional	
1. Non-sun-exposed location	**2 points** for basic criteria and two additional criteria
2. Size or shape variation	
3. Poikiloderma	1 point for basic criteria and one additional criterion
Histopathologic	1 point for clonality
Basic	
Superficial lymphoid Infiltrate	1 point for one or more criteria
Additional	
1. Epidermotropism without spongiosis	
2. Lymphoid atypia	
Molecular biological	
1. Clonal TCR gene rearrangement	
Immunopathologic	
1. 50% CD21, CD31, and/or CD51 T cells	
2. 10% CD71 T cells	
3. Epidermal or dermal discordance of CD2, CD3, CD5, or CD7z	

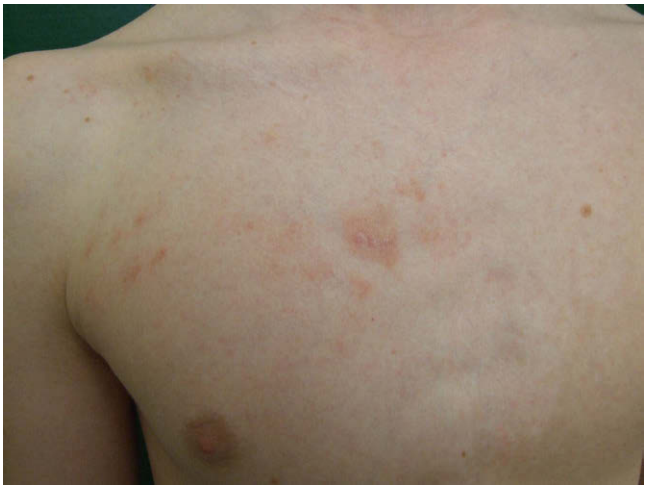


Figure 50.1 Patch or plaque early mycosis fungoides on the anterior chest.

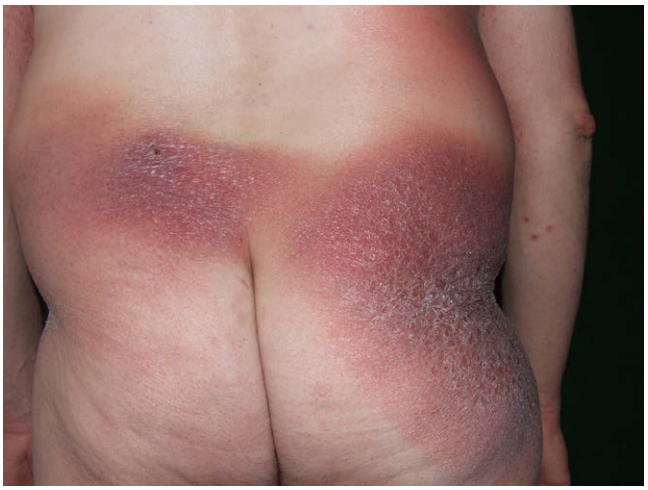


Figure 50.2 Infiltrated plaques defined as poikiloderma.

to early diagnosis of MF transformation are available in the literature.

Recent studies in a group of 26 cases and in a series of 45 patients with T-MF showed conflicting data about clinical features associated with a poor outcome. In the first one, poor survival is associated with early transformation (less than 2 years after initial diagnosis of MF) and advanced clinical stage at the time of T-MF (IIB–IV versus I–IIA). In the second older age (60 and older) and extracutaneous invasion (stage IV) were found correlated with a poor prognosis.

In our series, the median delay from the initial diagnosis of MF to documentation of the onset of a large-cell transformation was 3.6 years (range: 1–115 months) (12 months in Diamandinou *et al*. 1998) (Table 50.1). We also observed that fatal cases had a relatively shorter delay from initial diagnosis of MF to transformation. Survival time from transformation ranged from 12 months to 67 months (median: 27 months, according to data for Greer *et al*. 1988). As already published, our data demonstrate that advanced stage of the disease at the time of transformation (IIB and IV) adversely influences the prognosis: our four patients with fatal outcome were at least at stage IIB, and two patients in whom we had to administer systemic chemotherapy or bone marrow transplantation were at stage IVA. No or weak correlation between prognosis and age or β2 microglobulin or blood lactate dehydrogenase levels in univariate analysis has been evidenced in previous studies. In our series, age (younger or older than 60) was not significantly associated with prognosis.

Although histopathological criteria for the T-MF diagnosis are well defined with a skin biopsy showing large cells (≥4 times the size of a small lymphocyte) exceeding 25% of the infiltrate or forming microscopic nodules, a differential diagnosis of T-MF remains difficult. Vergier *et al*. (2000) have emphasized the necessity to differentiate large

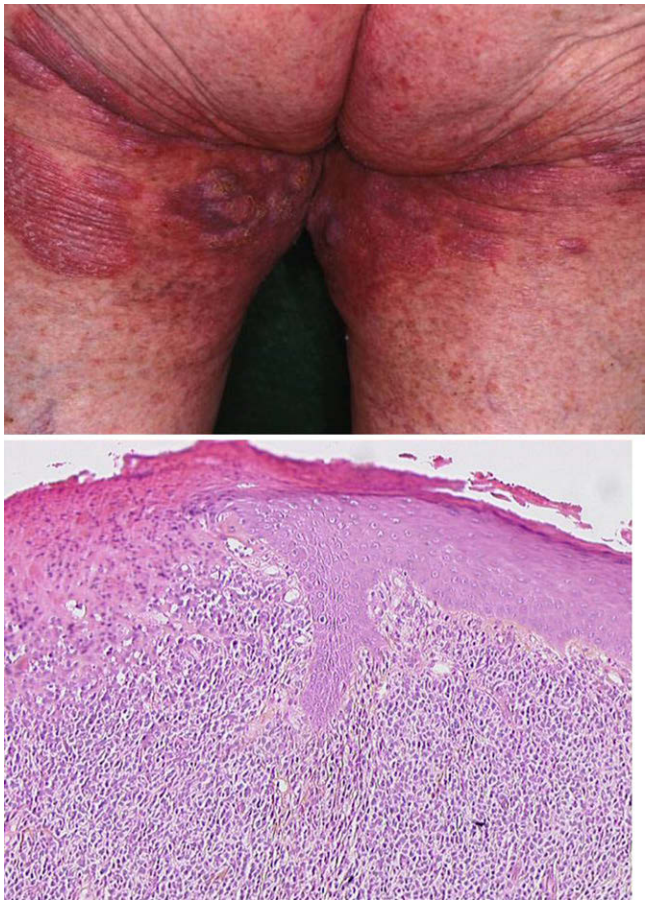


Figure 50.3 Transformed mycosis fungoides (clinical and pathology pictures). (Color Plate 50.1)

T-lymphocytes from histiocytes and macrophages because the prognosis of "granulomatous MF" is better than that of T-MF. Immunohistochemistry with anti-CD3 and CD68 antibodies could be used for that purpose. In our population of T-MF, CD68 immunostaining has been performed in order to better exclude histiocytic cells from the count of tumoral large cells.

Vergier *et al*. (2000) also stressed the point that the differential diagnosis between T-MF with CD30-positive cells and MF associated with CD30+ lymphoproliferative disorders (lymphomatoid papulosis or CD30+ large-cell cutaneous lymphoma), the later bearing a much better prognosis, can be very difficult. T-MF diagnosis can be regarded as highly probable when clinical transformation occurs within clinically typical MF lesions and in the coexistence of cerebriform lymphocytes mixed with fewer than 75% of CD30+ large T-cells.

As already described by Vergier *et al*. (2000), we reported that the patient's evolution is the most reliable criterion with which to distinguish CD30+ T-MF from MF associated with primary CD30+ large-cell lymphoma. This is in accordance with the usually favorable evolution of the CD30+ cutaneous lymphoproliferative disorders (CLPDs) and their marked tendency to spontaneously undergo regression. Apoptosis of tumor cells is considered a key mechanism in tumor regression. Proapoptotic proteins are expressed at high levels in CD30+ CLPD and may play a crucial role in mediating apoptosis-linked regression of tumors.

Recently Benner *et al*. confirmed that CD30 expression was a strong and independent predictor of improved survival, both in the total group of patients and in patients with transformation limited to the skin. Because patients may have a combination of favorable and unfavorable prognostic factors, they developed a prognostic index that may better predict prognosis and be a useful tool in selecting the appropriate treatment. For that purpose, the most discriminating independent prognostic factors for disease-specific survival were selected. For the total group of patients with transformed MF, these were the presence of generalized skin lesions, extracutaneous transformation, CD30 negativity, and folliculotropic MF. Patients with 0, 1, 2, 3, or 4 unfavorable prognostic factors had a 2-year disease-specific survival rate of 83%, 85%, 52%, 14%, and 33%, respectively. For the group of patients with only transformed skin lesions, CD30 negativity, folliculotropic MF, and the presence of generalized skin lesions were selected. Patients with 0, 1, 2, or 3 unfavorable prognostic factors had a 5-year disease-specific survival rate of 73%, 61%, 19%, and 0%, respectively. The accuracy of the prognosis index now has to be validated prospectively and may have an impact on therapeutic decisions.

In conclusion, transformation of MF occurs in about 8% of CTCLs, most often in the first years of the disease (median: 3.5 years); it is strictly correlated with a poor prognosis (median survival: 27 months). Markers of poor prognosis are the advanced initial stage of MF at transformation and the negativity of the CD30 immunostaining of the large transformed cells (the association of CD30− of the large cells with CD20+ B-cell peritumoral infiltrate).

3. Mycosis fungoides and Sézary syndrome: the same or distinct entities?

Sézary syndrome (SS) is a rare disease that occurs exclusively in adults. It is characterized by lymphadenopathy; erythroderma, which may be associated with marked exfoliation; edema; and lichenification, and it is intensely pruritic. Atypical lymphocytes with cerebriform nuclei (Sézary cells) are present in peripheral blood. SS is often designated as a leukemic phase or leukemic variant of MF. Because MF may sometimes present with erythroderma and peripheral blood involvement while rare SS patients may develop skin tumors, it was once thought that SS could arise from MF progressing from the skin into the circulation. But recent

works have demonstrated that this is almost never the case. To clarify the relationship between SS and MF, researchers studied extensively the phenotypes from both conditions. They showed that the SS blood specimen universally coexpressed the lymph node–homing molecules CCR7 and L-selectin as well as the differentiation marker CD27. By contrast, MF skin specimens lacked CCR7, L-selectin, and CD27 expression. Noteworthy is that CCR4 was highly expressed in both conditions and is currently being evaluated as a therapeutic target. The authors concluded that SS was a malignancy of central memory T-cells, whereas MF emerged from skin resident effector memory cells.

Both oncogenomic analysis and microRNA pattern expression were also shown able to distinguish, at the molecular level, SS from MF patients.

Because of the aggressive nature of SS compared with other subsets of CTCLs, such as erythrodermic MF, it is imperative to stratify and analyze this distinctive population separately. For instance, a differential expression of programmed death-1 (PD1) between SS and MF has been shown very recently. SS expressed PD1 in up to 89% of cases. Given this high expression of PD1, some have speculated on and suggested anti-PD1 therapy, specifically in well-delineated SS patients.

4. Is allogeneic stem cell transplantation useful in CTCLs?

Early-stage MF has an excellent prognosis and is treated with SDT. Aggressive forms of MF and SS require systemic therapy. Even with an increasing array of conventional and newer biologic agents, most patients with advanced-stage MF or SS experience a recurrent pattern of short-lived clinical responses followed by disease relapse or progression and death, either from refractory disease or from the complications of multiple lines of treatment. Currently, there is no standard of care for these patients, whose prognosis remains very poor. Hematopoietic stem cell transplantation (HSCT) is not so far included in the international guidelines due to the poor level of evidence of its efficacy.

Duarte *et al*. (2008) retrospectively reviewed the cases of autologous transplantation (HSCT) and collected 20 cases. In the overall experience of autologous HSCT for MF and SS patients, only one patient has remained alive with no evidence of posttransplant disease progression. Two additional patients achieved a second CR with conventional treatment following an early relapse posttransplant, and they remain disease-free at 22 and 84 months. Despite the short progression-free survivals, it would appear as if at least some patients could achieve a better control of their CTCL following relapse after autologous HSCT, which might remain as the only potential benefit from a procedure with no apparent curative potential for these patients.

In contrast to autologous HSCT, allogeneic HSCT (allo-SCT) avoids the risk of tumor contamination of the graft, which is derived from a healthy donor, and it can potentially deliver an additional graft-versus-leukemia effect. All published cases after allo-SCT following myeloablative or reduced-intensity conditioning (RIC) showed a decreased relapse rate and increased overall and event-free survival when compared to published data of conventional therapies. Duarte and colleagues (2010) recently published retrospective data from European Blood and Marrow Transplantation centers, which is the first large multicenter analysis of allo-SCT in CTCL patients. They demonstrated an incidence of relapse of 38% at one year and 47% at 3 years after allogeneic transplantation. Progression-free survival was 42% at 1 year and 34% at 3 years. The current progression-free survival at the last published follow-up was 52% in patients who received nonmyeloablative allo-SCT and 29% in patients who received myeloablative allo-SCT. The estimated overall survival rate was 66% at 1 year and 53% at 3 years. These noncontrolled results are promising and challenge the so far known outcomes after conventional treatment options. The use of RIC protocols makes allo-HCT feasible for elderly patients with MF and SS and for those with reduced organ capacity after multiple lines of therapy. In fact, RIC protocols seem to lead to better outcomes even in patients younger than 50 years in our MF and SS series, and they may be the choice for the majority of patients. Controlled studies to confirm the role of allo-SCT in CTCL patients are needed.

Selected reading

Benner MF, Jansen PM, Vermeer MH, *et al*. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood. 2012;119:1643–9.

Duarte RF, Canals C, Onida F, *et al*. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the Dummer R, Dreyling M. Primary cutaneous lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008;19(Suppl. 2):ii72–6.

Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2010;28:4492–9.

Trautinger F, Knobler R, Willemze R, *et al*. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer. 2006;42:1014–30.

CHAPTER 51

Hematopoietic cell transplantation in indolent non-Hodgkin's lymphoma

Saurabh Chhabra[1] and Ginna G. Laport[2]

[1]Medical University of South Carolina, Charleston, SC, USA
[2]Stanford University Medical Center, Stanford, CA, USA

1. Is there a role for autologous hematopoietic cell transplantation (HCT) as a consolidative strategy for follicular lymphoma (FL) in first remission?

The management of advanced FL remains ill-defined partly due to the large number of therapeutic options available. Patients with advanced FL and their physicians have numerous treatment options, including single-agent or combination chemotherapy, monoclonal antibodies (mAbs, including radioimmunoconjugates), and radiotherapy. These therapies have the potential to prolong progression-free survival (PFS), but none is known to provide a cure. As a result, there is no single standard front-line or second-line therapy, and no consensus as to the optimal sequence of the therapies.

High-dose therapy (HDT) with autologous HCT (auto-HCT) has been explored as consolidative therapy in first remission (CR1) and in the setting of disease relapse. Three randomized phase III trials from Europe evaluated the efficacy of auto-HCT vis-à-vis conventional chemotherapy followed by interferon-α maintenance (Table 51.1). Two of these three trials demonstrated a PFS advantage with auto-HCT. However, there was no overall survival (OS) difference between HCT and conventional therapy in all three studies. In fact, there was a significantly increased incidence of therapy-related malignancies in the HCT arms that mitigated the PFS advantage conferred by HCT. However, these trials were conducted in the pre-rituximab era, which limits the relevance of these data in current practice. This is further supported by fact that the PFS reported in the auto-HCT arms of the GELA (Groupe d'Etude des Lymphomes de l'Adulte) and GLSG (German Low-Grade Lymphoma Study Group) studies is comparable to the PFS of FL patients treated with rituxan RTX-containing front-line therapy in the contemporary cooperative group trials.

After the availability of rituximab (RTX), a randomized trial was conducted by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and Intergruppo Italiano Linfomi (IIL) that compared auto-HCT with standard therapy in high-risk FL patients. A total of 136 patients received upfront R-CHOP therapy and were then randomized to receive additional RTX or auto-HCT. With a median follow-up of 51 months, the results were consistent with those of the previous studies: an improved 4-year event-free survival (EFS) (61% versus 28%; $P < .001$) without any OS advantage with HCT. This trial also demonstrated that molecular remission was the strongest predictor of outcome and that the HCT arm had a higher incidence of molecular remission compared with conventional chemotherapy (80% versus 44%, respectively). Patients who relapsed after receiving chemotherapy were crossed over to the HCT arm. This group of relapsed FL patients ($n = 28$) had a 3-year EFS and OS of 68% and 81%, respectively, at a median follow-up of 30 months. Two meta-analyses also confirmed the improved PFS with auto-HCT for FL in first remission, without any OS advantage.

Based on the available data, auto-HCT as consolidation therapy is not recommended for FL patients in CR1. However, because the majority of the data come from trials that did not include RTX, longer follow-up is necessary in patients who received RTX with initial therapy and in the peri-HCT period to determine the efficacy of auto-HCT as a consolidative strategy for patients with FL in CR1.

2. What is the optimal timing for autologous HCT in the treatment of relapsed follicular lymphoma?

Auto-HCT has a more defined role in patients with relapsed FL than for those in CR1. Several studies, prospective and retrospective, have examined the outcomes after auto-HCT for relapsed FL, and they have reported high response

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 51.1 Randomized trials of chemotherapy versus autologous HCT (previously untreated).

	n	Preparative regimen	Progression-free survival (%)	Overall survival (%)	Follow-up (months)	Second cancers
German GLSG (2004)[a]	240	TBI/Cy	33 (non-HCT) 64 (HCT) *P* < 0.0001	NR	52	1% 6%
French GOELAMS (2009)[b]	166	TBI/Cy	39 (non-HCT) 64 (HCT) *P* = 0.004	80 76	108	1% 14%
French GELA (2006)[c]	401	TBI/VP/Cy	28 (non-HCT) 38 (HCT) *P* = 0.11	71 76	92	7% 14%
Italian GITMO (2008)[d]	136	Mitox/Mel/RTX	31(non-HCT) 68 (HCT) *P* < 0.001	80 81	51	2% 7%

Cy, cyclophosphamide; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GITMO, Gruppo Italiano Trapianto Midollo Osseo; GLSG, German Low-Grade Lymphoma Study Group; GOELAMS, Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang; Mitox, mitoxantrone; Mel, melphalan; NR, not reported; OS, overall survival; PFS, progression-free survival; RTX, rituximab; TBI, total body irradiation; VP, etoposide.
[a]From Lenz G, *et al.* Blood. 2004;104(9):2667–74.
[b]From Gyan E, *et al.* Blood. 2009;113(5):995–1001.
[c]From Sebban C, *et al.* Blood. 2006;108(8):2540–4.
[d]From Ladetto M, *et al.* Blood. 2008;111(8):4004–13.

rates, with 5-year PFS ranging from 40% to 50%, and one study reporting a 10-year PFS of 48%. With regard to prognostic factors, patients who have not been heavily pretreated (i.e., ≤3 prior regimens), those with chemosensitive disease, and those with a lower-risk Follicular Lymphoma International Prognostic Index (FLIPI) score at the time of auto-HCT had better OS (Figure 51.1).

The European Blood and Marrow Transplant Group (EBMT) reported a retrospective analysis of the outcomes of 693 FL patients who underwent auto-HCT. The 10-year PFS and OS were 31% and 52%, respectively. The post-HCT relapse rate was 54%, with relapse occurring at a median of 1.5 years (range: 0.08–13.5 years) after auto-HCT. The nonrelapse mortality (NRM) was 9%. Multivariate analysis revealed inferior survival with older age, chemoresistant relapse, and use of total body irradiation (TBI)-based conditioning. Sixty-four patients (9%) developed a second primary malignancy at a median of 7 years after HCT. Another German retrospective series of 241 FL patents who underwent auto-HCT showed a 10-year PFS and OS of 49% and 75%, respectively, with a follow-up of 8 years. A total of 47% patients relapsed at a median of 20 months (range: 2–128 months) after HCT. Five patients in this series developed a therapy-related malignancy.

The only randomized trial that prospectively addressed the role of auto-HCT compared with standard therapy in relapsed FL patients was the EBMT-sponsored CUP (chemotherapy vs. unpurged arm vs. purged arm) trial. A total of 140 FL patients with chemosensitive relapse (after salvage chemotherapy) were randomized (n = 89) to receive further chemotherapy, auto-HCT with a purged graft, or auto-HCT with an unpurged graft. The results demonstrated a PFS advantage and suggested an OS advantage of auto-HCT over conventional chemotherapy,

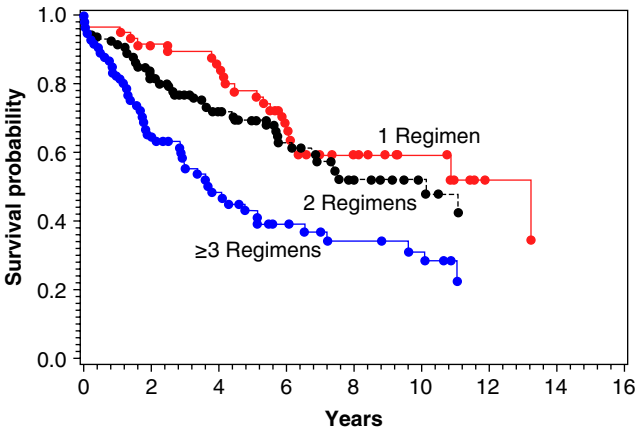


Figure 51.1 Overall survival based on the number of previous chemotherapy regimens received before hematopoietic cell transplantation (Source: Vose JM, *et al.* J Am Soc Blood Marrow Trans. 2008;14:36–42. Reproduced with permission of the American Society for Blood and Marrow Transplantation).

with a 4-year OS of 46% for the chemotherapy-only arm, versus 71% for the unpurged and 77% for the purged auto-HCT arms, with no significant benefit observed for those patients who underwent purging. The sample sizes in the HCT arms were too small to quantify the effect of *ex vivo* purging. There are two caveats to this trial: the first is inadequate power, as the trial closed early owing to slow accrual; and, second, RTX was not part of standard therapy when the trial was conducted, which makes the results less relevant today. Nonetheless, the results of the CUP trial are in line with those observed in the phase II studies, which included larger numbers of patients.

The GELA and Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) studies retrospectively evaluated the outcomes after auto-HCT compared with conventional salvage in 175 patients with FL in first relapse. Of these, 40% had had prior RTX and 40 patients (25%) underwent auto-HCT. With a median follow-up of 31 months, the 3-year OS was significantly superior in patients who proceeded to HCT compared with patients who did not (92% vs. 63%; $P = 0.0003$). In addition, this analysis did not show any effect of front-line RTX on the overall outcome. As with any retrospective study, the superior outcomes with HCT may be the result of selection bias, because only patients responding to salvage therapy underwent HCT.

In summary, FL patients who are beyond CR1 but are chemosensitive, do not have bone marrow (BM) involvement, and have a good performance status are optimal candidates for auto-HCT. However, for patients with limited disease involvement or an early stage at relapse, consideration should be given to involved-field radiotherapy with or without chemotherapy.

3. Does the "graft-versus-lymphoma" effect exist with allo-HCT for patients with follicular lymphoma?

Allogeneic HCT (allo-HCT) remains the only curative therapy for patients with FL. The existence of graft-versus-lymphoma (GVL) effect mediated by allogeneic donor T-cells is supported by the observation of lower relapse rates compared with auto-HCT. The degree of the GVL effect varies depending on the lymphoma histology, with indolent lymphomas such as FL being most susceptible to this effect and the high-grade or aggressive lymphomas being least sensitive. The effect of allo-HCT to induce a durable remission after the failure of auto-HCT is compelling evidence of the GVL effect. Regression of disease has been reported after withdrawal of immunosuppression in patients with FL who relapse after allo-HCT, and the effectiveness of donor leukocyte infusions (DLIs) in treating FL relapse after allo-HCT also provides strong evidence for the GVL effect. In earlier studies of allo-HCT for FL patients, myeloablative conditioning (MAC) regimens were primarily offered and resulted in lower relapse rates compared with patients receiving auto-HCT. Further evidence for the GVL effect is suggested by the plateau in the incidence of relapse over 2–5 years after allo-HCT, whereas a continuous trend of relapse is seen after auto-HCT in recipients. Two large registry studies from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT examined the outcomes after auto-HCT and MAC allo-HCT for patients with relapsed FL. In both analyses, the relapse risk was significantly lower in the allo-HCT group compared with auto-HCT, but the treatment-related mortality (TRM) was significantly higher in the allo-HCT group (30–38% compared to 8–15% after auto-HCT). As a result, OS was comparable between the auto-HCT and allo-HCT arms, as the significantly higher TRM in the allo-HCT group offset the advantage of lower relapse risk. The OS for the auto-HCT and allo-HCT groups ranged from 50% to 62%. Three single-institution retrospective analyses with MAC regimens for allo-HCT have also reported durable remissions in FL patients, with 5-year EFS ranging from 45% to 75%. As seen with auto-HCT, the chemosensitivity of FL at the time of transplant is the strongest predictor of outcome after allo-HCT.

Reduced-intensity conditioning (RIC) allo-HCT offers a lower risk of relapse and minimal risk of therapy-related myelodysplastic syndrome and acute myeloid leukemia when compared to auto-HCT, although the TRM is relatively higher with RIC allo-HCT. Unfortunately, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0202 trial that prospectively compared auto-HCT to RIC allo-HCT in FL closed early due to poor accrual (auto-HCT, $n = 22$; allo-HCT, $n = 8$). For the 30 patients in the study, 3-year PFS and OS were 63% and 73% after auto-HCT, and 86% and 100% after allo-HCT, respectively. Based on available data, it is acceptable to offer RIC allo-HCT with curative intent to younger FL patients who have relapsed or refractory disease and have a matched related or unrelated donor identified. Auto-HCT can also be considered for patients with chemosensitive FL in relapse. Although the optimal timing of HCT is a matter of debate, we generally consider the HCT option in patients who progress after 2–3 lines of therapies. Finally, allo-HCT can salvage a subset of patients with progression even after they have relapsed from an auto-HCT.

4. For follicular lymphoma patients undergoing allo-HCT, what is the optimal regimen: myeloablative or RIC?

A major advance in lowering the short-term TRM and morbidity of allo-HCT has been the advent of RIC regimens. RIC regimen–based allo-HCT relies more on the GVL effect of the donor T-cells than on cytoreduction from the conditioning regimen. RIC allo-HCT is based on the premise that adequate immunosuppression of the recipient facilitates

Table 51.2 Prospective trials of RIC allo-HCT for relapsed follicular lymphoma.

	n	Age, years (median)	Preparative regimen	PFS (%)	OS (%)	TRM (%)	Follow-up (months)
MD Anderson (2012)[a]	47	53	Flu/Cy/RTX	72	78	13	107
MD Anderson (2012)[a]	26	55	Flu/Cy/90^{Y}	85	88	8	23
CALGB (2011)[b]	44	53	Flu/Cy	75	81	9	55
GELTAMO (2010)[c]	37	50	Flu/Mel	57	54	24	52

CALGB, Cancer and Leukemia Group B; Cy, cyclophosphamide; Flu, fludarabine; GELTAMO, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea; Mel, melphalan; OS, overall survival; PFS, progression-free survival; RTX, rituximab; Y90, TRM, transplant-related mortality; Y90-ibritumomab tiuxetan.

[a]From Khouri IF, *et al.* Blood. 2012;119(26):6373–8.

[b]From Shea T, *et al.* BBMT. 2011;17(9):1395–403.

[c]From Piñana JL, *et al.* Haematologica. 2010;95(7):1176–82.

donor engraftment, without the need for significant debulking of the lymphoma. RIC allo-HCT has been used increasingly in FL patients and has resulted in durable remissions and lower NRM compared with MAC allo-HCT. The introduction of RIC regimens has significantly broadened patient eligibility: patients over the age of 70 years, those who had failed prior to auto-HCT, and patients with comorbid conditions that would preclude MAC should be considered for an allo-HCT using RIC regimens.

Table 51.2 provides results of four prospective RIC allo-HCT trials in relapsed FL patients. All four included patients who had failed prior auto-HCT, patients older than 60 years, and those who used a fludarabine (Flu)-based conditioning. With median follow-up ranging from 3 to 10 years, the disease-free survival (DFS) and EFS rates ranged from 43% to 75% and the OS from 52% to 81%. Chemosensitivity at the time of transplant was a consistent determinant of outcome.

In the trial reported by the MD Anderson group, 47 relapsed FL patients received the FCR [Flu, cyclophosphamide (Cy), and RTX] regimen that used a higher dose of RTX (three of the four doses were 1000 mg/m^2). The 11-year EFS and OS were 72% and 78%, respectively, with only three relapses observed, at a median follow-up of 107 months (Figure 51.2). Based on these impressive results, the BMT CTN launched a phase II multicenter study using the FCR conditioning regimen in relapsed FL patients who demonstrate chemosensitivity, and have a matched related donor (MRD) or matched unrelated donor (MURD) identified. This trial has already completed accrual, and results are pending.

The outcomes after MAC and RIC allo-HCT have not been formally assessed in a prospective fashion. However, two large registry studies directly compared the outcomes of FL patients who underwent either MAC or RIC allo-HCT. The RIC groups in both studies were significantly older, and a higher proportion had failed prior auto-HCT compared with the MAC group (Table 51.2). The CIBMTR analysis was confined to MRD allo-HCT (1997–2002) and failed to link survival benefit to a particular type of conditioning regimen. At 3 years, OS and PFS were 71% and 67% for the MAC group ($n = 120$), and 62% and 55% for the RIC arm ($n = 88$), respectively ($P > 0.05$). However, the rate of relapse and progression was significantly higher in the RIC group (relative risk of 2.94; $P = 0.04$). The EBMT, in contrast, evaluated MURD allo-HCT only, and on multivariate analysis showed the RIC group ($n = 87$) to have a lower NRM and a significantly prolonged PFS and OS compared to the MAC arm ($n = 44$), while the relapse rate was comparable between the two groups. Based on these two analyses, it has been suggested that an unrelated donor graft may be associated with a more robust GVL effect. Both studies found that chemoresistance and a worse performance status adversely affected NRM, OS, and PFS. A recent retrospective analysis from the CIBMTR also showed that chemosensitivity at the time of allo-HCT, rather than conditioning intensity, was a strong predictor of outcome in FL patients.

Thus, both retrospective and prospective data confirm that chemosensitivity, rather than conditioning intensity, is the most reliable determinant of outcome, and currently there is no absolute indication for a MAC regimen. The use of RIC regimens increased from 10% of allo-HCT in 1997 to 80% in 2002, establishing RIC allo-HCT as a standard for FL patients requiring an allo-HCT.

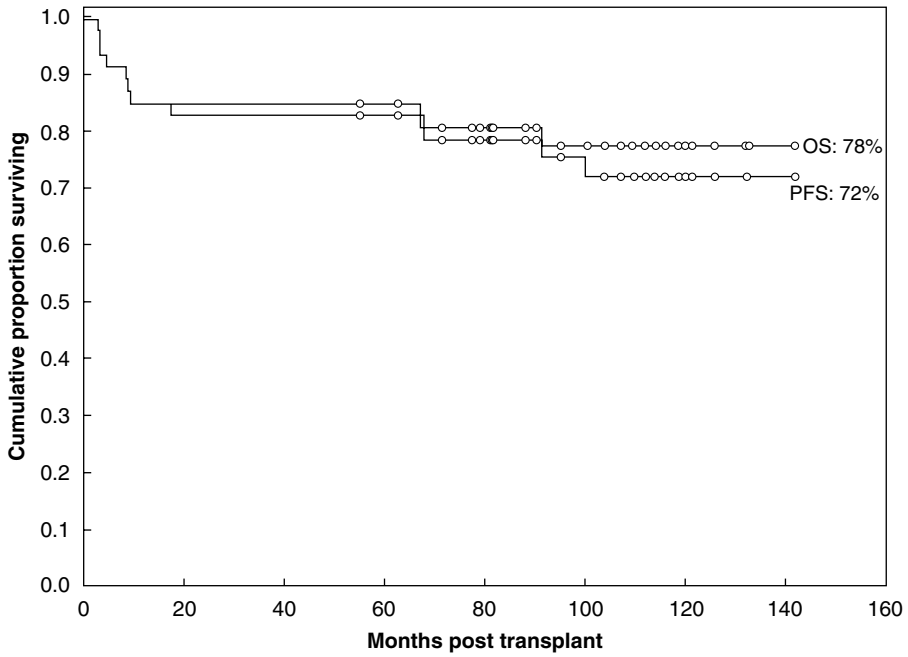


Figure 51.2 Overall survival (OS) and progression-free survival (PFS) rates after nonmyeloablative allogeneic hematopoietic cell transplantation with FCR [fludarabine, cyclophosphamide (Cy), and rituximab] conditioning (Source: Khouri IF, *et al.* Blood. 2012;119:6373–8. Reproduced with permission of the American Society of Hematology).

Selected reading

Al Khabori M, de Almeida JR, Guyatt GH, *et al*. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(1): 18–28.

Hari P. Carreras J. Zhang MJ, *et al*. Allogeneic transplants in follicular lymphoma: higher risk of relapse progression after reduced-intensity compared to myeloablative conditioning. Biol Blood Marrow Transplant. 2008;14(2);236–45.

Laport GG. Changing role of stem cell transplantation in follicular lymphoma. Hematology Am Soc Hematol Educ Program. 2012;2012:417–25.

Piñana JL, Martino R, Gayoso J, *et al*. Reduced intensity conditioning HLA identical sibling donor allogeneic stem cell transplantation for patients with follicular lymphoma: long-term follow-up from two prospective multicenter trials. Haematologica. 2010;95(7):1176–82.

Salles G, Ghesquieres H. Current and future management of follicular lymphoma. Intl J Hematol. 2012;96(5):544–51.

CHAPTER 52

Hematopoietic cell transplantation in diffuse large B-cell lymphoma

Syed A. Abutalib and Istvan Redei

Cancer Treatment Centers of America, Zion, IL, USA

Case study 52.1

You are requested to see a 61-year-old very successful hedge fund manager with diffuse large B-cell lymphoma (DLBCL). He comes to you for a third medical oncology opinion with recently diagnosed stage IIIB disease. He has excellent performance status. At the time of diagnosis, the LDH was above the upper limit of normal. His lymphoma does not have c-myc translocation or overexpress bcl-2 protein. The Hans criteria points toward the activated B-cell (ABC) subtype. The gene expression profiling (GEP) analysis confirms the ABC subtype. Approximately 8 weeks ago, he completed six cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) immunochemotherapy with positron emission tomography (PET) negativity. The cycles were given every 3 weeks. His assistant made an internet search and told him that he has a "high-risk" lymphoma. He informs you, "I'm a fixer and I want to be sure that my lymphoma does not come back ever."

• How would you explain to him the therapeutic and prognostic implications, especially of molecularly defined "ABC high-risk" lymphoma?

Numerous prognostic markers and indices are under investigation since the initial publication of the International Prognostic Index (IPI) model in 1993. The rationale behind such investigations stems from the inability of currently applied clinical prognostic model(s) to precisely capture the heterogeneity in outcomes experienced with delivery of category 1 NCCN recommended therapy. Obviously, this is due to the fact that DLBCL is not a single disease but encompasses various clinical and biologic subgroups. In the era of R-CHOP, the most applicable and widely acceptable prognostic models are the IPI and Revised IPI (R-IPI). Based on the age-adjusted (age >60) IPI model, this patient would be categorized into *high-intermediate* (HI) risk with a 5-year overall survival (OS) rate of 37%. And according to the R-IPI model, which appears to be a superior model in the rituximab era, the 4-year progression-free survival (PFS) and OS would be 53% and 55%, respectively. Using R-IPI, the best outcomes are achieved in patients categorized as *very good* risk with a remarkable 4-year PFS and OS of 94%. Notably, within these well-defined prognostic categories, layers of prognostic complexity remain. Indeed, utilizing the GEP method has the potential to refine the prognostic algorithm; however, not all genes within cell-of-origin (COO) classification have a strong prognostic significance. Importantly, as opposed to the highly curative strategies employed in acute promyelocytic leukemia (APL) following seminal discovery of the *PML–RARα* gene, the obstacle of isolating and targeting a disease-driving single gene in DLBCL remains a formidable challenge.

Intriguing retrospective data do exist in front-line settings, showing inferior PFS and OS in patients with GEP-defined ABC- versus germinal B-cell (GBC) DLBCL in the context of currently available therapies. A French group (the LNH98.5 trial) reported outcomes of 67 older adults with inferior OS rates in ABC ($n = 42$) versus GBC DLBCLs ($n = 25$) with a hazard ratio of 0.18 (0.04–0.76) in the context of R-CHOP therapy. The COO distinction remained statistically significant in a multivariate analysis for OS. Similarly, a study from the US National Institutes of Health (NIH) demonstrated PFS of 40% versus 75% ($P < .001$) with ABC and GBC

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

DLBCL, respectively, in patients treated with R-CHOP. Gutiérrez-García and colleagues (2010) from the University of Barcelona showed, in 52 patients, a 5-year PFS of 31% versus 76% ($P = .005$) in patients with ABC and GBC DLBCL, respectively. In Europe, a phase III molecularly guided randomized control trial (RCT), ReMoDL-B (ISRCTN 51837425), is ongoing. This is the first study with prospective GEP analysis as a means of stratifying randomization of DLBCL subgroups between treatment with R-CHOP or R-CHOP plus bortezomib. The goal of the trial is to determine if there is a subset of DLBCL in which bortezomib improves outcome. Altogether, despite unsatisfactory statistics procured with any of the aforementioned prognostic models, the recommended treatment, outside of a clinical trial, remains remarkably uniform within all risk categories in patients with stages III and IV DLBCL.

1. After hearing your explanation, he says, "So tell me, should I get ready for more chemotherapy and/or transplant, Doc, or should I get another opinion trans-Atlantic?" What do you recommend?

A. Front-line consolidation high-dose chemotherapy (HDT) and autologous hematopoietic cell transplant (auto-HCT)
B. Rituximab maintenance for 2 years.
C. Surveillance

This question highlights two important clinical issues in the management of DLBCL: (i) what are the optimal number of treatment (R-CHOP) cycles (e.g., 6 versus >6, especially in HI/HR risk category or ABC DLBCL)? And (ii) what is the highly debated role of frontline HDT and auto-HCT in DLBCL? The answers to these questions are not straightforward.

(i) The RICOVER-60 trial compared six and eight cycles with and without rituximab in 1222 patients ages 61 to 80 years with aggressive non-Hodgkin's lymphoma (NHL), but the cycles were every 2 weeks (R-CHOP14) instead of every 3 weeks (R-CHOP21). The authors concluded that six cycles should be the standard using R-CHOP-14. In our opinion, extrapolation of these data with R-CHOP21 in older adults with high-risk disease is an unsettled issue. The trial incorporated histologies other than DLBCL (20% of the patients did not have DLBCL) and <50% of the patients with aggressive lymphoma (all histologies included) had IPI >3. In our practice, we prefer R-CHOP21 ×6 cycles in the majority of adults with de novo (c-myc translocation negative and not transformed) DLBCL. However, European Society of Medical Oncology (ESMO) guidelines for DLBCL recommend R-CHOP21 ×8 in healthy older (age >60 to 80 years) adults with high IPI scores and R-CHOP21 ×6 in patients with low IPI scores or, alternatively, R-CHOP14 ×6 with an additional two doses of rituximab (total doses of rituximab ×8) for all healthy older (>60 years) patients up to age 80 years.

(ii) The majority of randomized clinical trials (RCTs) failed to demonstrate OS benefit with frontline auto-HCT in DLBCL. In addition, two meta-analyses (in 2003 and 2007) were unable to show OS benefit. On the contrary, detrimental effects with transplant were observed in low-risk IPI patients. The evidence for or against frontline auto-HCT in patients with high IPI scores continues to be debated especially following the SWOG 9704 study presentation during the American Society of Clinical Oncology (ASCO) meeting in 2011. This North American Intergroup was designed and approved prior to rituximab; however, the drug was incorporated into the CHOP regimen upon its availability. In this large RCT, patient with high-intermediate-risk (HI) and high-risk (HR) IPI received CHOP +/− rituximab ×5 and then were randomized to either three additional cycles of CHOP +/− rituximab ($n = 128$) or one additional cycle of CHOP +/− rituximab followed by auto-HCT ($n = 125$). Obviously, the randomization was performed only in patients who achieved greater than or equal to a PR ("chemosensitive disease"). The study was unable to demonstrate an OS benefit with front-line auto-HCT, not even in patients who received rituximab ($n = 72$). Rigorous subset analysis showed that only patients with HR IPI had OS benefit with auto-HCT, and a 2-year OS of 82% versus 64%; however, this was analyzed only in 44 and 40 patients in the auto-HCT and CHOP +/− R arms, respectively. Thus, these positive results beg caution to conclude that frontline auto-HCT comprise the best therapeutic strategy for HR IPI patients. For example, not all patients analyzed had DLBCL (78% of all patients in the study had DLBCL), only 32% of patients had HR IPI, rituximab was administered in approximately 48% of patients with B-cell lymphomas (not just DLBCL), and, finally, the analysis was exploratory. The final results of this study were recently published in NEJM. A separate French (GOELAMS 075) study did not demonstrate OS benefit with auto-HCT compared to R-CHOP. In fact, the 3-year EFS was superior with R-CHOP compared to auto-HCT (56% vs. 36%, respectively), with no impact of IPI risk categories on outcomes. The Italian Lymphoma Foundation (DLCL04) reported a 2 × 2 trial comparing R-CHOP14 with R-MegaCHOP in the first randomization, and auto-HCT versus continuation of the original induction regimen in the second randomization, in high-risk patients with DLBCL. The CR/unconfirmed CR (CR/CRu) rates were 70% for R-CHOP14 and 77% for R-MegaCHOP. With second randomization, there was a 2-year PFS in favor of the auto-HCT arm compared with the continuation-of-induction-chemotherapy arm. It was 72% for auto-HCT versus 59% for chemotherapy ($P = .008$), with no difference seen in OS. The therapeutic implications of interim PET scan is important and are discussed in Chapter 61. Presently, ABMTR guidelines (updated 2011) do not support frontline auto-HCT in

(*Continued*)

patients with either HI or HR IPI or R-IPI scores or GEP-defined ABC DLBCL. However, this discussion remains open for debate and investigation. In view of the benefit of auto-HCT in the salvage setting, it is likely that certain subgroups of newly diagnosed DLBCL patients may benefit from this strategy in the frontline setting. The ability to identify such patients based on clinical or biologic markers continues to evolve and is under intensive investigation.

2. Unfortunately, approximately 9 months following front-line immunochemotherapy, he develops severe B-symptoms; a PET–computed tomography (CT) scan reveals extensive fluoro-deoxyglucose (FDG)-avid lymphadenopathy at original sites. Repeat biopsy confirmed a relapse of ABC DLBCL. Bone marrow exam remains negative. What do you recommend?

A. R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin)
B. R-ICE (rituximab, ifosfamide, etoposide, and carboplatin)
C. R-GDP (rituximab, gemcitabine, dexamethasone, and cisplatin)
D. R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin)
E. R-MINE (rituximab, mesna, ifosfamide, mitoxantrone, and etoposide)
F. R-GemOx (rituximab, gemcitabine, and oxaliplatin)
G. R-DA-EPOCH (rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
H. Any of the above regimens is a reasonable option.

Salvage chemotherapy followed by auto-HCT is considered standard treatment for relapsed and refractory DLBCL. The choice of a specific salvage regimen prior to auto-HCT should take into consideration patient's comorbidities, physician comfort level with a particular regimen, and the regimen's ability to reduce disease burden without hampering the mobilization process. Achievement of complete response (CR2) is always preferred over partial response, but it is not a prerequisite to proceed with auto-HCT. Patients refractory to salvage regimens are not candidates for auto-HCT. These patients have a grim outlook with survival not more than a few months. In responding patients, PET scan negativity portends favorable outcomes for patients compared to a positive scan prior to auto-HCT (discussed in Chapters 40 and 61). Multiple salvage regimens have been developed, and there remains no standard of care. As such, there is no single best regimen; thus, patients should be encouraged to participate in clinical trials. It must be stated that outcomes are suboptimal even for patients responding and proceeding to auto-HCT. In the rituximab era, the landmark Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) intergroup study is a RCT that compared the two most commonly utilized salvage regimens, R-ICE and R-DHAP. In the CORAL trial, patients received either R-ICE or R-DHAP, and responding patents had BEAM (carmustine, etoposide, high-dose cytarabine, and melphalan) and auto-HCT, and then had second randomization between observation and rituximab maintenance for 1 year. Several important questions related to relapsed and refractory DLBCL were elegantly addressed in this phase III trial (reviewed in Table 52.1). Noteworthy, only half of the patients were able receive the intended auto-HCT. This was mainly secondary to progressive disease and highlights the key limitations of currently available salvage regimens. A larger RCT study (NCIC CTG LY12) with similar design under National Cancer Information Center (NCIC) sponsorship has been completed. In this study, R-GDP (gemcitabine, dexamethasone, and platinum) was compared with the R-DHAP regimen in patients with aggressive NHL (71% of the patients had DLBCL). The R-GDP was non-inferior to R-DHAP with less toxicity. Altogether, it is prudent to effectively incorporate novel agents, preferably early during the course of disease to improve on the inefficient outcomes demonstrated in the majority of patients with relapsed and refractory disease. Numerous experimental agents (Table 52.2) are in different evaluation phases, and it is hoped that they will be integrated into the treatment algorithm of DLBCL in the near future.

3. The patient received two cycles of R-DHAP and achieved CR2 by PET–CT criteria. What do you now recommend?

A. Auto-HCT
B. An additional four cycles of the R-DHAP regimen
C. Surveillance

The superiority of auto-HCT over conventional salvage chemotherapy for relapsed DLBCL was first demonstrated by the PARMA (1995) RCT. Although widely regarded as the standard approach for these patients, the relevance of this study to current management of relapsed DLBCL is uncertain. Eligibility to the PARMA study was restricted to patients younger than 60 years with a previous CR to frontline chemotherapy (CR1), and none of the patients had evidence of bone marrow involvement at diagnosis. Moreover, all patients in this study underwent bone marrow harvest as the source of autologous stem cell support, and the study was open to all patients with DLBCL according to the Working Formulation, which included histologies other than DLBCL. With dramatic improvements in supportive care and the advent of peripheral blood progenitor cell (PBPC) procurement for hematologic rescue, auto-HCT are now offered to older adults, patients who had not achieved CR1 with first-line therapy (but have chemosensitive disease with subsequent regimens), and, frequently, those with a history of marrow involvement. Keeping in mind these

Table 52.1 Relapsed and refractory diffuse large B-cell lymphoma (DLBCL) (data from CORAL study).

Treatment algorithm: R-ICE vs. R-DHAP → BEAM and Auto-HCT → rituximab versus observation

Question	Answer[a]	Comments
RICE and R-DHAP are comparable salvage regimens.	Yes	EFS: 26% vs. 35% ($P = .6$) at 3 years OS: 47% vs. 51% ($P = .5$) at 3 years
Did prior (front-line) rituximab-based regimen affect outcomes differently?	Yes	Probability of survival was 34% vs. 66% with and without rituximab, respectively.
Did relapse greater or less than 12 months affect outcomes differently?	Yes	3 year EFS was 20% vs. 45% for relapse >12 or <12 months, respectively.
Did prior (front-line) rituximab-based regimen affect outcomes differently if relapse was within 12 months of initial therapy?	Yes	3 year EFS was 21% (<12 months) vs. 41% (>12 months).
Did prior (front-line) rituximab-based regimen affect outcomes differently if relapse was >12 months following initial therapy?	No	No difference in EFS or OS between the two subgroups with or without rituximab exposure
Did secondary aaIPI had any bearing on prognosis?	Yes	3-year EFS with secondary aaIPI 2–3 was 18% vs. 40% for secondary aaIPI 0–1 ($P = .0001$).
Did patients with GBC DLBCL respond better to a salvage regimen compared to ABC DLBCL (COO defined by the Hans criteria)?	Yes	Retrospective analysis of the CORAL study showed PFS 70% and OS 74% for GBC DLBCL versus PFS 28%, and OS 40% for ABC DLBCL.
Did patients with GBC DLBCL fare better in outcomes with R-DHAP compared to R-ICE (COO defined by the Hans criteria)?	Yes	Retrospective analysis of CORAL study showed PFS at 3 years of 100% with R-DHAP and 27% with R-ICE. This needs confirmation by a prospective study.
Did patients with ABC DLBCL fare better in outcomes with R-ICE compared R-DHAP (COO defined by the Hans criteria)?	No	Retrospective analysis of the CORAL study showed equally poor outcomes in ABC DLBCL (via the Hans criteria) with either regimen.
Was incidence of c-myc greater in GBC DLBCL compared to ABC DLBCL by the Hans criteria?	Yes	Retrospective analysis showed that c-myc by FISH was positive in 17 patients with GBC DLBCL versus 10 patients with ABC DLBCL.
Was incidence of c-myc greater in GBC DLBCL compared to ABC DLBCL by GEP analysis?	Yes	Retrospective analysis showed that c-myc was more common in GBC DLBCL ($n = 3$), whereas no cases were associated with ABC DLBCL.
Does R-DHAP show OS improvement when compared to R-ICE in patients with c-myc (genetically defined) positive relapsed or refractory DLBCL?	No	Retrospective analysis showed that the type of salvage regimen, R-DHAP or R-ICE, had no impact on survival, with 4-year PFS rates of 17% vs. 19% and 4-year OS rates of 26% vs. 31%, respectively.
Were the majority of biological characteristics similar between diagnosis and relapse in the 45 matched-pair biopsies studied?	Yes	Retrospective analysis showed this to be true in 87% of the cases.
Did maintenance rituximab therapy following auto-HCT improve PFS?	No	The 4-year postautologous transplant EFS rates were 52% and 53% for the 122 patients with rituximab and the 120 patients in the observation group, respectively ($P = .7$).

aaIPI, age-adjusted International Prognostic Index score; ABC, activated B-cell; auto-HCT, autologous hematopoietic cell transplant; BEAM, carmustine, etoposide, high-dose cytarabine, and melphalan; COO, cell of origin; EFS, event-free survival; FISH, fluorescent in situ hybridization; GBC, germinal B-cell; OS, overall survival; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, etoposide, and carboplatin.

[a]Applicable to patients between the ages of 18 and 65 in the CORAL study.

(*Continued*)

Table 52.2 Experimental agents under investigation in diffuse large B-cell lymphoma (DLBCL).

Ofatumumab (anti-CD20 antibody)
Obinutuzumab (GA101) (anti-CD20 antibody)
Veltuzumab (anti-CD20 antibody)
Dacetuzumab (SGN-40) (anti-CD40 antibody)
Blinatumomab (MT 103) (bispecific anti-CD19 and CD3 antibody)
Epratuzumab (anti-CD22 antibody)
Inotuzumab ozogamicin (CMC-544) (anti-CD22 antibody conjugate with calicheamicin)
Pidilizumab (CT-011) (immune modulation via binding to PD-1)
Ipilimumab (MDX-010) (anti–CTLA-4 antibody)
Deacetylase inhibitors
Lenalidomide (immune modulation)
Fostamatinib disodium (splenic tyrosine kinase inhibitor)
PCI-32765 (Burton's tyrosine kinase inhibitor)
Bortezomib (nuclear factor kappa B (NF-κB) inhibitor)

modern practices, few retrospective data support the role of auto-HCT in the rituximab era. On behalf of the European Group for Blood and Marrow Transplantation (EBMT), 470 relapsed DLBCL patients in CR2 and before receiving auto-HCT were evaluated. The median duration of the first remission was <12 months in 49% of the patients; 119 patients did receive rituximab while 351 patients did not as part of initial therapy. The 5-year PFS and OS were 48% and 63%, respectively. The duration of post-autologous transplant PFS was longer than that before transplantation in 289 patients. When each patient was used as his or her own control, PFS after auto-HCT was longer than PFS before auto-HCT ($P < .001$). This difference in favor of post-auto-HCT remission was significant for patients with or without rituximab exposure. In a separate study, the Cleveland Clinic reported an almost similar observation in 226 consecutive patients treated with auto-HCT for relapsed DLBCL. They concluded that, even in the rituximab era, auto-HCT should remain the standard of care. In our opinion, patients responding to a salvage regimen, even those who obtain PR and with relapse >12 months following front-line therapy, should be considered for auto-HCT (due to lack of better therapies), but patients with early (<12-month) relapse and with responses less than CR should be considered for alternative therapeutic approaches, preferably a clinical trial with novel strategies and/or allogeneic transplantation.

4. You recommended auto-HCT. The patient read about different conditioning regimens for auto-HCT. He wants to know which one you would select and why. What do you recommend?

A. TBI and Cy (total body radiation and cyclophosphamide)
B. BEAM regimen
C. 90Y-Ibritumomab tiuxetan with BEAM regimen
D. 131-Iodine tositumomab with BEAM regimen

As described previously the role of auto-HCT in the treatment of relapsed DLBCL was defined more than a decade ago in a multicenter prospective randomized trial that compared auto-HCT versus a nontransplant approach. Presently, there is no standard conditioning regimen. Commonly used myeloablative (MA) regimens include BEAM, CBV (cyclophosphamide, carmustine, and etoposide), TBI-Cy, and BuCyVP-16 (busulfan, cyclophosphamide, and etoposide). Although there has been no RCT in this particular setting, comparative studies between TBI-based versus non-TBI-based regimens suggest higher rates of secondary hematologic and nonhematologic toxicities without any additional clinical benefit with TBI based regimens. Radioimmunotherapy (RIT) has been brought forward into the arena of conditioning regimens with hopes of eradicating disease more effectively without added toxicities of TBI. RIT delivers targeted radiation to lymphoma sites (primarily anti-CD20) while protecting other tissues. Two radiolabeled antibodies, iodine-131 tositumomab (Bexxar) and yttrium-90 ibritumomab (Zevalin), have been approved by the US Food and Drug Administration (FDA) to treat relapsed indolent lymphoma (discussed in chapter 62). Press *et al*. (2006) combined iodine-131 tositumomab (Bexxar) with etoposide and cyclophosphamide in the setting of relapsed NHL. Comparison of this regimen with historical TBI-based conditioning control demonstrated significant improvement in PFS and OS. Multiple phase II studies have been published that incorporated RIT to the conditioning regimen, showing lower treatment-related mortality (TRM) and promising efficacy. These promising phase II data paved the way for RIT to be tested in an RCT (CTN 0401) under the supervision of the Bone Marrow Transplant Clinical Trials Network (BMT CTN). The trial enrolled 224 adult patients with persistent or recurrent chemosensitive DLBCL. Prior to autologous transplant, patients were randomly assigned to R-BEAM versus BEAM plus conventional-dose iodine-131 tositumomab (I-BEAM). The 2-year PFS was 47.9% for I-BEAM and 48.6% for R-BEAM ($P = .94$). The 2-year OS rate of all randomized patients was 61% for I-BEAM and 65.6% for R-BEAM ($P = .38$). The TRM rate was 4.9% in the RIT-BEAM arm and 4.1% in the R-BEAM arm at 2 years following auto-HCT ($P = .97$). In summary, this phase III study was unable to recapitulate previously reported positive phase II data. In a separate study by Shimoni *et al*. (2012), standard-dose yttrium-90 ibritumomab tiuxetan (Zevalin) was added to BEAM (Z-BEAM) and was compared with a conventional

BEAM regimen in a small, randomized, multicenter study. Forty-three patients with chemosensitive DLBCL were randomized to one of the treatment arms. The PFS with Z-BEAM and BEAM was 59% and 30% at 2 years, respectively ($P = .20$). The OS was 91% and 62% at 2 years, respectively ($P = .05$). There was no significant added toxicity with the Z-BEAM regimen. Further large, well-designed, randomized studies are needed to evaluate the exact role of Z-BEAM as a conditioning regimen.

5. Your patient underwent a successful autologous hematopoietic progenitor cell collection following third cycle of R-DHAP. Subsequently, BEAM–HDT was administered. A posttransplant PET-CT scan remains negative, and he went back to work 2 months after auto-HCT. Now he asks, "Is there anything else that I can do to prevent relapse after autologous transplant?" What do you recommend?

A. Rituximab maintenance therapy for 2 years
B. Surveillance

One of the possible strategies to improve the outcome in patients with relapsed DLBCL is maintenance therapy following auto-HCT. Rituximab, a chimeric monoclonal antibody against CD20, is an essential component of the initial and salvage therapy for DLBCL. Rituximab maintenance or consolidation therapy after auto-HCT to target "minimal residual disease" is an appealing approach, especially in patients who had >12 months of CR1. Published data in follicular lymphoma showed a PFS advantage to rituximab maintenance therapy after auto-HCT. Maintenance rituximab therapy after auto-HCT in DLBCL has been evaluated in the context of short treatment courses administered soon after auto-HCT. Prolonged cytopenias and increased incidence of infections have been reported with this strategy. Phase II studies showed promising results. However, Haioun *et al*. (2009) reported no advantage of rituximab maintenance on 269 patients who were randomly assigned to either a control group or 4 weekly rituximab treatments after auto-HCT. In the CORAL trial (Table 52.1), there was no difference in EFS, PFS, or OS in the maintenance versus observation arm. The 4-year post-auto-HCT EFS was 52% in the maintenance arm versus 53% in the observation group ($P = .7$). A higher incidence of infections was reported in the maintenance arm after day 100. A subset analysis based on sex difference showed that there was a statistically significant difference in PFS between males and females at the time of second randomization ($P = .0135$) and after maintenance therapy ($P = .0044$). There was no such sex difference noted in the observation arm ($P = .5382$). The authors hypothesized that the lower PFS in males may be a result of hormone-related pharmacokinetic variation that caused higher rituximab clearance in males, which results in lower rituximab exposure. Of interest would be the final results of maintenance therapy in the NCIC LY12 trial. Early reports do not favor 1 year of rituximab maintenance therapy. Newer agents with better activity should also be explored following auto-HCT as maintenance therapy (Table 52.2). An example for this sort of approach would be the use of CT-011, which is a humanized anti-program death-1 (PD1) antibody. It blocks PD1 function and enhances the activities of natural killer (NK)-cells and T-cells against PD-L1-positive tumors. Gordon *et al*. (2011) reported results of 72 chemosensitive relapsed DLBCL patients who received three doses of CT-011 every 6 weeks, 30–90 days after auto-HCT. Compared with historical data, CT-011 resulted in improved PFS and OS in patients with relapsed DLBCL after auto-HCT with acceptable toxicity. Randomized phase III trials are warranted to confirm these intriguing findings. Other agents that are candidates for maintenance therapy include lenalidomide, bortezomib, and vorinostat.

6. The patient came back to see you for a 1-year posttransplant follow-up. He is very happy because his hedge fund did very well lately. Sadly, the CT scans showed new lymphadenopathy. The biopsy confirmed relapsed DLBCL. He tells you, "Doctor I must live—I have so many things to do." What do you recommend?

A. Salvage chemotherapy followed by second autologous transplant
B. Allogeneic HCT
C. Clinical trial
D. Hospice

The prognosis of the majority of DLBCL patients who relapse after auto-HCT is very poor, with an OS of less than 11% at 12 months. Conventional-dose salvage chemotherapy can induce remission in a small minority of patients. The results of a second auto-HCT are usually disappointing. Allo-HCT could be considered as a therapeutic option for these high-risk patients. Allo-HCT using a myeloablative conditioning regimen can achieve durable CRs. However, it has also been associated with exceedingly high nonrelapse mortality (NRM) of approximately 50%. The development of less intensive conditioning regimens that harness on graft-versus-lymphoma (GvL) effect has increased the number of patients who are candidates for this life-saving modality, including patients who relapse after auto-HCT. Recently, two retrospective analyses were published evaluating the results of allo-HCT in patients with DLBCL who relapsed after auto-HCT. The analysis of the EBMT database included 101 patients; conditioning regimens was nonmyeloablative (NMA) in 64 patients. The 3-year PFS and OS were 41% and 53% respectively. Patient with long remission after auto-HCT and with chemosensitive disease before allo-HCT had the best outcomes. Rigacci *et al*. (2010) analyzed 165 patients whose data were reported to the Gruppo

(*Continued*)

Table 52.3 Research agenda to improve outcomes in diffuse large B-cell lymphoma (DLBCL).

Development of better strategies upfront to eliminate relapses and minimize the incidence of refractory disease
Better understanding of the biology of the disease to allow personalized therapy, preferably early during the course of disease
Development of more robust prognostic models using both clinical and biologic parameters
Development of strategies to overcome rituximab resistance
Incorporation of newer agents targeting novel pathways without hampering the mobilization process in appropriate auto-HCT candidates
Incorporation of newer agents targeting novel pathways in nontransplant candidates
Methods to appropriately identify a correct subgroup of patients for autologous and allogeneic transplantation
Incorporation of newer, more effective, and less toxic agents in conditioning regimens with reduction in the incidence of secondary therapy-related malignancies
Integration of newer agents as part of maintenance therapy

Italiano Trapianto di Midollo Osseo (GITMO) registry; 70% of the patients received NMA conditioning regimens. The 1-, 3-, and 5-year OS were 55%, 42%, and 39%, respectively. The NRM was 28%. Interestingly, the 3-year OS was 27% in chemotherapy-refractory patients. These two retrospective registry studies that include relatively large numbers of patients indicate a role for allo-HCT in patients with DLBCL relapsing after auto-HCT. These data are also suggestive of a possible GvL effect because both PFS and OS curves seem to form a plateau in a heavily pretreated patient population. Clinical trial is also reasonable option. However, in this particular setting, there are no new agents that have curative potential (Table 52.3).

Case study answers

Case study 52.1

Question 1: Answer C
Question 2: Answer H
Question 3: Answer A
Question 4: Answer B
Question 5: Answer B
Question 6: Answer B

Selected reading

Gisselbrecht C. Is there any role for transplantation in the rituximab era for diffuse large B-cell lymphoma? Hematology Am Soc Hematol Educ Program. 2012;2012:410–6. doi:10.1182/asheducation-2012.1.410

Lenz G, Wright G, Dave SS, *et al*. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med. 2008;359:2313–23.

Oliansky DM, Czuczman M, Fisher RI, *et al*. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review. Biol Blood Marrow Transplant. 2011;17(1):20–47.

Stiff PJ, Unger JM,Cook JR *et al*. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med. 2013 Oct 31;369(18):1681–90.

Tilly H, Vitolo U, Walewski J, da Silva MG, *et al*. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol. 2012; 23(Suppl. 7):vii78–82.

CHAPTER 53

Hematopoietic cell transplantation in T-cell non-Hodgkin's lymphomas

Lori S. Muffly and Sonali M. Smith
The University of Chicago, Chicago, IL, USA

Introduction

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of uncommon non-Hodgkin's lymphomas (NHLs), arising from mature T-cells of postthymic origin and accounting for approximately 10% of all NHL cases in North America. Marked geographic variation exists regarding the frequency of various subtypes of PTCL worldwide. In North America, PTCL not otherwise specified (PTCL-NOS) is most common (34.4%), followed by angioimmunoblastic T-cell lymphoma (AITL; 16%) and anaplastic large-cell lymphoma (ALCL), ALK-positive (16%) and ALK-negative (7.8%). Extranodal natural killer (NK)- and T-cell lymphoma (ENKL) and adult T-cell leukemia and lymphoma (ATLL), which respectively account for only 5.1% and 2% of PTCLs in North America, are the most common subtypes on the Asian continent. With few exceptions, the various PTCLs share the common features of highly aggressive malignancies associated with poor clinical outcomes. With increasing spotlight on these rare NHLs, studies focused specifically on PTCL subtypes are emerging, leading to increasing understanding of disease biology, the development of novel therapies, and greater insight into the role of stem cell transplantation for PTCL.

Case study 53.1

A 51-year-old otherwise healthy man presents with stage IVB PTCL-NOS, with diffuse lymph node and bone marrow involvement.

• **What is the standard initial therapeutic approach for advanced-stage (Ann Arbor Stage III–IV) PTCL-NOS?**
PTCL-NOS is currently a provisional category in the 2008 World Health Organization classification as a heterogeneous group of nodal and extranodal mature T-cell lymphomas, which do not fit within any of the specifically defined mature T-cell entities. Morphologically, PTCL-NOS demonstrates paracortical or diffuse infiltrates with effacement of normal lymph node architecture, and it is more commonly associated with expression of CD3, CD4, and TCR β-chain, with frequent loss of CD5 and CD7. Variable expression of CD52 has been reported, and CD30 may be present but is most commonly absent. Epstein–Barr virus (EBV) is found in approximately 30% of all PTCL-NOS. Nearly all cases demonstrate clonal rearrangement of *TCR* genes. Gene expression profiling reveals that up to 20% of cases of PTCL-NOS have a gene expression profile characteristic of AITL, and another subgroup has features of cytotoxic T-cells that may represent a unique entity with a worse prognosis. The genetic heterogeneity portends that PTCL-NOS will eventually be segregated into more defined diseases.

PTCL-NOS represents the most prevalent PTCL subtype in Western countries, affecting mostly older adults with a median age at diagnosis of 60 years and a slight male predilection. Nearly 70% of patients present with advanced-stage disease, frequently with bone marrow involvement.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

The International Prognostic Index (IPI) is predictive of overall survival (OS) and failure-free survival (FFS) in PTCL-NOS, as is the more recently developed Prognostic Index for PTCL-NOS (PIT), which adds bone marrow involvement in addition to the IPI variables of age, performance status, and lactate dehydrogenase (LDH).

The historical treatment of PTCL has been modeled after that of diffuse large B-cell lymphoma, with conventional-dose, systemic, anthracycline-containing chemotherapy representing standard front-line therapy. However, it is clear that this approach is suboptimal for PTCL, with reported long-term survival rates of only 20–40%, and as low as 10% for those with high IPI scores. Further, the retrospective International T-Cell Lymphoma Project found no survival benefit with the use of anthracycline-containing combination chemotherapy relative to non-anthracycline-containing therapy for all PTCL subtypes, with the exception of ALK-positive ALCL, suggesting that different and more effective approaches are clearly needed.

Despite these poor results, few studies have challenged the front-line use of standard anthracycline-containing combination chemotherapy regimens. Based on promising phase II results, the Groupe Ouest Est d'Etude des Leucemies et Autres Maladies du Sang (GOELAMS) conducted a prospective phase III study in newly diagnosed PTCL comparing an alternating etoposide, ifosfamide, and cisplatin (VIP) and adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Sixty-five percent of patients had a confirmed diagnosis of PTCL-NOS. The investigators found that the VIP–ABVD regimen was more toxic and did not significantly improve 2- or 5-year event-free survival (EFS) as compared to CHOP. Additional groups have evaluated more intensive regimens, such as hyperC-VAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine), and have similarly reported no significant improvements relative to outcomes with CHOP. Several phase II studies have tested the use of alemtuzumab in combination with multi-agent chemotherapy in newly diagnosed PTCL, with reported high overall response rates (ORRs) of 60–90%; however, there were significant infectious complications, particularly when alemtuzumab was combined with fludarabine. Despite the infectious complications, the high activity with alemtuzumab-containing regimens prompted two ongoing phase III trials in Europe evaluating alemtuzumab plus CHOP as front-line therapy for PTCL. The Southwest Oncology Group (SWOG) evaluated the use of a gemcitabine-based regimen (platinum, gemcitabine, etoposide, and methylprednisolone (PEGS)) in newly diagnosed PTCL, with nearly one-half of study patients having a diagnosis of PTCL-NOS. Although tolerable, the PEGS regimen was not felt to be promising given the low ORR of 39% and a 2-year OS rate of only 30%. Finally, the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) retrospectively analyzed 343 patients with PTCL (22% PTCL-NOS) treated on phase II or III clinical trials and found that patients aged 60 and younger without an elevated LDH appeared to benefit from the addition of etoposide to CHOP (CHOEP), with significantly longer EFS and a nonsignificant trend toward improvement in OS. A Dutch trial incorporated CHOEP on a biweekly schedule as induction therapy prior to autologous stem cell transplantation with promising results, as discussed further in this chapter.

Thus, outside of a clinical trial, this 51-year-old with newly diagnosed advanced-stage PTCL-NOS should be offered front-line CHOP chemotherapy, with consideration for the addition of etoposide, as no other regimen has been proven to be more efficacious. However, given the relatively bleak outcomes of this disease with this approach, a clinical trial should always be offered if available.

The patient receives six cycles of CHOEP and enters a complete remission (CR) as evidenced by positron emission tomography and computed tomography (PET–CT) and repeat bone marrow examination.

• Should the treating oncologist recommend consolidation with high-dose chemotherapy and autologous stem cell transplantation (auto-SCT)?

Current data support the use of auto-SCT as consolidation therapy for patients with PTCL demonstrating chemosensitive disease following induction therapy, including PTCL-NOS. Recently, long-term results were reported from the Nordic Lymphoma Group's NLG-T-01 study, the largest prospective study to date evaluating upfront auto-SCT in PTCL. One hundred and sixty-six patients (mainly advanced stage, 39% with PTCL-NOS) with newly diagnosed PTCL (excluding ALK-positive ALCL, whose outcomes are favorable with conventional chemotherapy) were enrolled onto this multicenter study. Treatment consisted of dose-dense CHOEP (or CHOP for those over 60 years) given on a biweekly schedule, followed by auto-SCT for those achieving a partial remission (PR) or CR following induction. Using intention-to-treat analysis, with median follow-up of 60.5 months, the 3- and 5-year progression-free survival (PFS) rates were 48% and 44%, respectively; 3- and 5-year OS was 56% and 51%, respectively. The most impressive outcomes were seen in those patients with ALK-negative ALCL (5-year OS: 70%; PFS: 61%). Approximately one-fourth of patients experienced induction failure prior to transplant, and another 18% progressed or relapsed within the first 2 years of auto-SCT, with only 8% relapsing more than 2 years following transplant. These outcomes appear superior to the results of CHOP-like chemotherapy alone, which affords long-term survival rates on the order of 20–40% for the most common PTCL histologies. Retrospective analyses have reported even more favorable outcomes with upfront auto-SCT in PTCL, likely secondary to favorable patient selection, with long-

term PFS and OS ranging from 59% to 63% and from 62% to 63%, respectively, in several small series of mixed PTCL subtypes.

Clearly there is room for improvement, as substantial induction failures and frequent posttransplant relapses diminish the ability of PTCL patients to both undergo and receive benefit from auto-SCT. Across studies, approximately 25–40% of patients do not respond to induction therapy and thus never qualify for consolidative SCT. More effective induction strategies, as well as studies focused on eradicating minimal residual disease and preventing post-transplant relapse, are greatly needed. There are little data regarding the role of allogeneic stem cell transplantation (allo-SCT) in the frontline setting; however, it may be reasonable to consider allo-SCT for the rare PTCL subtypes, such as hepatosplenic T-cell lymphoma, that do not appear to benefit from conventional therapy or auto-SCT. There does, however, appear to be a long-term survival benefit for patients with the common histologic subtypes (PTCL-NOS, ALK-negative ALCL, and AITL) who undergo auto-SCT in first PR or CR, and this patient should therefore be offered consolidative auto-SCT.

Case study 53.2

A 49-year-old woman is referred for recommendations regarding her history of refractory, stage IIIB, ALK-negative anaplastic large-cell lymphoma (ALK− ALCL). Her treatment history includes six cycles of CHOP, and most recently three cycles of ifosfamide, carboplatin, and etoposide (ICE), with persistent biopsy-proven ALCL involving several retroperitoneal and inguinal lymph nodes. Her only medical comorbidity is well-controlled hypertension, and she continues to have an excellent performance status.

• What novel agents could be considered for this patient with refractory ALK− ALCL?

ALCL represents the second most common PTCL subtype seen in the United States. The disease is further characterized by the presence or absence of t(2;5)(p23;q35), which leads to fusion of the *ALK* gene on chromosome 2 with the *NPM1* gene on chromosome 5, resulting in overexpression of the anaplastic large-cell lymphoma kinase (ALK) protein. Several variant translocations involving *ALK* have subsequently been identified, but all partners result in expression of the ALK fusion protein. ALK-positive (ALK+) ALCL accounts for approximately 40–70% of all ALCL cases, with significant regional variation. ALK− ALCL is not always morphologically distinguishable from ALK+ ALCL, but is identified by the lack of ALK fusion protein. Cases of ALCL uniformly express strong CD30, and commonly express EMA, CD43, and CD4; CD3 is often absent.

Patients with ALK+ ALCL tend to be much younger (median ages: 34 vs. 58 years) than those with ALK− ALCL and have a strong male predilection. ALK+ ALCL has a clearly superior prognosis, with 5-year FFS and OS rates of 60% and 70% for ALK+ ALCL and 36% and 49% for ALK− ALCL, respectively, based upon the largest reported series of adult ALCL. Thus, many consider ALK+ and ALK− ALCL as two distinct diseases despite their morphologic similarities. As discussed in here, standard front-line therapy for ALCL consists of CHOP-like chemotherapy; however, if available, clinical trial enrollment is strongly preferred. Auto-SCT in first remission is recommended for transplant-eligible patients with ALK− ALCL, but does not clearly add benefit to the already favorable results with chemotherapy alone seen in ALK+ ALCL.

There is no standard salvage regimen for relapsed or refractory PTCL. Combination chemotherapy regimens commonly used as salvage for B-cell lymphomas have been routinely utilized in PTCL, with no available data regarding superior efficacy for any specific regimen. For patients with relapsed or refractory ALCL, the most exciting advance in recent years has been the development of brentuximab vedotin, a novel antibody–drug conjugate that targets CD30, delivering the anti-microtubule agent monomethylauristatin E. In August 2011, brentuximab vedotin was granted accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. Accelerated approval was based on the very favorable results of an international phase II study, where 58 patients with relapsed or refractory ALCL were treated with the single agent brentuximab vedotin, with remarkable response rates, including 57% achieving a CR. Common toxicities attributed to brentuximab vedotin include nausea, diarrhea, and peripheral neuropathy. The use of brentuximab vedotin for ALCL in the front-line setting in combination with multi-agent chemothotherapy is currently under study, as is the efficacy of brentuximab vedotin for patients with relapsed or refractory CD30-expressing NHL, including non-ALCL subtypes of PTCL.

Additional agents that have garnered FDA approval in recent years for relapsed or refractory PTCL include pralatrexate and romidepsin. Pralatrexate is a rationally designed, targeted antifolate that is similar to methotrexate but with greater affinity for the reduced folate carrier, leading to

(*Continued*)

selective accumulation in malignant cells. FDA approval for single-agent pralatrexate for relapsed or refractory PTCL was granted in September 2009, as a result of the response rates seen in the Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PROPEL) study. Of 109 evaluable patients with a mix of PTCL subtypes, the ORR was 29%, including 12 CRs (11%) and 20 PRs (18%). Thrombocytopenia, mucositis, and neutropenia are the most common grade 3 and 4 toxicities reported with pralatrexate. Romidepsin, a potent class 1 selective histone deacetylase inhibitor, was initially approved by the FDA in 2009 for cutaneous T-cell lymphoma. In 2011 romidepsin was approved for the treatment of patients with PTCL following at least one prior therapy, based on results of both an international phase II trial demonstrating an objective response rate of 25%, including a 15% CR and unconfirmed CR rate among 130 patients with relapsed or refractory PTCL, and a US National Cancer Institute–sponsored multicenter trial. Romidepsin was generally well tolerated, with nausea, fatigue, neutropenia, and thrombocytopenia being the most common adverse effects reported. Additional agents, such as bortezomib, lenalidomide, and bendamustine, are currently under investigation in the treatment of relapsed or refractory PTCL.

The patient described in this clinical vignette has ALK-negative ALCL that is refractory to at least one prior line of therapy. Thus, she is a candidate for brentuximab vedotin, which has been approved by the FDA for the treatment of systemic ALCL that has failed at least one prior combination chemotherapy regimen.

The patient receives brentuximab vedotin and enters a CR with a negative PET–CT. She continues to feel very well, with minimal neuropathy. A decision is made to proceed with a consolidative SCT.

- **What is the evidence for auto-SCT versus allo-SCT for patients with relapsed or refractory ALCL?**

In contrast to aggressive and/or intermediate-grade B-cell lymphoma, where high-dose therapy followed by auto-SCT has become the standard of care for relapsed or primary refractory disease, evidence from prospective randomized studies on salvage auto-SCT for PTCL is lacking. Multiple retrospective studies have evaluated auto-SCT for relapsed or refractory PTCL with conflicting results. These studies are limited by small populations of heterogeneous patients with varying histology, inclusion of patients receiving first-line auto-SCT, and varying patient follow-up. Additionally, selection bias due to the retrospective reporting of only those patients who actually received an auto-SCT further restricts the generalizability of these retrospective reports. Despite these limitations, subset analyses of patients with relapsed or refractory PTCL demonstrating chemosensitivity to second-line therapy reveal that salvage auto-SCT may be curative in a small proportion of patients. For example, in a series of 24 patients with relapsed or refractory PTCL of varying subtypes (excluding ALK-positive ALCL) who achieved PR or CR to second-line therapy and then underwent auto-SCT, 5-year PFS and OS were 24% and 33%, respectively.

The use of allo-SCT in relapsed or refractory PTCL has the advantage over auto-SCT of a potential graft-versus-lymphoma effect, albeit at the cost of increased toxicity. The largest series to date of allo-SCT in PTCL was reported in 2008 using data from the Société Française de Greffe de Moëlle-Thérapie Cellulaire (SFGM-TC) registry. Seventy-seven patients with confirmed PTCL who underwent allo-SCT between 1998 and 2006 were included; the majority of patients had ALCL or PTCL-NOS, and most received a myeloablative conditioning regimen (74%). It is not clear how many patients underwent allo-SCT in first remission versus relapse; however, 25% had received prior auto-SCT. Five-year treatment related mortality (TRM), EFS, and OS for all subtypes were 34%, 53%, and 57%, respectively. No significant differences were seen according to histopathologic subtypes or IPI score; however, more chemotherapy regimens prior to transplant and chemoresistant disease at transplant were both associated with worse outcomes. In a smaller, prospectively designed study, Corradini and colleagues (2004) demonstrated the efficacy of allo-SCT using a reduced-intensity conditioning (RIC) regimen in 17 patients with relapsed or refractory PTCL. 47% had failed upfront auto-SCT, and nearly all patients demonstrated chemosensitive disease prior to allo-SCT. With a median follow-up of 28 months, the estimated 3-year PFS and OS were 64% and 81%, respectively, with a very low TRM of 6%. Although these results warrant confirmation in larger prospective trials, they suggest that allo-SCT using a RIC regimen may result in reasonable long-term disease control and acceptable TRM in patients with relapsed or refractory PTCL.

Although limited by a lack of prospective randomized trials to better define the role of transplantation in relapsed or refractory settings, the currently available data support the use of allo-SCT in eligible patients as a reasonable option, with encouraging outcomes using RIC regimens. Therefore, this young, otherwise healthy woman with a history of refractory ALK− ALCL who has now achieved a CR with brentuximab vedotin should undergo evaluation for an allo-SCT as consolidation.

Case study 53.3

A 59-year-old woman presents with fever and an enlarging left inguinal lymph node. Her medical history is significant for stage IVB angioimmunoblastic T-cell lymphoma (AITL), diagnosed 3 years prior and treated with an intensive chemotherapy regimen that resulted in a CR. Inguinal lymph node biopsy confirms relapsed AITL, and additional work-up reveals the presence of bone marrow involvement.

• Should allo-SCT be considered for this otherwise healthy woman with relapsed AITL?

AITL is a PTCL subtype occurring primarily in older adults (median age: 65 years) and is more common in women than men. The typical morphologic presentation of AITL consists of partial or complete lymph node effacement by a polymorphous infiltrate of small to medium-sized cells admixed with a reactive population of small lymphocytes, histiocytes, plasma cells, and large lymphoid cells that are often infected by EBV. Between follicles, there is a proliferation of high endothelial venules. The neoplastic T-cells typically express CD4 or mixed CD4–CD8, CD10, CXCL13, and PD1, with hyperplasia of follicular dendritic cells and EBV+ CD20+ B-cells. AITL most commonly presents with advanced-stage disease and is frequently associated with autoimmune phenomena. In a minority of patients, AITL may follow an indolent course.

Historically, outcomes for AITL treated with conventional combination chemotherapy have been poor, with long-term OS rates of approximately 30%. Results appear to improve with the addition of high-dose therapy followed by auto-SCT in first remission; however, relapses remain problematic with this approach. For patients with relapsed disease, allo-SCT for transplant-eligible patients represents a viable option. In the largest published series, the European Group for Blood and Marrow Transplantation (EBMT) evaluated the outcomes of 45 patients who had undergone allo-SCT for AITL between 1998 and 2005. The median age was 48 years (range: 23 to 68 years); one-third had received at least two prior lines of therapy, and 15 patients had failed prior auto-SCT. Myeloablative conditioning was used slightly more frequently than RIC, and siblings were more commonly used than unrelated donors. Eight patients experienced disease relapse or progression after transplant, three of whom were salvaged with successful donor lymphocyte infusions or second allo-SCT. The 3-year PFS and OS for all patients were 53% and 64%, respectively, with a 1-year cumulative incidence of TRM of 25%. Intensity of the conditioning regimen was not associated with relapse rate or TRM; TRM also showed no association with age, donor type, or prior auto-SCT. Patients with chemosensitive disease at the time of allo-SCT had significantly better OS than those with refractory disease at the time of allo-SCT (81% vs. 37% at 3 years; $P = .002$).

For this patient with relapsed AITL, the optimal approach would be to proceed with salvage chemotherapy followed by allo-SCT, should she demonstrate chemosensitive disease. If she does not respond to salvage chemotherapy, overall outcomes are substantially inferior, and the use of a novel agent or regimen as part of a clinical trial may be preferred.

Case study 53.4

A 45-year-old Hispanic man is referred with a new diagnosis of ENKL, nasal type, with a large nasopharyngeal mass in addition to multiple axial skeletal lesions. He was noted to have a markedly elevated LDH, a normal albumin, and a mildly impaired performance status.

• What is the recommended treatment approach for newly diagnosed ENKL?

ENKL is a predominantly extranodal lymphoma representing up to 10% of all lymphomas in East Asia, but <1% in Western countries. The majority of cases originate in the nasal and paranasal region (60–90%), whereas a smaller proportion of patients may present with extranasal disease only. Phenotypic markers include CD2, cytoplasmic CD3, CD7, and CD56, as well as cytotoxic proteins such as TIA-1, granzyme B, and perforin, with frequent loss of CD3 and infrequent clonal rearrangement of the T-cell receptor genes. EBV is detected in nearly all cases, and is believed to play a role in lymphomagenesis. The median age of onset is 45–55, with a slight male predominance. Approximately 75% of nasal types present with localized disease, while extranasal ENKL most often presents with advanced-stage disease.

Major changes in the management of ENKL have occurred in the past few years based on the observations that radiation is a critical component of treatment and asparaginase is highly active in this disease. Prior to the early 2000s, there were no prospective clinical trials reported for ENKL; since then, however, there have been several practice-changing trials evaluating therapies for both localized and disseminated ENKL. Two early Korean studies evaluated the use of CHOP chemotherapy followed by involved-field radiation therapy (IFRT) in localized ENKL, and found that even with

(*Continued*)

dose-dense CHOP, the CR rate was 76%, and 3-year OS was only 67%. More recently, two prospective trials have reported superior results using concurrent chemoradiotherapy with the incorporation of non-multidrug-resistant (MDR) agents, as well as etoposide. The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted a phase I–II trial in newly diagnosed localized nasal ENKL, evaluating concurrent radiation therapy (RT) of 50 Gy and DeVIC (dexamethasone, etoposide, ifosphamide, and carboplatin). Twenty-seven patients were treated on the phase II portion of the study, with 2- and 5-year PFS and OS rates of 67% and 78%, and 63% and 70%, respectively. Subsequently, the Korean Consortium for Improving Survival in Lymphoma (CISL) conducted a multicenter phase II study evaluating cisplatin with concurrent RT of 40 Gy, followed by multiagent chemotherapy with VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone). Thirty patients were treated, with estimated 3-year PFS and OS of 80% and 86%, respectively. Notably, neither of these trials included central nervous system (CNS) prophylaxis or auto-SCT. The sum of these trials clearly establishes a role for RT in the management of localized ENKL with improved disease control and survival.

The prognosis of patients with advanced-stage nasal-type ENKL treated with conventional anthracycline-based chemotherapy is poor, with long-term OS rates of less than 20%. A collaborative group in East Asia therefore designed a novel induction chemotherapy regimen in 2004, composed of steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE). This regimen was evaluated in phase I and phase II studies that included newly diagnosed stage IV patients or those with disseminated or relapsed or refractory disease. In 38 evaluable relapsed patients, the ORR was 79%, with a CR rate of 45%. Grade 4 neutropenia and infection were frequent. Twenty-one patients underwent auto-SCT or allo-SCT after completing two cycles of SMILE. The 1-year OS was 55%, which was clearly superior to historical controls. A larger prospective study of 86 patients with newly diagnosed stage III–IV or relapsed or refractory disease who were ineligible for the phase II study reported similar results, with ORR of 81% and a CR rate of 66% after 1–6 cycles of SMILE. Twenty-four patients were transplanted after >2 cycles of SMILE. The estimated 5-year OS was 55%, with 4-year DFS of 64%. These results represent an impressive step forward in the treatment of disseminated ENKL. Questions remain regarding the role of transplantation in this disease, including the optimal timing and whether auto-SCT or allo-SCT leads to improved outcomes for various subsets of patients with ENKL.

The patient described in this clinical vignette is a young man with newly diagnosed, stage IV, nasal-type ENKL. He presents with a low albumin, which has been shown to be an unfavorable risk factor, but only a low-intermediate IPI score. Based on the presented data, he should be treated with the SMILE regimen.

Summary

Significant advances in the classification, description, and management of peripheral T-cell lymphomas have occurred in the past decade. However, these remain a very challenging set of heterogeneous diseases, and a key observation is that treatment paradigms geared toward aggressive B-cell lymphomas cannot be simply extrapolated to this population. Although many treatment approaches treat peripheral T-cell lymphomas as a single collective group, this will hopefully be refined so that more personalized management can be offered. The current generation of prospective trials and new agents being specifically developed for T-NHL hold promise that major advances with improved outcomes are forthcoming.

Selected reading

d'Amore F, Relander T, Lauritzsen GF, *et al*. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30:3093–9.

Dunleavy K, Piekarz RL, Zain J, *et al*. New strategies in peripheral T-cell lymphoma: understanding tumor biology and developing novel therapies. Clin Cancer Res. 2010;16:5608–17.

Kyriakou C, Canals C, Finke J, *et al*. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol. 2009;27:3951–8.

Le Gouill S, Milpied N, Buzyn A, *et al*. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol. 2008;26:2264–71.

Yang DH, Kim WS, Kim SJ, *et al*. Prognostic factors and clinical outcomes of high-dose chemotherapy followed by autologous stem cell transplantation in patients with peripheral T cell lymphoma, unspecified: complete remission at transplantation and the prognostic index of peripheral T cell lymphoma are the major factors predictive of outcome. Biol Blood Marrow Transplant. 2009;15:118–25.

PART 8

Plasma Cell Neoplasms and Related Disorders

CHAPTER 54

Smoldering multiple myeloma and monoclonal gammopathy of undetermined significance

Robert A. Kyle
Mayo Medical School, Rochester, MN, USA

Case study 54.1

A 58-year-old white female was hospitalized in November 1960 because of sudden low back pain while lifting. The hemoglobin was 12.4 g/dL. The serum protein electrophoretic pattern revealed a gamma spike of 1.4 g/dL. X-rays of the lumbar spine were negative. A bone marrow aspirate was diagnosed as multiple myeloma (MM). She was treated with chlorambucil and subsequently with urethane. The patient did not return for follow-up, but in November 1972 the hemoglobin was 13.4 g/dL and the beta-gamma spike (IgG lambda) was 1.9 g/dL. The bone marrow contained 10% plasma cells, and a metastatic bone survey was negative. There were no notable changes over the years.

She returned in April 1989 and was found to have a hemoglobin of 10.5 g/dL and a beta spike of 3.1 g/dL. A 24-hour urine specimen contained 270 mg of lambda light chain. A bone marrow biopsy revealed that 35% plasma cells and lytic lesions were present in a metastatic bone survey. An ultrasound examination revealed retroperitoneal nodes that upon biopsy showed a large-cell lymphoma [immunoglobulin M (IgM) kappa]. She was treated with cyclophosphamide, vincristine, and prednisone with some benefit but died in September 1990—30 years after a diagnosis of "multiple myeloma."

Comment: This woman was incorrectly diagnosed as having MM and treated with two ineffective agents without benefit. She remained asymptomatic with a diagnosis of monoclonal gammopathy of undetermined significance (MGUS), was untreated for almost 30 years, and then developed symptomatic multiple myeloma.

Mutiple choice and discussion questions

1. What is MGUS?

MGUS, introduced over 3 decades ago, is defined as the presence of a serum monoclonal (M) protein <3 g/dL, fewer than 10% monoclonal plasma cells in the bone marrow, no other B-cell proliferative disorders, and, most importantly, the absence of end-organ damage that can be attributed to the plasma cell proliferative disorder. End-organ damage is characterized by the presence of CRAB (hypercalcemia, renal insufficiency, anemia or bone lesions), which is related to the plasma cell proliferative disorder.

2. How is MGUS recognized?

Most cases are recognized when an M-spike is seen in the serum protein electrophoretic pattern when the patient presents with nondescript or no clinical symptoms. If a localized band or spike is found, immunofixation is needed to confirm the presence of an M protein. Patients should be screened for an M protein even if there is a low clinical suspicion of MM, Waldenström's macroglobulinemia (WM), amyloid light-chain (AL) amyloidosis, or a related disorder. In addition, some have recommended screening for MGUS in all patients with age-inappropriate osteoporosis or osteopenia.

3. What is the prevalence of MGUS in people ≥70 years of age in Olmsted County, Minnesota?

A. <1%
B. 2%
C. 5%
D. 10%

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

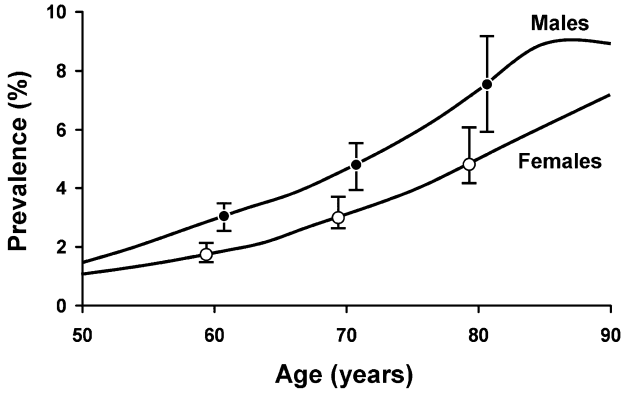


Figure 54.1 Prevalence of MGUS according to age. The "I" bars represent 95% confidence intervals. Years of age greater than 90 have been collapsed to 90 years (Source: Kyle, RA et al. NEJM. 2006;354:1362–9. Reproduced with permission of Massachusetts Medical Society).

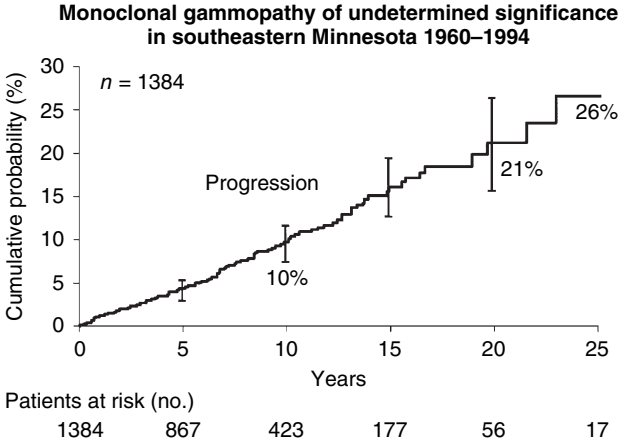


Figure 54.2 Probability of progression among 1384 residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) was diagnosed from 1960 through 1994. The curve shows the probability of progression of MGUS to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma (115 patients). The bars show 95% confidence intervals (Source: Adapted from Kyle RA *et al.* NEJM; 2002;346:564. Reproduced with permission of Massachusetts Medical Society).

MGUS was reported in 1–2% of adults in studies from Sweden, the United States, France, and Japan. The mean age at diagnosis is approximately 70 years, with fewer than 2% recognized before the age of 40 years. In Olmsted County, Minnesota, a population-based study involving 77% of residents who were 50 years of age or older (Figure 54.1) was performed. MGUS was found in 694 (3.2%) of this population. The prevalence was 5.3% in persons 70 years of age or older and 8.9% in men older than 85 years. The size of the M protein was $<1.5\,g/dL$ in 80% of the MGUS patients and $\geq 2\,g/dL$ in only 4.5%.

4. What is the cause of MGUS?

The cause of MGUS is not known. Radiation exposure, pesticides, obesity, and a familial element (which may be genetic or a shared environmental effect) may play roles.

5. What are the different classes of MGUS?

IgG constitutes about 70%, IgA accounts for about 10%, IgM is found in 15–20%, 3–5% have biclonal gammopathy of undetermined significance (two monoclonal proteins), and <1% are IgD. The clinical features of biclonal gammopathy are similar to those of MGUS. Kappa accounts for about two-thirds. The risk of progression of IgM MGUS was approximately 1.5% per year. Light-chain MGUS is defined as the presence of an abnormal FLC ratio with no heavy-chain expression and an increased concentration of the involved light chain. The prevalence of light-chain MGUS is 0.8% in Olmsted County.

6. What is the natural history of MGUS?

In a referral population of 241 patients seen at Mayo Clinic from 1956 to 1970, the actuarial risk of progression was 17% at 10 years, 34% at 20 years, and 39% at 25 years for a rate of approximately 1.5% per year. More than two-thirds of those who progressed developed MM. The interval from recognition of MGUS to the diagnosis of MM ranged from 1 to 32 years (median: 10.6 years). Only 6% were alive with no substantial increase of M protein after 3579 person-years of observation.

In order to eliminate the bias that occurs with referral populations, a population-based study of 1384 patients with MGUS from 11 counties of southeastern Minnesota were evaluated from 1960 to 1994. During a total of 11,009 person-years follow-up (median: 15.4 years; range: 0–35 years), MM, AL amyloidosis, WM, lymphoma with IgM monoclonal protein, plasmacytoma, or chronic lymphocytic leukemia developed in 8%. At 10 years, 10% had progressed; at 20 years, 21% had progressed; and at 25 years, 26% had progressed, for a rate of approximately 1% per year (Figure 54.2).

7. What are the risk factors for progression?

i. *Size of the M protein.* The size of the M protein at the time of recognition of MGUS is an important predictor of progression. Twenty years after recognition of MGUS, the risk of progression to MM or a related disorder was 14% for patients with an initial M protein value of $\leq 0.5\,g/dL$ and 49% in those with an initial M spike of $2.5\,g/dL$.

ii. *Type of serum M protein.* Patients who had an IgM or an IgA monoclonal protein had an increased risk of progres-

sion compared to those patients who had an IgG monoclonal protein ($P = 0.001$).

iii. *Bone marrow plasma cells.* The presence of more than 5% bone marrow plasma cells was an independent risk factor for progression; another study reported progression in 37% of those with an initial bone marrow plasmacytosis of 10% to 30%, compared to 6.8% when the plasma cell level was <10%.

iv. *Serum FLC ratio.* In a study of 1148 of the 1384 MGUS patients from southeastern Minnesota, we found an abnormal FLC ratio in 33%. The risk of progression in patients with an abnormal FLC ratio was higher than in patients with a normal ratio (hazard ratio = 3.5), and this was independent of the concentration and type of M protein.

Other features helpful in prognosis include the presence of abnormal plasma cells in the peripheral blood. A marked preponderance of abnormal plasma cells in the bone marrow as determined by flow cytometry is also associated with a significantly greater risk of progression to MM, as is reduction of uninvolved immunoglobulins. There is no convincing evidence at present that gene expression profiling predicts the risk of progression.

In our patients with elevated serum M protein ≥1.5 g/dL, the presence of IgA or IgM monoclonal protein and an abnormal serum FLC ratio had an absolute risk of progression at 20 years of 58% (high risk) compared to a risk of only 5% when none of these risk factors were present (low risk).

Plasma cell disorders developed in 10% of our southeastern Minnesota MGUS patients after 20 years of follow-up, while 72% had died of other causes (Figure 54.3).

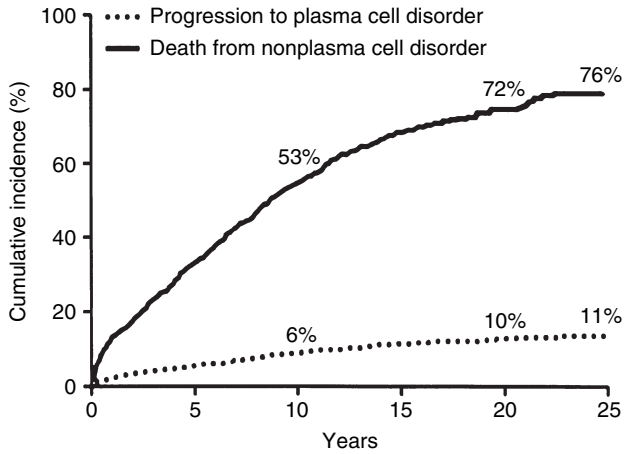


Figure 54.3 Rate of death from nonplasma cell disorders compared with progression to plasma cell disorders in 1384 patients with monoclonal gammopathy of undetermined significance (MGUS) from southeastern Minnesota (Source: Kyle RA, Rajkumar SV. Immunol Rev. 2003;194:112–39. Reprinted with permission of John Wiley & Sons).

8. What is the differential diagnosis of a patient with a monoclonal gammopathy?

A bone marrow aspirate and biopsy as well as a radiographic bone survey are suggested in all patients with an M protein ≥1.5 g/dL and in all patients who have abnormalities suggestive of a malignant plasma cell disorder in their complete blood count (CBC), calcium value, or creatinine level. Symptomatic MM is often associated with circulating monoclonal plasma cells in the peripheral blood, but this also occurs to a much lesser degree in MGUS. Fluorescence in situ hybridization (FISH) is not helpful in differentiating MGUS and MM because abnormalities may be found in both disorders.

9. How frequently is MGUS present prior to the diagnosis of multiple myeloma?

A. 20%
B. 50%
C. 80%
D. 100%

MM was recognized in 71 of 77,469 healthy adults enrolled in the nationwide population-based prospective prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial in which serially collected serum samples were obtained 2 to 9.8 years prior to the diagnosis of MM. MGUS was present in 100% 2 years prior to the diagnosis of multiple myeloma. At 5 years before the diagnosis of MM, 95% had an MGUS, whereas 82% had a recognizable MGUS for 8 or more years before the recognition of MM.

10. How often is MGUS recognized in an 80-year-old person in routine clinical practice at Mayo Clinic, Olmsted County, Minnesota?

A. 20%
B. 30%
C. 60%
D. 90%

At age 50 years, only 8% of the population with MGUS was recognized clinically. At 80 years of age, 33% of patients were recognized during routine clinical practice.

11. What is the duration of MGUS before it is recognized clinically?

A. Less than 1 year
B. 3 years
C. 5 years
D. 10 years
E. 15 years

We first determined the incidence of MGUS by using the MGUS prevalence data from Olmsted County, Minnesota, as well as follow-up of a large cohort of patients with clinically detected MGUS. The annual incidence of MGUS in

men was 120/100,000 population at the age of 50 years and increased to 530/100,000 at age 90 years. We estimated that 55% of men 70 years of age diagnosed as having MGUS had the condition for more than 10 years, and that 31% had MGUS for more than 20 years.

It is apparent that the increased prevalence of MGUS in older patients is not simply an accumulation of cases, but it is likely that the incidence of MGUS increases with advancing age. The clinician should keep in mind that in the majority of instances, the presence of a small MGUS is unrelated to the patient's current medical problem. We do not recommend screening for MGUS because there is no clinical benefit with screening and there are currently no known effective interventions for MGUS.

12. How does one manage MGUS?

At recognition of MGUS as well as at follow-up, the physician should be on alert for any symptoms or findings that suggest AL amyloidosis or MM. The CBC, serum calcium, and creatinine should be performed. If proteinuria is present, a 24-hour urine collection followed by electrophoresis and immunofixation is needed. Serum protein electrophoresis should be repeated 3–6 months after recognition because the M protein may represent an early MM or WM.

In patients with low-risk MGUS (serum M protein $<1.5\,g/dL$, IgG type, and a normal free light-chain ratio), the absolute risk of progression at 20 years is 5%, compared to 58% for the high-risk group. These low-risk patients may be followed at 3–5-year intervals.

Patients with high-risk MGUS have a serum M protein $>1.5\,g/dL$, an IgA or IgM isotype, or an abnormal FLC ratio. A bone marrow aspirate and biopsy and a metastatic bone survey should be performed. If the results of these tests are satisfactory, the patient should be followed with serum protein electrophoresis and a CBC in 3–4 months and, if stable, annually for life. Patients must always be told to contact their physician if there is any change in their clinical condition. Treatment is not indicated unless it is part of a clinical trial.

Smoldering (asymptomatic) multiple myeloma (SMM)

Case study 54.2

This 70-year-old male was found to have a hemoglobin value of 13.1 g/dL, an erythrocyte sedimentation rate of 86 mm/h, a gamma spike of 3.4 g/dL (IgG kappa), and a 24-hour urine specimen containing 0.3 g of kappa light chains in 1964. The bone marrow contained 16% plasma cells, but a metastatic bone survey was negative. The patient was not treated. He returned for regular visits but remained asymptomatic, and his laboratory studies were stable. In August 1983, the hemoglobin was 13.3 g/dL and the gamma spike was 2.7 g/dL. However, multiple lytic lesions were seen in the metastatic bone survey, and a compression fracture was present, but he had no bone pain. There were no clinical features of AL amyloidosis. His main medical problem was congestive heart failure from ischemic cardiomyopathy. He was not treated and died of refractory congestive heart failure in August 1984, but he did not develop bone pain. This patient represents SMM of 19 years duration.

13. What is SMM?

SMM is defined by the presence of an M protein $\geq 3\,g/dL$ and/or $\geq 10\%$ monoclonal plasma cells in the bone marrow but no evidence of end-organ damage. In a series of 276 patients with SMM, 59% developed SMM or AL amyloidosis during follow-up. The risk of progression was 10% per year for the first 5 years, was about 3% per year for the next 5 years, and after 10 years approached the 1–2% annual rate of MGUS (Figure 54.4).

In addition to the size of the serum M protein and number of bone marrow plasma cells, the FLC ratio (≤ 0.125 and ≥ 8) was an independent additional risk factor for progression.

Patients with one, two, or three risk factors (bone marrow plasma cells $\geq 10\%$, serum M protein $\geq 3\,g/dL$, and/or an abnormal FLC ratio) had progression rates of 25%, 51%, and 76% at 5-year follow-up.

14. How does one manage SMM?

At diagnosis, a CBC, calcium, creatinine, serum protein electrophoresis, and 24-hour urine collection for electrophoresis and immunofixation should be performed. A bone marrow aspirate and a metastatic skeletal survey are also required. The blood tests should be repeated in 2–3 months and, if stable, should be repeated every 4–6 months for one year; if still stable, the interval between evaluations can be lengthened to every 6–12 months.

Currently, the standard of care is observation, but patients at high risk of progression to symptomatic disease may benefit from lenalidomide and dexamethasone.

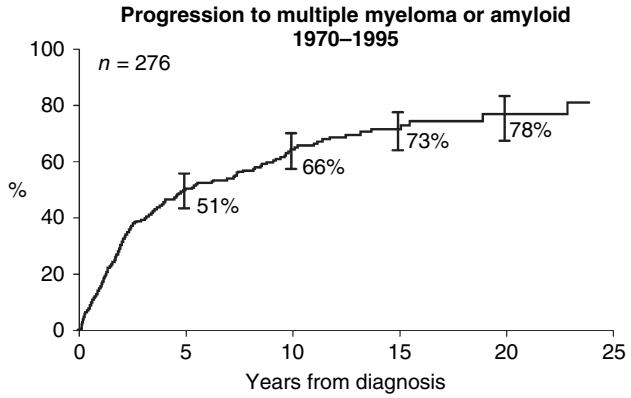


Figure 54.4 Probability of progression to active multiple myeloma or primary amyloidosis in patients with smoldering multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS). The "I" bar denotes 95% confidence intervals (Source: Adapted from Kyle RA, *et al.* NEJM. 2007;356:2582. Reproduced with permission of Massachusetts Medical Society).

15. What is idiopathic Bence Jones proteinuria [light-chain smoldering multiple myeloma (LC-SMM)]?

LC-SMM is defined as the presence of a monoclonal light chain in the urine $\geq$200 mg/day, the absence of an intact IgM protein (IgH expression) in the serum, and no evidence of MM, AL amyloidosis, or other related plasma cell disorders. This is the link between light-chain MGUS and LC-SMM. The cumulative probability of progression to active MM or AL was 20% at 5 years, 37% at 10 years, and 47% at 15 years.

The urine M protein ranged from 0.2 g daily to 4.7 g daily (median: 0.5 g/daily); 29% had >1 g daily. A monoclonal light chain was present in the serum on immunofixation in 62% of patients. The median bone marrow plasma cell level was 9% (range: 0–35%). The concentration of uninvolved (normal, polyclonal, or background) immunoglobulins was reduced in 62%. During 900 person-years of follow-up, 88% died. Twenty-seven patients developed symptomatic MM (relative risk: 140), and an additional seven patients developed AL amyloidosis (relative risk: 104). Thus, 93% have died or progressed. These patients do not require treatment and should be observed regularly in the clinic.

16. What is monoclonal gammopathy of renal significance (MGRS)?

MGRS is defined as a monoclonal gammopathy that does not meet the criteria of multiple myeloma but the monoclonal protein plays a prominent role in the pathogenesis of the disorder. It includes patients with light-chain deposition disease (LCDD), monoclonal immunoglobulin deposition disease (MIDD), light-chain proximal tubulopathy (with or without Fanconi syndrome), crystal-storing histiocytosis, heavy-chain deposition disease (HCDD), proliferative glomerulonephritis with monoclonal IgG deposits (usually IgG 3 kappa), and immunotactoid glomerulopathy. Therapy is indicated in these disorders despite the fact that they are characterized by small monoclonal immunoglobulins that do not constitute a diagnosis of MM.

Mutiple choice answers

Question 3: Answer C
Question 9: Answer D
Question 10: Answer B
Question 11: Answer E

Selected reading

Dispenzieri A, Katzmann JA, Kyle R, *et al*. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet. 2010;375(9727):1721–8.

Kyle RA, Therneau TM, Rajkumar SV, *et al*. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002;346(8):564–9.

Kyle RA, Therneau TM, Rajkumar SV, *et al*. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354(13):1362–9.

Landgren O, Kyle RA, Pfeiffer RM, *et al*. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009; 113(22):5412–7.

Therneau TM, Kyle RA, Melton LJ, 3rd, *et al*. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. Mayo Clinic Proc. 2012;87(11):1071–9.

CHAPTER 55

Risk stratification and response assessment in multiple myeloma and Waldenström's macroglobulinemia

Silvia Gentili[1] **and Sagar Lonial**[2]

[1]Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona, Ancona, Italy
[2]The Winship Cancer Institute of Emory University, Atlanta, GA, USA

Case study 55.1

A 59-year-old female is newly diagnosed with multiple myeloma (MM). Laboratory results show anemia, calcium and renal function that are normal, and an immunoglobulin A (IgA) kappa monoclonal protein that is 3.5 g/dl. The patient's β2-microglobulin (β2 m) is 3.1 mg/l and the albumin is 2.2 g/dl, so she has International Staging System stage II myeloma.

1. What is the role of the International Staging System (ISS) in the era of new drugs in MM?

A. It provides prognostic information
B. It is necessary in making therapeutic choices
C. It is considered to predict higher-risk disease
D. A and C

Multiple myeloma is a heterogeneous disease with variable disease courses, responses to therapy, and survival outcomes that range from less than 1 year in patients with aggressive disease to more than 10 years in patients with indolent disease presentation. Many studies have focused on the description of prognostic factors capable of predicting this heterogeneity in survival. Analysis of prognostic factors is essential to compare outcomes within and between clinical trials.

The Durie–Salmon Staging System (DSS) is used in patients with newly diagnosed MM to determine tumor burden and estimate survival. However, there are significant shortcomings with this system, correlated with the introduction of high-dose therapy and novel agents that are able to better reduce tumor burden, hence the need to introduce a new system.

At the present, the most widely applied prognostic system in myeloma is the International Staging System, which stratifies patients into three groups based on serum albumin and β2 m levels: stage I with β2 m < 3.5 mg/l and serum albumin ≥ 3.5 g/dl (median survival: 62 months); stage II, which is neither stage I nor stage III (median survival: 44 months); and stage III with β2 m ≥ 5.5 mg/l (median survival: 29 months).

Compared with the DSS, the ISS is more reproducible and easier to compute, and it reflects both patient and tumor factors, with β2 m being a measure of tumor bulk and renal function, while albumin is associated with the general state of the patient.

For the most part, the ISS has now replaced the Durie–Salmon staging system as it does represent a better way to assess outcomes. However, the ISS has some important limitations. A recent study demonstrated that in patients who are aggressively treated using upfront autologous stem cell transplantation (auto-SCT), the ISS does not improve the prediction of posttransplant outcomes compared with the DSS. The use of ISS to determine choice of therapy for individual patients remains unproven, and its validity with combination novel agent therapy still needs to be confirmed. We think the ISS should be supplemented and not necessarily supplanted. There is a clear need and consensus to add other markers to the ISS for predicting patient outcome. Avet-Loiseau *et al*. (2012) recently demonstrated that the combination of immunofluorescent in situ hybridization (iFISH) data with ISS significantly improves risk assessment in myeloma, versus ISS staging alone. Boyd *et al*. (2012) showed that by integrating the ISS and FISH lesions associ-

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

ated with short survival, it is possible to better identify a group of patients with a very poor outcome.

For a biologically heterogeneous disease, it is unlikely that any one clinical staging system can fully accommodate the factors that affect the outcomes.

Prior to the initiation of therapy, risk stratification of the MM helps predict the clinical course, although its use to risk adapt therapy decisions remains less clear. To this end, most clinicians agree that patients should be treated with the best induction regimen, and in the modern era of myeloma therapy, this typically represents a three-drug regimen using an immunomodulatory agent, a proteasome inhibitor, or both. The concept of how to best use genetic material identified at the time of initial diagnosis likely plays a major factor when considering how to approach maintenance therapy as all patients (standard or high risk) can achieve a major response following effective induction therapy; however, the durability of that remission is what may be risk dependent. As such, our group has adopted a risk-adapted maintenance strategy to prolong duration of remission and survival based upon the genetic risk at the time of diagnosis (Kaufman *et al*. 2012).

The incorporation of host factors, disease characteristics, serum free light chains (sFLCs), and radiography has been explored as possible additions to ISS to refine risk stratification. Age, performance status and comorbidities are prognostic factors and impact therapeutic decision making. It has been recently shown that, despite being enriched for higher-risk genetic subtypes, younger patients live longer, presumptively as a consequence of their ability to better tolerate treatment. Because of the lack of uniform availability of the data for analysis, which led to proposal of the ISS, there are a number of individual factors that still may have a significant role in identifying high-risk patients, such as lactate dehydrogenase, which was found to have significant influence in identifying risk. Baseline sFLC concentration may also provide useful prognostic information. Usmani *et al*. (2012) showed that extramedullary disease is more prevalent in genomically defined high-risk MM and, such as in other studies, is associated with shorter progression-free survival, even in the era of novel agents. Other features considered significant as individual factors are IgA, renal failure, and plasma cell leukemia, but if these features are sometimes useful, their general applicability is unknown, and there is a consensus that no change in treatment approach is currently indicated based on such single higher-risk features.

Regarding imaging, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI) probably also contribute meaningfully to prognostication. A recent study has reported that the presence of more than three fluorodeoxyglucose-avid focal lesions is the leading independent parameter associated with inferior overall and event-free survival. Walker *et al*. (2007) showed that the presence of focal lesions on MRI independently affected survival and that achieving MRI-directed complete remission has prognostic significance. But none of the imaging studies or results is currently recommended for inclusion in risk stratification.

However, it is essential that new prognostic indicators continue to be evaluated in prospective clinical trials.

This patient's initial diagnostic evaluation includes a unilateral bone marrow aspirate and biopsy evaluation with immunohistochemistry, cytogenetics, and fluorescence in situ hybridization (FISH).

2. What is the minimal FISH panel to stratify newly diagnosed MM patients?

A. t(4;14), del17p, and del(13q14)
B. t(4;14), t(14;16), and del17p
C. t(4;14), del17p, +1q21, and t(11;14)

There is a consensus that both cytogenetics and FISH play important and independent roles in risk stratification. The general purpose of risk stratification is not to decide time of therapy, but to prognosticate, and so it is applicable to newly diagnosed patients. Most myeloma experts recommend that either FISH or conventional cytogenetics, or preferably both, should be done at diagnosis in all patients.

Among all newly diagnosed patients, 15% harbor t(11;14), and in most series tested, it seems to be associated with a favorable outcome, but this effect is not strong enough to be statistically significant, and it may relate to heterogeneity within patients with t(11;14). In fact, some cases of MM with t(11;14) manifest with an aggressive phenotype such as plasma cell leukemia. Then, the global effect of t(11;14) on prognosis remains neutral. Translocation (4;14) is noted in about 15% of MM patients and has been associated with adverse prognosis in a variety of clinical settings. It does appear from an analysis performed by an Italian group that the use of bortezomib and an immunomodulatory agent at the time of diagnosis and in the setting of consolidation therapy (VTD) is able to overcome what has traditionally been the poor risk set of patients with t(4:14). This was also noted in an analysis of the TT3 series from Barlogie *et al*. (2007), where, in a much more intense treatment approach, the poor risk features of t(4;14) also appear to be eliminated. The significance of t(14;16) has recently been questioned. The Intergroupe Francophone du Myelome (IFM) group did not correlate this translocation with adverse survival, but several groups have shown that t(14;16) is associated with poor prognosis. Del(17p) is considered to be the most important molecular cytogenetic factor for prognostication, and in all series tested, it confers a very negative effect on survival. The prognostic influence of deletion 13 by iFISH was shown to disappear in the IFM study when patients

(*Continued*)

with simultaneous t(4,14) or del(17p) were excluded, indicating that the prognostic value of iFISH-detected deletion 13 was due to its frequent association with other known high-risk genetic abnormalities.

It is generally accepted that the t(4;14), t(14;16), and del 17p, demonstrated by FISH, confer an adverse outcome in myeloma. It has therefore been proposed that these abnormalities define "high-risk" myeloma, and at a bare minimum, a FISH panel for MM should include testing for t(4;14), t(14;16), and del 17p. There are some reports that the gain of 1q21 has been linked to adverse prognosis in a patient treated with tandem transplantation. However, its value as an independent FISH biomarker of adverse prognosis has not been validated by other groups. Recently, many studies have proposed that 1q analysis should be added to the diagnostic panel of FISH probes used in the routine assessment of prognosis in patients with MM. *Boyd et al*. (2012) demonstrated that t(4;14), t(14;16), t(14;20), +1q21 and del 17p can be used to define adverse prognosis in myeloma, and patients with the worst clinical outcome are identified by the cosegregation of more than one of these lesions. Another study recommended that the FISH testing panel should including testing for del 17p, chromosome 13 abnormalities, the five recurrent IgH translocations, and trisomy of any of the odd-numbered chromosomes; it was also showed that the presence of trisomies ameliorates the prognosis in patients with high-risk cytogenetics.

The expansion of a minimal panel to other probes may be desirable as it provides a more comprehensive assessment of the disease biology, clinical biology, clinical features, and likely outcome. Additionally, it is important that when FISH testing is performed, it is done using some method for identifying plasma cells in the mixed bone marrow aspirate. This can be done using light-chain staining to co-localize the FISH analysis on plasma cells, or using CD138 selection of plasma cells before performing FISH analysis. It is clear however, that if unselected FISH is performed, one runs the risk of incomplete staging as a negative result may be a false negative. The use of some plasma cell selection should be mandatory when assessing the risk status in a newly diagnosed myeloma patient.

Finally, recent reports suggested that novel approaches based on microarray technology should be used to achieve a more powerful prediction. Shaughnessy *et al*. (2007) have identified in 532 newly diagnosed myeloma patients, a set of 70 genes linked to shorter durations of complete remission, event-free survival, and overall survival. Decaux *et al*. (2008) also demonstrated in 182 patients that a set of 15 genes was able to identify the patients with the poorest prognosis. It is interesting to note that, although both these studies have included patients undergoing high-dose therapy, the 17 and 15 gene models do not share common genes. Novel gene expression profiling could be developed in the future, and it would be useful in risk stratification.

Case study 55.2

A 71-year-old male patient is newly diagnosed with symptomatic MM for the presence of bone disease detected by body X-ray and MRI. His laboratory results show an IgG kappa monoclonal protein that is 3.7 g/dl and a free light-chain (FLC) ratio that is 131. After completing six cycles of bortezomib-based therapy, his M-component protein has fallen to 0.5 g/dl, and his FLC ratio is normal.

1. Should be the sFLC assay be used to assess response in all MM patients?

A. Yes

B. No

The European Group for Blood and Bone Marrow Transplant, International Bone Marrow Transplant Registry, and American Bone Marrow Transplant Registry (EBMT–IBMTR–ABMTR) criteria were updated by the International Myeloma Working Group (IMWG) in 2006, and further modifications were subsequently proposed. The IMWG recognized the need for uniformity and published uniform response criteria that are to be used in future clinical trials.

Changes in the M-component level are the principal indicators used for response evaluation. The IMWG uniform response criteria were developed similarly to the EBMT criteria, and the major response categories, as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were maintained. CR is a negative immunofixation on the serum and urine, the absence of any plasmacytoma, and <5% bone marrow plasma cells. PR is a greater than 50% reduction of serum M-component and a greater than 90% reduction in 24 h urinary M-protein, or it is less than 200 mg in 24 h. The PD criteria require more than a 25% increase in the M-spike in monoclonal protein, but it has to be at least 0.5 g/dl if we are talking about a serum M-spike, and it has to be at least 200 mg/24 h if we are talking about a urine M-spike. The development of new bony disease or the observation of a new plasmacytoma and the development of hypercalcemia are also criteria for progression of disease. SD includes not meeting the criteria for CR, PR, or PD. The IMWG added two new response categories: very good partial remission (VGPR) and stringent complete response (sCR). The VGPR

category is a useful measure of depth response. It identifies patients with excellent responses that may have outcomes similar to those of patients considered to be in CR compared to those who merely have 50% reduction in their serum M-spike. So this requires a serum and urine M-protein detectable by immunofixation but not electrophoresis, or a more than a 90% reduction in serum M-protein and in 24 h urinary M-protein, or it is less than 100 mg in 24 h. The sCR category arises from the need to assess the exact magnitude of response in the era of new drugs, whereas CR was rarely observed with old conventional therapy. So sCR is defined as CR plus a normal SFLC ratio and the total absence of plasma cells in bone marrow by immunohistochemistry or immunofluorescence. This category has been refined recently to incorporate the use of flow cytometry to detect minimal residual disease on the basis of the presence of an aberrant immunophenotype. Low levels of residual disease may also be demonstrated using allele-specific polymerase chain reaction (PCR), and a further new category of molecular CR is proposed that is defined as the absence of disease by sequence-specific PCR methods with a sensitivity of 10^5. The minimal response (MR) category should be also reported separately in clinical trials for patients with relapsed or refractory myeloma.

Another important issue is the addition of response criteria for the patients with oligo-secretory or nonsecretory myeloma using the FLC assay. It is important to note that the FLC assay should not be used to assess response in patients with measurable levels of M-protein in either serum or urine. It has been shown that FLC response after 2 months of therapy is superior to early M-protein measurement to predict overall response, but it does not predict for overall or progression-free survival, and serial measurements of FLC do not appear to have added value in patients who have M-proteins measurable by electrophoresis.

Finally, the IMWG included a new category of clinical relapse, which reflects the fact that PD as defined does not necessarily indicate a need for further therapy, but should be evaluated by the presence of CRAB features (calcium elevation, renal insufficiency, anemia, and bone abnormalities) to identify progression requiring intervention.

These criteria will most probably change with time as the technology improves and more sensitive tests become available.

2. Is there a role for functional imaging methods in the response assessment for this patient?

A. Yes
B. No

In MM, the introduction of novel agents has allowed the achievement of unprecedented high rates of CR in patients, especially in young patients, a gain that translated into extended progression-free survival and overall survival. As a consequence, interest in the evaluation of the depth of response beyond the conventionally defined CR level has progressively grown. At the present, magnetic resonance imaging (MRI) and positron emission tomography (PET) with computed tomography (PET–CT) have increasingly important roles in the diagnosis and management of patients with MM, and in the near future, whole-body X-ray may be replaced by this more sensitive technique. In addition, these functional imaging methods have been proposed as an additional tool to increase the definition level of CR and to identify the persistence of residual disease outside of the bone marrow level.

MRI is the elective imaging technique for assessing the degree of bone marrow plasma cell infiltration. By using MRI in MM, it is possible to recognize five different patterns of marrow involvement and, between these, focal and diffuse patterns were associated with a higher tumor burden and reduced overall survival in MM patients. Moulopoulos *et al*. (1994) reported that a change in MRI pattern may correlate with response to therapy. Lecouvet *et al*. (2001) showed a significant correlation between an index for the assessment of spine MRI changes after transplant and treatment response. Walker *et al*. (2007) demonstrated that the resolution of lesions in MRI after total therapy is to be associated with a better prognosis. Hillengass *et al*. (2012) found an agreement between serological response and post-ASCT number of focal lesions detected by MRI.

PET–CT is an excellent imaging tool to monitor the response to treatment, owing to its ability to distinguish between active disease and fibrotic lesion. Recent studies have demonstrated that normalization of PET–CT correlated well with high-quality responses to therapy and that PET negativity preceded the achievement of conventionally defined CR, while a normal MRI pattern was reached later on. Combining PET–CT with laboratory data improves the accuracy of prediction of relapse and progression compared with each test alone.

However, based on the currently available evidence, the IMWG agreed that MRI and PET–CT findings will not be incorporated formally into the response criteria for the purposes of assessing depth of response, but a first approach should ideally be made within the context of a clinical trial.

In conclusion, further studies, with the inclusion of newer imaging techniques in future trials, are needed before the recommendation of using these functional imaging methods for assessing and monitoring responses to therapy.

Case study 55.3

A 63-year-old male patient, newly diagnosed with symptomatic MM, is treated with four cycles of bortezomib, thalidomide, and dexamethasone, and he achieves a CR. After induction, he goes to auto-SCT. He develops an sCR, and he continues only his treatment of bone disease with bisphosphonate zoledronic acid, but after only 9 months, he relapses.

1. What is the current role of minimal residual disease (MRD) assessment in MM?

A. It is useful to assess the depth of response
B. It provides prognostic information
C. It is necessary to evaluate the potential benefits of consolidation therapies
D. It is an exploratory endpoint in myeloma

In most hematologic malignancies, the quality of response to treatment, particularly achieving CR, is strongly associated with longer survival.

For many years, the major goal of MM therapy was to achieve PR or SD. With the introduction of high-dose therapy plus auto-SCT (HDT–auto-SCT) and novel agents upfront, the new goal became the achievement of CR. So CR may be defined as a surrogate marker for predicting outcome, and in the contest of transplant setting or in elderly patients treated with novel agents, the achievement of CR is associated with prolonged survival. Nevertheless, the current definition of CR is not fully satisfactory, and it presents some limitations such as low sensitivity; in fact, the amount of M-component does not directly reflect the residual tumor burden, as it only measures the product of secreting clone, and probably not all MM-plasma cells are secretory. Another pitfall of using the M-component to define CR is the prolonged clearance of residual immunoglobulins.

In conclusion, the definition of CR is suboptimal and requires further improvements both outside the bone marrow with imaging techniques such as MRI and PET–CT and at the bone marrow level.

MRD monitoring is defined as any approach aimed at detecting and possibly quantifying residual tumor cells beyond the sensitivity level of routine imaging and laboratory techniques. MRD can be assessed using several different approaches such as qualitative and real-time quantitative polymerase chain reaction (PCR) or multiparameter flow cytometry (MFC).

Ladetto *et al*. (2010) demonstrated that the achievement of MRD negativity by real-time quantitative PCR (RQ-PCR), following consolidation therapy, is associated with better outcomes in terms of PFS and OS; and that a dynamic increase in molecular tumor burden, detectable by RQ-PCR, predicts late-disease relapses several months before clinical recurrence. It is also important to note that the major predictive value of RQ-PCR is after consolidation but not at diagnosis and after auto-SCT, probably because the response level obtained at the end of the whole treatment is the most important outcome predictor. This suggests that even patients not achieving a maximum cytoreduction after ASCT have a good outcome if they achieve a major reduction in tumor burden after consolidation.

Paiva *et al*. (2008) showed, in a large series of uniformly treated patients with MM, that MRD evaluation by MFC 100 days after auto-SCT was the most relevant prognostic factor, and that the PFS and OS of patients with residual tumor plasma cells was shorter than those of patients with no detectable residual tumor cells. Recent study has also valuated the clinical impact of the immunophenotypic CR in the context of patients with high-risk cytogenetic disease; a Spanish group has reported that the presence of baseline of t(4;14), t(14;16), or del(17p) by FISH, and persistent MRD detected by MFC 100 days after auto-SCT, allows one to identify patients in CR at risk of early progression after HDT–auto-SCT. Thus, those two features were the only independent factors that predicted unsustained CR.

In MM, the most suitable method for MRD detection remains controversial. PCR is still slightly sensitive, although with the introduction of eight-color clinical flow cytometers, the sensitivity of immunophenotyping may reach a level similar to that of allele-specific oligonucleotide PCR (10^5 to 10^7). MFC is simpler, applicable to virtually all patients, fast, less expensive, and more usable in routine laboratory practice. The two approaches have been compared exclusively in a small single-center investigation, and neither was found to be definitively superior. So, at the present time, PCR and MFC should be regarded as complementary tools.

In conclusion, MRD evaluation by PCR or MFC seems to be a very useful technique for identifying patients who may be at risk of progression. Moreover, this analysis can contribute to the evaluation of the potential benefits of consolidation therapies. It is possible to monitor residual disease levels and to assess efficacy of treatment. Both techniques could identify two risk categories of patients with MM, based on the level of clonotypic plasma cells ($>10^4$ cells, high risk; $<10^4$ cells, low risk), who had significantly different outcomes. In the near future, the inclusion of MRD detection in the context of multicenter clinical trials as a secondary endpoint will allow a better comprehension of its prognostic power.

Case study answers

Case study 55.1

Question 1: Answer D
Question 2: Answer B

Case study 55.2

Question 1: Answer B
Question 2: Answer B

Case study 55.3

Question 1: Answer D

Selected reading

Cavo M, Rajkumar SV, Palumbo A. International Myeloma Working Group (IMWG) consensus approach to the treatment of multiple myeloma patients who are candidates for autologous-stem cell transplantation. Blood. 2011;117(23): 6063–73.

Dimopoulos M, Terpos E, Comenzo RL, *et al*. International Myeloma Working Group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple myeloma. Leukemia. 2009; 23:1545–56.

Fonseca R, Bergsagel PL, Drach J, *et al*. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210–21.

Ludwig H, Durie BG, Bolejack V, *et al*. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10,549 patients from the International Myeloma Working Group. Blood. 2008; 111:4039–47.

CHAPTER 56

Treatment of multiple myeloma

Cindy Varga, Claudia Paba Prada, Kenneth Anderson, and Paul Richardson
Dana-Farber Cancer Institute, Boston, MA, USA

Prognostic markers

Introduction

Multiple myeloma is a heterogeneous disease with both patient- and tumor-specific factors playing a role in predicting outcome. Overall survival in multiple myeloma is variable, with a current median of 7 to 10 years. Understanding both host- and tumor-derived factors is crucial for risk stratification, predicting outcome, and thus optimizing choices in therapy.

Prognostic markers can provide information about the aggressiveness of underlying disease and provide an assessment of risk when selecting potential treatment regimens.

Case study 56.1

A 64-year-old man presented to the emergency room with persistent lower back pain over a period of one month. X-rays of his thoracic and lumbar spine demonstrated the presence of compression fractures of the T12 and L1 vertebral bodies. Magnetic resonance imaging (MRI) of the spine revealed the presence of a large paraspinal soft tissue mass measuring 5.0 × 3.4 cm without evidence of spinal cord compromise. A biopsy of the soft tissue mass was consistent with plasmacytoma. Bone marrow biopsy revealed the presence of 70% CD138+ plasma cells. Initial laboratory studies were remarkable for a hemoglobin of 10.1 g/dl and an elevated total protein of 10.9 g/dl with an albumin level of 3.1 g/dl. Serum protein electrophoresis with immunofixation revealed an immunoglobulin G (IgG) kappa M-spike of 5.09 g/dl. The IgG level was elevated at 6510 mg/dl, and serum free kappa light chain was 822 mg/L with a K:l ratio of 94.7. B2 microglobulin was elevated at 5.6 mg/L. Renal function was within normal limits.

1. Which of the following parameters comprise Durie–Salmon (DS) staging? (Choose all that apply.)

A. Serum paraprotein level
B. Hemoglobin
C. Lactate dehydrogenase (LDH)
D. Albumin
E. Serum free light chain (SFLC) ratio
F. Beta-2 microglobulin
G. Creatinine
H. Total protein
I. Urinary light chains
J. Number of lytic bone lesions

The DS system of staging became a standard in multiple myeloma in 1975. Using multivariate regression analyses, it was demonstrated that tumor burden could be predicted by the (i) extent of bone involvement, (ii) level of hemoglobin, (iii) serum calcium levels, and (iv) paraprotein type or level in both serum and urine. Creatinine level (substage A: serum creatinine <2 mg/dL; and substage B: serum creatinine ≥2 mg/dL) further subclassified patients into lower and higher risk within the three stages of tumor mass.

2. What important prognostic parameters make up the International Staging System (ISS) for multiple myeloma?

A. Serum paraprotein level
B. Hemoglobin
C. LDH
D. Albumin
E. SFLC ratio
F. Beta-2 microglobulin
G. Creatinine

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

H. Total protein
I. Urinary light chains
J. Number of lytic bone lesions

In 2005, clinical and laboratory data were gathered on 10,750 previously untreated symptomatic patients with multiple myeloma from 17 different institutions worldwide. Possible prognostic factors were evaluated by univariate and multivariate analyses. The combination of both serum beta-2 microglobulin and serum albumin provided the simplest method of separating disease burden into three stages (stage I: B2M <3.5 mg/L, Alb ≥ 3.5 g/dL; stage II: neither stage I nor III; stage III: B2M ≥ 5.5 mg/L). The median survival for each stage was found to be 62 months, 44 months, and 29 months, respectively. The ISS demonstrated reproducibility and effectiveness in patients of various geographical locations (North America, Europe, and Asia) and across all age groups.

Case study 56.1 *continued*
Cytogenetic studies including fluorescent in situ hybridization (FISH) were performed on the bone marrow aspirate from the patients, and these identified a translocation between chromosomes 4 and 14 (t(4;14)) in 48% of the cells analyzed as well as a 17p deletion in 42% of cells analyzed.

3. What are the main cytogenetic abnormalities described in multiple myeloma?

There is increasing evidence that genetic heterogeneity is a primary driver of disease biology. Broadly, the genetic makeup of myeloma can be divided into two subtypes, hyperdiploid and non-hyperdiploid, with the former being generally more favorable than the latter. Hyperdiploid refers to the gain of various odd-numbered chromosomes in the clonal cell population, especially 3, 5, 7, 9, 11, 15, 19, or 21. This is observed in 50% to 60% of patients. Non-hyperdiploid encompasses hypodiploidy as well as a higher composition of translocations involving the immunoglobulin heavy-gene (IgH) locus of chromosome 14. The main IgH translocations in myeloma are t(11;14), t(4;14), t(14;16), t(6;14), and t(14;20).

Loss or deletion of chromosome 13 (del 13q) can be seen in almost 15% of patients by conventional cytogenetics and in as many as 50% by FISH analysis. In addition, one of the most important unfavorable molecular cytogenetic factors for prognostication is the 17p deletion found in 5–10% of patients.

At the Mayo Clinic, newly diagnosed myeloma patients are stratified into standard-, intermediate-, and high-risk disease using the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) classification.

4. What genetic abnormalities make up the standard-risk group? (Choose all that apply)

A. t(4;14)
B. t(11;14)
C. t(6;14)
D. t(14;20)
E. del 17p
F. Hyperdiploidy
G. Hypodiploidy
H. del13

t(11;14)
In general, patients with t(11;14) tend to have a less aggressive disease course with longer response durations and greater overall survival (OS). Since the introduction of novel agents, OS has improved broadly, and improvement in the prognosis of patients with both very adverse and less adverse cytogenetics have also become better. The incidence of t(11;14) ranges from 10% to 30% in patients with IgG, IgA, IgD, and lambda light-chain myeloma and results in the upregulation of cyclin D1. It is associated with CD20 expression, lymphoplasmacytic morphology, nonsecretory disease, and a serum monoclonal protein of less than 10 g/L (1 g/dL).

Hyperdiploidy
Patients with hyperdiploidy tend to have a more indolent course with longer treatment responses and OS. In a multivariate analysis of 208 patients, a non-hyperdiploid karyotype was the most significant adverse prognostic factor influencing OS. When compared with non-hyperdiploid myeloma, hyperdiploidy had significantly longer median OS (34 vs. 13 months).

Mutiple choice questions

1. What is the median overall survival of patients classified as standard risk?

A. 12 months
B. 24 months
C. 42 months
D. 80 months

Overall, patients with standard-risk myeloma have a median OS of 7 years.

2. What genetic abnormalities make up the intermediate-risk group? (Choose all that apply)

A. t(4;14)
B. t(11;14)
C. t(6;14)
D. t(14;20)
E. del 17p
F. Hyperdiploidy
G. Hypodiploidy
H. del13

t(4;14)

Several studies have shown that t(4;14) is associated with poor OS. Jaksic *et al*. (2005) determined that t(4;14)-positive patients are chemotherapy sensitive with 90% of patients achieving a partial response to VAD (vincristine, doxorubicin, and dexamethasone) therapy; however, early progression was common, with 26% of patients progressing before transplant and a median progression-free survival of only 14.1 months after transplant. More importantly, at relapse, resistance to alkylating agents was observed.

With the introduction of novel agents, San Miguel *et al*. (2008) compared the use of melphalan and prednisone with or without bortezomib in untreated patients with multiple myeloma who were ineligible for high-dose therapy. The efficacy of bortezomib therapy was evaluated in 26 patients with high-risk cytogenetics specifically, (t(4;14),t(14;16) translocation or 17p deletion). When compared to 142 patients with standard-risk cytogenetics, patients with t(4;14) had similar complete response rates (26%) with similar times to progression ($P = 0.55$) and OS ($P = 0.99$). It was concluded that the adverse prognosis of t(4;14) could be overcome with bortezomib therapy, and lenalidomide-based regimens have similarly been reported to be active in such patients; hence, this abnormality is now classified as intermediate risk rather than high risk in the 2012 update on the management and risk stratification of multiple myeloma.

Del 13q14

The presence of a 13q14 deletion used to be associated with significantly worse prognosis. This adverse prognostic factor was found to be independent of chemotherapy or high-dose therapy using single or tandem autologous transplantation, with multivariate analysis confirming the independent predictive value of 13q14 deletions for shortened survival. Its presence was also associated with a lower rate of response to chemotherapy. Deletions of 13q14 correlate with increased proliferative activity. However, the adverse prognostic impact of del(13) is less pronounced when detected by FISH than by conventional cytogenetics, which may be related to the potentially greater association between elevated plasma cell proliferation and del13 detected by metaphase cytogenetics. Treatment incorporating bortezomib may overcome the negative prognostic effects of del13 and produce outcomes independent of this mutation. Therefore, although previously considered high risk, as in t(4;14), deletion 13 is now classified as intermediate risk in the 2012 update on the management and risk stratification of multiple myeloma.

Hypodiploidy

Historically, patients with hypodiploid content had poorer responses to chemotherapy and shorter OS in several studies. Using univariate analysis, Smadja *et al*. (2001) found that among all the different chromosomal abnormalities, the chromosome number was the most important prognostic factor, with a median OS of 33.8 months for hyperdiploid patients compared with 12.5 months for hypodiploid patients ($P < .001$).

3. What is the median overall survival of patients classified in the intermediate-risk group?

A. 12 months
B. 24 months
C. 42 months
D. 80 months
E. 100 months

Overall, patients with intermediate-risk myeloma have a median OS of 42 months.

4. What genetic abnormalities make up the high-risk group? (Choose all that apply)

A. t(4;14)
B. t(11;14)
C. t(6;14)
D. t(14;20)
E. del 17p
F. Hyperdiploidy
G. Hypodiploidy
H. del13
I. t(14;16)

17p13

Although deletion of 17p is less frequently found in myeloma patients as compared to other malignancies, it continues to be a poor prognostic factor. The presence of 17p mutation is associated with significantly shorter OS (median 24.7 months), with serum levels of both beta 2-microglobulin and calcium higher in patients with deletion 17p, and a significant association with soft tissue plasmacytomas, as well as central nervous system involvement in rare instances.

t(14;16)

An initial series reported that t(14;16) was associated with a poor prognosis, despite the early incorporation of chemotherapy agents and tandem autologous transplantation. This translocation is associated with more aggressive underlying disease activity.

5. What is the median OS of patients classified in the high-risk group?

A. 12 months
B. 24 months
C. 42 months

D. 60 months
E. 100 months

High-risk multiple myeloma has a median OS of approximately 25 months. Interestingly, the coexistence of trisomies in high-risk myeloma can improve its negative prognosis, presumably because of grater genetic instability.

6. What is the prognostic significance of chromosome 1 abnormalities in multiple myeloma?

Chromosome 1 abnormalities are quite prevalent in patients with multiple myeloma and have been recently proposed as an important prognostic factor. Numerous studies have shown that abnormalities of both the short and long arms of chromosome 1 were associated with shorter survival. Multivariate analysis revealed that Amp1q21 was an independent adverse prognostic factor, associated with both rapid disease progression and poor outcome.

7. In which risk group does the patient in Case study 56.1 belong based on his cytogenetics?

A. Standard risk
B. Intermediate risk
C. High risk

The presence of the del17p13 mutation automatically places the patient in Case study 56.1 in the high-risk group. He is at risk of inferior response and shorter OS.

8. What is the role of SFLC as a prognostic factor in multiple myeloma?

An abnormal kappa–lambda free light chain (FLC) ratio is a sensitive marker for the degree of clonal expansion by malignant plasma cells. Studies have shown that patients with monoclonal gammopathy of unknown significance (MGUS) or smoldering multiple myeloma and who have an abnormal FLC ratio have a scientifically higher risk of disease progression. Patients who were found to have an abnormal FLC ratio (<0.03 or >32) have a significantly shorter OS when compared with patients with an FLC ratio between 0.03 and 32 (30 vs. 39 months, respectively). The patient in Case study 56.1 clearly has an abnormal ratio of 94.7.

Front-line therapy in symptomatic multiple myeloma

Myeloma diagnosis is broadly defined by the presence of 10% or more clonal plasma cells in the bone marrow and/or the presence of plasmacytomas that secrete a monoclonal immunoglobulin in serum and urine. Initiation of treatment should be considered for patients who have disease-related symptoms or evidence of organ dysfunction such as hypercalcemia (calcium level >11.5 g/dL), renal insufficiency (creatinine >2 mg/dL), anemia (hemoglobin <10 g/dL or 2 g< normal), and bone disease (lytic lesions, osteopenia, or osteoporosis). Patients with repeated infections and associated secondary hypogammaglobulinemia, or light-chain amyloidosis, should also be considered for systemic therapy. The approach to treatment is based on patient characteristics, including age, functional status, comorbid medical conditions, and risk stratification, which in turn determine eligibility for specific approaches such as high-dose chemotherapy and autologous stem cell transplantation (auto-SCT). The treatment outcomes of patients with multiple myeloma have significantly improved over the last decade with the introduction of novel, targeted therapies including proteasome inhibitors (such as bortezomib) and immunomodulatory drugs (iMIDs), including lenalidomide and thalidomide, all of which have improved OS from 3–4 to 7–10 years. The goal of induction therapy is to cytoreduce and consequently reduce organ impairment caused by monoclonal protein and plasma cell infiltration. Assessment of response is measured by a reduction in the concentration of the m-protein in the serum and/or urine and a decrease in the size of plasmacytomas, with the International Myeloma Working group and the European Group for Blood and Bone Marrow transplantation having established response criteria in this setting. Complete remission is considered an important treatment endpoint and represents an strong predictor of long-term outcomes.

Case study 56.2

A 56-year-old woman presented with a 4-week history of mid- and lower-back pain. She also reported progressive fatigue and dyspnea on exertion over the past 6 months. Initial X-rays of the spine demonstrated compression fractures of the T8 and T10 vertebral bodies. Laboratory studies were notable for anemia with a hemoglobin level of 8.4 g/dl. Her calcium level was normal as well as her kidney function. Serum protein electrophoresis with immunofixation revealed an IgG Kappa M-spike of 6.57 g/dl. Urine protein electrophoresis showed proteinuria with an Ig kappa monoclonal protein of 485 mg/L in 24 h. Beta 2 microglobulin was 6.0 g/dl, and albumin was 3.5 g/dl. Her bone marrow biopsy revealed 60% clonal plasma cell involvement. Cytogenetics studies revealed the presence of 13q deletion by metaphase analysis, and FISH was positive for 17p deletion in 15% of cells.

(*Continued*)

1. What is the most appropriate next step in the management of this patient?

A. Lenalidomide and dexamethasone
B. Melphalan, prednisone, and thalidomide
C. Lenalidomide, bortezomib, and dexamethasone
D. Carfilzomib and dexamethasone

Initial therapy for this patient should be based upon the fact that she is an auto-SCT candidate and she has high-risk disease based on her clinical stage and unfavorable cytogenetics, including del13q and del17p. Best choices for induction therapy are typically three-drug combinations, and the use of lenalidomide, bortezomib, and dexamethasone is one such approach, as this is a highly active regimen across all risk groups and is generally well tolerated. Lenalidomide and dexamethasone, while well tolerated and active, would not be sufficient without proteasome inhibition in this patient. Stem cell–toxic regimens that include melphalan should be avoided in patients who are candidates for auto-SCT since these interfere with adequate stem cell mobilization and contribute to genotoxic injury. Carfilzomib and dexamethasone are not yet approved for front-line therapy in multiple myeloma patients, but are approved for the treatment of relapsed and refractory disease, although the combination of carfilzomib, lenalidomide, and dexamethasone has shown considerable promise in early-phase studies in this setting.

Treatment strategies

Induction therapy for transplant-eligible patients

Patients with standard-risk disease can be treated with two or three drugs that include bortezomib or an iMID such as thalidomide or lenalidomide in combination with dexamethasone, with current practice favoring three-drug regimens given the excellent results seen with these combinations. Patients with high-risk disease are treated with highly active regimens of three or four drugs that include bortezomib to achieve maximum response and that have been shown to overcome poor prognostic factors such as t(4;14) and del 17p13. Newly diagnosed patients are usually treated with four to six cycles of therapy to achieve a maximum response before undergoing stem cell harvest. Early auto-SCT is more commonly used than at first relapse, although the decision is often based on response to initial therapy and the patient's preference. The optimal timing of transplantation remains an area of debate, and a large phase III clinical trial is currently underway to answer this question (NCT01191060; see http://www.clinicaltrials.gov).

Thalidomide and dexamethasone (TD)

TD has been shown in a phase III randomized trial to achieve a significantly higher overall response rate (ORR) compared to dexamethasone alone (63% vs. 41%; $P = 0.0017$). In a subsequent randomized, placebo-controlled, phase III study, the combination of TD showed an ORR of 64% compared to 46% with a significantly longer time to progression (22.6 vs. 6.5 months).

Lenalidomide and dexamethasone

Lenalidomide in combination with dexamethasone has been compared to placebo and dexamethasone in a phase III study. Lenalidomide and dexamethasone resulted in a higher ORR of 78% compared to 48% ($P < 0.001$), and superior 1-year progression-free survival. Rajkumar *et al.* (2010) randomized 445 patients to receive lenalidomide plus high-dose dexamethasone (RD) or low-dose dexamethasone (Rd), with a higher grade 3 or worse toxicity seen in the RD group (52%) compared to the Rd group (35%) during the first 4 months of therapy; and although there was a higher ORR in the RD group, the one-year OS was consequently superior in the low-dose group (96% vs. 87%; $P = 0.0002$).

Bortezomib and dexamethasone

The Intergroupe Francophone du Myelome (IFM) group randomized 482 newly diagnosed patients to induction therapy with VAD or bortezomib plus dexamethasone (VD). A second randomization was then performed to either receive or not receive two cycles of dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation therapy prior to auto-SCT. VD was superior to VAD induction with respect to rates of very good partial response (VGPR) or better (47% vs. 19%) and complete response (CR) or near CR (nCR: 21% vs. 8%). Clinical benefit associated with VD persisted after auto-SCT with improved rates of VGPR or better (41% vs. 29%) and CR or nCR (72% vs. 51%). Response rates were not improved in either treatment group by DCEP consolidation.

Bortezomib, thalidomide, and dexamethasone

A phase III study randomized 480 newly diagnosed patients to receive bortezomib, thalidomide, and dexamethasone (VTD) or TD as induction therapy before double autologous stem cell transplant, followed by consolidation therapy. After three cycles of induction therapy, the response rates were significantly higher in the three-drug combination therapy, including CR or nCR (31% vs. 11%) and VGPR or better (62% vs. 28%). Consolidation therapy after tandem transplant with the VTD regimen significantly increased the rates of CR (61%) compared to the TD (47%). The 3-year progression-free survival was significantly longer for the VTD group compared to the TD group (60 vs. 48%).

Bortezomib, lenalidomide, and dexamethasone

In a multi-center phase I–II study, 66 newly diagnosed patients received induction therapy with bortezomib, lenalidomide, and dexamethasone (RVD). All patients (100%) achieved PR or better, including VGPR in 75%, and 52% with CR or nCR in the phase II population. Reponses improved from cycles 4 to 8 in 75% of patients, with further improvement in 20 of 37 patients who continued RVD treatment beyond cycle 8 in the maintenance phase and impressive activity seen in patients with higher risk cytogenetics. The estimated 18-month progression-free survival and OS after a median follow-up of 21 months with or without transplant were 75% and 97%, respectively.

Bortezomib, cyclophosphamide, lenalidomide, and dexamethasone

The quadruple regimen of cyclophosphamide combined with lenalidomide, bortezomib, and dexamethasone was compared to bortezomib, cyclophosphamide, and dexamethasone (VCD) and to bortezomib, lenalidomide, and dexamethasone (VRd). All groups received maintenance therapy with weekly bortezomib. Following the interim analysis, the VCD arm was modified to add an additional dose of cyclophosphamide on day 15 (VCD-mod). VGPR or better was seen in 58%, 51%, 41%, and 53% of patients in the VDCR, VRd, VCD and VCD-mod arms, with a 1-year progression-free survival of 86%, 83%, 93%, and 100%, respectively. This trial demonstrated that VCD is a good choice for newly diagnosed myeloma patients, in particular those with any contraindication to IMiDs. No advantage was noted with VDCR over the three-drug combinations, and in fact increased toxicity with worse OS was seen. VRd incorporated significantly less dexamethasone than RVD in this study, which was associated with not only lower ORR than other studies of RVD but also greater neurotoxicity.

Carfilzomib, lenalidomide, and dexamethasone

Carfilzomib is a highly selective and irreversible proteasome inhibitor that has shown activity in relapsed or refractory patients and has significantly less neurotoxicity than bortezomib. In a phase I–II trial, 53 patients received carfilzomib in combination with lenalidomide and weekly dexamethasone. After a median of 12 cycles, PR or better was reported in 94%, and 62% achieved at least near-CR or better, with 24-month progression-free survival estimated at 92%. Tolerability was favorable with peripheral neuropathy observed in only 25% of patients, transient but significant shortness of breath in 15% and otherwise minimal cardiac toxicity seen.

Case study 56.3

A 48-year-old man presented with progressive generalized weakness, nausea, and bone pain. He had leukocytosis with a white blood cell (WBC) count of 15,000 with 5% circulating plasma cells, hemoglobin 7.2 g/dL, and a platelet count of 80,000/UL. His creatinine level was 3.9 mg/dL, and his calcium was 13.0 mg/dL, with an IgA of 6590 mg/dl, a lambda light chains of 612 mg/L, and a kappa–lambda ratio of 0.002. He was started on intravenous fluids and bisphosphonate therapy for hypercalcemia. A bone marrow biopsy showed a markedly hypercellular marrow with 90% involvement by dysplastic plasma cells. Conventional cytogenetics showed a complex karyotype, including t(4;16) in 10 metaphases. MRI demonstrated diffuse marrow involvement without compression fractures.

1. What is the most appropriate step in the management of this patient?

A. Vincristine, doxorubicin, and dexamethasone
B. Lenalidomide and dexamethasone
C. Perform plasmapheresis to improve renal function, and then start therapy with bortezomib, lenalidomide, and dexamethasone
D. Initiate therapy with cyclophosphamide, bortezomib, and dexamethasone
E. Refer the patient for immediate high-dose chemotherapy and stem cell transplantation

The patient has high-risk features, including renal failure due to high tumor burden and likely myeloma cast nephropathy. In addition, he has circulating plasma cells and requires urgent intervention. Bortezomib-based chemotherapy is preferred in patients who present with associated renal insufficiency. The combination of cyclophosphamide, bortezomib, and dexamethasone is an excellent choice and provides a high response rate; it can be used at full dose despite renal insufficiency. Lenalidomide and dexamethasone alone may not be sufficient and would require dose adjustment of lenalidomide for creatinine clearance. Delaying therapy for plasmapheresis is not recommended. The role of plasmapheresis in myeloma patients with acute renal failure is conflicting, with a Canadian study showing no significant benefit in outcomes for plasmapheresis in patients presenting with renal failure if effective systemic therapy is initiated immediately. High-dose chemotherapy and stem cell transplantation are options for this patient, but he needs cytoreduction first with induction therapy prior to this being pursued. Depending on his course, lenalidomide could then be integrated as part of induction and/or maintenance. Vincristine, doxorubicin, and dexamethaseon is no longer recommenced for initial therapy and considered obsolete.

Induction therapy for transplant-ineligible patients

Case study 56.4

An 80-year-old man with coronary artery disease and diabetes complained of progressive fatigue. Initial work-up revealed the presence of significant anemia with a hemoglobin of 9.3 g/dL. Serum protein electrophoresis did not detect an M-spike but immunofixation showed free kappa monoclonal proteins. He had normal immunoglobulin levels and a serum free kappa light chain of 5730 mg/L, with a lambda light chain of <1.01 mg/L and K:L ratio of 5673. A bone marrow biopsy revealed 50% involvement by monoclonal plasma cells consistent with myeloma. FISH mutational analysis was positive for t(4:14). Calcium level was normal, beta 2 microglobulin was 4.5 mg/L, creatinine was 1.8 mg/dL, and albumin was markedly low at 2.4 gm/dL. He had multiple small lytic lesions in the skull and throughout the spine on skeletal survey.

1. What treatment options would you offer?

A. Melphalan, prednisone, and lenalidomide (MPR), followed by lenalidomide maintenance
B. Melphalan, prednisone, and weekly bortezomib (MPV)
C. Bortezomib, lenalidomide, cyclophosphamide, and dexamethasone (CVRD)
D. Lenalidomide and high-dose dexamethasone

Given the patient's age and comorbid conditions, he is not an appropriate candidate for stem cell transplantation. Melphalan and prednisone have been the standard of care in this population and, with the introduction of novel therapies, have since been rapidly superseded by a combination of melphalan plus prednisone with either thalidomide or lenalidomide or bortezomib. The best choice of the regimens described for this elderly patient is MPV with weekly use of bortezomib, which is as effective as twice-a-week therapy with less neurotoxicity and a preferred choice given the patient's renal impairment as well as cardiac history. CRVD is an option of therapy, but this combination regimen has not been shown to be superior compared to three-drug regimens and may be more toxic, particularly in the context of this patient's age and comorbidities.

Other two-drug regimens such as lenalidomide plus dexamethaso and bortezomib plus dexamethasone in older patients are worth consideration in this setting, with appropriate dose adjustments to minimize toxicity. Patients with high-risk features are usually treated with three-drug combination regimens that include bortezomib, such as the RVD regimen. Thus, a modified schedule with a reduced dose of lenalidomide and bortezomib in this patient population, and the use of subcutaneous bortezomib (so-called RVd-lite), is currently being studied in non-transplant-eligible patients in a phase II clinical trial (NCT01782963; see http://www.clinicaltrials.gov).

Induction therapy for nontransplant candidates is usually administered to achieve a plateau phase of best response. At that point, different treatment strategies are considered, including continuation of treatment in the absence of significant treatment-related toxicities, maintenance therapy, or discontinuation of therapy and reinstitution at time of progression. However, recent data strongly favor continuous therapy and in particular results of the FIRST trial demonstrate significant clinical benefit for lenalidomide and dexamethasone administered until progression.

Melphalan-based combinations in the nontransplant population

Thalidomide

Elderly patients were randomly assigned to treatment with thalidomide and dexamethasone or MP ($n = 289$); TD resulted in a higher proportion of complete and very good remissions (26% vs. 13%) compared with MP, but OS was significantly shorter in the TD group. In a similar randomized, phase III trial, melphalan, prednisone, and thalidomide (MPT) were compared with melphalan and prednisone (MP) in newly diagnosed patients aged 60 years or older. The combined near-CR and CR rate among patients who received MPT was 28%, compared to 7% in the MP group. The IFM 01-01 trial randomly assigned patients 75 years or older to MP versus MPT. After a median follow-up of 47.5 months, the median PFS was significantly longer in the MPT group versus MP group (24.1 vs. 18.5 months), and the median OSS was 44 versus 29.1 months, respectively. A meta-analysis of the several trials in previously untreated transplant-ineligible patients has shown superior responses with MPT compared to MP.

Bortezomib

In the phase III VISTA trial, 682 transplant-ineligible patients with previously untreated myeloma were randomized to either bortezomib plus melphalan and prednisone (VMP) or MP alone. VMP was superior to MP in terms of the study's primary endpoint of time to disease progression (24 vs. 16.6 months) as well as CR rate (30% vs. 4%). At a median follow-up of 36.7 months, the 3-year OS rate was 69% in the VMP arm versus 54% in the MP arm, with longer follow-up at 5 years confirming sustained OS benefit.

Lenalidomide

A large phase III, double-blind, randomized study compared melphalan–prednisone–lenalidomide induction followed by lenalidomide maintenance (MPR-R) with melphalan–prednisone–lenalidomide (MPR) or melphalan–prednisone (MP) followed by placebo in patients 65 years of age or older with newly diagnosed multiple myeloma. Response rates were superior in the lenalidomide-containing regimens. While median PFS was similar between MRP and MP (14 vs. 13 months), patients receiving lenalidomide maintenance had a significantly prolonged median PFS (31 months).

Acknowledgements

The authors are very grateful for the expert assistance of Michelle Maglio in the preparation of this manuscript.

Case study answers

Case study 56.1

Question 1: Answer A, B, G, I, J
Question 2: Answer D, F
Question 4: Answer B, C, F

Case study 56.2

Question 1: Answer C

Case study 56.3

Question 1: Answer D

Case study 56.4

Question 1: Answer B

Mutiple choice ansewrs

Question 1: Answer D
Question 2: Answer A, G, H
Question 3: Answer C
Question 4: Answer D, E, I
Question 5: Answer B
Question 7: Answer C

Selected reading

Cavo M, Pantani L, Petrucci MT, *et al*. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012;120(1):9–19.

Fonseca R, Bergsagel PL, Drach J, *et al*. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210–21.

Neben K, Lokhorst HM, Jauch A, *et al*. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012;119(4):940–8.

Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046–60.

Rajkumar SV, Jacobus S, Callander NS, *et al*. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11(1):29–37.

Richardson PG, Weller E, Lonial S, *et al*. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679–86.

CHAPTER 57

Light-chain amyloidosis

David C. Seldin
Boston University, Boston, MA, USA

Case study 57.1

An 80-year-old man is referred to you for evaluation and treatment. The patient had been noted by his primary care doctor to have a monoclonal gammopathy of uncertain significance (MGUS) 10 years previously. Over the past year, the patient has developed dyspnea on exertion and signs of congestive heart failure, and he was placed on a diuretic and an angiotensin-converting enzyme inhibitor by his cardiologist. The cardiac evaluation has revealed increased wall thickness on echocardiography with diastolic dysfunction, and a cardiac magnetic resonance (CMR) study showed delayed gadolinium enhancement of the subendocardium consistent with amyloidosis. The cardiologist and primary care doctor have concluded the patient has light-chain amyloidosis (AL), and they are referring the patient to you for treatment.

1. Your next step is to:

A. Start the patient as soon as possible on treatment with melphalan and prednisone
B. Start the patient as soon as possible on melphalan and dexamethasone
C. Start the patient as soon as possible on treatment with CyBorD, the combination of cyclophosphamide, bortezomib, and dexamethasone
D. Refer the patient to a colleague for consideration of stem cell transplantation
E. Carry out additional diagnostic studies

Kudos to your colleagues for identifying a possible case of cardiac AL amyloidosis, a disease that can progress rapidly and is fatal without treatment. However, it would not be appropriate to treat this patient with chemotherapy without confirmation of the diagnosis. There are two essential steps in diagnosing AL amyloidosis: proving that amyloid fibrils are present, and proving that a plasma cell dyscrasia is responsible for the disease. The demonstration of amyloidosis can be accomplished by biopsy of the involved organ, in this case the heart, or by a less invasive aspiration of abdominal fat under local anesthesia, which is positive in 66–95% of patients with systemic amyloidosis, depending upon the type.

2. An abdominal fat aspirate is performed, dried on a slide, stained with Congo red dye, and examined under polarized light microscopy. Apple-green birefringence is seen. Now that you have proven the patient has amyloidosis, what should you do?

A. Start the patient as soon as possible on treatment with melphalan and prednisone
B. Start the patient as soon as possible on melphalan and dexamethasone
C. Start the patient as soon as possible on treatment with CyBorD
D. Refer the patient to a colleague for consideration of stem cell transplantation
E. Carry out additional diagnostic studies

You still have not established the diagnosis of AL amyloidosis. MGUS is not uncommon in an 80-year-old man; it occurs in about 7% of 80-year-old white males (data from Olmstead County, Minnesota), and the incidence in African Americans is 2–3 times higher. It is important to recognize that older men can develop an entity termed senile systemic amyloidosis (SSA) due to deposition of wild-type transthyretin (TTR), most commonly in the heart. The formal nomenclature for this would be ATTR(wt) to distinguish it from a hereditary form of amyloidosis due to production of a mutant TTR, ATTR(mut), a subtype of AF (familial amy-

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

loidosis). These patients should *not* be treated with chemotherapy. The TTR is synthesized in the liver, and chemotherapy would have no benefit.

3. How do you go about proving this is AL amyloidosis, due to aggregation and deposition of clonal immunoglobulin light chains produced by bone marrow plasma cells?

While the clinical presentation can favor one or the other (e.g., a patient whose parent had ATTRmut probably has the same diagnosis, whereas a patient who has multiorgan disease, or macroglossia, with a plasma cell dyscrasia undoubtedly has AL). In many cases, the clinical diagnosis should be confirmed using immunochemical or molecular testing. Most pathology laboratories are able to perform immunohistochemistry (IHC) for TTR, AA (secondary amyloidosis protein), and kappa and lambda light chains. If one of these is strongly positive and the others are negative, that is generally a reliable result. However, amyloid fibrils can bind antibodies nonspecifically, and if multiple antibodies are positive, the IHC is not helpful. Immunoelectron microscopy has more specificity but is not widely available. Many cases can be sorted out with mass spectrometric analysis of fibrils harvested from tissue sections using laser capture microdissection, which is available as a commercial test through the Mayo Clinical Laboratories. If the patient in question has TTR deposition by an immunochemical technique, gene sequencing should be done to distinguish a hereditable TTR mutant, versus the wild-type TTR that causes SSA.

Based on clinical presentation, there is a real possibility that this patient has two unlinked age-related conditions, MGUS and SSA, and does not need specific treatment for either. In that case, management would be supportive care to reduce heart failure symptoms. Drugs that stabilize TTR and reduce fibril formation, such as tafamidis and diflunisal, are under ongoing investigation.

4. If the workup reveals light-chain fibrils consistent with AL, what is the best treatment?

A. Start the patient as soon as possible on treatment with melphalan and prednisone
B. Start the patient as soon as possible on melphalan and dexamethasone
C. Start the patient as soon as possible on treatment with CyBorD
D. Refer the patient to a colleague for consideration of stem cell transplantation
E. Tailor treatment based upon the patient's performance status and comorbidities

There are no evidence-based guidelines for treatment of AL in older patients. In the era before the so-called novel agents for plasma cell diseases (proteasome inhibitors and immunomodulators), we were sometimes able to employ modified high-dose melphalan and autologous stem cell transplantation in patients up to age 80. However, the efficacy of the novel agents has shifted the risk–benefit ratio in older patients, and most centers would no longer consider transplant for patients this old, particularly with cardiac involvement, as risk of treatment-related mortality is high. Melphalan and prednisone is a regimen with a low response rate that largely has been superseded by melphalan + dexamethasone, as higher response rates were seen with the more intensive steroid regimen. However, in patients with cardiac amyloidosis, young or old, weekly dexamethasone is better tolerated than a consecutive 4-day regimen; even the weekly dosing may need to be modified to avoid exacerbation of congestive heart failure. I would suggest starting this 80 year old on no more than 20 mg dexamethasone weekly, with the expectation of needing to increase diuretics for a day or two after the steroid. While oral melphalan + dexamethasone is a convenient oral regimen, many hematologists now choose a bortezomib-containing regimen as first-line therapy for plasma cell diseases. Many centers would begin with bortezomib and dexamethasone on a weekly dose-reduced schedule in a patient this old (e.g., 1.3 mg/m^2 of bortezomib with 20 mg of intravenous dexamethasone). Weekly dosing will be more tolerable in terms of congestive heart failure, and it also has a lower incidence of neuropathy than biweekly dosing. Pharmacokinetic and pharmacodynamic data suggest subcutaneous administration is bioequivalent to the original intravenous regimen, and is an alternative. CyBorD is a highly effective three-drug combination regimen, but the original report did not note what the oldest treated patient was.

Case study 57.2

A patient is referred from primary care because they have a small "M spike," a monoclonal gammopathy, of 0.4 g/dL. The patient is a 50-year-old woman who has had fatigue over the past year, which has been attributed to menopause. To risk stratify her disease, you carry out appropriate testing, including a bone marrow biopsy, immunofixation electrophoresis (IFE) of serum and urine, and serum free light chains. These studies reveal 20% lambda monotypic plasma cells in the bone marrow, an immunoglobulin G lambda and free lambda monoclonal bands on serum IFE, and both albumin and lambda light chains in the urine. Lambda serum free light chains are elevated at 70 mg/L (normal: 5.7–26.3 mg/L) with a kappa of 5.0 (normal: 3.3–19.4 mg/L); the calculated kappa : lambda free light-chain ratio (FLCR) is 0.07 (normal: 0.26–1.65). The patient is not anemic or hypercalcemic, and she has no lytic lesions on a skeletal survey.

1. What is the diagnosis for this patient?

A. MGUS; no further workup is necessary at this time. Noninvasive studies should be repeated in 6 months and, if unchanged, every 1–2 years
B. Smoldering myeloma; no further workup is necessary at this time. Noninvasive studies should be repeated every 3–4 months
C. Unclear. Additional diagnostic studies should be done

This patient does not have MGUS, as the percentage of bone marrow plasma cells exceeds 10%. Could this patient have smoldering myeloma? Smoldering myeloma is diagnosed when the serum M protein is $\geq$3 g/dL *or* clonal bone marrow plasma cells are $\geq$10%, without the CRAB features of hypercalcemia, renal failure, anemia, or lytic bone lesions. Hematologically, the patient's plasma cell dyscrasia fits this diagnosis. However, for either MGUS or smoldering myeloma, there should be no end-organ disease or symptoms associated with the plasma cell dyscrasia. Why is she tired? Why does she have albuminuria?

2. What should the next step in her workup be?

A. 24-hour urine collection to assess urinary protein excretion
B. Electrocardiogram and echocardiogram
C. Measurement of NT-proBNP or BNP, and troponin
D. Referral to a psychiatrist
E. A, B, and C

To repeat: patients with MGUS or smoldering myeloma should have NO SYMPTOMS AND NO ORGAN DYSFUNCTION associated with their disease. A patient who appears to have MGUS or smoldering myeloma but has fatigue, dyspnea on exertion, edema, lightheadedness, peripheral neuropathy, GI symptoms, periorbital ecchymoses, hoarseness, macroglossia, or jaw or buttock claudication MUST be evaluated for amyloidosis. Delay in diagnosis of AL amyloidosis, particularly with cardiac involvement, can be fatal. As we have learned earlier, this patient should have an abdominal fat aspiration performed, with Congo red staining.

True or false? Patients with a cardiomyopathy due to amyloidosis would usually be expected to have:

3. Râles and/or elevated jugular venous pulse (JVP)

A. True
B. False

4. Increased voltage on electrocardiogram (ECG)

A. True
B. False

5. Sparkly pattern on echocardiogram

A. True
B. False

6. Increased interventricular septal diameter (IVSd) on echocardiogram

A. True
B. False

7. Delayed subendocardial gadolinium enhancement on CMR imaging

A. True
B. False

8. Elevated B-type natriuretic peptide (BNP) and/or troponin

A. True
B. False

Patients with amyloid cardiomyopathy usually have subtle signs of congestive heart failure, with râles, elevated JVP, or hepatojugular reflux on exam (a rise in the JVP with pressure on the abdomen or valsalva). Patients with amyloid cardiomyopathy have *decreased* voltage on ECG due to infiltration of the myocardium with fibrils; patients with long-standing hypertension leading to increased wall thickness have increased voltage. With modern high-resolution echocardiography, it is unusual to have "sparkles" reported by the echocardiographer, but there usually is diastolic dysfunction and an increase in the thickness of the IVSd. CMR shows a characteristic delayed gadolinium enhancement, as

well as increased wall thickness. BNP and troponin are now well described as cardiac biomarkers in amyloidosis, and they have prognostic as well as diagnostic significance.

This patient has the following findings, in addition to the hematologic findings described above: scant basilar râles and an elevated JVP with HJR; 1+ edema; nephrotic range proteinuria with 2.5 g protein excretion per day; low voltages in the limb leads of the ECG; an echocardiogram with an IVSd of 15 mm, normal ejection fraction, and grade I diastolic dysfunction; BNP and troponin that are slightly elevated; and Congo red staining fibrils on the abdominal fat aspirate. There is no family history of amyloidosis.

9. True or false? This patient should have an endomyocardial biopsy to establish the diagnosis of cardiac AL amyloidosis.

A. True
B. False

With a diagnosis of amyloidosis from the fat aspirate, there is no doubt this patient has systemic amyloidosis. The ECG and echocardiographic features, along with the elevated biomarkers, are diagnostic of cardiac amyloidosis. Thus, an endomyocardial biopsy is not required and would subject the patient to an unnecessary invasive procedure.

10. True or false? This patient must have mass spectrometry performed on the fat aspirate to diagnose AL amyloidosis.

A. True
B. False

Can we be certain of the diagnosis without molecular or immunochemical typing? This patient does not have SSA, as she is too young, and SSA is almost exclusively a disease of males. This patient has no family history of ATTR, and ATTR does not cause nephrotic-range proteinuria. This clinical presentation in a young woman with a plasma cell dyscrasia is diagnostic of AL amyloidosis. If she had cardiomyopathy only, or cardiomyopathy and peripheral neuropathy, and certainly if there was no evidence of a plasma cell dyscrasia, genetic testing for a mutant TTR and biochemical or immunochemical typing of the amyloid fibrils should be done.

11. True or false? Because of cardiac involvement and elevated biomarkers, this patient is not eligible for a stem cell transplant.

A. True
B. False

Although patients with cardiac involvement are at higher risk of complications during the course of a stem cell transplant, this patient, as described so far, has early-stage cardiac disease. Such patients can be transplanted successfully with excellent results. In contrast, the use of less rapidly effective therapies puts the patient at risk of progressive heart disease. The experienced centers that regularly treat patients with AL amyloidosis would at least consider this patient for high-dose melphalan chemotherapy and autologous stem cell transplantation (HDM–auto-SCT). In addition to biomarkers, functional assessments of cardiac capacity such as stair climbing, cardiopulmonary exercise testing, cardiac strain assessment by echocardiography, and cardiac perfusion testing are adjunctive tests that might help risk stratify this patient. With average times to response of 3–6 months, the use of oral melphalan + dexamethasone or lenalidomide + dexamethasone would not be advisable. The relative benefits of a bortezomib-containing regimen versus HDM–auto-SCT have not been tested in a randomized fashion. With more than 15 years of experience at this point with HDM–auto-SCT, centers that are careful in patient selection have low transplant-related mortality, and excellent and durable hematologic and organ responses. HDM–auto-SCT is still considered by most centers to be first-line treatment in suitable patients; clearly, proteasome inhibitors and immunomodulators are better choices in high-risk patients, and can be useable as consolidation therapy in patients who do not have an adequate response to HDM–auto-SCT. Bortezomib is the only proteasome inhibitor that has been extensively tested in AL amyloidosis patients, but studies are underway with carfilzomib and ixazomib (MLN9708), an oral proteasome inhibitor. Immunomodulators including thalidomide, lenalidomide, and pomalidomide have been used alone and in combination with other agents. Decisions among these options are highly individualized and should be made through consultation with a center that has extensive experience with evaluation and management of AL amyloidosis patients.

Case study answers

Case study 57.1

Question 1: Answer E
Question 2: Answer E
Question 4: Answer E

Case study 57.2

Question 1: Answer C
Question 2: Answer E
Question 3: Answer A ("True")
Question 4: Answer B ("False")
Question 5: Answer B ("False")
Question 6: Answer A ("True")
Question 7: Answer A ("True")
Question 8: Answer A ("True")
Question 9: Answer B ("False")
Question 10: Answer B ("False")
Question 11: Answer B ("False")

Selected reading

Cibeira MT, Sanchorawala V, Seldin DC, *et al*. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. 2011;118(16):4346–52.

Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol. 2011;29(14):1924–33.

Mikhael JR, Schuster SR, Jimenez-Zepeda VH, *et al*. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012;119(19):4391–4.

Reece DE, Hegenbart U, Sanchorawala V, *et al*. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood. 2011;118(4):865–73.

Seldin DC, Skinner M. Amyloidosis. In: Longo D, Fauci A, Kasper D, *et al*., editors. Harrison's principles of internal medicine. 18th ed. McGraw-Hill: New York, 2011.

CHAPTER 58

Waldenström's macroglobulinemia

Anita D'Souza and Morie A. Gertz
Mayo Clinic, Rochester, MN, USA

Mutiple choice and discussion questions

1. What is Waldenström's macroglobulinemia, and when should it be suspected?

Waldenström's macroglobulinemia (WM) is defined by the World Health Organization as a lymphoplasmacytic lymphoma (LPL) associated with a monoclonal immunoglobulin M (IgM) protein. The classic characteristic pentad of WM is (i) M-protein on serum protein electrophoresis confirmed to be (ii) IgM by immunofixation, with (iii) bone marrow evidence of lymphoplasmacytic lymphoma and, in some patients, evidence of (iv) hyperviscosity syndrome with (v) normocytic anemia. Using the Surveillance, Epidemiology, and End Results (SEER) data, WM represented 1.9% of all non-Hodgkin lymphoma. The median age at diagnosis was 73 years, with a predilection for men (5.4/million/year) as opposed to women (2.7/million), and a racial skewing toward Caucasians (4.1/million) rather than African Americans (1.8/million). First-degree relatives of patients with LPL–WM have a 20-fold increased risk of LPL–WM.

Other IgM-related conditions include IgM monoclonal gammopathy of undetermined significance (IgM <3 g/dl; no evidence of marrow infiltration >10%; and without symptoms of tumor mass or infiltrations, e.g., adenopathy, organomegaly, anemia, or IgM-mediated symptoms), smoldering WM (IgM >3 g/dl; marrow infiltration > 10%; and with no symptoms of tumor mass or infiltration or IgM-mediated symptoms), IgM-related cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, and amyloidosis.

2. Which of the following genetic changes is associated with WM?

A. t(11;18)
B. BRAF V600E
C. MYD88 L265P
D. NOTCH2

Using whole-genome sequencing, over 90% of patients with WM or non-IgM LPL have been found to have a common mutation, MYD88 L265P. This mutation also appears to be useful in differentiating LPL from other B cell lymphoproliferative disorders such as splenic marginal zone lymphoma. Furthermore, on metaphase cytogenetics, a deletion in the long arm of chromosome 6 (6q−) may be seen in 40–50% patients. Epigenetic dysregulation; aberrations in the phosphatidylinositol-3 kinase–mammalian target of rapamycin (PI3K–mTOR), nuclear factor kappa B, and Janus kinase–signal transducer and activator of transcription (JAK–STAT) signaling pathways; as well as bone marrow microenvironmental interactions may be other key factors that are involved in the pathogenesis of WM.

Case study 58.1

A 62-year-old male is diagnosed with WM. His hemoglobin is 11.4 g/dl, his white blood cell (WBC) count is 10,000/cu ml, and his platelet count is 102,000/cu ml. The IgM level is 6400 g/dl.

1. Based on this information, what is his risk category?

A. Low risk
B. Intermediate
C. High
D. Need more information

The International Staging System for Waldenström Macroglobulinemia identifies the following five factors associated with prognosis in WM: (i) age >65, (ii) hemoglobin <11.5 g/dl, (iii) platelet count <100,000/cu ml, (iv) beta2-microglobulin >3 mg/dl, and (v) monoclonal IgM >7 g/dl.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

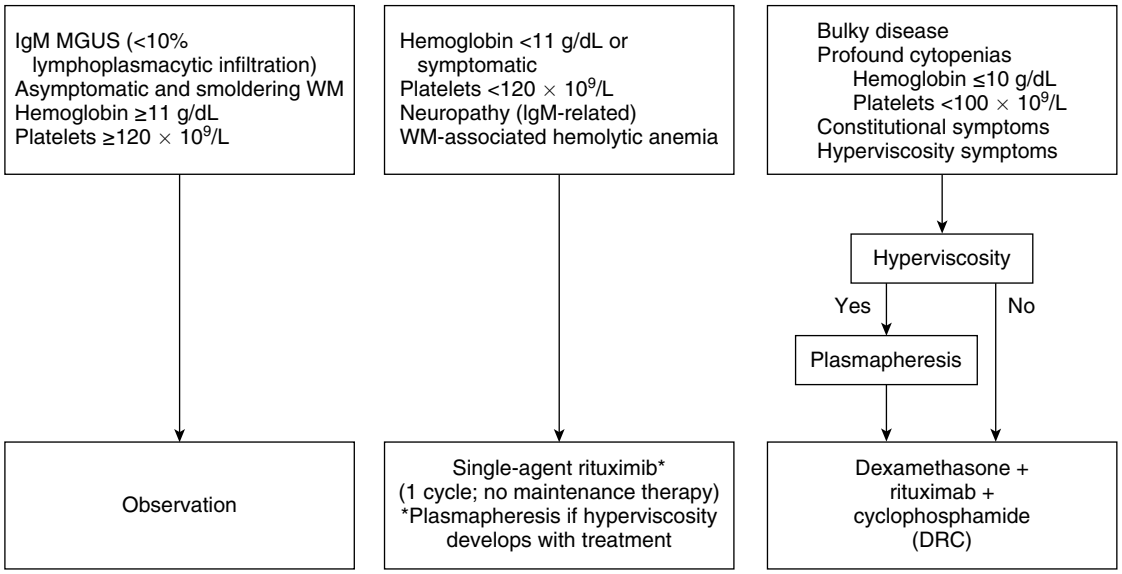


Figure 58.1 The Mayo Clinic approach to Waldenström's macroglobulinemia (WM). IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance (Source: Ansell SM, *et al*. Mayo Clin Proc. 2010;85:824–33. Reproduced with permission of Elsevier).

Based on the number of risk factors present, the risk category may be low (0 or 1 risk factor, except age), intermediate (age >65 or two risk factors), or high risk (>2 risk factors), which are associated with a median survival of 142.5, 98.6, and 43.5 months, respectively.

The staging system is notable for the absence of lactate dehydrogenase (LDH); however, LDH may have a role in separating the high-risk patients into two distinct categories.

2. The above patient is asymptomatic. His beta2 microglobulin and LDH are unremarkable; he has less than 10% involvement of the bone marrow with lymphoma. Does he need treatment?

He can be observed. Asymptomatic patients without significant cytopenias can be observed. Single-agent rituximab is rarely used but may be indicated for patients with isolated peripheral neuropathy or hemolytic anemia. Patients who need cytotoxic therapy are encouraged to go on clinical trials wherever possible. The standard of care at our institution at the current time is combination chemotherapy with dexamethasone, rituximab, and cyclophosphamide (Figure 58.1).

Case study 58.2

A 48-year-old male presents to his primary care doctor with blurred vision. He has had headaches and also notes nosebleeds. Examination reveals retinal venous dilation. Further work-up reveals a mild anemia with hemoglobin of 11.5 g/dl and a platelet count of 95,000/ ml^3. Chemistry shows normal creatinine and a total protein level of 9 g/dl.

1. What is going on with the patient?

A. Hyperviscosity syndrome
B. Dehydration
C. Thrombotic thrombocytopenia purpura
D. Amyloidosis

This is a potentially life-threatening complication of WM that is, fortunately, rarely encountered. The risk of hyperviscosity depends on the IgM level, and it is rare at an IgM level lower than 4 g/dl. Symptoms may be nonspecific, with generalized fatigue, dizziness, and lightheadedness. Bleeding can result with epistaxis, gingival bleeding, and retinal hemorrhages. Classic ophthalmologic findings include sausaging of retinal veins from venous engorgement, as seen on fundoscopic examination. Hyperviscosity syndrome is rare unless the serum viscosity exceeds 4 (normal ≤1.5 cpoise). Hyperviscosity syndrome can be treated immediately by the institution of plasmapheresis, followed by the institution of chemotherapy. Elevated viscosity without the presence of symptoms is not an indication for treatment. When single-agent rituximab is used, patients can develop an initial IgM flare that may result in hyperviscosity after the initiation of treatment. It is important to be watchful of the IgM and serum viscosity levels if single-agent rituximab is used with a low threshold for plasmapheresis. The other important implication of this observation is to not change therapy during a flare, as these patients can still respond to treatment.

Table 58.1 How response to Waldenström's macroglobulinemia (WM) treatment is measured (Source: Kimby E, *et al*. Clin. Lymphoma Myeloma Leuk 2006;6:380–3. Reproduced with permission of Elsevier).

Complete response	Disappearance of serum and urine M protein by immunofixation, histologic absence of malignant cells in bone marrow, resolution of lymphadenopathy or organomegaly, and no signs or symptoms attributable to WM
Partial response	≥50% reduction in serum M protein by electrophoresis, ≥50% decrease in adenopathy and organomegaly, and no new signs or symptoms of active WM
Minor response	≥25% but <50% reduction in serum M protein by electrophoresis; no new signs or symptoms of active WM
Stable disease	<25% reduction or increase in serum M protein by electrophoresis without progression of adenopathy and organomegaly or symptoms or signs attributable to WM
Progressive disease	≥25% increase in serum M protein by electrophoresis (on two measurements) or progression of clinically significant findings; symptoms or signs attributable to WM

2. How is response to treatment measured?

Response to treatment, as defined by a consensus panel at the Third International Workshop on Waldenstrom Macroglobulinemia, is defined in Table 58.1. There are a few important caveats to consider: (i) patients may have a delayed response, especially after purine analog and monoclonal antibody therapy, and best response may not be achieved until 6 months after treatment; and (ii) patients with minor responses may do just as well clinically as patients with better responses.

3. What are the different standard and novel therapies in WM?

The standard therapy for WM may be alkylator based (cyclophosphamide) or purine analog based (fludarabine and cladribine) with the anti-CD20 monoclonal antibody rituximab. Newer drugs include the alkylator bendamustine (bendamustine and rituximab), alemtuzumab, immunomodulatory drugs (lenalidomide and pomalidomide), and proteasome inhibitors (bortezomib and carfilzomib). Everolimus, the mTOR inhibitor, has high efficacy in WM with response rates up to 70% when used as a single agent. Perifosine, a protein kinase B (AKT) inhibitor; enzastaurin, a PI3K–AKT inhibitor; panobinostat, a histone deacetylase inhibitor; ofatumumab, a third-generation anti-CD20 monoclonal antibody; and ibrutinib, a Bruton tyrosine kinase inhibitor, are in various early stages of study in WM with promising results.

4. Is there a role for rituximab maintenance?

The benefit of maintenance rituximab therapy is controversial. A retrospective analysis of rituximab maintenance therapy in patients treated with rituximab-containing regimens indicated an improvement in progression-free and overall survival. Unlike with other low-grade lymphomas, maintenance rituximab has not been evaluated prospectively in WM. At our center, we do not routinely use maintenance rituximab therapy in all patients.

5. Should autologous stem cell transplantation be a front-line option?

Autologous stem cell transplantation produces durable responses with a low treatment-related mortality rate. For transplant-eligible patients, we routinely collect and cryopreserve peripheral blood stem cells, and patients, in particular younger patients, are considered for autologous stem cell transplantation in the front-line setting. Heavily pretreated patients (>3 regimens) and those who are chemorefractory at the time of transplantation are unlikely to benefit.

6. How is relapsed disease managed?

See Figure 58.2.

7. What about allogeneic stem cell transplantation?

Allogeneic transplantation is generally used in the investigational setting. As WM tends to occur at older ages, this makes allo-transplantation more difficult. The largest literature supporting allogeneic transplantation in WM comes from the European Bone Marrow Transplantation registry (304 patients, 2000–2011), in which patients who received reduced-intensity conditioning and myeloablative conditioning showed an overall survival of 62% and 66%, and 3-year response rates of 21% and 26%, respectively.

Cryoglobulinemia and related autoimmune disorders in WM

The monoclonal IgM protein can result in a number of autoimmune conditions. Type I cryoglobulinemia is common; all of the cryoglobulin is composed of the monoclonal IgM protein. Type I cryoglobulinemia tends to be an

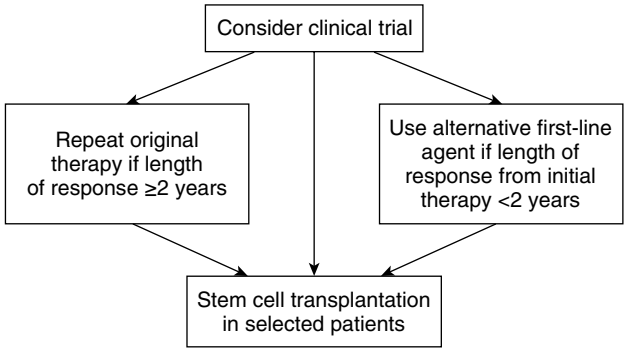


Figure 58.2 The Mayo Clinic approach for salvage therapy in Waldenström's macroglobulinemia (Source: Ansell SM, *et al.* Mayo Clin Proc. 2010;85:824–33. Reproduced with permission of Elsevier).

incidental finding without symptoms or signs. Type II cryoglobulinemia is composed of monoclonal and polyclonal immunoglobulins. Patients with mixed IgM–IgG cryoglobulinemia can have a variety of symptoms and signs related to cold sensitivity, purpura, arthralgias, and vasculitis. Type II cryoglobulinemia can have a marked effect on serum viscosity owing to the high thermal amplitude of the IgM–IgG cryoglobulin. Patients can also develop a cold agglutinin disease (CAD) from a monoclonal IgM directed against the red cell I or i antigen. Symptoms include acrocyanosis, Raynaud's phenomenon, and an immune hemolytic anemia on cold exposure. Last, the IgM protein can also attack neural proteins, resulting in immune neuropathies (see the "IgM-related neurologic manifestations" section). Asymptomatic type II cryoglobulinemia or CAD can be observed. Symptomatic patients with IgM-related autoimmune disorders can be treated with single-agent rituximab alone (if without bulky disease, cytopenias, or B symptoms), as shown in Figure 58.1. Patients with other symptoms related to WM are treated with cytotoxic therapy with rituximab.

Risk of amyloid light-chain (AL) amyloidosis

Primary systemic amyloidosis is a rare complication of WM. This should be considered when a patient has symptoms of peripheral neuropathy. This is an important complication to identify, as the development of amyloidosis can cause significant morbidity as well as mortality from organ involvement over the risk of progression of WM. In a series of 22 patients with IgM amyloidosis studied at the Mayo Clinic, patients tend to be older, with more peripheral nerve involvement and a lesser degree of cardiac involvement. Rarely, patients with WM can present with localized AL amyloidosis primarily affecting the lymph nodes. This tends to be a more indolent form of amyloidosis in which the amyloid deposition occurs peri-tumorally at the site of lymphoma cells without affecting distant organs. Treatment of IgM amyloidosis is similar to the treatment of primary systemic amyloidosis. There is some anecdotal evidence that treatment directed at the lymphoma cells with drugs such as rituximab may be of benefit.

IgM-related neurologic manifestations

The most common neurologic complication of WM is peripheral neuropathy. These may be seen as frequently as in half of all patients. The clinical presentation and neurologic findings are identical to those seen with IgM-MGUS (monoclonal gammopathy of undetermined significance) and are probably related to immune-mediated axonal loss. Known targets against which monoclonal IgM may be directed include myelin-associated glycoprotein (MAG) or sulfatide, but only a minority of patients have these autoantibodies. Other mechanisms of peripheral nerve damage may include direct infiltration of nerves by tumor cells, IgM directed against unidentified neural proteins, or other known complications of WM such as AL amyloidosis and cryoglobulinemia. Last, chemotherapeutic drugs such as bortezomib can worsen peripheral neuropathy.

The central nervous system can be affected in WM. Separate from hyperviscosity syndrome, rarely WM can involve the meninges, brain, and cerebrospinal fluid (CSF), which is termed Bing–Neel syndrome (BNS). In a review of 31 cases of BNS, patients may have evidence of lymphoplasmacytoid cells within the brain or CSF, or not, and presumably have an autoimmune mechanism mediated by IgM. White matter changes are seen on brain magnetic resonance imaging (MRI) in 65% of patients, and spinal cord syndromes were seen in 67% of patients. Treatment of the WM provided improvement in 42% of patients, with sustained responses from 6 months to 4 years.

Survivorship issues in W4M

The long survival and advanced age of presentation of WM have to be considered when selecting the most appropriate treatment. Treatment-associated morbidity is important to consider, with the risk of secondary infections from monoclonal antibody therapy, delayed response from purine analogs, myelodysplasia from fludarabine, and peripheral neuropathy related to bortezomib. Lastly, patients with WM are at an increased risk of developing a second malignancy, including diffuse large B-cell lymphoma, acute myeloid leukemia, and brain cancer.

Mutiple choice answer

Question 2: Answer C

Case study answers

Case study 58.1

Question 1: Answer D

Case study 58.2

Question 1: Answer A

Selected reading

Ansell SM, Kyle RA, Reeder CB, *et al*. Diagnosis and management of Waldenstrom macroglobulinemia: Mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines. Mayo Clin Proc. 2010;85:824–33.

Gertz M. Waldenstrom macroglobulinemia: my way. Leuk Lymphoma. 2012;54(3):464–71.

Issa GC, Leblebjian H, Roccaro AM, *et al*. New insights into the pathogenesis and treatment of Waldenstrom macroglobulinemia. Curr Opin Hematol. 2011;18:260–5.

Kastritis E, Kyrtsonis MC, Hadjiharissi E, *et al*. Validation of the International Prognostic Scoring System (IPSS) for Waldenstrom's macroglobulinemia (WM) and the importance of serum lactate dehydrogenase (LDH). Leuk Res. 2010; 34:1340–3.

Varettoni M, Tedeschi A, Arcaini L, *et al*. Risk of second cancers in Waldenstrom macroglobulinemia. Ann Oncol. 2012;23: 411–15.

CHAPTER 59

Autologous hematopoietic cell transplantation in multiple myeloma

Jean-Luc Harousseau[1] and Mohamad Mohty[2]

[1]French National Cancer Institute, Nantes, France
[2]University Pierre & Marie Curie, Paris, France

1. Is high-dose therapy plus autologous stem cell transplantation superior to conventional chemotherapy?

The concept of high-dose therapy (HDT) plus autologous stem cell transplantation (auto-SCT) was developed in the 1980s. The objective of auto-SCT was to support HDT in order to reduce the duration and toxicity of severe myelosuppression The Intergroupe Francophone du Myeloma was the first to conduct a randomized trial showing the superiority of HDT–auto-SCT compared with conventional chemotherapy in patients younger than 65 years of age, as regards response rate, event-free survival (EFS), and overall survival (OS). These findings were confirmed 7 years later by a larger study by the British Medical Council Research VII trial. Following these results; HDT–auto-SCT has become the standard of care in patients who are without severe comorbidities and younger than 65 years of age.

Overall, seven randomized studies have compared auto-SCT–HDT with conventional chemotherapy. While EFS was superior with HDT–auto-SCT in five out of seven trials, OS was significantly prolonged in only three trials. These results were confirmed by a meta-analysis that showed a significant benefit for HDT–auto-SCT in terms of EFS, but no benefit in terms of OS. This was partly explained by the impact of auto-SCT at relapse in patients initially treated with conventional chemotherapy. Therefore, the majority of myeloma experts recommended HDT–auto-SCT as part of initial therapy, whereas some experts considered that delayed auto-SCT (discussed later in this chapter) was a valuable approach. Overall, the use of HDT–auto-SCT was the major cause of OS improvement observed in younger patients before the introduction of novel agents (immunomodulators and proteasome inhibitors). However, in the vast majority of patients, relapses ultimately occurred and long remissions (and possible cures) were rare.

2. What is the optimal conditioning regimen prior to auto-SCT?

The first HDT regimen was the combination of intravenous (IV) high-dose melphalan (HDM) (140 mg/m^2) plus total body irradiation (TBI). In a randomized trial from the IFM, HDM alone at a dose of 200 mg/m^2 was superior to HDM plus TBI. Therefore, thus far, HDM 200 mg/m^2 is the most widely used regimen. However, to improve the efficacy of the HDT and auto-SCT results, several procedures were tested. Different groups have explored the use of combination HDT conditioning regimens using agents in addition to or replacing HDM. Recently, the Spanish group tested a combination of oral or IV busulfan combined with HDM. Unfortunately, better chemoreduction was associated with higher toxicity. The use of bortezomib in conjunction with high-dose melphalan proved to be safe, with nonrandomized data suggesting improved efficacy. However, until randomized results become available, HDM 200 mg/m^2 should remain the standard HDT prior to auto-SCT.

3. What is the best stem cell mobilization procedure prior to auto-SCT?

Hematopoietic stem cells (HSCs) usually circulate in only small numbers in peripheral blood (PB). Current mobilization strategies vary between centers, and some patients are unable to mobilize sufficient PB stem cell (PBSC) yields. The most widely used minimal cutoff for autologous HSCs to be infused is 2×10^6 CD34+ cells/kg recipient body weight. However, a significant amount of data suggests that a dose of 4×10^6 CD34+ cells/kg is likely to be an

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

optimal dose in terms of hematopoietic recovery. At present, there is no well-established evidence demonstrating a correlation between an autologous HSC dose and disease outcome. Monotherapy with granulocyte colony-stimulating factors (G-CSFs) is the most commonly used steady-state mobilization strategy. Currently, the G-CSF cytokines—filgrastim and lenograstim—are approved for the mobilization of autologous HSC. The recommended schedules are filgrastim 10 μg/kg/day for 4–6 consecutive days; apheresis to be performed on days 5 or 6; lenograstim 10 μg/kg/day for 4–6 days; and apheresis to be performed between days 5–7. Mobilization with cytokines alone is well tolerated, but their use can be limited by suboptimal PBSC yields. Adding chemotherapeutic agent(s) to cytokine therapy (aka the "chemomobilization" procedure) may increase PBSC yields and can potentially decrease the tumor burden. However, the time required to collect PBSCs is prolonged and becomes less predictable. Also, the incidence and severity of side effects with chemotherapy plus G-CSF are increased compared with G-CSF alone. The approved filgrastim and lenograstim doses for PBSC mobilization after myelosuppressive chemotherapy are 5 μg/kg/day each, starting within 1–5 days after completion of chemotherapy until the last apheresis. The most commonly used chemotherapy-based mobilization in myeloma relies on the use of high-dose cyclophosphamide (usual doses range from 2 to 4 g/m^2). The mobilization strategies can be optimized by different approaches: (i) remobilization with a steady-state approach, (ii) change in the chosen chemomobilization approach, or (iii) addition of new mobilization agents such as plerixafor. Plerixafor is a chemokine receptor 4 (CXCR4) antagonist that disrupts the interaction between the stromal deriving factor 1 (SDF1) and CXCR4, thereby enhancing the HSC mobilization effect of G-CSF. Plerixafor has been approved for the use in combination with G-CSF for autologous HSC mobilization in myeloma and lymphoma patients. The recommended dose is 240 μg/kg body weight/day approximately 6–11 hours prior to apheresis initiation following 4 days of G-CSF.

4. Which patients are candidates for auto-SCT?

Most randomized trials have included patients up to 65 years of age. Usually, auto-SCT is indicated for patients aged younger than 66 years with no severe comorbidity. Two clinical conditions may be discussed.

Patients over the age of 65. Auto-SCT is feasible in selected patients older than 65 years of age. However, results of published studies are obviously biased by selection criteria. Few randomized studies have included patients older than 65 years of age. In these studies, the doses of melphalan were reduced compared to those used in younger patients (100 mg/m^2 instead of 200 mg/m^2), but the transplant procedure was repeated twice (tandem transplants). In the Italian study, two courses of melphalan 100 mg/m^2 plus auto-SCT were superior to the standard chemotherapy regimen of melphalan–prednisone (MP). But the IFM group failed to confirm this result and showed that this approach was inferior to the combination of MP plus thalidomide. Therefore, in Europe, auto-SCT is rarely proposed in patients older than the age of 65.

Renal impairment. Although auto-SCT is feasible in patients with renal failure, toxicities of HDT are more frequent and more severe, and the doses of melphalan should be decreased. Patients with renal failure at the time of auto-SCT are currently excluded from auto-SCT programs, because no randomized trial has been performed in this context. However, renal impairment at presentation does not necessarily mean that auto-SCT will be contraindicated after induction therapy.

5. What is the objective of auto-SCT?

Compared to conventional-dose chemotherapy, HDT–auto-SCT improves the response rate and most importantly increases the complete response (CR) rate. In the context of HDT–auto-SCT, a significant relationship between CR or at least very good partial response (VGPR) achievement and the outcome has been clearly shown. Patients achieving CR have a longer progression-free survival (PFS). Therefore, the objective of HDT–auto-SCT has been to increase the CR rate. In the absence of new treatments, in the 1990s, the only possibility was to further increase dose intensity by developing the concept of double intensive therapy. Three randomized trials have shown a benefit in favor of double auto-SCT in terms of PFS, but two of them failed to show an OS benefit. The introduction of new agents (immunomodulators and proteasome inhibitors) in frontline regimens without HDT–auto-SCT has changed the scenario and raises the question of the place of HDT–auto-SCT in front-line therapy of multiple myeloma (MM). First, when combined with conventional-dose chemotherapy in elderly patients, these agents have been associated with high response rates as well and with CR rates that are comparable to those achieved with HDT–auto-SCT for younger patients. Second, these new agents have also been used in combination with HDT–auto-SCT with the objective of further increasing the CR rate and/or of upgrading the CR level. The addition of novel agents after and/or before HDT–auto-SCT has dramatically increased the post-auto-SCT CR rate (>40%) and the CR plus VGPR rate (> 60%). Maybe more importantly, the level of CR have been upgraded with the achievement of stringent CR(s-CR) with a normal k/l ratio (serum free-light chain assessment), immunophenotypic CR (with negative multiparameter flow cytometry), or even molecular CR. Achievement of immunophenotypic or molecular CR has been associated with longer PFS and might become a new objective of modern treatments with novel agents plus HDT–auto-SCT.

6. What is the best induction treatment prior to auto-SCT?

The objectives of induction treatment prior to HDT–auto-SCT are:

- to reduce the tumor burden in order to increase the post HDT–auto-SCT CR rate; and
- to decrease the plasma cell marrow infiltration in order to improve the quality of the graft.

The ideal induction treatment should be relatively safe and should spare normal hematopoietic precursors. Prior to novel agents, alkylating agents were avoided due to their hematopoietic toxicity, and the standard induction regimen was dexamethasone based, either high-dose dexamethasone alone or a combination of dexamethasone with nonalkylating cytotoxic agents like doxorubicin and vincristine in the so-called VAD regimen. A number of randomized studies have shown the superiority of induction regimens containing one or two novel agents (thalidomide or bortezomib) compared to VAD-based regimens. With these new regimens, the pre-auto-SCT was superior, yielding a higher CR rate and a higher CR plus n-CR or VGPR rate. More importantly, this better efficacy translated into a higher CR or CR plus n-CR or VGPR post transplantation. Therefore, VAD is no longer considered the standard induction treatment.

Three randomized studies have compared a two-drug induction (TD: thalidomide–dexamethasone; or VD: bortezomib–dexamethasone) with a three-drug regimen (VTD: bortezomib, thalidomide, and dexamethasone). In the three studies, VTD was significantly superior to the two-drug regimen and is now considered a standard induction regimen in Europe. There is no evidence that four-drug regimens are superior, and they may be more toxic.

The better response rate observed with new regimens is related to a better efficacy across all prognostic subgroups, including ISS III and poor-risk cytogenetics. There is currently no direct evidence that the higher CR plus n-CR rate achieved with these new regimens translates into a longer PFS because all of these studies had different post-auto-SCT treatments. However, there is an indirect argument in favor of the prognostic impact of a better induction treatment: the IFM group has shown that achieving at least a higher VGPR rate after induction was associated with a longer PFS.

7. What is the impact of consolidation therapy after auto-SCT?

The use of short-term consolidation therapy after HDT–auto-SCT aims to improve disease response through induction of a "deeper response." The first attempt was to repeat HDT–auto-SCT after a first auto-SCT, the so-called tandem transplantation approach that was pioneered by the Arkansas group. In three randomized trials, double auto-SCT significantly prolonged PFS compared to single auto-SCT. However, for many investigators, the benefit in terms of OS was too marginal to justify such an aggressive procedure. It is indeed widely accepted that consolidation therapy should rely on a highly efficient combination of drugs with limited toxicity and be administered for a limited period of time. Experiences testing consolidation therapy in myeloma remain scarce because they started in the era of novel therapies. Initial results suggested that novel agents after auto-SCT may further increase the rate of high-quality responses and improve both PFS and OS. In patients with good response after auto-SCT, consolidation therapy not only increases the CR rate but also upgrades the level of response and even yields molecular remissions that are associated with longer PFS. The largest consolidation therapy results are derived from an Italian randomized phase III study that assessed the superior efficacy of VTD versus TD as induction therapy before double auto-SCT for newly diagnosed myeloma patients. In this randomized study, superior CR and nCR rates and extended PFS were demonstrated with VTD versus TD as induction therapy before, and consolidation after, double auto-SCT. A recent per-protocol analysis specifically assessed the efficacy and safety of consolidation with VTD or TD. Before starting consolidation, CR/nCR rates were not significantly different in the VTD and TD arms .After consolidation, CR and CR/nCR rates were significantly higher for VTD-treated versus TD-treated patients. VTD consolidation significantly increased CR and CR/nCR rates, but TD did not, and 3-year postconsolidation PFS was significantly longer for the VTD group. Thus, VTD consolidation therapy significantly contributed to improve clinical outcomes observed for patients randomly assigned to the VTD arm of the study. Data from other reports are consistent with the above findings of the clinical benefit of consolidation therapy after auto-SCT. In another randomized trial, the use of bortezomib as single-agent consolidation therapy was compared with no consolidation in a population of bortezomib-naïve patients and proved to be a superior approach. The interest of a second auto-SCT compared with consolidation therapy and the respective impact of consolidation and maintenance (see Chapter 8) are unknown, and randomized studies addressing these questions are underway.

8. What is the impact of maintenance therapy after auto-SCT?

When discussing treatment strategies, the terms "consolidation" and "maintenance" therapy are often used synonymously, although they identify two treatment approaches with different goals. In contrast to consolidation therapy—which should, by definition, be short term—maintenance therapy is generally assumed to be long term and typically

aims to reduce the risk of progression or relapse and to prolong OS. Therefore, maintenance therapy should ideally rely on a gentle treatment for a prolonged period, with long-term safety being a major issue.

Given its efficacy in different myeloma treatment settings, and being an oral agent, thalidomide was tested in different randomized trials as a candidate drug maintenance treatment. Although these studies varied in design, dose, and duration of thalidomide treatment, most of them showed a significant benefit in terms of response rates (i.e., CR and/or VGPR) and/or PFS. However, OS was not significantly prolonged in all studies, and a shorter OS after relapse could be observed in some studies in the thalidomide group. Also, prolonged treatment with thalidomide was associated with a high risk of peripheral neuropathy, fatigue, and different other side effects, all of which represent a serious obstacle to the wider use of the drug in the maintenance setting.

In the transplant-eligible myeloma population, two large placebo-controlled multicenter randomized trials could establish the potential benefit of long-term use of lenalidomide maintenance. Both studies could show a dramatic improvement of PFS in patients receiving low-dose lenalidomide after auto-SCT until progression. In one of these studies (the Cancer and Leukemia Group B study), longer PFS translated into a significantly longer OS. In both trials, lenalidomide was as superior in all predefined prognostic subgroups. Treatment was well tolerated. However, in both studies, an unexpected overincidence of secondary malignancies (both solid tumors and hematologic malignancies) was described. The pathophysiology of these secondary malignancies is still yet to be deciphered. At present, long-term maintenance with lenalidomide cannot be recommended to all patients because OS benefit is not yet widely established, and because of the concerns about long-term safety. Ongoing studies are focusing on determining the optimal duration of maintenance therapy and the profile of patients who might benefit most from lenalidomide maintenance. Obviously, the combined use of both consolidation and maintenance therapies is still controversial.

9. What are the outcomes with novel agents plus auto-SCT in MM?

The use of novel agents as part of the induction treatment prior to HDT–auto-SCT has significantly increased the post-auto-SCT CR rate. With triple combinations such as VTD, CR rates >40% and CR plus VGPR rates of 60–80% can now be achieved. Although there is no direct evidence that this higher CR rate translates into a better outcome in the absence of trials looking only at the prognostic impact of induction treatment, it has been shown that achieving CR or at least VGPR before auto-SCT is associated with a longer PFS.

The use of post-auto-SCT consolidation with novel agents further increases the CR rate up to 60% or upgrades the level of CR to stringent, phenotypic, or even molecular CR. As a consequence, PFS is prolonged; for example, in the Italian experience with VTD as induction and consolidation therapy and double auto-SCT, the estimated 5-year PFS was 62%.The use of novel agents as maintenance therapy after auto-SCT significantly prolongs PFS. The most striking results have been obtained with lenalidomide. The use of novel agents at all phases of therapy was initiated by the Arkansas group. Long-term results of the so-called Total Therapy 3 are the best ever achieved, with 5-year EFS and OS of, respectively, 69% and 72%. Moreover, out of the 62% of patients who achieved CR, 82% retained CR 5 years later. However, whether all phases of this complex and aggressive strategy, including double auto-SCT, are needed in all patients is unknown. Randomized trials are needed to determine the respective impacts of consolidation (with a second auto-SCT or with novel agents) and of maintenance therapy.

10. What is the role of auto-SCT as salvage therapy?

Almost all patients ultimately relapse, and no plateau is observed in the survival curves. At the time of disease recurrence, there is no one standard salvage approach, but instead various therapeutic options are available, including novel agents-based therapy, which is administered for a fixed duration of time or until progression.

When a frozen autologous graft is still available, it is also possible to repeat high-dose therapy in patients who previously responded to the front-line application of high-dose melphalan and auto-SCT. Over time, several reports have demonstrated the feasibility of this salvage strategy. The majority of data is derived from retrospective studies and is based on experiences with small numbers of selected patients. In this setting, PFS has been shown to range from 7 to 22 months, and the treatment-related mortality was acceptable, ranging from 0% to 8%. Various prognostic factors for prolonged PFS have been described, such as the duration of response to the first high-dose therapy or the number of lines of therapy prior to salvage auto-SCT. Currently, it is realistic to assume that repeat administration of high-dose melphalan with auto-SCT can be considered for salvage therapy if the interval between prior auto-SCT and relapse is $\geq$1.5–2 years. Prolonged duration of remission after the first auto-SCT is associated with improved PFS and OS after second auto-SCT.

11. Should newly diagnosed patients with MM have upfront or late auto-SCT in myeloma?

Until recently, the available research evidence demonstrated that the use of HDT followed by auto-SCT should be the preferred treatment option for young myeloma

patients, because HDT–auto-SCT was associated with a significant improvement in outcome. However, already in the initial period when HDT–auto-SCT was compared with conventional chemotherapy, whereas almost all randomized studies showed longer PFS, the OS benefit was less clear partly because some patients received auto-SCT as salvage therapy for relapse in the conventional chemotherapy arm. As a consequence, one must acknowledge that auto-SCT could improve OS whether performed early, as first-line therapy, or late as rescue treatment. Nevertheless, a global consensus was strongly in favor of early front-line auto-SCT.

Recently, based on the impressive results achieved with novel agents, including those achieved in elderly patients not receiving auto-SCT, the dogma of mandatory early front-line auto-SCT versus late rescue auto-SCT in the younger population was challenged by many investigators. For instance, the lenalidomide–dexamethasone combination was evaluated by different investigators as primary therapy both in young patients who did not wish to undergo auto-SCT and in older patients who were not candidates for auto-SCT. Another study tested the lenalidomide–bortezomib–dexamethasone combination. The later studies showed that such modern combinations may also yield high complete remission rates and promising PFS estimates. Moreover, these treatments are rather well tolerated and may be given for longer periods. Interestingly, patients who did not receive auto-SCT upfront might still receive it at the time of relapse. Therefore, the role of upfront auto-SCT is being questioned in many centers worldwide. Ongoing randomized trials comparing upfront auto-SCT versus novel agents and no transplant till relapse will allow a definitive answer to this question. In the first of these sorts of trials, preliminary analysis in a study by Palumbo and colleagues (2010), suggests that auto-SCT reduces the risk of progression but does not improve OS. Longer follow-up is needed. It is actually possible that some subgroups of patients may still need upfront auto-SCT in combination with novel agents.

Selected reading

Attal M, Harousseau JL, Stoppa AM, *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma: Intergroupe Francais du Myelome N Engl J Med. 1996;335:91–7.

Mohty M, Ho AD. In and out of the niche: perspectives in mobilization of hematopoietic stem cells. Exp Hematol. 2011;39: 723–9.

Palumbo A, Bringhen, S, Petrucci MT, *et al*. Intermediate dose melphalan improves survival of myeloma patients aged 50–70. Blood. 2004;104:3052–57.

Fenk R, Liese V, Neubauer F, *et al*. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. Leuk Lymphoma. 2011;52:1455.

Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies Blood. 2011;118:3205–11.

CHAPTER 60

Allogeneic hematopoietic cell transplantation in multiple myeloma

Jasleen Randhawa[1], Veerpal Singh[2], and Parameswaran Hari[1]

[1]Medical College of Wisconsin, Milwaukee, WI, USA
[2]Fox Valley Hematology Oncology, Elgin, IL, USA

Introduction

Due to our inability to cure multiple myeloma (MM) with current therapies, including autologous stem cell transplantation (auto-SCT), there has been a sustained interest in allogeneic hematopoietic cell transplantation (allo-HCT) given its use of a myeloma-free donor cell graft and the possibility of a donor-driven, immune-mediated graft-versus-MM effect. Based on reporting to the Center for International Blood and Marrow Transplant Research (CIBMTR), fewer than 300 patients underwent an allo-HCT for MM between 2010 and 2011.

The evolution of the allogeneic approach in MM

• What are the risks of allo-HCT in MM, and how has the field evolved over time?

Historically, allo-HCT preceded by classic myeloablative conditioning was of limited applicability except in very young patients, and it was associated with unacceptable treatment-related mortality (TRM) of 40–60%. The allo-HCT arm of the US Intergroup S9321 study was terminated after an early TRM of 53% was observed. However, allo-HCT survivors demonstrated a plateau survival at 22% with no late relapse events, indicating a likely cure.

The advent of nonmyeloablative and reduced-intensity conditioning (NST–RIC) approaches in the 2000s led to more patients receiving allo-HCT using these regimens. A CIBMTR analysis demonstrated a major practice switch to NST–RIC-based allo-HCT with concomitant reduction in the numbers of myeloablative allografts. Lower-intensity conditioning also resulted in expanded eligibility, with older MM patients receiving allo-HCT and increasing numbers of allo-HCT performed after auto-SCT in a tandem auto-SCT–allo-HCT fashion. Interestingly, survival after allo-HCT did not improve over time since the decline in TRM was negated by an increase in relapse risk in later years.

Several phase II studies were reported utilizing the strategy of an initial auto-SCT followed (usually 3–6 months later) by lower-intensity allo-HCT using NST–RIC. The rationale was to uncouple myeloablation (achieved by the auto-SCT) from the immune-mediated benefits of the allo-HCT approach. Excellent short-term (24-month) outcomes could be achieved with TRM ranging from 11% (for related donor grafts) to 26% (for unrelated donor grafts). Median event-free survival (EFS), however, was disappointing at 3 years, and the median time to progression was 5 years. Five-year overall survival (OS) and EFS were 64% and 36%, respectively, with patients transplanted within 10 months of initial therapy having 5-year OS of 69% and EFS of 37%. The lack of an apparent cure with ongoing late relapses was disappointing.

Randomized trials

• Are there modern randomized prospective trial data regarding the role of upfront allo-HCT in MM?

Several randomized trials (summarized in Table 60.1) have attempted to evaluate the tandem auto-SCT–allo-HCT approach versus tandem auto-SCT in the upfront transplant setting. Bruno *et al*. (2009) randomly assigned patients (on sibling donor availability) to allo-HCT versus a second tandem auto-SCT after initial induction and a first auto-SCT. Eighty patients with an HLA-identical sibling were assigned to 2 Gy (Gray) total body irradiation (TBI)-based

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 60.1 The autologous stem cell transplantation (auto-SCT)–allogeneic hematopoietic cell transplantation (alloHCT) approach versus tandem auto-SCT in the upfront transplant setting.

Author	*N* total / *N* allo	Trial setting	Conditioning	CGVHD allo-HCT	TRM	OS	PFS	Conclusion
Bruno *et al.* (2007/2009)	245/58	Postinduction biological assignment based on sibling match donor	MEL auto-SCT followed by TBI 2 Gy vs. MEL doses 100–200 mg/m^2	32%	10%	Median 80 vs. 54 months $P = 0.01$	Median 35 vs. 29 months $P = 0.02$	Clear benefit for allo-HCT in intention to treat donor vs. no donor analysis
Garban *et al.* (2006)	284/65	Parallel prospective studies limited to high-risk disease	MEL 200 auto-SCT followed by FLU-BU + ATG alloSCT vs. MEL 200 auto-SCT	42%	11%	Median 34 vs. 48 months $P = 0.07$	Median 19 vs. 22 months $P = 0.58$	30% did not complete allo-HCT. No benefit to allo-HCT in this study
Rosinol *et al.* (2008)	110/25	Limited to patients not in CR after a first auto-SCT	FLU-MEL allo-SCT vs. auto-SCT	66%	16%	Median NR vs. 58 months $P = 0.9$	Median 20 vs. 26 months $P = 0.4$	Higher CR rate after allo-HCT but no survival benefit
Knop *et al.* (2009)	199/126	Limited to patients with 13q– by FISH Unrelated donor grafts in 60%	MEL 200 auto-SCT followed by FLU-MEL vs. MEL 200 auto-SCT	N/R	13%	3 year OS 60% vs. 72% $P = 0.22$	N/R	Largest trial in high-risk patients and with unrelated donors
Gahrton *et al.* (2013)	357/108	Postinduction biological assignment based on sibling match donor	MEL 200 auto-SCT followed by FLU-TBI2 Gy vs. MEL 200 auto-SCT	54%	13%	8 yr OS 49% vs. 39 % $P = 0.03$	8yr PFS 22% vs. 12% $P = 0.02$	Allo-HCT with lower risk of relapse and with improved PFS. Benefit for higher-risk del 13 subset.
Krishnan *et al.* (2011)	710/226	Postinduction assignment based on availability of matched sibling donor	MEL 200 auto-SCT followed by TBI 2 Gy allo-HCT vs. MEL 200 auto-SCT	54%	11%	3 year OS 77% vs. 80%	3 year PFS 43% vs. 46%	Allo-HCT with no benefit
Lokhorst *et al.* (2012)	Not strictly a randomized study—donor vs. no donor analysis of HOVON 50		MEL 200 auto-SCT followed by TBI 2 Gy allo-HCT	64%	16%	6 year OS 55% in both groups	6 year PFS 28% (donor group) vs. 22% no donor	No benefit to having a family donor but allo-HCT was by center preference. Relapse lower for those with donors.

ATG, antithymocyte globulin; BU, busulfan; CGVHD, chronic graft-versus-host disease; Flu, fludarabine; Gy, gray; HCT, ; MEL, melphalan; N/R, not reported; OS, overall survival; PFS, progression-free survival; TBI, total body irradiation; TRM, treatment-related mortality.

allo-HCT, and 82 patients to a second auto-SCT. After a follow-up of 7 years, median OS was not reached ($P = .02$) and PFS was 39 months ($P = .02$) in the 58 patients who received an allograft whereas OS was 5.3 years and EFS 33 months in the 46 who received two autografts. In those achieving complete remission (CR) after allo-HCT, 53% were in continuous CR compared with 19% in CR following tandem auto-SCT. This was the first randomized study that showed an advantage for allo-HCT over auto-SCT in MM and indicated that CR achieved after allo-HCT was durable.

Other prospective randomized studies have demonstrated discordant results. In the BMT CTN (Blood and Marrow Transplant Clinical Trials Network) 0102 multicenter study, tandem auto-SCT and auto-SCT–allo-HCT arms were similar for the primary endpoint of 3-year

progression-free survival (PFS) (46% in the tandem auto-SCT group vs. 43% in the other). Higher-risk patients also did not benefit from the auto-SCT–allo-HCT approach in terms of 3-year PFS.

Another randomized European study has now, with extended 8-year follow-up, continued to show improved PFS and OS for the tandem auto-SCT–allo-HCT approach versus tandem auto-SCT. At 96 months, PFS and OS were 22% and 49% versus 12% ($P = 0.027$) and 36% ($P = 0.030$) favoring tandem auto-SCT–allo-HCT. Relapse was lower in the allo-HCT cohort (60% vs. 82%; $P = 0.0002$), although TRM was higher in this cohort. Interestingly, patients who relapsed and progressed following allo-HCT had a significantly higher OS than the patients who relapsed after tandem auto-SCT. The graft-versus-MM effect is thought to have played a major role in this phenomenon.

Meta-analyses of the published allo-HCT versus auto-SCT studies have concluded that while CR rates are higher for allo-HCT, a consistent survival benefit cannot be demonstrated. In summary, while allo-HCT induces high CR rates and provides superior antirelapse potential compared with auto-SCT, TRM rates remain prohibitive. In the absence of a clear-cut survival advantage across studies and with recent improvements in induction and maintenance therapy, some experts have suggested the end of allo-HCT in MM. However, MM is still incurable with novel induction followed by auto-SCT, and while two randomized studies have shown a survival benefit for allo-HCT, no study has suggested an inferior outcome with allo-HCT. It is also notable that these allo-HCT trials were performed in patients who had not received highly effective modern induction regimens.

• What accounts for the discrepancy between randomized studies?

The discordant outcomes are likely due to variations in the conditioning regimens employed, patient selection, MM risk profile, length of follow-up (shorter for the negative BMT CTN study), and the use of agents such as ATG (antithymocyte globulin), which may reduce the potential for graft-versus-MM effect.

• How strong is clinical evidence for a graft-versus-MM effect?

Several lines of evidence exist. Myeloma (idiotype)-specific CD4 T-cell response could be transferred from an immunized marrow donor to patients in early studies. The success of donor lymphocyte infusions (DLIs) in patients with residual or progressive MM after allo-HCT is corroborative. Although the durability of responses after DLI is modest, the occurrence of GVHD (acute or chronic) after DLI seems to be the most powerful predictor of a response. The prospective BMT CTN 0102 study and a retrospective CIBMTR study also found that the occurrence of chronic GVHD after allo-HCT correlated with freedom from progressive MM. In vitro or in vivo T-cell depletion has been associated with higher relapse rates and a need for DLI after allo-HCT in MM.

• Who are the patients for whom current standard approaches are ineffective and allo-HCT is reasonable?

• Define ultra-high-risk MM.

The persistent risk of higher TRM and the prospect of chronic graft-versus-host disease (GVHD) limit the use of allo-HCT to younger patients with MM. Even in younger patients with MM, prospective data from the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the German Multicenter Myeloma Group (GMMG) study HOVON-65–GMMG-HD4 indicate that with bortezomib-based induction followed by single or tandem auto-SCT and consolidation–maintenance strategies, durable long-term remissions can be achieved. Allo-HCT should therefore be limited to those with exceptionally high risk of early relapse with current standard approaches.

The term "ultra-high-risk MM" is used to characterize patients who by baseline risk stratification have an estimated median survival of 24 months or less. This subgroup includes those presenting with International Staging System (ISS) stage 3 disease and with specific genetic abnormalities such as deletion 17p, immunoglobulin heavy-chain gene translocations t(4;14) or t(14;16), and chromosome 1q21 amplification (>3 copies). Since the outcomes for these patients remain poor despite the best available alternative therapies, allo-HCT may be considered despite the risk of higher TRM and GVHD. In the uncommon situation of a relatively young (<50 years old) ultra-high-risk patient, even higher-intensity myeloablative conditioning followed by allo-HCT is reasonable as long as patients are aware of their unfavorable prognosis and are willing to accept the risks of conditioning.

A subanalysis of the HOVON-65 International Stage (ISS GMMG-HD4 study identified a high-risk subgroup (comprising approximately 18% of patients) characterized by the presence of del(17p13), t(4;14), and 1q21 (>3 copies) and a high ISS score of II or III. Median PFS for this group was only 18.7 months. Those relapsing early (≤18 months from transplant) after modern novel agent-based induction and auto-SCT represent another group where allo-HCT may be considered.

Practice point

In patients with ultra-high-risk MM, it is our policy to offer upfront allo-HCT to patients if they are eligible for allo-HCT by virtue of young age, performance status, and comorbidity score.

• When should allo-HCT be offered in the disease course of MM—upfront or at relapse?

As a curative-intent procedure and as an adjunct and alternative to an auto-SCT, allo-HCT has the best long-term outcomes and highest curative potential when it is part of a planned upfront strategy in newly diagnosed patients. Since deferring allo-HCT to relapse helps avoid the potential early TRM, there is interest in offering it to patients relapsing after auto-SCT.

However, a recent CIBMTR analysis and several single-center studies have suggested that for the multiply relapsed patient in the salvage setting, allo-HCT does not offer significant advantages in survival or a prospect of cure. In the CIBMTR study, 152 patients, all of whom received an NST–RIC allo-HCT after relapse following a prior auto-SCT (50% relapsing within 24 months), were analyzed. Even with a relatively acceptable TRM of 13% in the first year, the 3-year PFS and OS were 6% and 20%, respectively. It appears that the benefit is highest when allo-HCT is used earlier in the disease course and when used as a strategy for consolidation of a remission.

Practice point

In relapsed MM, it is our policy to offer allo-HCT to patients who are in therapy-sensitive early relapse and after they achieve a deep remission such as a very good partial response (VGPR) or CR. We do not offer allo-HCT to multiply relapsed patients or those with uncontrolled MM.

Case study 60.1

Genetically defined high-risk myeloma in the young patient

A 34-year-old man presented with IgA lambda multiple myeloma (stage III ISS). Bone marrow biopsy showed 60% plasma cells on marrow aspirate with karyotypic chromosome 13 deletion and deletion of 17p on fluorescent in situ hybridization (FISH) analysis. After initial induction with bortezomib, lenalidomide, and dexamethasone, he achieved a partial remission. Subsequently, he underwent an auto-SCT and achieved a VGPR. HLA typing identified a matched sibling donor.

• Is there a role for allo-HCT for this patient?

Deciding on allo-HCT for the high-risk MM patient in practice

The biological factors that influence risk and prognosis in myeloma need to influence the choice of therapy in order to deliver the best risk-adapted approach to patients. Biologic risk at diagnosis differentiates patients into three risk groups—high, intermediate, and standard. According to the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) guidelines, in the absence of concurrent trisomies, patients with t(4;14) are considered intermediate risk, while 17p deletion, t(14;16), and t(14;20) are considered high risk. In those with intermediate risk driven by t(4:14), a bortezomib-based induction therapy followed by bortezomib-based maintenance may overcome the higher risk. Additionally, there are some patients for whom current tests do not capture their true risk, which is subsequently revealed by refractoriness to novel agent therapy or rapid relapses following such therapy.

High-risk MM patients may acquire new clonal abnormalities and present with aggressive, rapidly growing relapses and sometimes secondary plasma cell leukemia. The benefits of novel agent therapy have not accrued to this subgroup, either. A more aggressive approach to therapy with the intent to produce a deep CR and prevent relapse is warranted in these patients. In the absence of an effective established standard of care, these patients should be enrolled in clinical trials whenever possible. In the most recent update of the European Group for Blood and Marrow Transplantation (EBMT) NMAM study, at a median follow-up of 96 months, 21% of patients with the higher-risk del 13 abnormality receiving tandem auto-SCT–allo-HCT were progression free versus 5% in the tandem auto-SCT group. Hence, a survival benefit was noted with tandem auto-SCT–allo-HCT in spite of the higher TRM associated with the regimen.

Practice point

It is our practice to offer allo-HCT either on a clinical trial or as standard of care to younger eligible patients with well-defined high-risk features (Table 60.2). This philosophy is based on the proven benefit of allo-HCT in multiple randomized trials as the best antirelapse strategy and also with the expectation that with careful patient selection, TRM can be reduced significantly. The benefits of a prolonged PFS after allo-HCT in patients with high-risk disease, while exciting, may still be enhanced by maintenance strategies (discussed further in this chapter). The risks associated with the procedure in terms of TRM and GVHD have to be acknowledged.

Update

Patient went on to receive a RIC allogeneic transplantation from a matched, related sibling donor and is in continuous CR at 4 years of follow-up.

Table 60.2 Who, when, and how of allogeneic HCT for MM (authors' practice).

A. PATIENT FACTORS

Age: Approximately 15% of patients with MM are <55 years old. Allo-HCT is an option in these patients.
Performance status (PS) and comorbidity: Allo-HCT is feasible with low TRM in those with good PS and low comorbidity scores. We use PS and comorbidity score as exclusion criteria to lower TRM.
Younger patients with MM (<55 years) with good PS and low comorbidity scores are considered allo-HCT eligible at our center.

B. DISEASE FACTORS

Newly diagnosed MM—myeloma risk stratification: We attempt karyotypic, plasma cell—enriched FISH-based and gene expression profiling (GEP)-based (Arkansas model) risk stratification in allo-HCT eligible patients at diagnosis.
If any of the following are discovered, we proceed to donor search:
1. Ultra-high-risk MM: defined by ISS stage 3 or a high plasma cell proliferation index *and* the presence of any or a combination of the following specific genetic changes: del(17p), chromosome 1 q gains, t(14:20), t(14:16), OR a high-risk gene expression profile.
2. Primary plasma cell leukemia
3. Primary refractory MM: patients who are refractory to or progressing on combination therapy involving both full doses of lenalidomide and a proteasome inhibitor (bortezomib or carfilzomib) after four cycles
4. Relapsed MM: Early relapse after auto-SCT: defined as those relapsing with clinical disease (*not* biochemical progression) within 18 months after induction and auto-SCT. These patients are considered if they achieve a VGPR or better disease status with salvage therapy.
We offer allo-HCT consultation to eligible patients fulfilling the above criteria for short survival with current therapies and auto-SCT

C. DONOR EVALUATION

Ideal donor: Matched sibling or an unrelated donor matched at all A, B, C, and DR loci using high-resolution typing.
If an ideal donor has been identified, allo-HCT is offered either on a clinical trial protocol or as standard of care for patients defined above AFTER risks and benefits have been discussed.
Alternative donor: If an ideal donor is not available, *we offer allo-HCT using a haploidentical or other mismatched donor only on a clinical trial protocol and only for those without an ideal donor.*

D. CONDITIONING THERAPY

For those who have not had an auto-SCT or are more than 1 year from an auto-SCT, we offer myeloablative or reduced-intensity regimens. Nonmyeloablative regimens are not used.

E. POST-ALLOTRANSPLANT THERAPY

At day 100, in patients with no GVHD and with adequate performance status, we initiate maintenance therapy either on a clinical trial or as standard of care with lenalidomide or bortezomib, with intent to continue such therapy for 3 years.

Case study 60.2

Plasma cell leukemia

A 54-year-old man presented with pancytopenia and significant peripheral blood plasmacytosis (absolute plasma cell count >20,000/mm^3). Bone marrow biopsy revealed CD56-positive, CD38-positive, kappa-restricted plasma cells at 87% in the bone marrow with t(11;14) translocation. Free light-chain analysis demonstrated a kappa excess, and an immunoglobulin G (IgG) kappa monoclonal spike was demonstrated in the serum and urine. A diagnosis of primary plasma cell leukemia (PCL) was made.

- **What transplant options are suitable for this patient? Is there a role for allo-HCT for PCL in first remission?**

Primary PCL is an aggressive neoplasm, and patients generally present at a younger age and with worse performance status at diagnosis compared to MM patients. Also, PCL patients have a higher incidence of extramedullary involvement with extensive bone disease. Although the importance of cytogenetic abnormalities in PCL is not fully clear, t(4;14), del(1p21), and *MYC* gene rearrangements have been associated with poor outcomes.

(*Continued*)

In a comparison from the EBMT, patients with PCL receiving auto-SCT (compared to MM patients) were more likely to suffer TRM and achieve a CR, but OS was inferior to that of the MM patients since responses were not sustained. A CIBMTR study of 97 primary PCL patients reported a 3-year PFS and OS of 34% and 64%, respectively, while 50 allo-HCT recipients (16 with NST–RIC regimens) demonstrated a PFS of 18% and OS of 56% in the NST–RIC cohort with a significant relapse rate of 39%. Although inconclusive, these data suggest that in PCL (as in MM), the benefits of lower relapse rates following allo-HCT are often offset by the high TRM.

Practice point
In young persons with PCL, given the extremely high risk of relapse after an auto-SCT, the option of allo-HCT should be explored, and its risks and benefits should be discussed. At our center, for patients with PCL who are at very high risk of early relapse, allo-HCT is offered in first remission.

Update
The patient achieved a stringent complete remission with initial bortezomib, thalidomide, dexamethasone, cisplatin, adriamycin, cyclophosphamide, and etoposide (VDTPACE) combination chemotherapy followed an auto-SCT. He then received a matched sibling donor allo-HCT in first CR and continues in CR on lenalidomide maintenance post allo-HCT.

- **Is there a role for maintenance after allogeneic HCT?**

Lenalidomide

Lenalidomide (LEN), a potent antimyeloma agent that also upregulates natural killer (NK)-cells and NK-T-cells, has been shown to improve time to disease progression and OS when used as ongoing maintenance therapy after auto-SCT. LEN maintenance after allo-HCT is attractive since the graft-versus-MM effect could be augmented by LEN-induced stimulation of the alloreactive lymphocytes and NK-cells. Laboratory data suggest that in the post allo-HCT setting, LEN may induce disease response and also GVHD. Additionally, LEN may augment the efficacy of antimyeloma vaccines. In another study, objective responses to salvage treatment with lenalidomide were noted in 83% (including 29% CR) of patients relapsing after an allo-HCT. However, 31% developed or exacerbated an acute GVHD, which was significantly associated with an improved antimyeloma response.

In practice, LEN maintenance after allo-HCT may be fraught with special risks and limited in feasibility. In the HOVON 76 trial of maintenance lenalidomide starting 1–6 months after allo-HCT for newly diagnosed MM, 53% developed GVHD, 37% acute GVHD (at a median of 18 days on LEN), and 17% chronic GVHD, leading to premature discontinuation of therapy in 43% of the patients. Becker *et al*. (2010) have reported the use of LEN maintenance starting at a median of day 96 post transplant in 30 high-risk patients after allo-HCT with lower GVHD rates ($\geq$grade 3 in 17%). PFS and OS at 1 year from initiation of lenalidomide were 68% and 88%, respectively, suggesting a benefit and manageable GVHD risk.

Bortezomib

The intrinsic antimyeloma activity of proteasome inhibitors (PIs) and their ability to suppress GVHD without mitigating the graft-versus-MM effect make bortezomib an attractive option for post-allo-HCT maintenance. More studies are needed to define the role of bortezomib and other PIs in the planned maintenance post-allo-HCT setting given their efficacy in GVHD prevention.

Measuring the efficacy of allo-HCT and defining deeper remissions after allo-HCT

- **Does measurement of minimal residual disease provide clues to relapse risk?**

Deeper levels of remission after therapy in MM correlate with superior PFS, but no level of remission that equates to a cure has been defined. In a study of patients in CR following allo-HCT, those who were polymerase chain reaction negative for plasma cell clone-specific markers were relapse-free at 5 years. In another study, compared with auto-SCT recipients, allo-HCT recipients were more likely to be in molecular CR (MCR), which in turn predicted for lower relapse rates. These results support the concept that MCR is associated with longer relapse-free survival and reduced relapse rates. However, the presence of MCR does not equate with cure, and such testing is not routinely available outside of research. Similar depths of remission can possibly be assessed by monitoring for the presence of aberrant plasma cells in marrow aspirates using multiparameter flow cytometry at serial time points. Those with no malignant plasma cells at both 3 and 6

months post auto-SCT were noted to have a 5-year overall survival of 100% in early studies. Minimal residual disease techniques validated in the auto-SCT setting may translate to allo-HCT recipients too and identify those requiring additional maintenance or immune-based interventions posttransplant.

- **How is relapse after allo-HCT treated? Is it different from relapse after chemotherapy or auto-SCT?**

Treatment options for relapsed MM after allo-HCT include DLI alone or in combination with salvage chemotherapy. Novel agents and combinations involving novel agents have been used successfully. A higher risk of GVHD has been reported in those treated with LEN, but special precautions other than close monitoring are not needed.

- **What are the risks and benefits of DLIs?**

DLIs are able to induce a clinically meaningful graft-versus-MM effect in some patients relapsing after allo-HCT but with a risk of inducing severe GVHD. In a series of 54 patients, DLI yielded OS and CR rates of 52% and 17%, and acute and chronic GVHD in 57% and 47% patients, respectively. Disease control from DLIs was superior for those in remission and for those who developed GVHD. Another strategy is the use of prophylactic DLIs at defined time periods (usually 6 months) or in graded incremental T-cell doses for improving donor-derived T-cell immunity and to convert those with partial chimerism to full donor hematopoiesis. An exciting area of research is to use specific donor-derived T-cells directed at myeloma-associated antigens such as WT1 or antigens in the cancer testis antigen family.

Practice point

Our practice is to offer DLI after salvage therapy to augment donor immunity in patients who relapse after allo-HCT.

The future of allo-HCT for MM

Whether tandem auto-SCT–allo-HCT approaches are beneficial for high-risk MM is not entirely clear and should be further assessed in future trials designed for this subgroup of patients.

Selected reading

Bruno B, Rotta M, Patriarca F, *et al*. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med. 2007;356:1110–20.

Bruno B, Rotta M, Patriarca F, *et al*. Nonmyeloablative allografting for newly diagnosed multiple myeloma: the experience of the Gruppo Italiano Trapianti di Midollo. Blood. 2009;113:3375–82.

Gahrton G, Iacobelli S, Bjorkstrand B, *et al*. Autologous/reduced-intensity allogeneic stem cell transplantation versus autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 2013;121(25):5055–63.

Garban F, Attal M, Michallet M, *et al*. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood. 2006;107:3474–80.

Knop S, Liebisch P, Hebart H, *et al*. Allogeneic Stem Cell Transplant Versus Tandem High-Dose Melphalan for Front-Line Treatment of Deletion 13q14 Myeloma – An Interim Analysis of the German DSMM V Trial. ASH Annual Meeting Abstracts. 2009;114:51.

Krishnan A, Pasquini MC, Logan B, *et al*. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol. 2011;12:1195–203.

Kumar S, Zhang MJ, Li P, *et al*. Trends in allogeneic stem cell transplantation for multiple myeloma: a CIBMTR analysis. Blood. 2011;118:1979–88.

Lokhorst HM, van der Holt B, Cornelissen JJ, *et al*. Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study. Blood. 2012;119:6219,25; quiz 6399.

Rosinol L, Perez-Simon JA, Sureda A, *et al*. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood. 2008;112:3591–3.

van de Donk NW, Kroger N, Hegenbart U, *et al*. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. Bone Marrow Transplant. 2006;37:1135–41.

PART 9

Special Issues in Hematology

CHAPTER 61

Role of PET scan in lymphomas

Matthew A. Lunning and James O. Armitage
University of Nebraska Medical Center, Omaha, NE, USA

Case study 61.1

A 52-year-old man is referred from his primary care physician after a contrast-enhanced computed tomography (CT) scan for epigastric fullness and early satiety demonstrated diffuse adenopathy below the diaphragm. An excisional biopsy of a right inguinal lymph node demonstrated diffuse large B-cell lymphoma (DLBCL). A bone marrow biopsy was negative for involvement with lymphoma. You clinically surmise the patient has stage IIA disease. To complete staging, you order a positron emission tomography (PET)–CT.

1. What is the likelihood the patient will have evidence of extranodal disease leading to stage IV disease?

A. 5–10%
B. 20–25%
C. 40–60%
D. 80–90%

PET–CT remains a more sensitive and specific modality for the initial staging of both Hodgkin and, in this case, aggressive non-Hodgkin's lymphomas (DLBCL). In a retrospective study, the sensitivity and specificity of PET–CT for nodal involvement was, respectively, 94% and 100% and for extranodal disease was 88% and 100%. In comparison, contrast-enhanced CT for extranodal disease had an inferior sensitivity and specificity of 50% and 90%, respectively. The knowledge of sites of lymphoma prior to treatment may result in stage migration, a change in therapy, and the duration of therapy. A questionnaire-based examination of the utility of PET–CT in staging of lymphomas resulted in a change in stage in 44% of cases reviewed, with 21% being upstaged. PET–CT findings resulted in intermodality and intramodality changes in 42% and 10%, respectively. PET–CT is essential in the work-up of newly diagnosed DLBCL.

Case study 61.2

A 72-year-old woman with Ann Arbor stage IIIA DLBCL has tolerated four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) on an every 21-day schedule. The patient has had a significant reduction in her palpable disease burden on clinical exam and normalization of her lactate dehydrogenase (LDH). You order a PET–CT to confirm your clinical suspicion, and it shows a near-complete remission except for residual lymph node avidity in an aortocaval lymph node with a delta standardized uptake value (SUV) of 13 (20 to 7).

1. How would you recommend proceeding based on the PET–CT findings?

A. Order a biopsy to confirm primary refractory disease
B. Switch to curative second-line therapy, and refer for autologous stem cell transplantation

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

C. Transition to palliative therapy
D. Continue R-CHOP for a total of six cycles, and repeat PET–CT 4–6 weeks after completion

Interim PET–CT in DLBCL has become more in vogue as the test becomes readily available. To date, the results of interim scanning remain murky; however, a negative interim PET–CT does carry a high negative predictive value. However, there remain several current barriers to recommending interim PET–CT. These barriers include no standard time for interim scanning (e.g., after cycles 2, 3, or 4); what constitutes a positive or negative scan, considering the high interreader disagreement; and whether there should be different values used in the interim setting compared to those for pre- and posttreatment PET–CT. Furthermore, many other variables such as timing of last chemotherapy and growth factor use may lead to false-positive PET–CT. The Deauville criteria, a 5-point visual-based system used in interim PET–CT evaluation, has been used effectively in Hodgkin lymphoma, but has not been as effective in DLBCL. At this time, outside of a clinical trial, interim PET–CT for DLBCL remains investigational unless there is clinical concern for primary progressive disease. It should be noted that the end-of-treatment PET–CT has been shown to be predictive of event-free survival, progression-free survival, and overall survival.

2. A biopsy was performed for this patient. She asks the likelihood that the positive PET–CT finding will represent residual DLBCL. What value would you quote her?

A. 90%
B. 60–70%
C. 35–45%
D. 10–20%

While ordering an interim PET–CT is controversial in DLBCL, what to do with an interim PET–CT report that does not explicitly state "no evidence of avid lymphadenopathy" remains one of the most debated clinical conundrums. Few studies evaluating the utility of interim PET–CT have performed biopsies on accessible PET–CT "positive" lesions at this juncture. Given the concern for false-positive interim PET–CT lesions in advanced-stage DLBCL, Moskowitz and colleagues (2010) performed biopsies on patients with a positive interim PET–CT as defined by International Harmonization Project criteria. In 97 patients with advanced-stage DLBCL, 38 patients were deemed PET–CT positive after four cycles of accelerated R-CHOP; however, only 5 (13%) patients had evidence of viable DLBCL in the biopsy specimen. Confounding variables in this study include the schedule of the rituximab-containing regimen, and the timing of the interim PET–CT resulting in PET–CT positivity. However, these data, while limited to a single center, bring concern regarding the utility of interim PET–CT.

Case study 61.3

A 28-year-old woman with a history of Ann Arbor stage IIB Hodgkin lymphoma was treated with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) for six cycles 5 years ago. She has remained without evidence of disease with a residual 3.2 cm PET-negative anterior mediastinal lesion since the end of therapy. She had a recent upper respiratory infection that prompted a chest X-ray, which noted fullness in the hilum. A PET–CT was performed, which demonstrated bilateral hilar adenopathy with a maximum SUV (SUVmax) of 18; the residual mass is 3.0 cm and remains PET negative.

1. What nonlymphomatous lesion is PET avid?

A. Calcified granuloma
B. Sarcoidosis
C. Simple cyst
D. None of the above

Hodgkin lymphoma is a unique disease in that <1% of the lymphomatous lesion is composed of the malignant Reed–Sternberg (RS) cells, but rather surrounds the RS cell in a sclerotic and inflammatory cell meshwork. A mediastinal mass is often a hallmark of Hodgkin lymphoma. However, nearly as common is a residual mass (>1.5 cm) after completion of the therapy. As a result, the metabolically incorporated [18F] fluoro-2-deoxyglucose (FDG) portion of the PET–CT has become imperative in assessing the response to treatment in Hodgkin lymphoma. In this case, a relapse of Hodgkin lymphoma after 5 years would be uncommon but not unheard of; however, this scenario should raise the clinical suspicion for other PET–CT-avid causes in the differential. Sarcoidosis is a known PET-avid inflammatory lesion. Furthermore, the finding of sarcoidosis after a subsequent lymphoma diagnosis is a known event. Given the significant implications of relapsed Hodgkin lymphoma, a biopsy of the avid lesion is imperative prior to initiating second-line therapy for Hodgkin lymphoma.

Case study 61.4

A 67-year-old man presents with fever, severe hemolytic anemia, and the finding of a polyclonal gammopathy on serum immunofixation. A work-up for fever of unknown origin is commenced with a contrast-enhanced CT demonstrating small-volume lymphadenopathy above and below the diaphragm. An excisional biopsy of an enlarged axillary lymph node revealed angioimmunoblastic T-cell lymphoma.

1. What is the likelihood that a PET–CT will demonstrate additional sites of disease?

A. 80–90%
B. 40–50%
C. 10–20%
D. 0%

Peripheral T-cell lymphomas (PTCLs) account for 10–15 percent of newly diagnosed non-Hodgkin's lymphoma. The three most common subtypes are peripheral T-cell lymphoma not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma, and anaplastic large-cell lymphoma, and these represent nearly 80% of the cases diagnosed. Given the rarity of the diagnosis, an extensive literature does not exist regarding the utility of PET–CT in the evaluation of common subtypes of PTCL. In a retrospective review of 135 patients with numerous PTCL subtypes, over 90% of the cases reviewed were found to be avid, including those with mycosis fungoides, an indolent cutaneous T-cell lymphoma. In a recent report from the same group, 95 patients excluding primarily cutaneous subtypes retrospectively assessed how PET–CT affected the initial staging of PTCL. In all, 96% of all cases were PET avid with PET identifying additional lesions in 50% of the cases reviewed compared to conventional staging techniques. The most common additional site of disease was other nodal (25%) and bone (11%). Interestingly, despite the significant additional sites of disease being found by PET–CT a change in stage occurred in only 5% of the cases and did not change therapy in any cases. A likely explanation for this disparity is that PTCL more commonly presents with more advanced-stage disease. PET–CT remains a useful part of the work-up in PTCL.

Case study 61.5

A 42-year-old woman presents with a right pretibial skin lesion. A dermal biopsy demonstrated extranodal NK- and T-cell lymphoma (NK/TCL), nasal type. Her whole-blood Epstein–Barr virus (EBV) level is 2300 copies/uL. A PET–CT demonstrates focal avidity with an SUV of 9 in the right pretibial lesion.

1. The patient has no sino-nasal complaints. How would you proceed?

A. Refer to radiation oncology for definitive therapy
B. Admit to hospital for intensive multiagent chemotherapy
C. Refer to an ear, nose, and throat physician for direct nasal inspection and random biopsies
D. Initiate outpatient R-CHOP

NK/TCL is an uncommon PTCL subtype representing 10% of all newly diagnosed cases of PTCL. EBV is felt to be an essential piece for lymphomagenesis. NK/TCL has a significant tropism for extranodal presentations most commonly in the nasopharynx, but extranasal sites including the intestine, testes, skin, and others have been reported. The role of PET–CT is often to identify other sites of disease outside of the nasopharynx to ensure correct staging and proper treatment. In a series of 19 patients with newly diagnosed NK/TCL, PET–CT identified all extranodal sites of disease compared to 61% by conventional staging techniques. Other groups have shown that PET–CT is also important in the staging of NK/TCL given the prognostic and treatment differences between localized and disseminated NK/TCL. Despite the PET–CT lacking avidity in the nasopharynx, direct nasal inspection with random biopsies would ensure accurate staging and appropriate treatment recommendations.

Case study 61.6

A patient with DLBCL is scheduled to have a PET–CT to evaluate for response after treatment.

1. Which of the following factors is unlikely to affect the PET–CT result?

A. Recent pneumonia
B. Time from last meal
C. Hip prosthesis
D. HIV status

The incorporation of low-dose CT to standard PET scans has increased the diagnostic accuracy as well as decreased the time to obtain a scan by 30–40%. However, several limitations for each modality still exist and must be noted prior to ordering a PET–CT to avoid false-positive results. It is

(*Continued*)

well established that PET–CT will identify recent sites of inflammation (i.e., recent pneumonia) and is an expensive way to diagnose or document such illness. Therefore, documenting a recent illness on the requisition or avoidance of PET–CT during an episode would be helpful to avoid false-positive tests. The patient's blood sugar at the time of the PET–CT can drastically affect the final reading in two instances: if the blood sugar is high, it will compete with the uptake of the radiotracer at sites of importance, and high insulin levels may lead to uptake of radiotracer in normal tissues. Contacting the radiology department for consideration of patients with diabetes is often necessary. For those without diabetes, avoidance of food for up to 5 hours appears standard. The role of immune competence in PET–CT is of recent interest. Specifically in AIDS-related lymphomas, PET–CT should be used with caution. In a study of 31 interim PET–CTs in patients with HIV-associated DLBCL, the positive predictive value of an interim scan was 15%, and it was notably lower at the end of treatment at 7% (Dunleavy 2010). Lastly, metal implants are well known to cause streaking artifacts on CT, resulting in overestimation of uptake values. However, high-density metals like those used in hip prosthesis result in lack of emission of PET photons, leading to a cold area rather than higher avidity.

Case study 61.7

A 50-year-old woman has been diagnosed with grade 2 follicular lymphoma.

1. Which statement is true regarding the place of PET scans in her care?

A. It is of marginal value since only ~50% of patients with low-grade follicular lymphoma have a positive PET scan.
B. A negative PET scan at the end of therapy is the most powerful predictor of a durable remission.
C. Most patients with grade 2 follicular lymphoma will have an SUVmax on PET scan of 10–20, and an SUVmax of <5 makes this diagnosis unlikely.
D. Patients with low-grade follicular lymphoma almost always receive rituximab as part of their treatment, and rituximab administration invalidates the use of a PET scan for at least 3 months after the last dose.

Patients with low-grade follicular lymphoma almost always have an abnormal PET scan. However, in contrast to DLBCL, the SUVmax in patients with low-grade follicular lymphoma is rarely more than 10–15. Patients with grade 3 (i.e., high-grade) follicular lymphoma can have a SUVmax comparable to that seen in DLBCL.

Changes in PET scans following therapy reflect the impact of the drugs on the cancer, and individual anticancer drugs such as rituximab do not, by themselves, affect the outcome of a PET scan. For most lymphomas that are regularly PET avid, a posttreatment PET scan is one of the most, if not the most, powerful predictors of outcome. This has been more controversial in low-grade follicular lymphoma. However, a recent report by Troutman *et al*. (2011) looked at the patients who participated in an international trial of induction chemotherapy that included rituximab and were then randomized to maintenance rituximab versus observation. The study showed that maintenance rituximab improved the treatment outcome of patients who responded to induction therapy, including an improvement in patients who achieved an initial complete remission. When patients from this study who received PET scans before and after therapy were evaluated, it was found that PET scanning was the most powerful predictor of treatment outcome. Patients who remained PET positive after induction therapy had significantly poorer outcome than those who achieved a remission. When the results were compared to assignment of treatment response using a CT scan, PET scan was a more powerful predictor of outcome. Patients who were PET negative and in complete remission by CT scan did better than patients who were PET positive and in complete remission by CT scan. Patients who were determined to not be in complete remission by CT scan, but were in complete remission by PET scan, had a better outcome than those who remained PET positive, and they had an outcome comparable to those patients who were PET negative and had a CT complete response.

Mutiple choice questions

1. How often is the Ann Arbor stage altered as a result of incorporating PET into the care of patients with Hodgkin lymphoma?

A. Less than 5%
B. 35%
C. 65%
D. 90%

The alteration of stage by incorporating PET scans into routine staging tests of patients with Hodgkin lymphoma has varied from study to study. The standard imaging for patients with Hodgkin lymphoma before the advent of PET scanning was the CT scan. When these two methods have been compared, PET scanning is much more sensitive than and almost as specific as CT scans. When PET changes the stage of a patient with Hodgkin lymphoma, it can be to

either upstage or downstage. In a significant number of these patients whose stage is altered, the treatment strategy will be changed. In several series of patients, the chances of change in disease stage in patients who underwent a PET scan in addition to other imaging were 8–41% in patients with Hodgkin and non-Hodgkin's lymphoma. Thus, the performance of PET scans in patients with Hodgkin lymphoma as an initial staging maneuver is the imaging study most likely to provide an accurate Ann Arbor stage on which to base therapy.

Case study 61.8

A 30-year-old woman received two cycles (i.e., four treatments) of ABVD for stage IIA Hodgkin lymphoma that presented with disease involving the neck and mediastinum. The maximum SUV in the staging PET scan was 15.5. One day before the scheduled third cycle of ABVD, a repeat PET scan showed reduction in the maximum SUV in all sites, with the highest being 3.0 in the mediastinal lymphadenopathy (i.e., maximum SUV in the liver: 3.0; estimated maximum SUV in the non-involved mediastinum: 1.8).

1. Which statement is most correct regarding the interpretation of the PET scan in this patient?

A. The patient has failed to achieve a complete remission, and the treatment should be changed to BEACOPPesc (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone).
B. The patient has a <50% chance to be cured if she completes six cycles of ABVD.
C. At the present time, this type of early restaging has no proven impact on treatment decisions and should not be done.
D. If the patient completes six cycles of ABVD, she has at least a 70% chance of freedom from relapse for 2–3 years after completing treatment.

Several factors need to be taken into account in interpreting interim PET scans. These include the overall prognosis of the patient, the timing of the interim scan, and the degree of improvement in the PET scan in relation to the pretreatment scan. This patient had limited-stage Hodgkin lymphoma where previous studies have shown a high chance to be free of disease 2 or 3 years after completing therapy with ABVD alone. Her PET scan after two cycles of ABVD (i.e., the most frequent time to do interim scans in published trials in Hodgkin lymphoma) had markedly improved from the pretreatment scan, but the SUVMAX had fallen to approximately that of the background in the liver, and was not clearly "negative." When these patients complete ABVD, their ultimate outcome will depend on what the PET scan shows when it is repeated after completion of therapy. In one study, for the patients who were PET positive on interim scan but PET negative by the end of therapy, the 2-year failure-free survival was 92%—not different than the 96% found for patients who were PET negative on both images. In another series of patients who had a positive PET scan after two or three cycles of ABVD, the overall progression-free survival was 71% compared with 90% whose interim scan was negative. As in the previous study, however, patients whose positive interim PET scan turned negative by the end of therapy did not show an adverse impact of the early positive PET scan.

There is evidence that BEACOPPesc has a higher initial cure rate in patients with poor-risk Hodgkin lymphoma than treatment with ABVD. However, evidence for a significant advantage in patients with limited-stage disease, even with the borderline PET scan after two cycles of ABVD, is much less clear. Interim PET scanning in Hodgkin lymphoma is being studied as a way to improve treatment outcome by either decreasing or increasing the intensity of therapy based on the results of the scan, and it might become standard in the management of patients with early-stage Hodgkin lymphoma.

Case study 61.9

A 28-year-old man had been treated for stage IIA Hodgkin lymphoma 2 years previously with six cycles of ABVD, and he achieved a complete remission and then had a PET–CT scan done every 6 months as part of a surveillance program to detect early relapse. Previous PET–CT scans had been normal. On this occasion, the examination showed a new lymph node in the mediastinum with an SUV of 5. The patient is asymptomatic and has a normal physical examination, and laboratory studies including complete blood count and sedimentation rate are normal.

1. What is the chance that a biopsy of the abnormal lymph node will show Hodgkin lymphoma?

A. 15%
B. 35%
C. 55%
D. 75%

When routine PET–CT scans are done attempting to find early, asymptomatic recurrence, what one is doing is screening for relapse. The mathematics of screening tests for any

(*Continued*)

disease has been a subject for considerable study. The chances for any screening test to yield a true positive depend upon the sensitivity and the specificity of the test being studied and particularly on the frequency of the event (in this case, recurrent Hodgkin lymphoma) in the population being screened.

Various reports have tried to identify the chances of a patient with Hodgkin lymphoma relapsing on any particular day. Radford *et al*. (1997) found relapse on average in 1 in 68 visits to their clinic. Most of the data for screening to date has used CT scanning, where the sensitivity is in the range of 60–65% and the specificity in the range of 90–95%. PET–CT scans have a higher sensitivity but a much lower specificity. Thus, using these numbers in the formula for screening tests suggests that patients who are in asymptomatic remission would have no more than a 10–15% chance of a positive biopsy.

Even this percentage is probably high since most studies have found relapses to be more often seen in patients who come to clinic for unscheduled visits complaining of new symptoms. In addition to the low likelihood of benefit, patients who have an abnormal PET–CT scan will almost always have a biopsy because the physicians won't want the risk of ignoring the positive test. These biopsies can be associated with morbidity and mortality. Also, medical imaging is a major cause of radiation exposure in the United States and carries its own risks.

Until a study has been completed that shows an improvement in survival with surveillance imaging for patients with curable lymphomas in remission, these tests should not be routinely done.

2. Patients with lymphoma undergoing PET–CT scans at the time of initial staging, restaging, or surveillance for relapse occasionally will have an abnormal finding in an area not typical for the lymphoma in question. This raises a concern about the possibility of a second malignancy. Which of the following tumor types has a high likelihood of being positive on a PET scan, and thus incidentally being discovered in these settings?

A. Colon cancer
B. Esophageal cancer
C. Breast cancer
D. All of the above

While PET scanning has a major role in the management of patients with lymphoma, it also can be abnormal in other cancers. In addition to the malignancies noted here, the authors have incidentally discovered renal cell carcinoma, melanoma, thyroid cancer, lung cancer, pancreas cancer, and bladder cancer in patients with lymphoma undergoing PET imaging. In a patient who ought to be in remission from lymphoma, or in whom the PET results do not seem to make sense, it is important to consider the possibility that the abnormality on PET scan might represent a second malignancy.

3. How long after completing therapy for lymphoma should one wait before performing a restaging PET–CT scan?

A. At least 3 weeks after completing either radiation therapy or chemotherapy
B. At least 12 weeks after completing either radiation therapy or chemotherapy
C. At least 3 weeks after completing radiation therapy and 12 weeks after completing chemotherapy
D. At least 12 weeks after completing radiation therapy and 3 weeks after completing chemotherapy

Animal models have suggested posttreatment inflammatory changes for up to 2 weeks after chemotherapy and at least 2–3 months after radiation therapy or chemoradiotherapy. The possibility that PET scans performed earlier might lead to inappropriate treatment recommendations led to the recommendations of the imagining subcommittee of the International Harmonization Project in Lymphoma.

4. Which unusual presentation of lymphoma might be uniquely discovered using a PET–CT scan?

A. Neurolymphomatosis
B. Adrenal involvement
C. Sinus involvement by nasal NK/TCL
D. Colon involvement by mantle cell lymphoma

Neurolymphomatosis is an unusual presentation of DLBCL involving the peripheral nerves. It can lead to confusing clinical syndromes where the differential diagnosis includes viral infection, vasculitis, amyloidosis, and other causes of peripheral nerve injury. Patients presenting with this syndrome often represent diagnostic dilemmas, and considerable time passes from their initial symptoms to making the diagnosis. The diagnosis is based on a biopsy showing infiltration of a peripheral nerve by malignant B-cells.

PET–CT scanning seems to be uniquely useful in identifying sites for biopsy in this type of unusual presentation of lymphoma. The exam shows multiple small nodular lesions extending along peripheral nerves. Neurolymphomatosis appears to be more often seen as a relapse of primary or transformed DLBCL rather than the initial presentation of this lymphoma.

5. PET scans have been proposed as a way to determine if a residual mediastinal mass in a patient who has been treated for Hodgkin lymphoma represents active disease. If a patient with a residual mediastinal mass undergoes a PET scan, and the test is negative (i.e., uptake less than that in the background mediastinum or liver), what is the chance that the patient will relapse on subsequent follow-up?

A. 10%
B. 30%
C. 50%
D. 70%

Residual mediastinal masses are frequently seen in patients with Hodgkin lymphoma after apparently successful therapy when the patient initially presented with a large mediastinal mass. The determination of the presence of residual tumor versus fibrotic mass has represented a significant clinical problem. In the past, patients who had a significant reduction in the size of the mass that then remained stable were often thought to be in complete remission, although radiation therapy was generally administered to these patients. Weihrauch *et al*. (2001) found that 16 of 19 patients whose residual mediastinal mass was negative on PET scan stayed in remission in contrast to 4 of 10 patients whose PET scan was abnormal. Mikhaeel *et al*. (2000) described 49 patients with Hodgkin lymphoma or aggressive non-Hodgkin's lymphoma who had a residual mediastinal mass. They found that 21 of 23 patients who had a negative PET scan stayed in remission (i.e., including all the patients with Hodgkin lymphoma) in contrast to a relapse seen in eight of nine patients whose residual mediastinal mass was abnormal on PET scan. These results, and others, support the current recommendation that negative PET scan at the end of therapy is the best indicator of complete remission and freedom from relapse in patients after treatment for Hodgkin lymphoma or non-Hodgkin's lymphoma.

Case study answers

Case study 61.1

Question 1: Answer B

Case study 61.2

Question 1: Answer D
Question 2: Answer D

Case study 61.3

Question 1: Answer B

Case study 61.4

Question 1: Answer B

Case study 61.5

Question 1: Answer C

Case study 61.6

Question 1: Answer C

Case study 61.7

Question 1: Answer B

Case study 61.8

Question 1: Answer D

Case study 61.9

Question 1: Answer A

Multiple choice answers

Question 1: Answer B
Question 2: Answer D
Question 3: Answer D
Question 4: Answer A
Question 5: Answer A

Selected reading

Elstrom RL, Leonard JP, Coleman M, *et al*. Combined PET and low-dose, noncontrast CT scanning obviates the need for additional diagnostic contrast-enhanced CT scans in patients undergoing staging or restaging for lymphoma. Annals Oncol. 2008;19(10):1770–3.

Juweid ME, Stroobants S, Hoekstra OS, *et al*. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25 (5):571–8.

Schoder H, Meta J, Yap C, *et al*. Effect of whole-body (18)F-FDG PET imaging on clinical staging and management of patients with malignant lymphoma. J Nucl Med. Aug 2001;42(8): 1139–43.

Trotman J, Fournier M, Lamy T, *et al*. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol. 2011;29(23):3194–200.

CHAPTER 62

Radioimmunotherapy in lymphomas

Reem Karmali and Stephanie A. Gregory
Rush University Medical Center/Rush University, Chicago, IL, USA

Radioimmunotherapy (RIT) combines a radiation-emitting radionuclide with an anti-CD20 monoclonal antibody to treat B-cell non-Hodgkin's lymphoma (NHL). The two approved agents are ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab. RIT is approved for treatment of patients with relapsed or refractory follicular lymphoma, including patients with rituximab refractory disease.

There are some differences in the approvals between the two agents. The label for ^{131}I-tositumomab also includes patients with transformed lymphomas, and ^{90}Y-ibritumomab tiuxetan was approved in 2009 for use as consolidation therapy after induction chemotherapy for patients with follicular lymphoma who achieve a partial or complete remission after first-line chemotherapy.

RIT studies demonstrate favorable efficacy and safety profiles in follicular lymphoma with the primary toxicity being reversible myelosuppression. Many studies have demonstrated higher overall response rates and durations of response when used earlier in the treatment algorithm for follicular or indolent lymphoma. This chapter asks a number of questions that will drive home the nuances of RIT use.

Multiple choice questions

1. A patient presents in consultation with relapsed follicular lymphoma to discuss RIT. Which of the following criteria would exclude the patient from receiving RIT?

A. Greater than 25% bone marrow involvement
B. Platelet count of $\geq$100,000/mm^3
C. Absolute neutrophil count of 1800/mm^3
D. Prior stem cell transplant

Prior to receiving RIT, adequate hematopoietic reserve must be established as myelosuppression is clearly the dose-limiting toxicity. As such, recommendations are that the marrow should have less than 25% lymphoma burden with normal cellularity of at least 15%, and peripheral blood counts should demonstrate an absolute neutrophil count of $\geq 1500 \times 10^6$/L and a platelet count $\geq 100{,}000 \times 10^6$/L. ^{90}Y-ibritumomab tiuxetan is dosed at 0.4 mCi/kg for a pretreatment platelet count of at least 150,000/mm^3 and 0.3 mCi/kg for a platelet count ranging between 100,000/mm^3 and 149,000/mm^3. Similarly, impaired marrow reserve is also assumed in those who have received external beam radiation to more than 25% of the marrow or with a history of failed stem cell transplant. Although prior high-dose therapy has been a contraindication to RIT in the past, it is now felt that reduced-dose RIT can be administered safely in patients treated with prior high-dose therapy with stem cell support provided there is adequate marrow reserve. Candidates should not be restricted on the basis of a high-risk clinical presentation—patients with high International Prognostic Index (IPI), extranodal involvement, or chemoresistance have been shown to derive benefit from RIT. Reasonable response rates have also been reported in patients with high tumor burden, including bulky disease, although these rates are not as high (68%). In previously treated patients, caution should be exercised to exclude a preexisting myelodysplastic syndrome (MDS) with fluorescence in situ hybridization (FISH) or conventional cytogenetics prior to RIT therapy.

2. A female patient with newly diagnosed follicular lymphoma asks you what the differences are between ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab. She is concerned about what the implications are for her child as she is a single mother. You indicate:

A. Ibritumomab is better than tositumomab.
B. Ibritumomab is a beta emitter while tositumomab is a gamma emitter, making it preferred to isolate patients receiving tositumomab from children for a short period of time after dosing.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

C. Long-term side effects of ibritumomab include hypothyroidism.
D. The bioscan is a good predictor for altered ibritumomab biodistribution and should always be used.

With a newly diagnosed follicular lymphoma, this patient is not eligible for RIT monotherapy. Please see indications for use of these agents as stated in the introduction. Chemoimmunotherapy induction followed by RIT consolidation is, however, a reasonable option. ^{131}I-tositumomab (BEXXAR®, GlaxoSmithKline) and ^{90}Y-ibritumomab tiuxetan (Zevalin®, Spectrum Pharmaceuticals, Inc.) are the only two US Food and Drug Administration (FDA)-approved radioimmunotherapeutic agents currently available in the United States for indolent lymphomas. ^{131}I-tositumomab is a gamma emitter composed of a murine IgG2a λ anti-CD20 antibody conjugated to ^{131}I. Clinical trials with ^{131}I-tositumomab predate those with ^{90}Y-ibritumomab tiuxetan, allowing for more reliable long-term follow-up and understanding of toxicities. Due to the nature of its emissions, radiation safety, including keeping away from children and pregnant women, should be followed for 1 week after a therapeutic dose, a precaution that has resulted in its falling out of favor. Other side effects of ^{131}I-tositumomab include hypothyroidism and myelosuppression. ^{90}Y-ibritumomab tiuxetan, however, is a beta emitter with minimal risk of exposure. Data comparing the efficacy of ^{90}Y versus ^{131}I in therapeutic effect are conflicting. Of note, analysis of data in 253 patients showed that the ^{111}In imaging dose and bioscan were not reliable predictors of altered ^{90}Y biodistribution. Thus, the requirement for a bioscan for ^{90}Y has been removed by the FDA.

3. A 59-year-old male was diagnosed with follicular lymphoma 6 years ago after presenting with bulky lymphadenopathy and B-symptoms to his primary care provider. The decision was made to treat this patient with R-FND (rituximab, fludarabine, mitoxantrone, and dexamethasone) for six cycles, the patient achieving a CR. However, 3 years later, the patient relapsed, and this time he underwent retreatment with R-FND followed by RIT consolidation. Today he presents with fatigue, dyspnea on exertion, and petecchiae. Lab work demonstrates pancytopenia. This patient likely has:

A. Therapy-related MDS
B. Relapsed follicular lymphoma
C. Transformed follicular lymphoma
D. Active infection

RIT conjugates are relatively new on the market, making information on long-term sequelae limited. Concern for an increased propensity for developing therapy-related myelodysplastic syndrome (t-MDS) and/or acute myeloid leukemia (AML) with RIT has been raised. However, to date, this has not been verified. In retrospective analyses of relapsed or refractory indolent lymphoma patients receiving RIT, 2.5–3.0% cases of MDS or AML have been reported. This incidence is no different from that described in patients receiving alternative therapies for their lymphoma with an annualized rate of 0.7% per year in RIT patients compared to an annualized rate of 1.0–1.5% per year after treatment with alkylating agents. There is some suspicion that prior exposure to purine nucleoside analogs may be compounding this effect by further damaging the stem cell environment. More recently, in an update of the prospective phase III First-Line Indolent Trial (FIT) using RIT consolidation in the front-line setting, no difference in rates of MDS and AML cases were seen in the ^{90}Y-ibritumomab versus the control arm (3% versus 1%, $P = 0.063$) with 66.2 months of follow-up. However, prolonged cytopenias were seen with patients receiving induction with fludarabine-based regimens as compared to other chemotherapeutic agents.

4. A 54-year-old female presents with a new diagnosis of follicular lymphoma. She asks about her options for therapy and has been entertaining the idea of RIT. Which of the following are false regarding RIT?

A. There are no phase III data comparing RIT consolidation to rituximab maintenance in the front-line setting for indolent lymphoma.
B. Data supporting the use of RIT consolidation in the front-line treatment of indolent lymphomas are limited to phase II data, making the decision to use RIT consolidation less appealing.
C. Both rituximab maintenance and RIT consolidation have been shown to improve progression-free survival (PFS) in the front-line treatment of follicular lymphoma.
D. RIT consolidation appears to provide benefit across all Follicular Lymphoma International Prognostic Index (FLIPI) risk groups.

FIT is a phase III study that established ^{90}Y consolidation after chemotherapy induction as an effective option in the front-line treatment of follicular lymphoma. 414 patients were randomized to ^{90}Y-ibritumomab tiuxetan consolidation or observation, with the consolidation arm resulting in prolonged median PFS across all FLIPI risk groups [36.5 versus 13.3 months; hazard ratio (HR) = 0.465] and improved responses [partial response (PR) to complete response (CR) conversion of 77% with a final CR of 87%]. The PRIMA trial demonstrated similar results with the use of rituximab maintenance in a comparable population. In the PRIMA study, 1019 patients achieving CR or PR with first-line chemoimmunotherapy induction were randomized to either rituximab maintenance or observation. Although overall survival (OS) did not differ between groups, PFS was significantly improved with rituximab maintenance (74.9 vs. 57.6%; HR = 0.55). Rituximab maintenance also delayed time to next treatment and improved

quality of response, with a 52% conversion rate of PR to CR and a final CR rate of 71.5%. Although there are no head-to-head comparisons of ^{90}Y consolidation versus rituximab maintenance to date, there are two phase III trials currently underway addressing this question in indolent NHL: the ZAR study, an investigator-initiated study, is expected to report early results comparing ^{90}Y with rituximab maintenance in NHL soon; and an expanded head-to-head study of ^{90}Y versus rituximab maintenance in follicular lymphoma (RoZetta study) is currently accruing.

5. True or false? Consolidation with RIT earlier in the treatment paradigm for indolent lymphomas results in improved CRs and longer durations of response.

A. True
B. False

This question addresses the issue of optimizing RIT efficacy with earlier use in the treatment of indolent lymphomas. The first trials with RIT were conducted in patients with relapsed or refractory low-grade or follicular lymphoma who had received a median of four prior therapies. Overall response rates (ORRs) in these patients were as high as 74% with CR rates approaching 20%. Gordon *et al*. (2004) published results of a phase III study reporting response rates of 80% with CRs of 34% and a doubling of median DOR using ^{90}Y in relapsed or refractory low-grade or follicular NHL patients who had received fewer (a median of two) prior therapies. Soon after, we conducted a pooled analysis of 10 studies using ^{131}I-tositumomab in over 1000 patients and showed an inverse correlation in response rates and median duration of response with number of prior therapies. In fact, median duration of response was not reached in patients receiving RIT front-line with 40 months of median follow-up. Similar results were reported by Emmanoulides *et al*. (2006) for patients receiving ^{90}Y as RIT. This paved the way for studies incorporating RIT earlier in the treatment paradigm of indolent lymphomas. Most recently, the phase III FIT demonstrated an ORR of 90% with a CR rate of 54% with chemotherapy induction and a conversion of PRs to CRs with RIT consolidation resulting in an overall CR rate of 87% in these patients. The FDA has since expanded ^{90}Y label to include use in previously untreated follicular NHL patients who have achieved partial or complete response to first-line chemotherapy. RIT monotherapy as front-line treatment remains investigational.

6. True or false? RIT consolidation has not shown any benefit in the frontline treatment of advanced-stage mantle cell lymphoma (MCL)

A. True
B. False

RIT has shown some benefit in the MCL population as demonstrated in a number of phase II trials but remains investigational. One group of investigators demonstrated efficacy of sequential ^{131}I-tositumomab followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in untreated advanced-stage MCL unable to move onto transplant consolidation. Although not applicable to current practices of chemoimmunotherapy induction, results of this study showed reasonable responses: ORR to RIT was 83% [CR and unconfirmed CR (CRu) 46%; PR 38%], and ORR after chemotherapy consolidation was 86% (CR and CRu 67%, PR 19%). Perhaps short durations of response seen here could be attributed to lack of rituximab versus sequence of RIT and chemotherapy. Recently, Smith *et al*. (2012) reported the results of E1499, addressing the safety and efficacy of ^{90}Y-RIT consolidation following chemoimmunotherapy, an approach more applicable to patients with MCL in the front-line setting at present. Patients received an abbreviated course of R-CHOP (CHOP plus rituximab) followed by ^{90}Y-RIT. More than half of the population in this study had intermediate- or high-risk Mantle cell lymphoma International Prognostic Index (MIPI) scores. ORR in these patients was 82% with 55% CR/CRu. Median time to treatment failure was 34.2 months, providing a 50% prolongation of time to treatment failure over that expected for R-CHOP $\times$ 6 alone and an estimated 5-year OS rate of 73%. RIT effect, however, appears limited in relapsed or refractory MCL; in a phase II study conducted by Wang *et al*. (2009), patients who had received a median of three prior therapies were given ^{90}Y-ibritumomab tiuxetan monotherapy, achieving a median OS of 21 months and event-free survival (EFS) of only 6 months. But improved EFS was noted in responders to RIT, patients with nonbulky disease, and those demonstrating chemosensitivity with prior regimens. Of note, data pertaining to RIT with either autologous or allogeneic stem cell support in MCL are encouraging but also investigational.

7. A 74-year-old male is diagnosed with high-risk diffuse large B-cell lymphoma (DLBCL). He undergoes R-CHOP $\times$ 6. He is concerned about relapse and asks if there are any additional measures that may provide further benefit. You indicate:

A. RIT consolidation in the front-line settings for large-cell lymphoma has shown promise and warrants further study.
B. Rituximab maintenance provides benefit in DLBCL.
C. No additional options are available for patients with relapsed DLBCL who are non–transplant candidates.
D. The choice of salvage therapy in DLBCL is allogeneic stem cell transplantation.

Since the addition of rituximab to CHOP, a number of strategies have aimed at further improving overall response and survival outcomes in the DLBCL, including dose dense

or intense chemoimmunotherapy, rituximab maintenance, and RIT consolidation. Although results for dose-dense and intense therapy are equivocal with a worse toxicity profile and no benefit has been shown with rituximab maintenance in the front-line setting for the treatment of DLBCL, the opposite is true for RIT consolidation.

Phase I and II trials have reported on the efficacy of RIT in the relapsed or refractory and the front-line settings. In an initial phase I–II trial of ^{90}Y- ibritumomab tiuxetan, responses were seen in 43–58% patients with relapsed or refractory DLBCL, including complete remissions of 33%. Similarly, a multicenter phase II study assessed the role of ^{90}Y- ibritumomab tiuxetan in 104 elderly transplant-ineligible patients with relapsed or refractory DLBCL. The overall response rate was 44% higher in patients who were rituximab naïve. More recently, RIT consolidation has been investigated in the front-line setting for DLBCL. Two studies have demonstrated efficacy and safety of R-CHOP-21 followed by ^{90}Y in high-risk elderly DLBCL patients. We conducted a similar study at our own institution, this time using R-CHOP-14 followed by ^{90}Y consolidation in patients with high-risk disease defined by IPI, tumor bulk, or molecular subtype using Hans criteria. We were able to demonstrate improved response rates with a CR rate of 95% and an 80% PR-to-CR conversion rate post RIT consolidation. After a median follow-up of 50.8 months, the PFS and OS for the entire cohort were 73% and 79%, respectively.

In view of these findings, we believe that data on RIT consolidation in aggressive lymphomas are encouraging but should not be adopted as a standard approach outside of a clinical trial. We reserve further recommendations on this matter pending results of the ZEST trial, a phase III trial addressing survival outcomes in patients with DLBCL older than 60 years of age treated with RIT consolidation after achieving a CR with R-CHOP or R-CHOP-like therapy.

8. A 59-year-old male is diagnosed with follicular lymphoma and treated with R-CHOP with complete remission. Three years after treatment, he notices a brisk increase in cervical lymphadenopathy making it difficult to swallow. His lactate dehydrogenase is 680, and his uric acid is 10.1. A biopsy of a cervical lymph node reveals transformed histology. He has read that RIT can be used in transformed lymphoma. Is this true or false?

A. True
B. False

In one of the earliest phase III trials with ^{90}Y, patients with relapse or refractory low-grade, follicular, or transformed lymphoma were randomized to either ^{90}Y or rituximab. 73 patients were included in the RIT arm, including nine patients with transformed lymphoma (12% of the total population in the RIT arm). ORRs in the ^{90}Y versus rituximab arms were 80% and 56%, respectively ($P = 0.002$) with an ORR of only 56% in the transformed group receiving RIT. Although this did not translate into an increased time to progression, durable responses of >6 months were much higher in the RIT arm (64% versus 47%, $P = 0.030$). Similar outcomes were seen with ^{131}I. In fact, in a meta-analysis of five clinical trials with ^{131}I-tositumomab or tositumomab, 71 patients with transformed lymphoma (28% of total) were included. Once again, lower ORRs were noted in patients with transformed histology in multivariate analyses, with CR predicting for durable response. Despite available data for both RIT agents in this setting, only ^{131}I-tositumomab has been approved in transformed lymphoma. Of note, in Richter's transformation, RIT is not effective. Tsimberidou *et al*. (2004) treated seven patients with ^{90}Y, none of whom responded, with a median time to disease progression of 41 days.

9. True or false? RIT can provide responses in relapsed primary cutaneous B-cell lymphomas and be considered an option for salvage therapy

A. True
B. False

Some data suggest that RIT may be useful in treating extranodal sites of lymphoma. In a small study of 10 patients with relapsed primary cutaneous B-cell lymphoma (PCBCL), Maza *et al*. (2008) were able to demonstrate that RIT is an effective treatment option. Seven of these patients had primary cutaneous follicle center lymphoma, whereas three had the more aggressive diffuse large B-cell lymphoma leg-type. ORR and CR rates were 100%. Median time to relapse was 12 months, making this a reasonable option for second-line therapy.

10. A 63-year-old male with relapsed follicular lymphoma is referred to you for evaluation for further treatment. He has noticed increased B-symptoms in the last month. He has received several prior therapies, including rituximab, R-CVP (rituximab, cyclophosphamide, and prednisone), and ^{131}I tositumomab. His last treatment was RIT 1 year ago, resulting in minimal toxicity and a reasonable duration of response. The patient asks if another course of ^{131}I or ^{90} Y would be beneficial. You explain:

A. There are no data looking at retreating with RIT in patients with previous response to RIT.
B. Hematologic toxicity with a second dose of RIT is significantly higher than with the initial dose.
C. Retreatment with RIT is useful in patients who did not achieve response with their first dose.
D. Retreatment with I-131 following a previous response can produce second durable responses.

Although there are no data to support retreatment with ^{90} Y, ^{131}I-tositumomab retreatment has been studied. In an important phase II trial of patients with NHL who were

heavily pretreated and had previously responded to ^{131}I (defined as a response of $\geq$3 months), Kaminski *et al*. (2005) demonstrated that retreatment with ^{131}I could produce second durable responses. In 32 patients, ORR was 56% (CR 25%). Median duration of response in patients with CR was 35 months, with five patients obtaining a response ranging from 1.8 to 5.7 years. Importantly, retreatment did not seem to increase hematologic toxicity. However, 16% of patients did develop MDS, all of whom had received multiple courses of chemotherapy and/or radiation (a median of five therapies) in addition to retreatment with RIT. Thus, retreatment with ^{131}I appears to be an option at relapse with the stipulation that caution should be exercised in patients who are heavily pretreated because of the increased incidence of MDS and AML. Moreover, retreatment is not approved by the FDA.

Mutiple choice answers

Question 1: Answer A
Question 2: Answer B
Question 3: Answer A
Question 4: Answer B
Question 5: Answer A ("True")
Question 6: Answer B ("False")
Question 7: Answer A
Question 8: Answer A ("True")
Question 9: Answer A ("True")
Question 10: Answer D

Selected reading

Gregory SA, Hohloch K, Gisselbrecht D, *et al*. Harnessing the energy: development of radioimmunotherapy for Patients with non-Hodgkin's lymphoma. Oncologist. 2009;14(Suppl. 2):4–16.

Hagenbeek A, Radford J, Van Hoof A, *et al*. 90Y-ibritumomab tiuxetan (Zevalin) consolidation of first remission in advanced-stage follicular non-Hodgkin's lymphoma: updated results after a median followup of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 patients. Blood. 2010(ASH Annual Meeting Abstracts);116:594.

Kaminski MS, Tuck M, Estes J, *et al*. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med. 2005;352:441–9.

Smith MR, Li H, Gordon L, *et al*. Phase II study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone immunochemotherapy followed by yttrium-90-ibritumomab tiuxetan in untreated mantle-cell lymphoma: Eastern Cooperative Oncology Group Study E1499. J Clin Oncol. 2012;30(25):3119–26.

Zinzani PL, Rossi G, Franceschetti S, *et al*. Phase II trial of short-course R-CHOP followed by 90Y-ibritumomab tiuxetan in previously untreated high-risk elderly diffuse large B-cell lymphoma patients. Clin Cancer Res. 2010;16:3998–4004.

CHAPTER 63

Radiation oncology consultation for hematologic malignancies

Chris R. Kelsey and Leonard R. Prosnitz
Duke University Medical Center, Durham, NC, USA

Case study 63.1

A 55-year-old male presented with a 2-month history of an enlarging, painless right neck mass. The mass was mobile, measuring 3 cm in dimension. Excisional biopsy demonstrated diffuse large B-cell lymphoma (DLBCL). Bone marrow biopsy was negative, lactate dehydrogenase was within normal limits, and positron emission tomography and computed tomography (PET–CT) demonstrated hypermetabolic adenopathy confined to the right neck. He denied fevers, drenching night sweats, or unexplained weight loss. Thus, the stage is IA. The patient received four cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), and postchemotherapy PET–CT showed a complete remission (CR) (Figure 63.1).

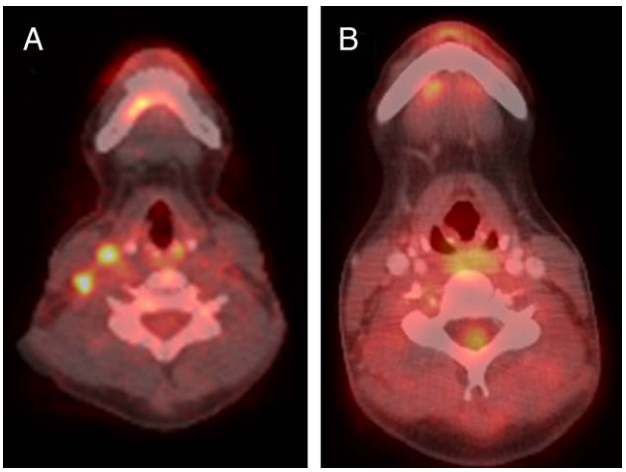


Figure 63.1 PET-CT of the neck showing hypermetabolic lymph nodes in the right neck (A), which resolved after chemotherapy (B). (Color plate 63.1)

• Is consolidation radiation therapy (RT) necessary if a CR by PET is achieved after R-CHOP for DLBCL?
The randomized trials that demonstrated that consolidation RT decreases the risk of relapse after CHOP were all conducted in the pre-rituximab and pre-PET era. With more effective systemic therapy (rituximab) and improved chemotherapy response assessment (PET), some have contended that if a CR is achieved by PET, then consolidation RT is no longer necessary.

No phase III trials, however, in the rituximab–PET era have as yet addressed this issue. Retrospective studies evaluating patients in a CR by PET after R-CHOP have shown that RT still decreases the risk of relapse, in both early and advanced disease. It must be remembered that a negative PET does not necessarily indicate that all disease has been eradicated. A critical mass of tumor cells is necessary for a PET signal to be detected. There are currently no radiological studies that can detect microscopic disease. Thus, the standard of care remains consolidation RT after chemotherapy for localized DLBCL.

The contrasting clinical scenario also deserves attention, specifically a persistently positive PET scan after completion of chemotherapy. If a patient with localized disease has clearly not responded well to chemotherapy, treatment options include high-dose chemotherapy and autologous stem cell transplantation or RT to the local area. Few studies have compared the two. Historical data indicate that ~50% of patients achieve long-term failure-free survival with RT alone for stage I disease but much inferior results for stage II (~20%). Therefore, we favor the transplant approach for stage II patients and an individualized approach for stage I. Prior to a fairly radical change in treatment such

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

as stem cell transplant, biopsy confirmation of active disease is mandatory.

For a patient who has responded well clinically but has a positive postchemotherapy PET scan, proceeding with consolidation RT is still a reasonable option, perhaps using a higher total dose (~40 Gy). Clinical outcomes are best when the PET is negative after chemotherapy, but a significant percentage of patients who are still PET positive remain disease-free after consolidation RT.

This patient received 30 Gy of consolidation RT to the right neck. Treatment was well tolerated with transient odynophagia and fatigue.

Case study 63.2

A 40-year-old female noticed a lump in her left inguinal region that did not resolve with antibiotics. She was otherwise asymptomatic. No other abnormalities were apparent on physical examination. An excisional biopsy was performed, showing grade 2 follicular lymphoma. PET–CT revealed hypermetabolic lymphadenopathy in the left external iliac lymph node chain, postoperative changes in the left inguinal region, but no evidence of disease elsewhere. Bone marrow biopsy was negative.

• What is the optimal treatment for localized follicular lymphoma: RT, chemoimmunotherapy, a combination approach, or observation?

The great majority (~80%) of patients with follicular lymphoma present with advanced disease. The treatment for advanced follicular lymphoma has been transformed by the introduction of rituximab, which when combined with chemotherapy decreases the risk of relapse and improves survival. However, relapses inevitably occur. Follicular lymphoma is still considered an incurable malignancy. Indeed, initial observation of selected patients with advanced but asymptomatic follicular lymphoma is still considered appropriate. For the minority of patients with localized disease, most published guidelines recommend involved-field RT. This is based on multiple retrospective studies with long-term follow-up showing 10-year failure-free survival of ~50% with low radiation doses (24–30 Gy), with few relapses occurring thereafter. With short follow-up, the National LymphoCare Study demonstrated that combined approaches using chemotherapy, rituximab, and/or RT were associated with a lower risk of relapse compared with RT alone, although no differences in survival were noted.

With the recognition that neither chemotherapy nor immunotherapy is curative in advanced follicular lymphoma, the minimal morbidity and cost of low-dose involved-field RT, which provides long-term disease control in a significant proportion of patients, suggest that this is still an excellent initial treatment strategy for localized disease. Furthermore, data from the Surveillance, Epidemiology, and End Results (SEER) program showing superior survival in patients who receive RT for stage I follicular lymphoma support this recommendation. Reserving systemic therapy until systemic disease develops remains a valid strategy. Further studies should investigate the addition of rituximab-containing chemotherapy to RT for localized disease.

This patient achieved a CR with 30 Gy of involved-field RT. No systemic therapy was utilized.

Case study 63.3

A 23-year-old female presented with cough, chest discomfort, and drenching night sweats. Several small lymph nodes were palpable in the left neck. Chest X-ray showed widening of the mediastinum, greater than one-third of the maximum transverse diameter of the chest. Erythrocyte sedimentation rate was 80. PET–CT showed a hypermetabolic 14 cm mediastinal mass with suspicious left cervical adenopathy. Excisional biopsy of a left cervical lymph node showed nodular sclerosis Hodgkin lymphoma.

• What is the appropriate goal in the treatment of early-stage Hodgkin lymphoma: progression-free survival or overall survival?

This patient has early-stage, unfavorable Hodgkin lymphoma. Although randomized trials have consistently demonstrated improved disease control with chemotherapy plus consolidation RT, the concern for late effects of RT have led some to advocate for chemotherapy alone. The customary argument is that RT will lead to lethal complications, and even if omitting RT leads to a higher risk of relapse, these patients will be salvaged with high-dose chemotherapy and autologous stem cell transplantation, and long-term survival will be preserved.

This assertion, however, has not been adequately tested. In general, the best chance of cure is with the first course of therapy. Only about 50% of patients who undergo autologous stem cell transplant will achieve long-term disease control, and some patients who relapse will never proceed with transplant. Furthermore, the toxicity of low-dose conformal RT is dramatically less than historical approaches

that utilized ~40 Gy to large fields, with significantly less cardiotoxicity and a much lower risk of second cancer induction. The most important scientific question is not whether RT should be utilized in Hodgkin lymphoma (it remains the single most active modality), but in whom. Many current studies are evaluating whether interim PET response will help elucidate which patients are most likely to relapse after chemotherapy alone and would be most likely to benefit from adjuvant RT.

In this particular patient, the standard approach per the German Hodgkin Study Group HD11 study would be four cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by 30 Gy RT. Our approach for patients with bulky mediastinal adenopathy is generally six cycles of ABVD followed by 20 Gy of consolidation RT if the postchemotherapy PET is negative.

Case study 63.4

A 45-year-old male presented with escalating pain in the low back. Physical exam was unremarkable. X-ray shows a lytic lesion involving the L5 vertebral body, confirmed on CT (Figure 63.2) and magnetic resonance imaging (MRI). Skeletal survey showed no other abnormalities. A CT-guided biopsy demonstrated a plasma cell neoplasm. Bone marrow biopsy showed 3% polyclonal plasma cells. There was a detectable monoclonal protein on serum protein electrophoresis. Laboratory work was otherwise unremarkable.

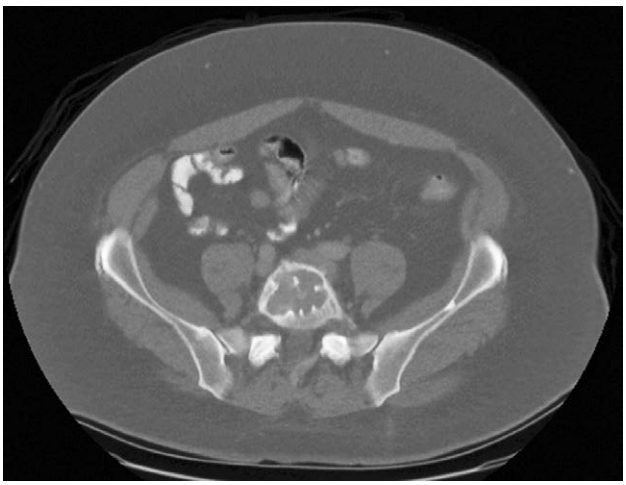


Figure 63.2 CT of the lumbar spine, bone windows, demonstrating a lytic lesion involving the L5 vertebral body.

- **What dose of RT should be administered for a solitary plasmacytoma?**

This patient has a solitary plasmacytoma of bone. Only 5–10% of patients with plasma cell neoplasms present with a solitary tumor. Solitary plasmacytomas develop at osseous sites in 80% of cases and in extramedullary sites, most commonly in the upper aerodigestive tract, in the remaining 20% of cases. The treatment of choice is RT. Multiple myeloma will develop in approximately 70% of patients with osseous presentations and 35% of patients with extramedullary disease.

Given the rarity of this disease, the optimal dose of RT has not been well established through formal studies. Doses up to 50 Gy have been recommended in older texts. Local control, regardless of dose, is achieved in most patients. From a global perspective, the risk of developing myeloma, particularly for patients with osseous disease, is the biggest competing risk. The largest study to date was a multicenter analysis of 258 patients with solitary plasmacytomas, both osseous and extramedullary. The 5- and 10-year probability of local control was 86% and 78%; this did not differ between osseous and extramedullary sites. No clear improvement was noted when doses greater than 30 Gy were prescribed. The primary factor affecting local control in patients receiving RT was the size of the tumor.

For this patient, a dose of 40 Gy was prescribed, a good balance between controlling the tumor yet limiting the risk of treatment-related complications. Approximately 12 months later, he developed pain in the upper back and was found to have progressed to multiple myeloma.

Case study 63.5

A 45-year-old female underwent upper endoscopy for persistent epigastric discomfort that responded only partially to initiation of a proton pump inhibitor (PPI). A mass was noted in the body of the stomach. Biopsy showed extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) with evidence of ***Helicobacter pylori*** infection. The disease was confined to the stomach on subsequent staging studies. The patient was treated with amoxicillin and clarithromycin with continuation of the PPI. Her abdominal pain resolved. Upper endoscopy 3 months later showed a persistent, but much smaller, mass in the stomach. Biopsy confirmed persistent MALT lymphoma with negative staining for ***H. pylori***.

• When should RT be utilized in a patient with H. pylori–positive gastric MALT lymphoma with persistent disease after antibiotics?

The majority of patients who are diagnosed with gastric MALT lymphoma have evidence of ***H. pylori*** infection. Remarkably, studies have consistently shown that eradication of the infection leads to durable CRs. Approximately 80% of patients achieve a CR with antibiotics; this will prove durable in ~70% of cases. Thus, ~50% of patients with gastric MALT lymphoma will have long-term remissions with antibiotics. RT is efficacious in those patients who are ***H. pylori*** negative, do not respond to antibiotics, or relapse after antibiotics.

It is important to realize that responses can occur slowly after antibiotics. Although the majority of patients achieve a CR by the time of repeat endoscopy 3 months after antibiotics, for some patients it may take up to 2 years or longer for a CR to be achieved. As long as the lymphoma is regressing on serial endoscopy, a watch-and-wait policy is appropriate. There are factors that have been associated with a higher risk of failing antibiotics. These include deep gastric wall invasion, nodal involvement, and the translocation t(11;18).

For this particular patient, with resolution of symptoms and disease regression on endoscopy, continued observation was recommended.

Case study 63.6

A 70-year-old female developed an erythematous, slightly raised patch on her right flank. On exam, it was about 3 cm in diameter, not ulcerated, without suspicious lesions elsewhere. A punch biopsy showed a CD30+ lymphoproliferative disorder. PET–CT showed no hypermetabolic abnormalities. The patient was referred to radiation oncology for consideration of treatment.

• How does one distinguish between lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma (C-ALCL), and when is it appropriate to proceed with RT?

CD30+ lymphoproliferative disorders encompass the entities LyP and C-ALCL, the former considered a benign skin disorder and the latter considered a malignant skin lymphoma. There are no pathological findings that distinguish LyP from ALCL with absolute certainty, including monoclonality. Although there are subtle clinical and pathological hints that help distinguish between the two, the most important factor is clinical presentation and behavior. In particular, LyP, by definition, is a self-limiting, chronic skin disease that is characterized by spontaneous regression of lesions, typically within 3 months of presentation. Although spontaneous regressions can occur with C-ALCL, this is far less common, and persistent lesions that do not regress are the primary means of distinguishing these two processes. Thus, a careful history and serial examinations are critical to discriminate between these two disorders.

Patients with C-ALCL have an excellent prognosis. They typically present with localized disease, which responds well to RT. Although recurrences develop in 30–40% of patients, they typically occur in skin distant from the initial site and are often amenable to a second course of RT.

In this patient, further observation was advocated. When she returned 2 months later, the patch had largely resolved and ultimately disappeared with longer follow-up, with minor residual pigmentation changes that can occur with LyP.

Case study 63.7

A 65-year-old male presented to his primary care provider with a 3-week history of headache, nausea, and personality changes. His physical exam was unremarkable. An MRI showed a single, homogeneously enhancing mass in the left frontal lobe (Figure 63.3). HIV testing was negative. A stereotactic biopsy showed DLBCL, and further staging studies demonstrated confinement to the central nervous system (CNS). He underwent a high-dose methotrexate-based regimen and achieved a CR by MRI.

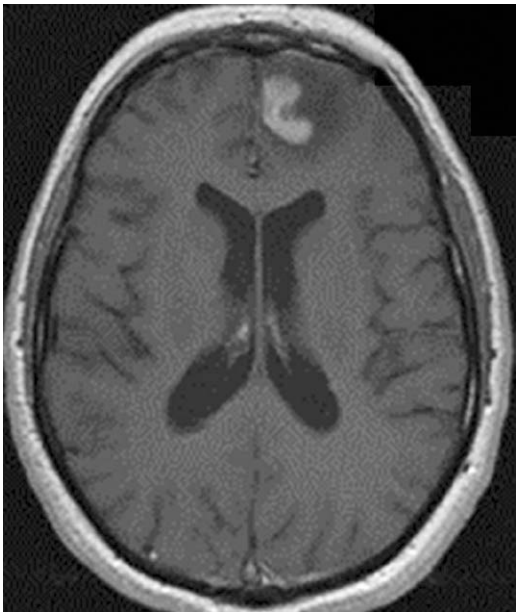


Figure 63.3 T1 MRI of the brain with contrast demonstrating a single homogeneously enhancing mass in the left frontal lobe.

• Should whole-brain radiation therapy (WBRT) be utilized in a patient with primary CNS lymphoma (PCNSL) achieving a CR to high-dose methotrexate?

PCNSL is a rare extranodal non-Hodgkin's lymphoma that occurs in both immunocompetent and immunosuppressed patients, although with different presentations. WBRT was historically the treatment of choice, with CR achieved in up to 80% of patients. Unfortunately, with WBRT alone, relapse rates were high and the median survival was ~12–18 months. High-dose methotrexate regimens, with or without WBRT, have become the treatment of choice, with an improvement in median survival to ~50–60 months in many studies.

The contribution of WBRT after high-dose methotrexate regimens is controversial. Although WBRT may decrease the risk of relapse, it is often counterbalanced by increased toxicity. In older patients (>60 years), conventional doses of WBRT (45 Gy) have been associated with unacceptably high rates of severe neurotoxicity, including dementia. When a CR is achieved, lower doses of RT may decrease the risk of relapse but avoid the toxicity of full-dose WBRT. However, longer follow-up will be required to confirm these initial findings.

In this particular patient, after much discussion regarding the risks and benefits of WBRT, given his age the patient elected to forgo further therapy.

Case study 63.8

A 58-year-old female presented with an unexplained 10 kg weight loss and vague chest discomfort without systemic symptoms. Her physical exam was unremarkable. Chest X-ray showed a possible mediastinal mass, confirmed on CT imaging. A PET–CT showed multiple hypermetabolic mediastinal and celiac lymph nodes. Mediastinoscopy revealed DLBCL. Bone marrow biopsy was negative; the lactate dehydrogenase was not elevated. She had stage IIIA disease. Initial treatment consisted of six cycles of R-CHOP, achieving a CR by PET.

• Is there value to consolidation RT in advanced DLBCL?

R-CHOP is the backbone of treatment for patients with advanced DLBCL. Various strategies have been investigated to improve outcomes in this group of patients, including the use of more intense chemotherapy than CHOP and high-dose chemotherapy and autologous stem cell transplantation. Consolidation RT is infrequently employed but appears, based on both prospective and retrospective studies, to improve local control and decrease the overall risk of relapse.

Patients with widespread disease not amenable to comprehensive RT may be treated to sites of bulk disease if present. More limited disease presentations, such as that described in this case, are amenable to consolidation treatment to all sites of original involvement. Compared with patients with early-stage disease, more cycles of chemotherapy are often utilized, which may allow for a lower dose of RT.

This particular patient was treated with six cycles of R-CHOP and 19.8 Gy in 1.8 Gy fractions to both the mediastinum and upper abdomen.

Selected reading

Deckert M, Engert A, Bruck W, *et al*. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. Leukemia. 2011;25(12):1797–807.

Dreyling M, Ghielmini M, Marcus R, *et al*. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22(Suppl. 6):vi59–63.

Kelsey CR, Beaven AW, Diehl LF, *et al*. Radiation therapy in the management of diffuse large B-cell lymphoma: still relevant? Oncology. 2010;24(13):1204–12.

Kelsey C, Beaven A, Diehl L, *et al*. Combined-modality therapy for early-stage Hodgkin lymphoma: maintaining high cure rates while minimizing risks. Oncology. 2012;26:1182–93.

Ruskone-Fourmestraux A, Fischbach W, Aleman BM, *et al*. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. Gut. 2011;60(6):747–58.

PART 10

Special Issues in Hematopoietic Cell Transplantation

CHAPTER 64

Donor and graft selection in allogeneic hematopoietic cell transplantation

Jose Leonel Ochoa-Bayona and Claudio Anasetti

H. Lee Moffitt Cancer Center, Tampa, FL, USA

Introduction

Donors can be categorized according to (i) genetic makeup, as identical (syngeneic) in the case of twins, or disparate (allogeneic) in all other cases; (ii) relationship to the recipient, as related (R) when family members are considered, or unrelated (UR); (iii) degree of human leukocyte antigen (HLA) disparity as matched (M) or mismatched (MM) with the recipient at one or more HLA alleles—most common are matched related donors (MRDs) and matched unrelated donors (MUDs), but utilization of MMRDs or MMUDs is increasing, and less common are family members who are genotypically identical for one haplotype and partially matched for the other (haploidentical); and (iv) anatomic source of hematopoietic progenitor cells, as bone marrow (BM), peripheral blood (PB), or umbilical cord blood (UCB). Center for International Blood and Marrow Transplant Research 2005–2009 data for allogeneic stem cell sources for recipients age 20 and older indicated that approximately 80% received PB, 15% BM, and 5% UBC. Nearly half of the donors were related donors, and the others unrelated. Most of the evidence for donor and graft selection comes from large-registry and some single-institution studies, and only a few randomized control trials (RCTs). Important endpoints are survival, engraftment, graft failure, and graft-versus-host disease (GVHD).

Case study 64.1

A 40-year-old male with an FLT3-positive, NPM1-negative, normal-cytogenetics acute myeloid leukemia (AML) is undergoing a second cycle of induction chemotherapy; his day 14 bone marrow is hypoplastic with 20% residual blasts, consistent with primary induction failure AML. He has three younger siblings who have undergone HLA typing; one of them is HLA identical to the patient by DNA-based high-resolution testing at HLA-A, B, C, DRB1, and DQ.

1. What would you do next?

A. Recommend allogeneic stem cell transplant using this HLA-identical sibling donor

B. Recommend haploidentical transplant using one of his other siblings

C. He is not a transplant candidate as he is not in remission

Transplantation for primary induction failure AML is associated with a 20–30% probability of long-term survival. HLA matching is the cornerstone for the selection of sibling and unrelated donors. HLA matching impacts survival, graft failure, and GVHD risk. For sibling donors, in practice, donor selection starts with HLA typing of the available full siblings. HLA genes are located in the short arm of chromosome 6 and are codominantly inherited as a single haplotype from each parent. The chance that two siblings share two identical haplotypes is 25%. HLA typing to determine HLA-A, B, C, DRB1, and DQB1 haplotypes at the allele level is currently performed using DNA-based high-resolution methods. However, serology was used for HLA-A, B, and DR typing in the past, and it is still performed by some laboratories. Early studies demonstrated a 2% risk of graft failure for genotypically identical siblings compared to 12% with incompatible siblings using HLA typing by serology. Most recent registry studies report graft failure of 1% or less with genotypically identical siblings and fully matched unrelated donors in the era of DNA-based high-resolution HLA

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

testing. The goal standard for HLA typing is high-resolution testing. Because mismatching at DQB1 does not impact survival or GVHD as the other alleles do, an 8/8 donor is consider a fully matched donor. Matched related hematopoietic stem cell transplantation (HSCT) remains the gold standard to which other alternative hematopoietic stem cell sources are compared.

2. What stem cell product would you choose?

A. Peripheral blood stem cells
B. Bone marrow stem cells
C. Either product based on center expertise, patient needs, and donor preferences

The results from trials comparing BM versus PB for MRD transplantation have yielded inconsistent results. However, a meta-analysis from nine randomized trials demonstrated that PB led to faster engraftment and carried an increased risk of extensive chronic GVHD. There was improvement in disease-free survival and overall survival, but only for patients with high-risk disease. Decision analysis demonstrated 7-month superiority for PB stem cell (PBSC) transplantation for patients with high-risk disease. However, for patients with low risk for relapse, BM remains the optimal stem cell product. For this patient with high-risk disease, who has already been neutropenic for a prolonged period of time, evidence supports the selection of PBSCs from an HLA-matched sibling donor.

Case study 64.2

A 34-year-old Caucasian female with BCR–ABL-positive acute lymphoblastic leukemia (ALL) is in first remission (CR1) after two cycles of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) plus a tyrosine kinase inhibitor, with persistently positive polymerase chain reaction for BCR–ABL. You are considering allogeneic stem cell transplantation for this patient; she is concerned about long-term GVHD risks. She does not have any siblings. An unrelated donor search reveals three 8/8 fully matched donors.

1. What donor would you select?

A. A 21-year-old male with a history of anxiety, who will only agree to donate bone marrow under general anesthesia
B. A 55-year-old female with several pregnancies
C. A 50-year-old male from whom the collection center will provide only PBSCs

The role of matched related allogeneic HSCT was tested on UKALL12/E2993, confirming superiority over chemotherapy in the pre-imatinib era. Conversely, the role of unrelated allogeneic HSCT in this setting is less well defined, but single-center reports support that it is feasible and reasonable. The most appropriate donor will be the 21-year-old male. PBSCs versus bone marrow stem cells for unrelated-donor HSCT has been recently addressed in an RCT. In this study, there was no difference in overall survival, rate of relapse, or acute GVHD regarding the anatomic source of hematopoietic progenitor cells. There was a slightly higher risk of graft failure with BM (9% vs. 3%) but a lower risk of chronic GVHD (41% vs. 53%). PB was associated with 7-day earlier engraftment. This patient is concerned regarding the risk of GVHD, which potentially would be lower using this donor. Recipients who have received immunosuppressive chemotherapy are at lower risk for graft failure, and BM will be appropriate. In contrast, recipients with high risk for BM failure, such as patients never receiving cytotoxic chemotherapy or reduced-intensity regimens, may be better served by peripheral stem cells. The other donors are less appropriate because older donors (>45 years) have been associated with worse survival; also, a female donor with prior pregnancies and donating PBSCs more likely will lead to higher risk for GVHD.

Case study 64.3

A 20-year-old, previously healthy male presented with fever, intermittent mouth sores, and purpura for 2 weeks. His absolute neutrophil count is 100, platelets 12,000, and hemoglobin 9. His peripheral blood smear reveals normochromic anemia without leukoerythroblastosis. Bone marrow biopsy revealed 5% cellularity, and he had normal cytogenetics and FISH and normal flow cytometry. He has been started on cyclosporine A and antithymocyte globulin; thus far, he has not responded. He does not have any siblings. Unrelated donor search reveals multiple potential 8/8 matched donors, and typing is underway.

1. What stem cell source do you request?

A. Peripheral blood stem cells
B. Bone marrow
C. T-cell-depleted graft

For a young patient with severe aplastic anemia who does not have an identical sibling and has not responded to immunosuppression, unrelated allogeneic HSCT should be the next line of therapy. Unmanipulated BM remains the stem cell product of choice for patients with severe aplastic anemia. Registry studies have compared the outcomes for bone marrow and PBSC in HLA-matched siblings and unrelated HSCT. In HLA-matched siblings, the rates of engraftment and chronic GVHD were similar for PB and BM regardless of the age, but chronic GVHD and overall mortality were higher for PB in patients younger than 20 years. Five-year probabilities of OS were 73% and 85% after PB and BM, respectively, in patients younger than 20 years and 52% and 64% for those older than 20 years. Another registry study has compared BM to PB in unrelated HSCT in severe aplastic anemia, demonstrating similar engraftment rates but higher acute GVHD (HR 1.6), and mortality risks (HR 1.6), which were independent of age. A BM stem cell dose of at least 2×10^6 CD34+ cells/kg should ideally be given because a low BM cell dose increases the risk of graft failure.

Case study 64.4

A 53-year-old male with stage IV, immunoglobulin H (IgH) unmutated, deleted 17p chronic lymphocytic leukemia (CLL) has received six cycles of fludarabine, cyclophosphamide, and rituximab. He has attained a morphological CR, but flow cytometry still identifies a small population of CD5 and kappa light-chain restricted lymphocytes. He only has one sibling who is just a haplotype identical; an unrelated donor search reveals four 9/10 matched donors at HLA-A, B, C, and DRB1 but mismatched at DQ, respectively. He seeks your advice regarding if he should proceed with transplantation.

1. What would you recommend regarding transplantation and, if so, donor selection?

A. Proceed with transplant using a DQ-mismatched donor
B. Defer transplant until relapse, and continue maintenance rituximab
C. Consider enrollment in a study using a new B-cell monoclonal antibody for minimal residual disease

Historically, donor selection for HSCT relied on serological testing for donor and recipient identity for the HLA-A, B, and DR antigens. However, a large degree of diversity of the HLA genes became apparent with testing using molecular methods; consequently, many serologically identical, unrelated donors and recipients were found to have mismatches of two unique alleles of the same antigen. Most recently, large-registry studies have demonstrated that such allelic differences are clinically relevant, increasing the risks of graft failure, GVHD, and mortality. In a large-registry study, high-resolution DNA matching for HLA-A, B, C, and DRB1 (8/8) was the minimum level of matching associated with the highest survival. A single mismatch, detected by low or high DNA testing, at HLA-A, B, C, and DRB1 (7/8) was associated with a higher mortality (relative risk: 1.25) and one-year survival of 43% compared to 52% for 8/8 matched patients with good-risk disease; mismatches at two or more alleles compounded the risk. Single mismatches at HLA-B and C were somewhat better tolerated than mismatches at HLA-A and DRB1. Conversely, mismatches at HLA-DQ, DP, and other donor factors were not associated with survival. Therefore, a well-matched 8/8 is the standard donor source for unrelated HSCT. There is an approximately 10% decrease in survival for each allele mismatched at HLA-A, B, C, and HLA-DRB1. The outcomes from URD transplants are better compared with alternative treatments for patients with high-risk CLL. Unrelated-donor PB and BM were equal in survival, but PB led to faster engraftment and higher risk of chronic GVHD; BM was associated with higher graft failure but lower GVHD.

Case study 64.5

A 62-year-old female with trisomy 11 AML attained a CR1 and completed consolidation; AML relapsed 1 year later, and she attained a second complete remission (CR2) after induction with cladribine and cytarabine; she has an excellent performance status. The only available sibling has a history of breast cancer. An unrelated donor search revealed only potential mismatches at HLA-A and DRB1. However, several 4/6 and 5/6 HLA-A, B at low-resolution, and HLA-DRB1 at high-resolution UCB units with more than 3.5×10^7 nucleated cells have been identified.

1. What would you do next?

A. Continue consolidation chemotherapy as the patient is unfit for UCB transplantation
B. Inform the patient that she is a good transplant candidate, and consider a single UCB transplant
C. Consider a double UCB transplant
D. Keep the unrelated search open for 6 more months, hoping that a better unrelated donor will register

Many patients who may benefit from transplantation may lack a suitable matched (or mismatched at no more than one locus) related or unrelated donor. Despite an earlier higher transplant-related mortality, transplantation of HLA-mismatched UCB has demonstrated similar long-term leukemia-free survival to other alternative donors. The present standard for selecting UCB units uses lower-resolution matching and does not typically include matching at HLA-C. Units are selected based on the total nucleated-cell dose ($>2.5 \times 10^7$ cells/kg at cryopreservation) and donor-recipient matching at HLA-A and B at the antigen level and HLA-DRB1 at the allele level. It has been recently demonstrated that transplant-related mortality was higher in HLA-C-mismatched transplants compared with those matched, as it was for two, three, or four mismatched loci. For patients whose larger unit is $<2.5 \times 10^7$, double cord blood transplantation is an option. Results from a randomized trial recently presented at the 54th ASH meeting demonstrated no survival advantage after double UCB compared to single UCB transplant in children with hematological malignancies. It is hoped that in the future, cord blood expansion or enhanced cell-homing technology will allow even safer UCB transplantation in adults from a single small cord unit.

Case study 64.6

A 30-year-old male with T-cell lymphoblastic leukemia has just moved to your community where he has a better family support. He was diagnosed 2 years ago and entered CR after hyper-CVAD. He relapsed one month ago and was reinduced with nelarabine, attaining a CR. He has three healthy younger siblings and parents living locally; siblings are 5/8 or 6/8 matched. Previously an unrelated donor search was performed, but no matches were found; there was one 4/6 matched cord unit that contained 1.5×10^7 NC/kg, as he is moderately overweight.

1. What would you recommend to this patient?

A. Refer him for haploidentical sibling peripheral stem cell transplantation to a local academic transplant center for his enrollment in an ongoing clinical trial
B. Continue nelarabine consolidation because his likelihood of long-term survival with it is similar to what he would have after stem cell transplant
C. Continue nelarabine for palliation, and start discussing hospice

A small nucleated cell dose on a UCB unit carries a high risk of graft failure and in an overweight recipient is a less suitable option. He should be referred for participation in clinical trials of haploidentical transplantation to investigate methods to improve engraftment and reduce GVHD and transplant-related mortality, which are the major challenges. For patients lacking a matched sibling or MUD, or when there is not enough time to make additional arrangements and commit an unrelated donor due to rapid disease progression, the only two available alternatives for stem cell donor sources are haploidentical transplantation from a mismatched family member or UCB transplantation. A suitable MUD may not be identified for approximately one-third of the patients. This problem may be greater for ethnic minorities. Earlier single-center studies demonstrated that haploidentical HSCT was feasible, but with substantial risk for graft failure (12%), and GVHD and nonrelapse mortality exceeding 50%. Nevertheless, a multicenter study recently reported engraftment rates of 96%, GVHD grades 2–4 of 32%, 1-year nonrelapse mortality of 45%, relapse of 7%, and 1-year OS probability of 62% and PFS of 48%; a double cord study by the same network reported engraftment rates of 94%, GVHD grades 2–4 of 40%, 1-year nonrelapse mortality of 24%, and relapse of 31%; 1-year OS probability was 54%, and PFS was 46%. These results continue to show the continuous uncertainty in setting priorities between haploidentical and cord transplantation.

Case study 64.7

A 42-year-old female nurse with refractory cytopenia and multilineage dysplasia, intermediate risk-2 MDS has attained a CR after six cycles of azacytidine. She is returning to discuss with you recommendations for MRD or MUD transplantation. The patient is homozygous at HLA-A. Her only sister is a 9/10 mismatch at HLA-A. Two 8/8 HLA-matched unrelated donors have been identified. While reviewing the literature, she has read that additional matching for HLA-DP has been identified as an additional factor that could positively affect transplant outcomes. She would like your guidance before making a decision.

1. What would you recommend to the patient?

A. Recommend against using her sister because there is a high risk of graft failure when the recipient is homozygous at one HLA class I loci

B. HLA-DP is unlikely to affect transplant-related mortality or severe acute GVHD risk, and typing is not recommended

C. You will review this further and discuss her case in the tumor board

Recipient homozygosity at the mismatched HLA locus was associated with a risk of graft failure of approximately 70% in a small study, and for this reason this donor should be avoided by a patient who has not been previously treated with cytotoxic chemotherapy. If a match is not available, the preferred mismatch should be at a locus for which the recipient is heterozygous. In this case, selecting an HLA-matched URD will be a better option. When additional typing at HLA-DP is performed, ~80% of recipient–donor pairs are mismatched at one allele and ~40% are mismatched at two alleles. It is clear from transplant outcome studies that not all HLA mismatches result in poor clinical outcome. Mismatching at the HLA-DP locus was not associated with worse survival. However, HLA-DPB1 disparity is associated with increased severe acute GVHD, transplant-related mortality, and decreased relapse. DPB1 mismatches have been categorized as nonpermissive or permissive depending on whether or not they are associated with a worse clinical outcome, as immunogenicity varies among disparities between distinct pairs of DPB1 alleles.

Case study 64.8

A 50-year-old female with refractory cytopenia and multilineage dysplasia, 2% blasts and normal cytogenetics, MDS intermediate-1 is referred in consultation. She had mild improvement on transfusion requirements after six cycles of azacytidine, but she remains transfusion dependent and she is alloimmunized. She had three prior pregnancies. Her only sister is a haplotype identical match. Two HLA 8/8 MUDs have been identified. She has donor HLA-specific alloantibodies to one of the donors with whom she is additionally mismatched at HLA-DPB1; this donor is immediately available. She is a fully DPB1 matched and carries no donor-specific HLA antibodies against the second donor, who will be available in 2 months.

1. Which donor would you select for this patient?

A. HLA-DPB1 mismatched to whom the patient has donor HLA-specific alloantibodies

B. HLA-DPB1 matched to whom the patient does not have HLA-specific antibodies

C. Delay transplantation until there is evidence of disease progression

HSCT recipients may become alloimmunized to foreign HLA antigens through pregnancy or blood transfusion. The resulting antibodies may be directed against mismatched HLA antigens of stem cell donors. Although the etiology of graft failure remains elusive for most of the patients, the presence of donor-directed HLA class I (A, B) and II (DP) donor-specific antibodies was associated with increased risk of graft failure in recipients possessing antibodies compared to controls in a retrospective study of patients in whom pretransplant serum samples were available. Even though mismatching at HLA-DP does not impact survival, if a recipient has HLA antibodies directed against a mismatched DP-type donor, there may be an increased risk of graft failure. Thus, HLA antibody screening is indicated for potential HSCT recipients. If HLA antibodies are present, a thorough assessment of the antibody specificity and donor mismatches is warranted. Desensitization methods to remove the alloantibody with rituximab or plasma exchange before stem cell transplantation could be tried but remain unreliable. Donors to whom the recipient has HLA alloantibodies should preferably be avoided.

Case study 64.9

A 30-year-old male with relapsed normal-cytogenetics acute myelogenous leukemia has attained a second remission. At the time of his first remission, he was evaluated for transplant. He did not have siblings, and unrelated donor search identified several HLA 8/8 MUDs, but he decided to pursue conventional consolidation chemotherapy. Now, he has decided to proceed with transplant. He asks you regarding the role of killer-cell immunoglobulin-like receptor (KIR) in transplant outcomes, which he has read about in the internet.

1. What would you recommend to the patient?

A. You will check with your referral transplant programs to see if they have any prospective studies using KIR genotyping to assess its role in donor selection
B. Typing for KIR is unlikely to affect leukemia relapse, and it is not recommended
C. You will review this further and discuss his case in the tumor board

Of all the cancers treated with allogeneic HSCT, acute myeloid leukemia is the most sensitive to natural killer (NK)-cell reactivity. NK-cell function is controlled by inhibitory and activating signals through cell surface receptors, including the KIRs. Most persons have multiple activating KIRs, of which KIR2DS1 is the only one known to play a role in both NK-cell activation and tolerance through its recognition of HLA-C type 2 molecules. KIR2DS1-positive NK-cells isolated from HLA-C type 1–positive individuals become activated and cytotoxic to target cells. In HLA-C type 2 homozygous individuals, NK-cells that exclusively express KIR2DS1 are hyporesponsive. A large retrospective study evaluating the clinical effects of donor KIR genotype and donor and recipient HLA-C genotypes demonstrated that leukemia relapse risk was decreased using KIR2DS1-positive, HLA-C type 1 homo- or heterozygous donors; donor and recipient HLA-C type 2 homozygosity was associated with higher relapse; and KIR3DS1, which is frequently in positive linkage disequilibrium with KIR2DS1, did not affect leukemia relapse but was associated with decreased nonrelapse mortality. In this patient at high risk for leukemia relapse, participating in a study to prospectively evaluate the effect on KIR on leukemia relapse will be the most appropriate answer. However, if KIR information is already known on the available donors, which is not routine, a KIR2DS1-positive donor who is not HLA-C 2 homozygous will be appropriate.

Case study answers

Case study 64.1

Question 1: Answer A
Question 2: Answer A

Case study 64.2

Question 1: Answer A

Case study 64.3

Question 1: Answer B

Case study 64.4

Question 1: Answer A

Case study 64.5

Question 1: Answer B

Case study 64.6

Question 1: Answer A

Case study 64.7

Question 1: Answer A

Case study 64.8

Question 1: Answer B

Case study 64.9

Question 1: Answer A

Selected reading

Anasetti C, Logan BR, Lee SJ, *et al*. Peripheral blood stem cells versus bone marrow from unrelated donors. N Engl J Med. 2012;367:1487–96.

Eapen M, Klein JP, Sanz GF, *et al*. Effect of donor-recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. Lancet Oncol. 2011;12:1214–21.

Kollman C, Howe CWS, Anasetti C, *et al*. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood. 2001;98:2043–51.

Lee SJ, Klein J, Haagenson M, *et al*. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007;110:4576–83.

Spellman S, Bray R, Rosen-Bronson S, *et al*. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. Blood. 2010;115:2704–8.

CHAPTER 65

Preparative regimens in allogeneic hematopoietic cell transplantation for malignant hematological diseases

Robert J. Soiffer

Dana-Farber Cancer Institute, Boston, MA, USA

Traditionally, conditioning regimens prior to hematopoietic cell transplantation (HCT) were designed to provide the highest dose of chemoradiotherapy tolerated by the patient with the hope of complete tumor eradication. Agents and modalities with nonoverlapping toxicities were combined to limit nonhematopoietic organ complications. The sole function of the conditioning regimen in autologous hematopoietic cell transplantation (auto-HCT) is destruction of residual tumor cells. In contrast, in the allogeneic setting, the conditioning regimen serves an additional function, providing sufficient immune suppression to prevent rejection of donor cells, permitting engraftment of both hematopoietic progenitors and immune effector. We now know that donor immune effectors cells, particularly T-cells but also perhaps natural killer (NK)-cells and B-cells, play a critical role in eliminating residual recipient malignant cells in allo-HCT. This potent graft-versus-tumor (GVT) effect forms the rationale for the use of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning regimens designed to provide adequate immune suppression to promote engraftment without producing organ toxicity. It is hoped that reductions in transplant-related mortality due to collateral tissue damage often induced by ablative conditioning regimens will more than counterbalance the compromise of antitumor cytotoxicity when reduced-dose conditioning is employed. Reduced-intensity regimens allow allo-HCT to be offered to older patients and those with comorbidities that would normally preclude high-dose therapy.

There is no single standard conditioning regimen that has been established in phase III trials as clearly superior in either the ablative or reduced-intensity setting. There are limited numbers of randomized trials comparing regimens, and the most data are derived from phase II or retrospective analyses. Choice of regimen is usually based upon a number of factors such as diagnosis, disease stage (not clinical stage), and comorbidities. This chapter will address the conditioning options available for allo-HCT, and explore some of the controversies surrounding the selection of specific regimens.

Multiple choice questions

1. A 32-year-old man presents with acute myelogenous leukemia (AML) with adverse cytogenetics. He has achieved a complete remission with anthracycline and cytosine arabinoside. He tolerated induction therapy well, although he experienced a vancomycin-resistant enterococcus bacteremia that cleared with prolonged antibiotic therapy. He has received two cycles of high-dose ara-C intensification. An 8/8 human leukocyte antigen (HLA)-matched unrelated donor has been identified, and allo-HCT is planned. Of the following, which would be the most reasonable choice of conditioning regimen for him?

A. Cyclophosphamide 60 mg/kg 2× plus 1200 cGy fractionated total body irradiation (fTBI)

B. Cyclophosphamide 60 mg/kg 2× plus 1000 cGy unfractionated TBI

C. Fludarabine and single-dose 200 cGy TBI

D. Cyclophosphamide 60 mg/kg 2× plus 1575 cGy fTBI

In general, for a man of this age, a myeloablative regimen would be considered and a TBI-based regimen would be reasonable. Fractionating the dose of irradiation is felt to be less toxic to healthy tissue, allowing for escalation of the total dose. Unfractionated radiation in this range (option B) has been associated with significant hepatic and

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

pulmonary toxicity and is associated with inferior outcome. The optimal number of fractions and their ideal distribution (i.e., over how many days) have not been fully settled. The absence of standardization across studies with reference to energy source, shielding, schedules, and concomitant chemotherapy makes it challenging to determine the best schedule. Higher doses of fractionated radiation such as 1575 cGy (D) have actually been associated with lower relapse rates than 1200 cGy but at the cost of increased nonrelapsed mortality from both direct organ damage and graft-versus-host disease (GVHD). Recently, two studies (retrospective and prospective phase II) reported that a myeloablative regimen with cyclophosphamide and intravenous busulfan is associated with better overall survival (OS) compared to total body radiation and cyclophosphamide in adult patients undergoing allo-HCT for AML. Nonmyeloablative regimens (C) may be less toxic and equally efficacious as traditional regimens, such as option A. However, they are generally reserved for older patients or those with significant comorbidities. A prospective randomized trial of myeloablative conditioning versus RIC is being conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) for patients with AML and myelodysplastic syndrome (MDS). It is possible we will learn that in certain circumstances bigger isn't better.

2. A 46-year-old woman has been treated for non-Hodgkin's lymphoma for the past 9 years. She received treatment with several lines of therapy and underwent an autologous transplant 2 years ago. She remained in remission for 20 months but then relapsed. Salvage therapy has resulted in an excellent partial remission, and her doctors have recommended an allogeneic transplant. She has an HLA-identical sister who will serve as the donor. Of the following, which would be the most reasonable conditioning regimen for her?

A. Cyclophosphamide, etoposide, and carmustine
B. Cyclophosphamide 60 mg/kg 2× plus 1200 cGy fTBI
C. A reduced-intensity regimen of alkylating agent plus fludarabine
D. Cyclophosphamide 60 mg/kg 2× plus following intravenous busulfan 0.8 mg/kg every 6 h for 16 doses

High-dose ablative regimens (A, B, and D) have all been utilized with some success in patients who have undergone a prior transplant. However, organ-specific toxicity is significant, particularly veno-occlusive disease (VOD). It is more common practice to utilize RIC in part to minimize toxicity with the understanding that immune-mediated graft-versus-tumor (GVT) effects are likely the primary mechanism for disease control. In addition, in patients with lymphoproliferative disease, RIC is being utilized more commonly than myeolablative regimens even in younger, fit individuals. Cyclophosphamide, busulfan, and melphalan, and low-dose single-fraction TBI, have all individually been combined with fludarabine to constitute reduced-intensity regimens. They have not been tested head-to-head in a prospective randomized trial, and there is no convincing evidence that one regimen is superior to any other.

3. A 63-year-old man diagnosed with AML in second remission is scheduled for allogeneic transplant from a matched unrelated donor. He has no major comorbidities. Of the following, what would be the most appropriate conditioning regimen?

A. Intravenous busulfan 6.4 mg/kg plus fludarabine 120 mg/m^2 administered over 4 days
B. Busulfan and fludarabine, as above, with alemtuzumab
C. Busulfan and fludarabine, as above, with rabbit antithymocyte globulin (ATG)
D. Any of the above

Both answers B and C represent forms of in vivo T-cell depletion (TCD), alemtuzumab and ATG. Such in vivo TCD was thought to serve several purposes. One function was to reduce the incidence of GVHD. The other purported benefit was to immune-suppress the recipient to prevent graft rejection, which was thought necessary in light of the reduction of chemotherapy-conditioning doses. Unfortunately, no large prospective randomized studies have been performed to address the need for alemtuzumab or ATG in the RIC setting to promote engraftment. Retrospective registry studies from both the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Bone Marrow Transplantation Registry do not suggest any benefit in terms of engraftment or survival for patients receiving these in vivo TCD strategies. Indeed, some suggest that these antibodies so deplete GVT activity as to negatively impact progression-free survival.

4. Prospective randomized trials have demonstrated which of the following?

A. Busulfan–cyclophosphamide (Bu-Cy) conditioning is superior to Cy–TBI in young patients with MDS.
B. Cy–TBI is superior to RIC in adult patients with acute lymphoblastic leukemia (ALL).
C. Cy–TBI is superior to Bu–Cy in first remission (CR1) AML.
D. High-dose busulfan–fludarabine (Bu-Flu) is superior to Bu–Cy for patients with AML–MDS.
E. Etopside–TBI is superior to cyclophosphamide–TBI in patients with ALL.

Historical retrospective single-center data may suggest answers A, B, D, and E, but no large prospective randomized studies support those claims. Several prospective

randomized trials from the late 1980s and early 1990s indicated that TBI-based therapy led to superior outcomes compared to busulfan-based regimens in AML CR1 patients. No differences in outcomes were noted when patients were transplanted for chronic myeloid leukemia. The difference was driven in part by lower relapse rates in the TBI arms. However, more recent retrospective studies from the CIBMTR refute those results. It is possible that significant imbalances in the cytogenetic and molecular aberrations in the two arms of earlier trials led to differences in relapse. Also, the less reproducible pharmacokinetics associated with oral busulfan utilized in those early studies may have influenced outcomes. In general, results for pediatric patients with ALL have been superior with TBI-containing regimens compared to non-TBI regimens, although convincing data are not available in older adults.

5. TBI has been associated with which of the following side effects?

A. Growth retardation in children
B. Cataracts
C. Hypothyroidism
D. Cognitive disorders
E. All of the above

All of these side effects are often dose related. Transplantation at a younger age may also be a risk factor. While other contributing factors such as steroid use or chronic GVHD may play a role in complications such as cataracts and second cancers, it is clear that TBI is implicated in all these sequelae and has fueled interest in both non-TBI and RIC regimens. Long-term complications are not limited to recipients of TBI. Busulfan-containing regimens have been associated with long-term complications of bronchilitis obliterans, alopecia, and second cancers.

6. Veno-occlusive disease of the liver has been most often linked to which of the following?

A. Cy–TBI
B. Bu–Cy
C. Bu–Flu
D. Fludarabine–melphalan

VOD can be seen after conditioning with any of the regimens listed above, although it has been classically identified with the Bu–Cy regimen. When pharmacokinetic testing is performed and doses are adjusted to avoid toxic exposures, the incidence appears to be less frequent. The introduction of intravenous busulfan may have led to a reduction in VOD as a consequence of more consistent drug levels compared to the oral formulation. Some investigators have argued that it is the cyclophosphamide as much as the busulfan that contribute to VOD development, and certainly incidence seems less frequent in high-dose Bu–Flu compared with Bu–Cy. VOD can even be seen in some reduced regimens containing alkylating agents.

7. In which clinical scenario have traditional ablative regimens (CY–TBI, BU–CY, etc.) been associated with superior survival when compared to RIC or nonmyeloablative conditioning?

A. AML in first remission
B. CLL
C. AML beyond first remission
D. All of the above
E. None of the above

As there have been limited prospective trials to date examining dose intensity, it is not surprising that the answer here might be E. Even retrospective studies have not as yet been able to convincingly demonstrate the superiority of an ablative regimen when patient risk factor and comorbidities are taken into account. One might think it logical to assume that in more advanced disease such as AML beyond CR1, higher-dose conditioning might have an advantage. However, that may not indeed be so as patients beyond CR1 have already demonstrated resistance to high-dose chemotherapy, suggesting that the therapeutic advantage of transplant lies in GVT effects, not in chemotherapy-mediated cytotoxicity.

8. A 46-year-old patient with aplastic anemia is scheduled to undergo an allogeneic transplant from an HLA-matched unrelated donor. She had been treated with horse ATG and cyclosporine but had an inadequate response. She has received 18 units of red blood cells prior to transplant. What should her conditioning regimen include?

A. Cyclophosphamide and 1200 cGy TBI
B. Cyclophosphamide and horse ATG
C. Fludarabine and low dose TBI (200 cGy) and rabbit ATG
D. Cyclophosphamide and rabbit ATG
E. Any of the above

In general, for patients with aplastic anemia, the goal of conditioning is immunologic rather than cytotoxic. The history of prior transfusion might increase allo-sensitization and therefore could favor the use of a more intensive conditioning. The high-dose Cy–TBI regimen might not be appropriate due to its toxicity. Low-dose TBI with fludarabine alone may not be sufficiently immunosuppressive to prevent rejection. A cyclophosphamide- and ATG-based regimen is most commonly employed in these circumstances. Often times, if a patient has been exposed to ATG derived from one source, a different ATG product source may be used, although no data indicate this is necessary. Recent prospective randomized studies have suggested that equine ATG is superior to rabbit-derived (thymglobulin) ATG in the primary treatment of aplastic anemia, but

no such definitive data exist with respect to transplant conditioning.

Multiple choice answers

Question 1: Answer A
Question 2: Answer C
Question 3: Answer D
Question 4: Answer C
Question 5: Answer E
Question 6: Answer B
Question 7: Answer E
Question 8: Answer D

Selected reading

Bashey A, Owzar K, Johnson JL. Reduced-intensity conditioning allogeneic hematopoietic cell transplantation for patients with hematologic malignancies who relapse following autologous transplantation: a multi-institutional prospective study from the Cancer and Leukemia Group B (CALGB trial 100002). Biol Blood Marrow Transplant. 2011;17:558–65.

Bunin N, Aplenc R, Kamani N, *et al*. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant. 2003;32(6):543–8.

Champlin RE. Busulfan or TBI: answer to an age-old question. Blood. 2013;122(24):3856–7.

Deeg HJ, Storer B, Slattery JT, *et al*. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. Blood. 2002; 100(4):1201–7.

Soiffer RJ, Leradeamacher J, Ho V, *et al*. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Blood. 2011;6963–70.

CHAPTER 66

T-cell depletion in allogeneic hematopoietic cell transplantation

Jenna D. Goldberg and Miguel-Angel Perales

Memorial Sloan Kettering Cancer Center *and* Weill Cornell Medical College, New York, NY, USA

Introduction

Graft-versus-host disease (GVHD) contributes significantly to transplant-related morbidity and mortality (TRM), with an associated mortality rate of 10–25% after hematopoietic cell transplantation (HCT). The risk of grade II–IV acute GVHD in recipients of human leukocyte antigen (HLA)-matched related donor (MRD) and matched unrelated donor (MUD) grafts approaches 35–50% and 40–70%, respectively, with the use of current immunosuppressive regimens. Long-term immunosuppression is required in 30–40% of patients who develop GVHD. The recognition that GVHD was mediated by donor-derived T-cells led to preclinical and clinical exploration of T-cell depletion to reduce the risk of GVHD. The use of ex vivo T-cell-depleted (TCD) grafts has significantly reduced the risk of GVHD without the need for posttransplant immunosuppression. In this chapter, we will focus on the use of ex vivo T-cell depletion or CD34 selection of the graft rather than the use of in vivo antibodies such as antithymocyte globulin (ATG) or alemtuzumab.

1. What methods are used for T-cell depletion of the graft?

Although the most commonly used method of T-cell depletion currently relies on positive selection of CD34+ hematopoietic stem cells from the graft, over the years several different approaches have been used (Table 66.1). These differ primarily in the use of negative versus positive selection. Negative selection can be achieved through either physical methods such as counterflow elutriation or soybean lectin agglutination (SBA) and sheep red blood cell (sRBC)–rosette depletion (E-rosetting), or immunological methods using monoclonal antibodies. Monoclonal antibodies can be used with or without complement, or can be conjugated to toxins. Antibodies can have narrow specificities, such as T10B9 targeting the α/β T-cell receptor (TCR$\alpha\beta$), or broad specificities, such as a combination of antibodies targeting CD2, CD4, and CD8. More recently, removal of T-cells from the graft has been achieved through positive selection of CD34+ cells using immunomagnetic beads. In earlier studies, CD34+ selection of peripheral blood stem cells (PBSCs) was performed on the ISOLEX 300i magnetic cell selection system (Baxter, Deerfield, IL), followed by E-rosetting. Current studies are using immunomagnetic beads on the CliniMACS cell selection system (Miltenyi Biotech, Gladbach, Germany) for CD34+ selection. The CliniMACS system can also be used to negatively select grafts through depletion of CD3 and CD19 cells or depletion of TCR$\alpha\beta$ T-cells.

When assessing data from clinical trials reporting the use of TCD grafts, it is critical to review the specific approach used. In particular, the specific populations being removed from the graft (T-, B-, and NK-cells and all nonhematopoietic stem cells), the degree of T-cell depletion, the stem source (bone marrow vs. peripheral blood stem cells), the degree of HLA match (matched vs. mismatched vs. haploidentical), and the use of posttransplant GVHD prophylaxis (standard vs. reduced vs. none) can have a significant impact on clinical outcomes. The degree of T-cell depletion is a particularly critical factor. In recipients of TCD marrow grafts from HLA-identical donors, the risk of GVHD was shown to increase if the graft contained $>1 \times 10^5$ T cells/kg. For example, the CliniMACS system can achieve a 5-log reduction in T-cells, whereas the ISOLEX 300i system achieves a 3.5-log reduction, requiring additional T-cell

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 66.1 Examples of methods used for T-cell depletion of stem cell grafts.

Method	Number of patients	Donor	BM versus PBSC	Degree of depletion	GVHD prophylaxis	Acute GVHD	Graft Failure
Physical methods							
CCE	22	HLA–MRD	BM	2 logs	CSA or MTX or none	Yes (patients w/o PPX)	1/22
CCE	38	HLA–MRD	BM	2–3 logs Standard T-cell dose given (10^6/kg)	CSA	45%	0
SBA–E	31	HLA–MRD	BM	2.5–3 logs	None	3/26	5/31
SBA–E	39	HLA–MRD	BM	2.8–3 logs	None	0	0
SBA–E	54	HLA–MRD	BM	3 logs	None	0	0
Immunological methods							
Monoclonal antibodies	14	HLA–MRD	BM	2 logs	None	2/13	0
Monoclonal antibodies	20	HLA–MRD	BM	2–3 logs	CSA	3/19	7/20
Monoclonal antibody	20	HLA–MRD	BM	2 logs	MTX or CSA	3/20	5/20
Immunotoxin	38	HLA–MRD	BM	2.5 logs	CSA or MTX	3/37	6/37
Monoclonal antibody or Immunotoxin	71	HLA–MRD or HLA–MMRD	BM	2 logs	10/19 MTX All MTX	23% 50%	4%
Monoclonal antibody	41	HLA–MRD or HLA–MMRD	BM	1.5–2 logs	None	15% 42%	0/34 1/7
Monoclonal antibody	170	HLA–MRD or HLA–MUD	BM	1.5–2 logs	None	20% 42%	1/170
Magnetic beads							
CD34 selection	104	Haplo	PBSC	4.5 logs	None	8/100	9%
CD34 selection	50	HLA–MRD	PBSC	Not indicated	CSA or CSA + steroids	16%	0
CD34 selection + E-rosetting	52	HLA–MRD	PBSC	5 logs	None	8%	0
CD34 selection + E-rosetting	29	HLA–MUD or HLA–MMUD	PBSC	5 logs	None	9%*	1/29
CD34 selection +	44	HLA–MRD	PBSC	4.9 logs	None	22.7%	0
CD3–CD19 depletion	29	Haplo	PPSC	4.4 logs	None	48%	0

BM, bone marrow; CCE, centrifugal counterflow elutriation; CSA, cyclosporine A; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; MMRD, mismatched related donor; MRD, matched related donor; MTX, methotrexate; PBSC, peripheral blood stem cells; PPX; pramipexole; SBA–E, soybean lectin agglutination and E-rosette depletion.
*Report includes 29 patients who received PBSC grafts and six patients who received BM grafts. GVHD is reported for the whole study.

depletion through E-rosetting. Therefore, the differences between T-cell depletion methods can have a significant impact on clinical outcomes, including the risk of graft failure, GVHD, and relapse.

2. What is the impact of T-cell depletion on engraftment?

A potential consequence of T-cell depletion is a higher risk of graft rejection. In fact, early studies of T-cell depletion were associated with higher rates of graft rejection than those observed among recipients of conventional grafts, with reported graft failure rates as high as 27%. These clinical results confirmed preclinical data that donor-derived T-cells facilitate engraftment. Following modifications of the conditioning regimen, and in particular the use of ATG to promote engraftment, several centers have reported consistent engraftment with TCD grafts using a variety of approaches for T-cell depletion, including CD34 selection.

3. What is the impact of T-cell depletion on GVHD?

The main goal of using a TCD or CD34-selected graft is to reduce the risk of both acute and chronic GVHD. This result has been achieved in most studies, although to varying degrees. The risk of GVHD generally has correlated with the extent of T-cell depletion. Studies using methods that result in a 1–2 log depletion of T-cells generally have rates of acute GVHD from 15% to as high as 50% when mismatched donors are used. This includes studies in which posttransplant GVHD prophylaxis is given. In contrast, the risk of both acute and chronic GVHD decreases significantly when the degree of T-cell depletion is 3-log using bone marrow or 4–5-log using PBSCs. For example, studies performed at Memorial Sloan Kettering Cancer Center (MSKCC) that achieved a 5-log reduction in T-cells using CD34 selection followed by E-rosetting have reported incidences of acute GVHD (limited to grade II) of 8%, and chronic GVHD of 9% in recipients of matched related grafts, and incidences of acute and chronic GVHD of 9% and 29%, respectively, in recipients of MUDs. None of the patients received GVHD prophylaxis beyond T-cell depletion of the graft. Interestingly, in the setting of MRDs, ATG was not required for engraftment when patients were conditioned with total-body irradiation (TBI), thiotepa, and fludarabine. Results from single-center studies have been validated in a Blood and Marrow Transplant Clinical Trials Network multicenter study (BMT CTN 0303), in which 44 patients with acute myeloid leukemia (AML) in first or second remission (CR1 or CR2, respectively) were conditioned with TBI, thiotepa, and cyclophosphamide with rabbit ATG followed by a TCD PBSC allogeneic graft from an HLA-identical sibling donor. The incidence of acute GVHD grade II–IV was 22.7%, and the incidence of extensive chronic GVHD was 6.8% at 24 months. Importantly, these results are in the setting of PBSC grafts. Finally, this approach has also been used successfully with grafts from haploidentical donors. Aversa *et al*. (2005) reported a series of 104 patients with acute leukemia (AML: 37; acute lymphoblastic leukemia (ALL): 37) who received CD34-selected PBSC grafts from haploidentical donors after conditioning with TBI, thiotepa, fludarabine, and ATG. Graft failure was observed in 7 of 101 evaluable patients, and acute GVHD developed in 8 of 100 patients.

4. What is the impact of T-cell depletion on relapse?

One of the main reasons for increased disease-free survival after allogeneic HCT (allo-HCT) compared to autologous HCT (auto-HCT) is the recognition of the tumor by donor-derived T cells, the so-called graft-versus-leukemia (GVL) effect. There is both preclinical and clinical data to support GVL effects in allo-HCT. Therefore, a potential and significant limitation of T-cell depleting the graft is an increase in relapse. This was illustrated in patients with chronic myeloid leukemia (CML) in a retrospective study in which 46 patients who underwent TCD transplants were compared to 40 patients who had conventional grafts. The 3-year probability of relapse was higher in the TCD group than in the non-TCD group (62% vs. 24%; $P = .0003$). After donor lymphocyte infusion (DLI), however, 17 of 20 patients in the TCD group and two of three patients in the non-TCD group achieved a complete remission. While the CML experience clearly supports the critical role of GVL in allo-HCT, results in studies with patients with AML or ALL report comparably low rates of relapse after TCD HCT. For example, in the BMT CTN 0303 study, the relapse rate for patients with AML in CR1 was 17.4% at 36 months. We recently reported our results in 56 adult patients with ALL, including 27 patients in CR1, 18 in CR2, and 11 in third remission (CR3) or greater. With a median follow-up of 6.1 years, the cumulative incidence of relapse for the entire cohort was 0.23. These results are consistent with those reported by the Perugia group, who found a probability of relapse of 0.12 for patients with AML and 0.28 for patients with ALL who underwent TCD HCT in CR1 or CR2. To further assess the impact of T-cell depletion on relapse in patients with AML in CR1, we performed a retrospective analysis of 115 patients who received TCD grafts after ablative conditioning at MSKCC and compared them with a cohort of 181 patients who received unmodified grafts after conditioning with busulfan–fludarabine and GVHD prophylaxis with tacrolimus–minimethotrexate at MD Anderson Cancer Center (MDACC). There were no significant differences in the rate of relapse at 3 years between TCD and unmodified graft recipients (18% vs. 25%; $P = 0.3$).

5. What is the impact of T-cell depletion on immune recovery?

Allo-HCT is associated with deficiencies in the recovery of T- and B-cells that are associated with increased rates of infections, disease relapse, and the development of secondary malignancies. Although several factors contribute to these immune defects, the use of either in vivo (with alemtuzumab or ATG) or ex vivo T-cell depletion has marked effects on immune recovery. Studies of thymic output have shown lower T-cell receptor rearrangement excision circles (TRECs) in recipients of TCD allografts compared to unmodified allograft recipients. These differences, however, abated beyond 9 months. Delayed thymic output translates into delayed recovery of total and naïve CD4+ T-cells, prolonged inversion of the CD4–CD8 ratio, and delayed recovery of T-cell mitogen responses, which is associated with an increase in Epstein–Barr virus–associated lymphoproliferative disorders and opportunistic infections in the first year posttransplant. Studies of T-cell receptor (TCR) diversity in allo-HCT patients using 5′-RACE polymerase chain reaction with deep sequencing have shown more rapid recovery in a diversity in recipients of conventional grafts compared to those receiving TCD grafts. It should be noted, however, that GVHD also has a significant impact on immune recovery through direct effects on the thymus, particularly because of the immunosuppressive drugs required to treat GVHD. In the MSKCC–MDACC retrospective study, six (5%) and two (1%) patients died of infections within 100 days posttransplant in the TCD and unmodified groups ($P = 0.04$), respectively. Despite these differences in infectious deaths, there were no significant differences in 3-year relapse-free survival (RFS) and overall survival (OS) rates.

6. Are there potential strategies to enhance immune recovery post-HCT?

One strategy that has been used clinically to decrease posttransplant T-cell deficiency has been to add back a fixed dose of T-cells to the graft, based on the relationship between T-cell dose and risk of GVHD. Beyond this direct approach, a significant effort in preclinical models has focused on novel strategies to enhance posttransplant T-cell recovery. A number of these are now in clinical development, including interleukin-7 (IL7), keratinocyte growth factor (KGF), growth hormone (GH), and sex steroid ablation. We recently published results of a phase I trial of recombinant human IL7 (rhIL-7, CYT107, and Cytheris) in recipients of a TCD allo-HCT and demonstrated enhanced immune recovery, both quantitative and qualitative, without causing significant GVHD or other serious toxicity. A randomized study investigating the potential role of KGF and sex steroid ablation on immune recovery post TCD–HCT is currently ongoing (NCT01746849).

7. What are the potential advantages of CD34 selection of the graft?

The main advantage of the use of a CD34-selected graft is the significant reduction in acute and chronic GVHD. This is particularly relevant in patients who do not have a fully matched donor. Another advantage of CD34-selected grafts is the fact that no posttransplant GVHD prophylaxis is required. The ability to avoid calcineurin inhibitors eliminates the renal toxicity associated with their use in allo-HCT, and it allows the inclusion of patients with underlying renal dysfunction, including older patients. It also increases the ability to use ablative regimens in older patients, in whom the combined toxicity of an ablative regimen and posttransplant GVHD prophylaxis that includes a calcineurin inhibitor and methotrexate represents a dose-limiting toxicity. As a result, older patients receiving conventional grafts are typically treated with reduced-intensity or nonablative conditioning regimens, which are associated with higher rates of relapse in acute leukemias. Finally, the use of a CD34-selected graft also represents the ideal platform for posttransplant immunotherapy with adoptive cell therapy targeting minimal residual disease. This approach has the potential advantage of overcoming any loss of GVL without affecting the benefit of reduced GVHD.

8. Which patients are candidates for a CD34-selected graft?

In the absence of randomized data, it is reasonable to consider the following factors when deciding on the use of a CD34-selected graft in a patient: (i) the underlying disease and disease status, (ii) the degree of donor matching, and (iii) patient comorbidities. Clinical data support the use of CD34-selected grafts in patients with AML, ALL, myelodysplastic syndrome (MDS), and high-grade non-Hodgkin's lymphoma (NHL) in remission based on similar relapse data to those seen after conventional grafts. This is particularly relevant in patients without a fully matched donor, in whom the risk of GVHD would be a limiting factor. Furthermore, patients able to tolerate an ablative regimen but for whom GVHD or nephrotoxicity may be limiting are also potential candidates. Another group of patients who are candidates for CD34-selected grafts are those with nonmalignant conditions, for whom the GVL effect does not offer any benefit. This includes patients with congenital disorders, such as severe combined immune deficiency. Finally, patients who have donors with autoimmune diseases would in theory benefit from a CD34-selected graft, although there are no published data on this.

Conclusions

T-cell depletion has now been under investigation for over 3 decades, with few studies comparing outcomes with

those of patients receiving unmodified grafts. As noted in this chapter, results from the MSKCC–MDACC comparative study demonstrated similar RFS and OS after TCD and conventional transplants from related and unrelated donors in patients with AML in CR1, but a significant reduction in GVHD in the TCD cohort. A prior retrospective study of 146 patients with hematological malignancies did not show significant differences in survival, GVHD rates, and quality of life between patients who received TCD and unmodified grafts, although the method of T-cell depletion used only achieved a 1–2-log reduction in T cells. In the only prospective randomized phase II–III trial, the incidence of acute GVHD was lower after TCD–HCT, but there was no difference in survival. This study also used older methods of T-cell depletion that only achieved 1–2 logs of depletion. A recent analysis of the BMT CTN 0303 trial's patients compared to a subset of patients on BMT CTN 0101 who received a conventional transplant for AML in CR1 or CR2 showed no differences in rates of graft rejection, leukemia relapse, TRM, and disease-free and overall survival rates. Two-year rates of chronic GVHD were lower with TCD grafts than conventional grafts (19% vs. 50%, respectively; $P < .001$), and TCD was associated with a higher GVHD-free survival rate at 2 years (41% vs. 19%; $P = .006$).

The use of CD34-selected grafts overcomes one of the major limitations of an allogeneic HCT, namely, the morbidity and mortality associated with GVHD. This approach should be considered in patients with AML, ALL, MDS, and high-grade NHL in CR1 or CR2, whether using a matched related or unrelated donor and particularly in the setting of a mismatched donor. The main limitations remain the need for graft manipulation, the requirement for an ablative conditioning regimen, and delayed immune reconstitution. The risk of relapse appears to be increased in diseases in which the main benefit of an allo-HCT is GVL, and therefore routine use of CD34 selection is not recommended in patients with these diseases. Future randomized studies are needed to better define the indications of CD34-selected grafts.

Selected reading

Bayraktar UD, de Lima M, Saliba RM, *et al*. Ex vivo T cell depleted versus unmodified allografts in patients with acute myeloid leukemia in first complete remission. Biol Blood Marrow Transplant. 2013;19(6):898–903.

Goldberg GL, Zakrzewski JL, Perales MA, *et al*. Clinical strategies to enhance T cell reconstitution. Semin Immunol. 2007;19: 289–96.

Goldberg JD, Linker A, Kuk D, *et al*. T cell-depleted stem cell transplantation for adults with high-risk acute lymphoblastic leukemia: long-term survival for patients in first complete remission with a decreased risk of graft-versus-host disease. Biol Blood Marrow Transplant. 2013;19:208–13.

Pasquini MC, Devine S, Mendizabal A, *et al*. Comparative outcomes of donor graft CD34+ selection and immune suppressive therapy as graft-versus-host disease prophylaxis for patients with acute myeloid leukemia in complete remission undergoing HLA-matched sibling allogeneic hematopoietic cell transplantation. J Clin Oncol. 2012;30: 3194–201.

Perales MA, Goldberg JD, Yuan J, *et al*. Recombinant human interleukin-7 (CYT107) promotes T-cell recovery after allogeneic stem cell transplantation. Blood 2012;120:4882–91.

CHAPTER 67

Prevention and treatment of relapse following hematopoietic cell transplantation

Robert Chen, Sandra Thomas, and Stephen J. Forman
City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Introduction

Allogeneic and autologous stem cell transplant are therapies that are utilized to cure either patients with high-risk hematologic malignancy in first remission or those patients who suffer a relapse and have little or no other potential curative options. Autologous transplant historically has been utilized as a way of delivering high-dose chemotherapy to eliminate residual tumor cells, using cryopreserved stem cells to reestablish both hematopoiesis and immune reconstitution after clearance of the drugs. The major risk of the procedure in the autologous setting is recurrence of the disease, something that is, unfortunately, common in both Hodgkin and non-Hodgkin's lymphomas and multiple myeloma, which are the major indications for the use of this approach.

For those patients undergoing allogeneic transplantation, the goal is similarly cure, but relies, in large part, on the graft-versus-tumor (GVT) effect mediated by the donor immune cells, be it from a related, unrelated, or cord blood donor. Although originally almost all transplants utilized high-dose chemoradiotherapy or a high-dose chemotherapy regimen alone, over the last decade, with increasing understanding of the role of the GVT effect, reduced-intensity transplant regimens have been utilized and have now been applied to the care of older patients with hematologic malignancy, especially acute leukemia and myelodysplasia. Although the risks of the transplant are different in the autologous and allogeneic settings, the major problem for many patients is relapse of the disease. This risk is related, in large part, to the disease status of the patient prior to transplant, the molecular nature of the genetic abnormalities associated with that disease, and the extent of prior therapy. Patients who are in remission tend to do better than those who are not in remission at the time of transplant, and now disease assessments include measurements of minimal residual disease (MRD) to further quantitate the burden of disease going into transplant and its impact on transplant outcomes. Thus, pretransplant, conditioning regimen, and post-transplant intervention strategies are being explored to reduce the chances of relapse and lead to better outcomes The clinical scenarios described in this chapter focus on the dilemma faced by physicians in assessing patients for transplant and dealing with the aftermath, should there be a relapse of the disease.

Case study 67.1

• **Is there a role for a second allogeneic transplant in patients who suffer a relapse after a first transplant?**
A 35-year-old man with FLT3-positive acute myeloid leukemia (AML) underwent allogeneic transplantation utilizing a myeloablative total body irradiation (TBI) conditioning regimen from a human leukocyte antigen (HLA)-matched sibling. Following transplantation, he developed some acute graft-versus-host disease (GVHD) that resolved with increased immunosuppression. The medications were subsequently discontinued, and he did not develop any evidence of chronic GVHD. Eighteen months after transplant, while off immunosuppression, he developed fatigue, and a blood count showed circulating blasts consistent with relapse of his disease. Among the various therapeutic ques-

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

tions are: is there a role for a second allogeneic transplant to treat his disease and, if so, which time, conditioning, and donor type would be best?

Relapse after allogeneic transplantation remains a major problem and requires a thoughtful discussion with the patient as to how to manage what was initially intended as a curative therapy. Among the choices are no further therapy with palliative care, withdrawal of immunosuppression to elicit a therapeutic GVT response, re-induction chemotherapy with the same or different agents, donor lymphocyte infusions with or without preceding chemotherapy, and, in some specific cases, depending upon the response, second transplant with or without preceding chemotherapy. There are a number of clinical nuances that influence this judgment, including whether there was any antecedent GVHD; the current status of the patient's organ function; the willingness of the donor, either sibling or unrelated, to provide more cells; and, importantly, the time between transplant and relapse; also, the specific characteristics of the leukemia contribute to the difficulty of the decision. And, of course, the question arises whether any patients who undergo second allogeneic transplant after relapse from a first transplant are likely to be cured.

Despite the apparent heterogeneity of studies that have addressed this issue, several principles have emerged to help guide patients, families, and physicians. In general, most centers will use the same donor for both the first and second transplant, and most patients will undergo re-induction therapy in order to reduce the disease burden, knowing that the outcome for any transplant is improved if the patient is in remission. Typically, patients who underwent a TBI-based regimen for initial transplant would receive a non-TBI myeloablative regimen for their second transplant. However, with the increased appreciation of the role of a graft-versus-leukemia effect in facilitating cure of leukemia, reduced-intensity transplant regimens have been used for patients in this situation.

Patients with chemosensitive disease in remission who have had a long initial remission (defined as greater than 6–12 months after the first transplant) and who never developed any GVHD are likely the ones who benefit most from a second transplant. Conversely, when patients have had a very short remission and did not respond to re-induction chemotherapy, they are unlikely to benefit from a second allogeneic transplant. In those patients who do undergo a second transplant in a second remission of their disease and who had no significant chronic GVHD the first time, it is generally advised to taper the post-transplant immunosuppression more quickly in order to harness a therapeutic GVT effect in the post-transplant setting. In addition, patients who had both acute and chronic GVHD but, despite this, suffered a relapse and thus had an ineffective GVT effect are less likely to benefit from a second transplant from the same donor. In this setting, the decision to undergo a second transplant needs to be weighed against the associated comorbidities that contribute to transplant-related mortality and the use of another donor. Sometimes when there is a second match within the family, transplant will be done with a different donor in an attempt to harness a more effective immune system, and for patients who have had a longer remission, it is worth considering an unrelated donor.

Case study 67.2

• Should patients with relapsed AML or acute lymphoblastic leukemia (ALL) undergo re-induction therapy before allogeneic transplant?

A 37-year-old man with pre-B ALL (CD19+), Philadelphia chromosome negative, with normal cytogenetics presented with a white blood cell (WBC) count of 60,000, hemoglobin of 4 g/dl, and a platelet count of 20,000. The diagnosis was confirmed by bone marrow and peripheral blood analysis, and hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) chemotherapy was initiated. It was his physician's assessment that, based on his age, lack of BCL/ABL mutation, and the fact that he achieved a remission with chemotherapy in the first cycle, transplant was not indicated. He had four siblings, but none of them were typed at the time of diagnosis. He then received alternating cycles of hyper-CVAD part A and part B, but prior to initiation of treatment with cycle 4A, he remained pancytopenic, not having recovered from the previous cycle. Because of concerns about the status of the marrow and continuing therapy, a bone marrow biopsy was performed that showed approximately 40% lymphoblasts of a very similar phenotype and no additional chromosome abnormalities.

Most induction regimens use intensive chemotherapy to achieve a remission, followed by consolidation and, in the case of ALL, maintenance therapy, with many patients being cured with this approach. However, for patients who suffer a relapse of disease, the treatment options are limited.

(*Continued*)

Depending upon the duration of remission, sometimes the same drugs can be effective in achieving a second remission, particularly if the first remission was greater than 1–2 years. For patients whose remission lasted less than 6 months, the 1-year overall survival has been 14%, but if greater than 18 months, it has been reported to be 57%. Therefore, the ability to achieve a second remission is contingent upon several clinical and biological factors. Although patients who relapse will have reduction of the leukemic burden with additional treatment, it is very rare for a patient to be cured by this approach. Among a large number of patients who had relapsed in the German ALL study, no patient without transplant survived more than one year after relapse. Therefore, the salvage therapies in transplant-eligible patients should be viewed as a bridge to transplant. For patients who achieve a second remission without any limiting organ toxicities that would preclude proceeding to transplant and who have a donor, the cure rate can be as high as 50%. The major problem, however, for those patients with a relatively short remission is that the treatment options are somewhat limited, as in the case discussed here.

For patients with relapsed AML, there are some new treatment options utilizing hypomethylating-based therapy, combined with histone deacetylase inhibitors or lenalidomide, or the use of FLT3 inhibitors to achieve a remission as bridges to transplant. New drug development in ALL has been more limited, but recently promising options, especially those including immunologic approaches, are being developed. These include BiTE® immunotherapy, an approach that fuses an antibody fragment recognizing the CD19 antigen on pre-B ALL, to an anti-CD3 antibody fragment that engages a local T-cell response to elicit the patient's immune system in tumor cell killing. These studies have shown an impressive rate of response and depth of remission (MRD negative) and can act as a bridge to transplant. This approach is being tested, both as treatment of relapsed patients, such as the one described here, and as part of upfront treatment to combine both chemotherapy and immunotherapy in the initial treatment of the disease. In addition, immunoconjugates that deliver a drug directly to $CD19^{+}$ cells, as well as the use of genetically altered T-cells that can recognize CD19, are also being explored as novel approaches to treat ALL patients. These novel approaches, will give patients a better option for achieving a second remission after relapse of the disease and facilitate a more successful transplant. Thus, even for patients with disease relapsing relatively early, new options are evolving that may change the outcome, hopefully achieving a minimal disease state that would improve the chances of cure after an allogeneic transplant. Similar approaches focusing on myeloid antigen targets are being developed for AML that could also serve as bridge therapies to transplant.

For patients with an early relapse after a relatively short remission (ALL and AML), if a donor can be identified quickly, early transplant without re-induction therapy can sometimes lead to a cure. To facilitate this, it is prudent to do family typing at diagnosis in all adult patients with ALL or AML, as this will help determine the transplant strategy in case of relapse or even failure to achieve a first remission. In the above-noted case, we would advise re-induction therapy with either chemotherapy or, if eligible, an immunotherapy protocol and, of course, typing the siblings.

Case study 67.3

• Is there a benefit to hypomethylating therapy in the management of patients with myelodysplastic syndrome (MDS) who are candidates for allogeneic transplantation?

A 57-year-old woman who was treated for stage II breast cancer with dose-dense cyclophosphamide, doxorubicin, and taxane developed pancytopenia 3 years after completion of her primary therapy while on antihormone therapy (her tumor was ER/PR positive and Her2/neu negative). She was noted on routine follow-up to be pancytopenic, and a bone marrow biopsy was performed that showed her to have morphologic evidence of myelodysplasia with approximately 12% blasts in the marrow and a chromosome abnormality showing deletion 7. At the time of diagnosis, her hemoglobin was 9 g/dl, platelet count 50,000, and WBC count 3200 with no blasts in the blood. HLA typing was performed, and she did not have a match in her family, but a preliminary search of the donor registries identified multiple 10/10 allele-level matches.

This patient developed a late complication of chemotherapy that can be seen for chemotherapy-treated patients with breast cancer, lymphoma, Hodgkin lymphoma (HL), or multiple myeloma, namely, the development of secondary myelodysplasia resulting from exposure to chemotherapeutic agents, often combined with radiation. As noted here, HLA typing was performed and she was found not to have a sibling match , but there were numerous allele-level 10/10 matches in the registry who could be evaluated for transplant within a few months of diagnosis. The question is often raised as to whether there is any benefit to hypomethylating therapy, which is the major therapeutic option existing for patients with this disease, compared to proceeding directly to transplant? Although reasoning by analogy to other forms of acute leukemia implies that the disease

burden at the time of transplant affects the outcome, the issues in management of myelodysplasia are less clear, and no formal studies have been done that actually address this question. In general, for patients with high-risk MDS, physicians do use hypomethylating therapy to improve hematopoiesis, reduce the leukemia cell burden, and improve the patient's overall condition prior to transplant, but the number of cycles to be utilized and the timing of transplant are less clear. For instance, many physicians will initiate hypomethylating therapy but, when the donor is identified, proceed directly to transplant. This is influenced, in part, by the idea that not all patients respond to hypomethylating therapy and some patients actually progress while on it, thus resulting in a worse hematologic condition going into transplant. There is now a national study attempting to address the role of transplantation versus other therapies in the management of older patients with primary myelodysplasia, which will help to answer part of this question, but it is specifically designed to answer whether transplant is of benefit in such patients. Recent studies have also suggested that for patients with secondary myelodysplasia, such as in the case discussed here, transplant can rescue them from the sequelae of this disease, with over 50% of the patients becoming long-term disease-free survivors. In this setting, if the patient had an HLA-matched sibling donor and otherwise was in good condition, most transplant physicians would proceed directly to transplant without intervening steps of hypomethylating-based therapy. However, for those patients who may have a more protracted search of the registries, a trial of hypomethylating therapy to at least stabilize, if not reduce, the burden of disease would be appropriate before proceeding to transplant when a donor is identified.

Ideally, it would be best if we knew whether patients who respond to hypomethylating therapy have an improved outcome, but such studies have not been formally done. For instance, if the outcome was exactly the same, it would obviate the need for a bridge to therapy with hypomethylating-based agents. However, if the outcome was better for those patients who responded, then strategies to implement this in more patients, including achievement of remission, would be appropriate. There is also the question as to whether patients who respond well to hypomethylating therapy should delay or even forgo transplant? The field would suggest that the duration of response of hypomethylating therapy is very limited and that the outcome for patients who relapse is dismal. For patients with both primary high-risk myelodysplasia and secondary myelodysplasia, transplant seems to be the better option, with the role of hypomethylating therapy yet to be defined.

Case study 67.4

• Is there a role for allogeneic transplantation for patients who have recurrent lymphoma after autologous transplantation?

The patient is a 35-year-old woman who had stage IIB nodular sclerosing Hodgkin lymphoma, with disease confined to the chest and supraclavicular lymph nodes. The mediastinal mass at the time of diagnosis measured approximately 8 cm, and she presented with cough, respiratory symptoms, fever, and feeling poorly. After initial staging, she was started on adriamycin, bleomycin, vinblastine, and dacarbazine and achieved a complete remission, which was documented after the first two cycles and then again after completion of therapy. She was then followed regularly by her physician, but was noted to become anemic with microcytic indices, and a repeat positron emission tomography–computed tomography (PET–CT) scan showed recurrence of the disease, both above and below the diaphragm and sites of previous disease as well. After re-induction therapy with ifosfamide, carboplatin, and etoposide (ICE), she achieved a near-complete response measured by PET–CT scan criteria, then underwent autologous transplant following a cyclophosphamide, carmustine, and etoposide transplant regimen, but showed evidence of recurrent disease within a year of transplant. HLA typing was performed, and she was found to have a match with her brother and, thus, was considered for allogeneic transplantation.

The primary therapy for patients with large-cell lymphoma and HL who have relapsed after primary chemotherapy is re-induction therapy, followed by autologous hematopoietic cell transplant. The original studies performed years ago demonstrated that those patients who received only continued or palliative chemotherapy had inferior disease-free survival compared to patients who underwent autologous hematopoietic cell transplant. Despite this improvement, there are still many patients who relapse after autologous cell transplant. This is true for both Hodgkin and non-Hodgkin's lymphoma, and there are prognostic features that suggest the outcome can be predicted. For instance, for those patients with diffuse large B-cell lymphoma (DLBCL) who have had prior rituximab-based cyclophosphamide,

(*Continued*)

doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy, patients who relapsed within the first year or who failed to achieve a PET-negative remission after primary therapy were at high risk for relapse even after autologous hematopoietic cell transplant. The same is true for HL, and the question is whether there is a role for allogeneic transplantation for patients who have recurrent lymphomas if they failed an autologous transplant? For patients with DLBCL, some progress has been made in developing allogeneic transplant regimens, although the efficacy of the graft-versus-tumor effect in this particular histology is less clear. Some studies utilizing novel approaches, particularly radioimmunotherapy-based regimens. In contrast to patients with DLBCL, patients with relapsed mantle cell lymphoma (MCL), who often have autologous hematopoietic cell transplant as part of their primary therapy, are exquisitely sensitive to the GVT effects, and an allogeneic transplantation can consistently cure a proportion of patients with this disease. In patients with Hodgkin's lymphoma the challenges are different. Historically, these patients have been heavily pretreated with both chemotherapy and radiation therapy, and the transplant-related toxicity following allogeneic transplantation has been quite significant, with only a small proportion of patients getting through the transplant and being cured of their disease. However, recent data suggest that patients who have relapsed and respond well to re-induction therapy, predominantly with brentuximab vedotin, do quite well after transplant, with encouraging one-year survival. The same thing is true for low-grade lymphoma where the results of allogeneic transplantation have been probably the most impressive, likely due to a higher susceptibility to the GVT effect in these patients. Currently, there are a number of options for patients with low-grade lymphoma, so the actual timing of allogeneic transplantation is less clear, but even those patients who have recurred after more than 2–3 prior regimens can still benefit from such an approach utilizing predominantly reduced-intensity transplant regimens that focus predominantly on harnessing a GVT effect.

Case study 67.5

• Is there a role for maintenance therapy following autologous or allogeneic transplant?

The patient is a 57-year-old man who presented with stage IIIB DLBCL, activated B-cell type, who was treated with six cycles of R-CHOP and achieved a complete remission, documented by PET-CT scan. He returned to work and had no further symptoms. Approximately 6 months later, he was noted on routine evaluation to have recurrent palpable adenopathy; subsequent biopsy of PET-CT avid lymph node confirms recurrent disease of similar histology. He was treated with re-induction therapy with rituximab–ICE (R-ICE) chemotherapy, achieved a partial response, and underwent autologous stem cell transplant with high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy. Scans performed on day 50 after transplant showed him to be in complete remission.

Although this patient has done well after autologous stem cell transplant, his prognosis after the procedure was actually quite poor based on the prognostic features of his relatively short duration of complete remission after primary therapy, his exposure to rituximab, and the fact that he achieved only a partial response to the re-induction chemotherapy. Although in remission after transplant, his risk of relapse is probably in excess of 70–75%, and studies are now ongoing to ask the question of whether there is a role for maintenance therapy in lymphoma, very similar to what is used for multiple myeloma. In general, all patients undergoing transplant for multiple myeloma receive some form of maintenance therapy, usually with lenalidomide or bortezomib-based chemotherapy, often in conjunction with dexamethasone, anywhere from 1 to 3 years depending upon tolerance and, in some cases, geographic, if not national, standards for the disease. Thus, multiple myeloma patients, in contrast to patients undergoing transplant for other hematologic malignancies, almost always undergo maintenance therapy, while it is rare for nonmyeloma indications. However, the relapse rates for autologous transplantation for HL, MCL, and large-cell lymphoma are of such a magnitude that questions are now being posed as to whether maintenance therapy should be considered for these patients. Although no formal studies have been performed, among the options being considered are the administration of lenalidomide post-transplant for patients with DLBCL, and the use of Bruton's tyrosine kinase inhibitors or proteasome inhibitors after autologous transplant for large-cell lymphoma and MCL. Brentuximab vedotin is being tested as maintenance therapy in patients who have completed transplant for HL, and there is potential for the use of genetically modified T cells-cells targeted on $CD19^{+}$ cells for patients with MCL or DLBCL. Interest in these agents, in

part, reflects the concern that few recent innovations within the transplant regimen have led to improvements in disease control, combined with the recognition that there are prognostic factors that predict which patients are most likely to relapse after autologous stem cell transplant. Thus, the patient in this case would be an ideal candidate for maintenance therapy, although the agent of choice is unknown designed to reduce the disease burden that may persist even after the high-dose chemotherapy (discussed in Chapter 59).

Selected reading

Fielding AK, Richards SM, Chopra R, *et al*. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109:944–50.

Forman SJ, Rowe JM. The myth of the second remission of acute leukemia in the adult. Blood. 2013;121:1077–82.

Khouri IF, Saliba RM, Erwin WD, *et al*. Nonmyeloablative allogeneic transplantation with or without 90yttrium ibritumomab tiuxetan is potentially curative for relapsed follicular lymphoma: 12-year results. Blood. 2012;119:6373–8.

Thakar MS, Forman SJ. ASH evidence-based guidelines: is there a role for second allogeneic transplant after relapse? ASH Education Book. 2009:414–18.

Yahng SA, Yoon JH, Shin SH, *et al*. Response to pretransplant hypomethylating agents influences the outcome of allogeneic hematopoietic stem cell transplantation in adults with myelodysplastic syndromes. Eur J Haematol. 2013;90:111–20.

CHAPTER 68

Acute graft-versus-host disease

Andrew C. Harris and John E. Levine

University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

Case study 68.1

You are consulting a 54-year-old man for consideration of hematopoietic cell transplantation (HCT) as therapy for high-risk acute myeloid leukemia. He asks how you plan to collect stem cells for his transplant and how that may affect his risk for posttransplant complications. He has read about graft-versus-host disease (GVHD) and is particularly fearful of this transplant complication.

1. True or false? Peripheral blood stem cell (PBSC) grafts are associated with an increased risk for acute GVHD when compared to bone marrow grafts.

A. True
B. False

Although some initial studies implicated that PBSC grafts imparted greater risk for acute GVHD, larger and more recent randomized studies have shown no difference in risk between bone marrow and peripheral blood grafts, which report GVHD rates of 50–80%. In a recently completed randomized clinical trial specifically designed to compare the two graft sources from unrelated donors, however, patients receiving marrow grafts experienced increased graft failure (9% vs. 3%; $P = 0.002$) and decreased risk for chronic GVHD (41% vs. 53%; $P = 0.01$) when compared to those receiving PBSCs. The 2-year incidence of relapse (approximately 25%) and rates of overall survival (approximately 50–55%) appear to be comparable between graft sources.

Umbilical cord blood offers a potential graft source for patients who do not have suitably matched donors. Transplants using single umbilical cord blood units confer decreased risk for GVHD when compared to blood or PBSC grafts regardless of whether the donor is related or unrelated (hazard ration (HR): 0.4–0.45). Importantly, GVHD risk from cord bloods mismatched at up to two loci at human leukocyte antigen A (HLA-A), -B, or -DRβ1 is comparable to that of fully HLA-matched unrelated donor marrow or PBSCs, and risk was less than that from HLA-mismatched unrelated donor marrow or PBSCs (HR: 0.66). The decreased absolute number of T-cells and the predominance of naïve T-cells in the graft may explain why cord blood grafts are more tolerant of HLA disparity than marrow or PBSC grafts, and delayed count recovery and increased infectious complications are observed after cord blood transplantation.

The small cell dose available from a single cord blood unit is often insufficient for adult patients and obese children; the minimum acceptable pre-cryopreservation cell dose is 2.5×10^7 TNC/kg, and lower cell doses have been associated with poor engraftment and high nonrelapse mortality (NRM). Investigators have studied the transplantation of two cord blood units to overcome this limitation and have reported reliable engraftment and promising survival. While engraftment can be facilitated with the use of two cord blood grafts, early reports demonstrated an increased risk for acute GVHD (HR: 2–6.1). However, patients receiving double cord transplants since 2005 have experienced comparable GVHD rates to those receiving single cord blood units according to registry data.

You identify an HLA-matched, unrelated donor and plan for HCT for this patient. He asks you what conditioning regimen you intend to provide and if the choice will have an impact on his risk for GVHD.

2. Which stem cell transplant conditioning regimen is associated with the greatest risk for acute GVHD?

A. Total-body irradiation (TBI)-based myeloablative conditioning
B. Busulfan-based myeloablative conditioning
C. Reduced-intensity conditioning

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Tissue damage from the HCT conditioning regimen plays a key role in the cytokine model of acute GVHD pathophysiology. This model identifies three steps that lead to the development of GVHD. First, host tissue damage caused by the conditioning regimen activates host antigen-presenting cells (APCs). The activated host APCs then stimulate donor T-cell proliferation and differentiation. This culminates in cellular (e.g., cytotoxic T-lymphocytes and natural killer (NK) cells) and inflammatory cytokine and protein (e.g., tumor necrosis factor alpha (TNFα) and interferon gamma) effectors, causing host tissue damage and apoptosis. This model may help explain the decreased risk for GVHD observed after reduced-intensity conditioning regimens, as reported in multiple studies (relative risk (RR): 0.1–0.3). Interestingly, myeloablative doses of TBI have consistently increased the risk for GVHD above the risk from other myeloablative conditioning regimens (HR: $\geq$1.4), suggesting that the immunologic response to TBI-induced tissue damage differs from that to chemotherapy.

He mentions reading in a newspaper about "T-cell depletion" and that it decreases the likelihood of experiencing GVHD. He asks you about the risks associated with this strategy.

3. What posttransplant complications are associated with T-cell depletion?

A. Infection
B. Relapse
C. Graft failure or rejection
D. Posttransplant lymphoproliferative disorder (PTLD)
E. All of the above

While T-cell depletion reduces the risk of acute GVHD, the lack of donor T-cells puts the patient at significant risk of other complications. All of the listed complications are sequelae of the reduced number, or absence, of T-cells. One of the first techniques used for ex vivo T-cell depletion involved two steps. Agglutination of lymphocytes with soybean lectin was followed by exposure to sheep red blood cells (which causes formation of e-rosettes of residual lymphocytes) that were subsequently removed from the stem cell product. This technique results in a 2.5- to 3-log decrease in T-cell content of the graft, which obviated the need for posttransplant GVHD prophylaxis and led to good engraftment rates and low incidence of complications. However, this method of depletion is highly operator dependent and labor intensive, and thus has not been widely adopted. Other ex vivo T-cell depletion methods include the incubation of the graft with T-cell-specific (e.g., anti-CD3) antibodies in various combinations, antithymocyte globulin or alemtuzumab (of which both may also be used for in vivo depletion), counterflow centrifugation elutriation, and column-based immunologic CD34+ cell selection. CD34+ cell collection results in a 4–5-fold decrease in T-cells and can also be safely performed without posttransplant GVHD prophylaxis; it is now the most commonly used method of ex vivo T-cell depletion due to the relative ease of this technique. Champlin *et al*. (2000) compared the efficacy of the different techniques (excepting CD34+ selection) through a retrospective analysis of Center for International Blood and Marrow Transplant Research (CIBMTR) data and found that, while all methods of T-cell depletion reduced the risk for acute GVHD with similar efficacy to each other, patients receiving T-cell depletion with anti-T-cell antibodies of narrow specificity had superior survival when compared to other methods (RR: 0.61–0.73, $P \leq 0.03$).

The BMT Clinical Trials Network performed a phase II trial of CD34+ selected grafts from HLA-matched sibling donors for 44 patients with acute myeloid leukemia and reported 100% engraftment, 23% incidence of grade II–IV GVHD through day 100, 21% NRM, and 59% overall survival at 2 years; 11% of patients experienced lethal infections, including Epstein–Barr virus–associated PTLD. When compared to contemporaneous patients receiving T-replete HLA-matched sibling donor transplants, the investigators observed a trend toward decreased GVHD (39% vs. 23%; $P = 0.07$), with no difference in overall survival. A similar trial was performed using CD34+ selected unrelated donor HCT, including partially HLA-mismatched grafts, which reported 9% incidence of grade II–IV GVHD, 21% incidence of infection- or PTLD-related death, and 6% relapse incidence at 4 years. Although an uncommon complication of hematopoietic cell transplantation, the risk of PTLD is dramatically increased by T-cell depletion, with a 3–15-fold increase in RR depending on the depletion strategy.

Due to the inability to find suitably matched donors for all patients who might benefit from HCT, T-cell depletion strategies have been applied to haploidentical HCT in an attempt to expand the donor pool for patients who do not otherwise have a sufficiently matched donor. Early attempts at haploidentical HCT without T-cell depletion resulted in extremely high rates of lethal GVHD and/or graft failure. T-cell depletion of haploidentical grafts is most commonly performed by either ex vivo CD34+ cell selection or in vivo through the administration of posttransplant high-dose cyclophosphamide. T-cell depletion has significantly increased the safety of haploidentical HCT, but high rates of lethal infections, relapse, and graft rejection remain significant limitations to its wider use; these complications tend to occur at different frequencies depending on the method of T-cell depletion and the patient population. Aversa *et al*. (1998) reported 26% mortality due to infection at 1 year in patients receiving CD34+ cell selected haploidentical HCT for high-risk leukemia. Luznik *et al*. (2001) reported a 1-year relapse rate

(*Continued*)

of 51% after nonmyeloablative conditioning and high-dose posttransplant cyclophosphamide for hematologic malignancy; patients with sickle cell anemia treated with a similar strategy experienced graft rejection rates of 43%.

You plan for a myeloablative conditioning regimen for this patient and now need to determine what GVHD prophylaxis strategy to use.

4. What are the common immunosuppressive strategies used for GVHD prophylaxis, how do they work, and how does one choose between strategies?

The common strategies focus on the manipulation of T-cells, through either diminishing or limiting T-cell numbers or modulating their activity. Aside from T-cell depletion as a method of GVHD prophylaxis, there are several other strategies commonly used. Chemotherapeutic agents such as methotrexate and cyclophosphamide induce T-cell apoptosis. Calcineurin inhibitors such as tacrolimus and cyclosporine inhibit T-cell activation and proliferation, primarily through the inhibition of interleukin-2 (IL2) gene activation. Mycophenolate mofetil inhibits purine metabolism essential to lymphocyte proliferation. Sirolimus inhibits response to IL2, thus preventing the activation of T-cells. For more in-depth discussion of these medications, please see the recent review by Ram and Storb (2013).

5. How does one determine which medications to administer for GVHD prophylaxis?

There is no universal consensus on the best GVHD prophylaxis regimen, and the choice is often guided by institutional preference. A clinician must consider multiple factors when determining which medications to use, including GVHD, graft rejection, and relapse risks, as well as the patient's underlying medical conditions and medications.

Outside of T-cell depletion strategies, almost all centers administer a calcineurin inhibitor in combination with at least one other agent for GVHD prophylaxis because multiagent GVHD prophylaxis is more efficacious than single-agent strategies (HR: 0.4–0.5). In a recent survey of European centers, most favor a combination of calcineurin inhibitor and a short course of methotrexate, often consisting of four doses. Methotrexate has hepatic, renal, and mucous membrane toxicities, so it should be used with caution in patients with evidence of liver or kidney dysfunction, or in patients with severe mucositis. Furthermore, methotrexate should be avoided in patients with pleural effusions or ascites because these fluid collections can act as reservoirs for the drug, which can lead to prolonged exposure and increased toxicity. For patients who cannot receive methotrexate, many clinicians will administer mycophenolate mofetil or sirolimus in concert with the calcineurin inhibitor. Mycophenolate mofetil is often favored following reduced intensity or nonmyeloablative conditioning regimens or when using umbilical cord blood grafts.

The use of antithymocyte globulin or alemtuzumab during the conditioning regimen can help facilitate engraftment in patients at risk of graft failure, but these medications can also help protect against GVHD (HR: 0.2–0.5). Thus, patients receiving HLA-mismatched grafts will commonly receive one of these medications, and some centers administer these medications to all unrelated donor transplant recipients. Patients receiving HCT for benign hematologic disorders (e.g., severe aplastic anemia) or receiving T-cell-depleted grafts also routinely get antithymocyte globulin during conditioning. Ongoing studies are currently investigating the use of alemtuzumab during conditioning for other benign hematologic disorders such as sickle cell anemia and beta-thalassemia.

6. Which of the following GVHD prophylaxis strategies is associated with the lowest risk of acute GVHD?

A. Tacrolimus
B. Tacrolimus–methotrexate
C. Cyclosporine A–methotrexate
D. Methotrexate

Tacrolimus and methotrexate prophylaxis significantly decreased the risk for GVHD when compared to cyclosporine and methotrexate (56% vs. 74%) in a large, randomized clinical trial; multiple studies have reproduced this finding, including a retrospective analysis of over 5000 patients through the CIBMTR (odds ratio (OR): 0.65–0.79). The lack of universally standardized tapering schedules for immunosuppression makes retrospective comparative studies difficult to interpret, however, and tapering practices differ from one institution to the next. Furthermore, tapering schedules frequently vary between patients within any single institution, with factors such as donor type, degree of HLA match, and conditioning regimen intensity and relapse risk influencing the therapeutic plan.

Other GVHD prophylaxis regimens have been compared to calcineurin inhibitor–methotrexate strategies. Tacrolimus with mycophenolate mofetil has been compared to tacrolimus–methotrexate or cyclosporine–methotrexate in small randomized studies; no difference in the incidence of GVHD was seen between the treatment arms in either study. A national phase III study comparing the efficacy of tacrolimus–sirolimus to tacrolimus–methotrexate as GVHD prophylaxis has recently closed to accrual; results have not yet been published.

The patient receives his transplant and is discharged from the hospital on post-HCT day 19. He returns to your clinic 5 days later with a complaint of new-onset diarrhea. You are concerned that he may have developed GVHD and make arrangements for upper and lower gastrointestinal (GI) endoscopy with biopsies.

7. Which causes of post-HCT GI symptoms are difficult to distinguish from acute GVHD on biopsy?

A. Mycophenolate mofetil use
B. Cytomegalovirus (CMV) enteritis
C. Chemotherapy or TBI effect
D. Proton pump inhibitor use
E. All of the above

GVHD is diagnosed clinically. Biopsies, however, may provide supportive evidence for the diagnosis. Apoptosis is the hallmark histologic finding of acute GVHD, but biopsies can frequently be interpreted as normal or equivocal; thus, a clinician should initiate therapy if he or she has sufficient suspicion for GVHD despite a lack of confirmatory tissue pathology.

Clinicians often assess suspected GI GVHD through esophagogastroduodenoscopy and/or colonoscopy/sigmoidoscopy with accompanying biopsy acquisition. On endoscopy, gastrointestinal mucosa may frequently have a normal appearance and biopsies may miss areas of active GVHD, thus providing false-negative results. Furthermore, several other common posttransplant toxicities can cause apoptosis, thus mimicking GVHD. Pathologists have difficulty making the diagnosis of GVHD in the first 3 weeks following the conditioning regimen due to apoptosis caused by chemotherapy and/or radiation. Proton pump inhibitor use may cause apoptosis observed on gastric biopsies, and mycophenolate mofetil toxicity is difficult to histologically differentiate from GVHD, although distribution may afford some clues. Both CMV and cryptosporidium infections can cause apoptosis in the gut mucosa, although immunologic staining for these pathogens can help discriminate them from GVHD. Thus, contextual interpretation of histologic findings is essential for HCT patients.

The endoscopic report states the mucosa was unremarkable, and biopsies come back with rare apoptotic cells, but the pathologist cannot definitively make the diagnosis of GVHD based upon the biopsy. The patient continues to have multiple episodes of watery diarrhea each day and does not develop rash or hyperbilirubinemia. You elect to admit him to initiate systemic corticosteroid therapy for GVHD. He states that he has had seven or eight bouts of diarrhea daily for the past 4–5 days and asks if the amount of diarrhea affects his likelihood of survival.

8. Which GVHD onset characteristics are associated with poor outcomes?

GVHD severity is assessed by the degree of involvement of the three target organs: skin, liver, and GI tract. Although some centers utilize different GVHD scoring systems, the

Table 68.1 Modified Keystone graft-versus-host disease (GVHD) staging criteria used by the BMT Clinical Trials Network (Source: Data from Sullivan KM. In: Blume KG, *et al.*, eds. Thomas' Hematopoietic Cell Transplantation, 3rd ed. Oxford: Blackwell Publishing Ltd; 2006. p. 633–44).*

Stage	Skin	Liver (bilirubin)	Gut† (stool output/day)
0	No GVHD rash	<2 mg/dl	Adult: <500 ml/day Child: <10 ml//kg/day
1	Maculopapular rash <25% body surface area (BSA)	2–3 mg/dl	Adult: 500–999 ml/day Child: 10–19.9 ml/kg/day Or persistent nausea, vomiting, or anorexia, with a positive upper gastrointestinal (GI) biopsy.
2	Maculopapular rash 25%–50 BSA	3.1–6 mg/dl	Adult: 1000–1500 ml/day Child: 20–30 ml/kg/day
3	Maculopapular rash >50% BSA	6.1–15 mg/dl	Adult: >1500 ml/day Child: >30 ml/kg/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and/or desquamation >5% BSA	>15 mg/dl	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of volume)

*Overall clinical grading is as follows (grade based upon highest target organ stage): grade 0: no stage 1–4 of any organ; grade I: stage 1–2 skin without liver or gut involvement; grade II: stage 3 rash, and stage 1 liver or gut involvement; grade III: stage 0–3 skin with stage 2–3 liver or GI GVHD ; grade IV: stage 4 skin, liver, or GI involvement (stage 4 gut as grade IV is a modification from the originally reported Keystone criteria, which includes stage 4 gut as grade III GVHD).
†Gut criteria have been modified from the original Keystone criteria as follows: grossly bloody stool may be reported as stage 4 GVHD (previously no scoring for frank GI hemorrhage).

(*Continued*)

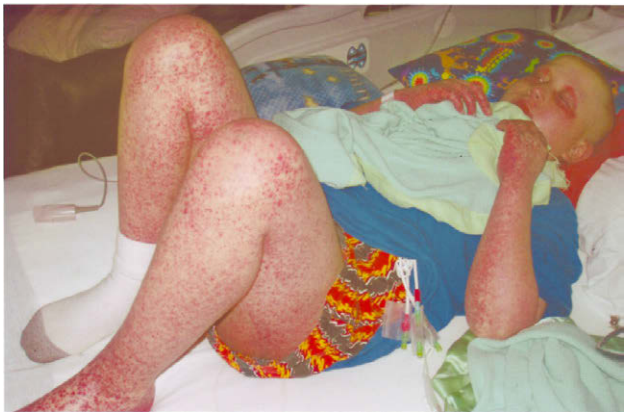


Figure 68.1 Patient with diffuse graft-versus-host disease (GVHD) rash (Source: Courtesy of M. Hartwell).

BMT Clinical Trials Network uses the modified Keystone staging system in GVHD clinical trials in an attempt to standardize GVHD staging (see Table 68.1). The modified Keystone staging system is perhaps the most widely used. Skin GVHD classically manifests as a pruritic erythematous maculopapular rash (Figure 68.1), and severity is scored by degree of skin involvement. Liver GVHD presents as cholestatic jaundice, with increased severity ascribed to higher levels of hyperbilirubinemia. Gastrointestinal GVHD can affect the upper GI tract, causing nausea, vomiting, and/or anorexia, and/or it can affect the lower GI tract, resulting in secretory diarrhea or, in its most severe form, severe pain, ileus, and/or GI hemorrhage.

Severe (grade III–IV) GVHD has reproducibly been associated with increased risk for mortality (HR: 1.5–2.6). Severe lower GI and/or liver involvement frequently occurs in grade III–IV GVHD; thus, it is unsurprising that involvement by these organs at GVHD onset increases the risk for NRM (HR: 2.4–4). Skin and upper GI GVHD does not appear to strongly influence NRM.

For patients with lower GI GVHD, several studies have demonstrated that on multivariate analysis, the onset clinical stage of GI GVHD correlates with NRM. Stage 2 or greater GI GVHD results in a 1.5–3-fold increased risk for nonrelapse mortality.

9. Can any additional tests be performed to aid in making the diagnosis of GVHD or help with prognostication?

No additional clinical tests are currently available to help with making the diagnosis or help clinicians determine the prognosis for patients with GVHD. Researchers have recently described several plasma biomarkers, however, that are elevated at the onset of GVHD and may help predict treatment response and NRM. Two of these biomarkers, elafin and REG3α, may help discriminate GVHD from other causes of posttransplant rash or diarrhea, respectively. Additionally, higher concentrations of biomarkers at GVHD onset—either individually or as biomarker panels—have correlated with increased risk for NRM. While not yet clinically available, sample collection for biomarker measurement is being incorporated into multicenter clinical trials to help determine how best to use GVHD biomarkers in clinical care.

10. What is the appropriate first-line therapy for GVHD, and what is the likelihood that the patient will respond to initial therapy?

There is a paucity of medical literature surrounding the management and natural history of GVHD that presents as isolated skin GVHD with $\leq$50% body surface area involvement (grade I GVHD), but many patients are treated with topical steroids in the absence of systemic therapy. Many clinicians elect to treat grade I GVHD systemically, however, especially if there is increased risk for progression to more severe GVHD as in the setting of GVHD presenting very early in the post-HCT course or after receiving an HLA-mismatched allograft. At our institution, 58% of patients who presented with grade I GVHD progressed to more severe GVHD, and 78% of patients were treated with systemic steroids within one month of diagnosis.

For patients with grade II–IV GVHD, treatment with 2 mg/kg or methylprednisolone (or equivalent dosing of other corticosteroids) is the most widely used first-line therapy, although some centers prefer to start patients on lower steroid doses ($\geq$1 mg/kg) and increase to 2 mg/kg if their GVHD is unresponsive or progressive without significant increased risk for treatment failure or mortality. Large studies report response rates (complete or partial) of 55–65% at 4 weeks of therapy.

11. Have any additional agents been proven to improve outcomes if administered as "upfront" therapy?

No single therapy when added to steroids has improved response and/or survival when compared to steroids alone in randomized clinical trials. Treatments investigated in randomized controlled trials include IL2 blockade (daclizumab or basiliximab), TNFα blockade (infliximab), and antithymocyte globulin. A phase III, multicenter, randomized, double-blind clinical trial performed by the BMT Clinical Trials Network investigating the addition of mycophenolate mofetil to systemic steroid therapy was recently halted due to futility. Agents that have shown promise in phase II trials, but have not been definitively tested in phase III trials, include etanercept (a 69% CR rate), denileukin diftitox (a 41–50% CR rate in steroid-refractory GVHD), and pentostatin (a 63% CR rate in steroid-refractory GVHD); sirolimus monotherapy

has shown potential efficacy in a retrospective report (a 50% CR rate).

The patient demonstrates no clinical response to systemic corticosteroid therapy, but he does develop hyperglycemia and hypertension and experiences reactivation of CMV secondary to this treatment. You want to add an additional therapy to his GVHD treatment, but want to avoid immunosuppressive medications due to viremia. You perform a literature search, read about extracorporeal photopheresis (ECP), and wonder if this may help your patient.

12. Is there a potential role for ECP in the treatment of acute GVHD?

Yes. Although few studies report the use of ECP for acute GVHD, the initial results show some potential benefit for patients with steroid-resistant or -dependent GVHD, with response rates of 50–70% at 3 months after initiation of ECP and improved survival. Although not yet clearly elucidated, the leading theory on ECP's mechanism of action is through three main effects: (i) induction of apoptosis of activated T-cells; (ii) phagocytosis of the apoptotic T-cells by antigen-presenting cells, resulting in a switch from proinflammatory to immunotolerant cytokine production; and this (iii) induces regulatory T-cells (T_{regs}).

13. What are some potential causes of death that this patient might experience that are directly related to acute GVHD?

A. Progressive or nonresponsive GVHD
B. Infection
C. Chronic GVHD
D. All of the above

There are several causes of death that are associated with GVHD and that comprise a majority of the NRM following allogeneic transplantation. First, progressive, steroid-refractory GVHD can be directly fatal. There are other indirect causes of death that are related to acute GVHD and/or its treatment. Patients requiring immunosuppressive therapy above and beyond GVHD prophylaxis medications are at increased risk for life-threatening infections that would not occur otherwise. Lastly, acute GVHD is a major risk factor for chronic GVHD, which is a significant contributor to late mortality following HCT.

Case study answers

Case study 68.1

Question 1: Answer B ("False")
Question 2: Answer A
Question 3: Answer E
Question 6: Answer B
Question 7: Answer E
Question 13: Answer D

Selected reading

Deeg HJ. How I treat refractory acute GVHD. Blood. 2007;109: 4119–26.

Harris AC, Ferrara JL, Levine JE. Advances in predicting acute GVHD. Br J Haematol. 2012;160(3):288–302.

Levine JE, Logan BR, Wu J, *et al*. Acute graft-versus-host disease biomarkers measured during therapy can predict treatment outcomes: a Blood and Marrow Transplant Clinical Trials Network study. Blood. 2012;119:3854–60.

Martin PJ, Rizzo JD, Wingard JR, *et al*. First and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2012;18(8): 1150–63.

Ram R, Storb R. Pharmacologic prophylaxis regimens for acute GVHD: past, present and future. Leuk Lymphoma. 2013;54(8): 1591–601.

CHAPTER 69

Chronic graft-versus-host disease

Carrie L. Kitko and Daniel R. Couriel

University of Michigan Blood and Marrow Transplant Program, Ann Arbor, MI, USA

Chronic graft-versus-host disease (cGVHD) remains the leading cause of morbidity and mortality for long-term transplant survivors. The reasons for this discrepancy are multifactorial, but some of the main contributors are incomplete understanding of the pathophysiology, lack of appropriate animal models that recapitulate the human disease, and, until recently, variable definitions for diagnostic and response criteria. In 2005, the National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease published a series of articles to help standardize the clinical approach to these patients, and promoted new interest in this important posttransplant complication. The scenarios in this chapter will highlight our current understanding of the clinical assessment and treatment of cGVHD.

Case study 69.1

A 55-year-old patient who received an allogeneic hematopoietic cell transplant (HCT) for high-risk myelodysplastic syndrome (MDS) has returned closer to home after his day 100 post-HCT evaluation, and plans to have his routine follow-up visits in your clinic.

1. Which of the following would increase his chance of developing cGVHD?

A. Human leukocyte antigen (HLA) mismatch between donor and recipient
B. History of prior acute graft-versus-host disease (GVHD)
C. Use of peripheral blood stem cells as graft source
D. Use of a female donor into a male recipient
E. Older patient age
F. All of the above

Known risk factors for the development of cGVHD include prior acute GVHD, use of peripheral blood stem cells as a grafting source, use of a female donor for a male recipient, older patient age, and use of an HLA-mismatched and/or unrelated donor. Flowers *et al*. (2011) retrospectively analyzed 2941 adult and pediatric HCT recipients in order to confirm these previously reported risk factors. These investigators reported a 34% cumulative incidence of cGVHD at 2 years post-HCT with a median time to onset of 162 days post-HCT. Anasetti *et al*. (2012) recently reported that recipients of peripheral blood stem cell grafts experienced a significantly increased incidence of cGVHD when compared to bone marrow recipients (53% vs. 41%; $P = 0.01$).

The patient received an 8 out of 8 HLA-matched unrelated donor transplant from a female donor following a reduced-intensity conditioning regimen. He developed biopsy-proven mild skin acute GVHD at day 45 posttransplant that resolved following treatment with topical therapy alone. His tacrolimus taper was started at day 90, with a plan to taper monthly until discontinuation around day 180.

2. What are some of the diagnostic features of cGVHD for which the patient should be monitored during your subsequent follow-up visits to guide your decision to continue the tacrolimus taper?

A. Oral mucosal changes, including lichenoid markings and hyperkeratotic plaques
B. Skin changes, including poikiloderma, lichen planus–like features, lichen sclerosis–like features, sclerotic features, and morphea-like features

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

C. Joint stiffness or contractions secondary to sclerosis
D. A and B are correct.
E. All of the above

The median time to cGVHD diagnosis is approximately 6 months post-HCT, and new-onset cGVHD is rarely diagnosed beyond one year. Disease manifestations can be highly variable, and almost every organ system can be involved. The NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease published a series of articles that aimed to standardize the diagnosis, classification, and response criteria for cGVHD. This system replaced the "limited" versus "extensive" classification system first described in 1980.

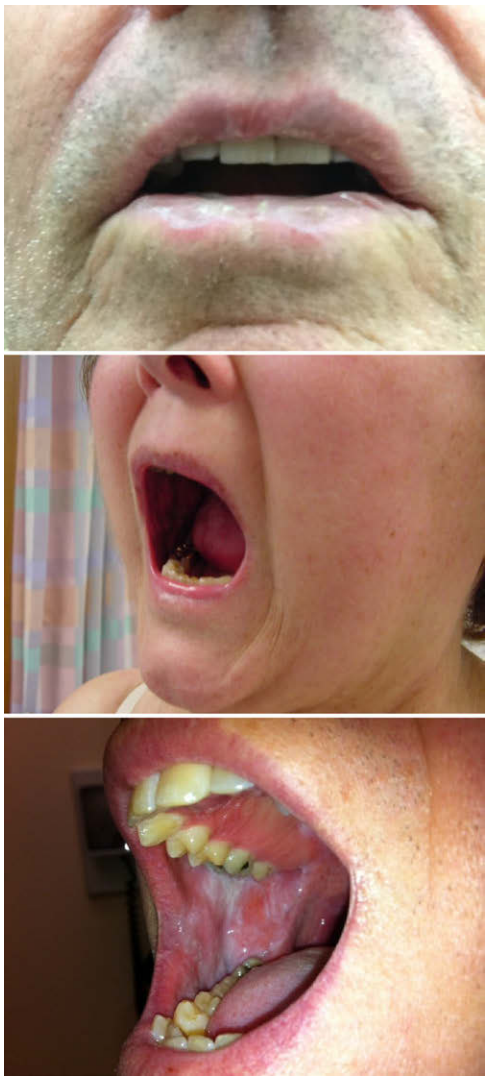


Figure 69.1 Diagnostic oral manifestations of chronic graft-versus-host disease (cGVHD). Top: Lichenoid cGVHD of the lips. Middle: Restricted mouth opening due to sclerotic cGVHD. Bottom: Lichenoid changes to buccal mucosa consistent with cGVHD. (Color plate 69.1)

Filipovich *et al*. (2005) proposed an extensive list of diagnostic features (sufficient to establish the diagnosis of cGVHD), distinctive features (present in cGVHD, but insufficient alone to establish the diagnosis), other features (known to be associated with cGVHD, but not frequent enough to be diagnostic or distinct), and common features (seen in both acute and chronic GVHD) seen in the eight commonly affected organs (see Table 69.1). A photo atlas of diagnostic features is included (Figures 69.1, 69.2, and 69.3). The presence of any of the diagnostic manifestations of cGVHD can establish the diagnosis without a confirmatory biopsy, while the diagnosis of cGVHD cannot be established without additional confirmatory testing when only distinctive features are present.

The patient is evaluated in your office on day 120. He has no signs of GVHD, so you taper his tacrolimus. He returns

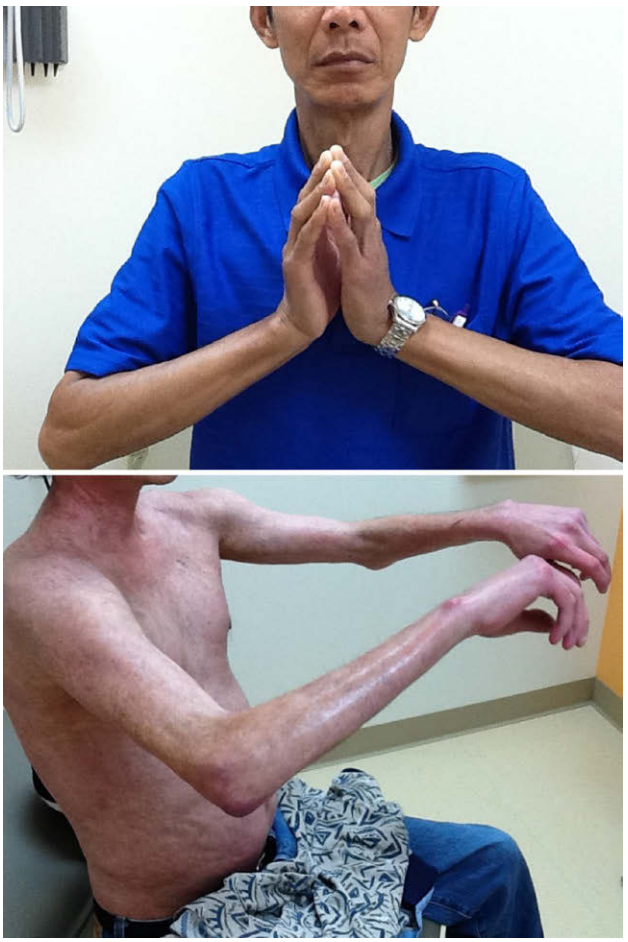


Figure 69.2 Diagnostic musculoskeletal manifestations of chronic graft-versus-host disease (cGVHD). Top: Fasciitis and restriction of the range of motion (ROM). Bottom: Sclerotic cGVHD of the skin with restricted ROM.

(*Continued*)

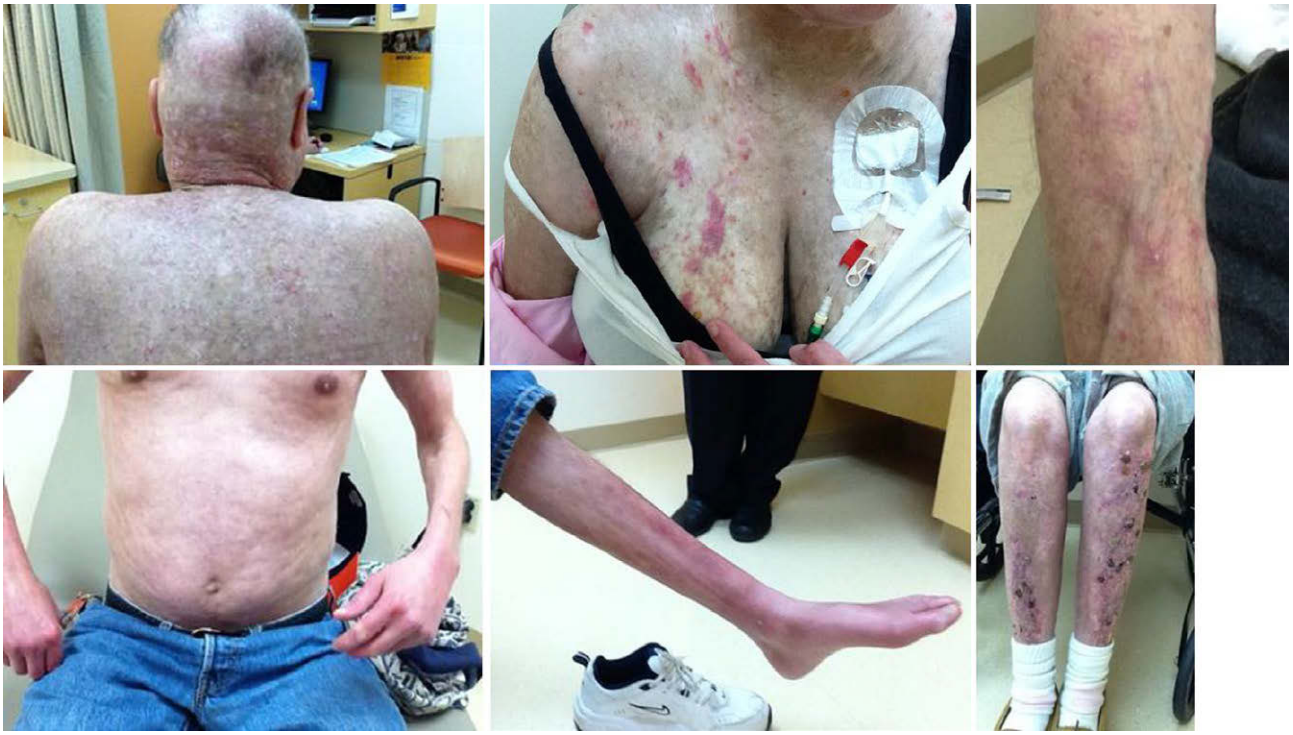


Figure 69.3 Diagnostic skin manifestations of chronic graft-versus-host disease (cGVHD). Top left: Lichen sclerosus. Top middle: Lichen planus–like changes, surrounded by lichen sclerosus. Top right: Lichen planus–like rash. Bottom left: Subcutaneous sclerosis. Bottom middle: Sclerosis of the dermis and subcutaneous tissues, with a "pipe stem" appearance to the leg. Bottom right: Severe sclerosis with overlying erosions and ulcerations.

for follow-up on day 150 and presents with new symptoms that are concerning for GVHD.

3. Match the symptoms with the correct classification of late acute GVHD, classic cGVHD, or overlap syndrome.

1. An erythematous, maculopapular rash
2. New onset of dry, gritty eyes; oral sensitivity; and lichenoid changes and erythema on bilateral buccal mucosa
3. New nausea, anorexia, elevated liver enzymes, mild restriction in range of motion in prayer position, and a sclerotic rash with some erythema on arms bilaterally

A. Classic cGVHD
B. Overlap syndrome
C. Late or recurrent acute GVHD

In 2005, the NIH cGVHD Consensus Project redefined the classification system based upon the presenting clinical characteristics of GVHD. Filipovich et al. (2005) defined erythematous skin lesions, nausea, vomiting, diarrhea, and liver enzyme abnormalities as acute GVHD regardless of the time post-HCT of presentation. Classic cGVHD is defined by the presence of diagnostic, distinctive, and other features outlined in Table 69.1 at any time post-HCT. If a patient presents with both classic chronic symptoms and "common" symptoms (Table 69.1), his or her GVHD is classified as overlap syndrome.

Thus, scenario 1 in this question has features consistent with acute GVHD, without the classic features of cGVHD, and would be considered late-onset or recurrent acute GVHD. Scenario 2 describes only classic cGVHD features. Scenario 3 has features common to both acute and chronic GVHD, consistent with overlap syndrome.

During your visit with the patient at day 150, he complains of moderate eye and mouth dryness, general pruritus, and new mild transaminitis (less than twice the upper limit of normal). He appears well on physical exam. His mucous membranes appear slightly dry but are otherwise pink and without discrete lesions, his sclerae are non-injected, and there are no abnormal skin or abdominal findings, including the absence of hepatosplenomegaly.

Although the patient does not have any diagnostic signs of cGVHD, you are concerned that these findings may progress in the near future. You requested that he return in 2 weeks for reassessment.

Table 69.1 Signs and symptoms of chronic graft-versus-host disease (cGVHD).

Organ or site	Diagnostic	Distinctive	Other features	Common
Skin and scalp	Poikiloderma Lichen planus–like features Sclerotic features Morphea-like features Lichen sclerosus–like features	Depigmentation, scarring or nonscarring alopecia	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle Onycholysis Pterygium unguis Nail loss		
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucoceles Mucosal atrophy Pseudomembranes Ulcers		Gingivitis Mucositis Erythema Pain
Eyes		New-onset dry, gritty, or painful eye Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Vaginal scarring or stenosis	Erosions Fissures Ulcers		
GI Tract	Esophageal web Strictures or stenosis in the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive
Liver				Total bilirubin, alkaline phosphatase, ALT, or AST $>2\times$ upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology		BOOP
Musculoskeletal	Fascitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis	Edema Muscle cramps Arthralgia or arthritis	

ALT, alanine aminotranferease; AST, aspartate aminotransferase; BOOP, bronchiolitis obliterans organizing pneumonia; PFTs, pulmonary function tests.

(*Continued*)

4. What changes to the physical exam or laboratory analysis at the return visit would warrant the initiation of systemic therapy for cGVHD?

A. Symptoms and exam are completely unchanged from prior visit.
B. Mouth sensitivity has increased, and patient is altering diet to find foods that do not aggravate his symptoms. Examination of the oropharynx reveals erythema and lichenoid changes to the buccal mucosa bilaterally. Weight, eye complaints, and transaminitis are all unchanged.
C. Eye and mouth findings are stable, but patient now has an erythematous lichenoid skin rash on 65% body surface area (BSA), increased skin pruritus, and transaminitis.

The NIH Consensus Project scores each organ individually, and these scores are integrated into an overall score. Mild disease would include patients with the involvement of only 1 or 2 organs (excluding the lungs) with a maximum individual organ score of 1 (no significant impairment of daily living). Moderate disease involves any patient with an individual organ score of 2 (significant impairment of daily living), or if there is mild lung involvement (score of 1). Severe disease is defined as patients with any individual organ with a score of 3 (major disability), or lung involvement with a score of 2 or 3.

Answer A is incorrect because there are no diagnostic manifestations of cGVHD. Answer B is incorrect because the patient's disease is still mild to moderate and would likely benefit from a trial of topical therapy. Answer C is correct because he has a diagnostic manifestation of cGVHD (lichenoid skin rash) that involves more than 50% of his BSA, which is considered severe (score = 3) and warrants systemic therapy for treatment of his severe cGVHD.

5. What would be considered appropriate initial systemic treatment for new-onset moderate or severe cGVHD?

A. Increase tacrolimus dose to achieve therapeutic levels.
B. Referral to dermatology for initiation of extracorporeal photopheresis (ECP).
C. Prednisone 1 mg/kg/day (or equivalent dose of other steroid)
D. Referral back to transplant center for consideration of a clinical trial.

Table 69.2 Secondary treatment for chronic graft-versus-host disease (cGVHD) (summary of results of therapies reported from 2009 to 2013).

Treatment	Study type	No. of patients	% Overall response	Overall survival
Extracorporeal photopheresis (ECP)	Retrospective	102	53	78% (1 year)
	Retrospective	82	79	69% (3 years)
	Retrospective	71	61	53% (1 year)
	Retrospective	58	65	44% (6.6 years)
	Retrospective	43	65	70% (1 year)
	Crossover	29	57	
	Phase II	23	70	78% (4 years)
	Phase II	9	67	
Imatinib	Retrospective	39	31	85% (1.5 years)
	Phase I/II	19	79	84% (1.5 years)
	Phase I	15	40	
	Retrospective	14	50	75% (1.5 years)
	Phase I/II	9	22 (pulmonary)	78% (1.5 years)
Interleukin-2	Phase I	29	12/23 evaluable	
Mesenchymal stem cell infusions	Phase I/II	19	74	78% (2 years)
	Phase I/II	8	50	3/8 died
	Phase I	7	57	5/7 died
mTOR inhibitor	Phase II	35	63	41% (2 years)
	Retrospective	34	76	72% (3 years)
Pentostatin	Phase II	51	53%	60% (3 years)
	Retrospective	18	56%	34% (1 year)
Alemtuzumab and rituximab	Phase I/II	15	100	90% (1 year)
Rituximab	Meta-analysis	111	66	
	Phase II	37	86	72% (1 year)
	Phase II	20	61	
	Retrospective	9	0	3/9 died
Tocilizumab	Retrospective	2	1/2	
Ultraviolet B phototherapy (narrow band)	Retrospective	10	80	

E. A and D
F. C and D

Systemic corticosteroid therapy has been the standard of care for the last 30 years, and no prospective clinical trial of alternative or combination upfront treatment of cGVHD has demonstrated superior efficacy. There have been a total of six randomized phase III studies for initial treatment of cGVHD reported to date. The commonly accepted starting dose of prednisone is 1 mg/kg/day, with varying suggested tapers. Steroid taper is generally recommended to begin within 2–4 weeks of improvement in disease manifestations, with the goal of transitioning to alternate day therapy within 4–8 weeks of taper initiation. Patients should anticipate prolonged therapy, with a median duration of therapy ranging from 2 to 3 years, and up to 10% of patients require immunosuppression 7 years after diagnosis of cGVHD.

Patients unresponsive to steroids receive secondary therapy. A comprehensive overview of secondary therapies is beyond the scope of this chapter, but a table has been included to review commonly recommended options (Table 69.2).

The patient is started on prednisone 1 mg/kg and returns to the transplant center for a multidisciplinary assessment of his cGVHD. He enrolls on a national study investigating the role of adding an additional immunosuppressive agent shortly after diagnosis of cGVHD. He appears to have a partial response to this treatment one month into the study, with improvement (but not resolution) of his skin rash, normalization of his liver enzymes, and improvement in his oral and ocular symptoms.

6. What ancillary or supportive care treatments will be important to provide to this patient as he remains on treatment for cGVHD?

A. Antibiotic prophylaxis
B. Referral to ophthalmology
C. Referral to dentist
D. Referral to dermatology
E. All of the above

While primary systemic therapy for the treatment of cGVHD is aimed at decreasing systemic alloreactivity, ancillary and supportive care can help alleviate cGVHD symptoms and minimize secondary sequelae of cGVHD and its therapy. Prevention of infectious complications is essential due to the long duration of immunosuppressive therapy expected for patients with cGVHD. The NIH cGVHD Consensus Project includes formal recommendations for ancillary and supportive care.

Case study answers

Case study 69.1

Question 1: Answer F
Question 2: Answer E
Question 3: Answer 1 – C, 2 – A, 3 – B
Question 4: Answer C
Question 5: Answer F
Question 6: Answer E

Selected reading

Couriel D, Carpenter PA, Cutler C, *et al*. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic vraft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Tranplant. 2006;12(4):375–96.

Flowers ME, Inamoto Y, Carpenter PA, *et al*. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood. 2011;117(11):3214–9.

Flowers ME, Parker PM, Johnston LJ, *et al*. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. Blood. 2002;100(2):415–9.

Inamoto Y, Flowers ME. Treatment of chronic graft-versus-host disease in 2011. Curr Opin Hematol. 2011;18(6):414–20.

Pavletic SZ, Martin P, Lee SJ, *et al*. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Tranplant. 2006;12(3):252–66.

SECTION 2

Oncology

PART 1

Central Nervous System Tumors

CHAPTER 70

Primary brain tumors

Barbara J. O'Brien and Mark R. Gilbert
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Epidemiology, tumor classification, and prognostic and predictive markers

1. What is the basis of the current classification system for primary brain tumors, and what are the limits of this classification system?

Primary brain tumors rarely spread outside the central nervous system (CNS), precluding the use of the conventional TNM (tumor, node, and metastasis) staging system. Therefore, brain tumors are classified histopathologically, with subtype designation based on morphologic similarity to normal brain cells, and grade of malignancy based on features such as pleomorphism, mitoses, vascular proliferation, and necrosis (Table 70.1). Currently, the standard system is from the World Health Organization (WHO), and grading is used to predict biological behavior and inform treatment decisions. However, the histopathologic diagnosis of glioma has inherent subjectivity and is prone to significant interobserver variability, particularly in differentiating grade II from grade III gliomas, and "pure" tumors from "mixed" oligoastrocytomas (Figures 70.1, 70.2, 70.3, 70.4, and 70.5). Although a useful guide, the WHO criteria have limitations in predicting response to treatment and prognosis for individual patients, as histologically similar tumors often are significantly heterogeneous in regard to sensitivity to treatment and clinical behavior. The classification of gliomas is shifting from a histomorphologic grading system to a more objective and diagnostically accurate classification, based on a molecular profile, or signature, stratifying gliomas into groups based on expected response to particular treatments and overall survival.

2. Is the incidence of brain tumors increasing?

Although a slight increase in the incidence of gliomas has been reported over the past few decades, this apparent increase is likely secondary to diagnostic advances and greater availability of neuroimaging, as well as changes in brain tumor classification and reporting. The reason for a reported rise in primary central nervous system lymphoma (PCNSL) is more ambiguous. The increased incidence is in part explained by the HIV/AIDS epidemic, although the incidence in the HIV population has leveled off since the arrival of highly active antiretroviral therapy (HAART). Several studies suggest the incidence has also increased in immunocompetent individuals, despite a lack of identifiable environmental or behavioral risk factors.

Brain tumor statistics may be found on the Central Brain Tumor Registry of the United States (CBTRUS) website (http://www.cbtrus.org), and the Surveillance, Epidemiology, and End Results (SEER) website (http://website.seer.cancer.gov).

3. Do cell phones, viruses, and other environmental factors cause brain tumors?

Although some studies suggest environmental exposures as risk factors for brain tumor development, the epidemiological literature on brain tumors is for the most part inconclusive. The only proven risk factors for brain tumors are rare hereditary syndromes, ionizing radiation exposure, and immunosuppression resulting in PCNSL, and these account for only a small proportion of cases. The association between cell phone use and brain tumor risk is inconclusive. Other factors with unconvincing and/or conflicting

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 70.1 Grading characteristics of World Health Organization (WHO) glioma histologic subtypes.

WHO grade	Histologic subtype	Histologic features
Grade I	Pilocytic astrocytoma	Hypercellularity
Grade II	Astrocytoma Oligodendroglioma Mixed oligoastrocytoma	Cellular atypia and Hypercellularity
Grade III	Anaplastic astrocytoma Anaplastic oligodendroglioma Anaplastic mixed oligoastrocytoma	Nuclear atypia and mitoses
Grade IV	Glioblastoma	Microvascular proliferation and/or necrosis

associations include infectious agents, epilepsy, head trauma, N-nitroso compounds, mercury, chlorinated water, tobacco, hair dye and hair spray, air pollution, petroleum, pesticides, and dental X-rays.

4. Is there a familial risk of brain tumors?

Genetic susceptibility to gliomas is suggested by tumor aggregation ("clusters") in families, genetic cancer syndromes, linkage analyses, and lymphocyte mutagen sensitivity, although the vast majority of tumors are sporadic. Syndromes associated with brain tumors include neurofibromatosis 1 and 2, tuberous sclerosis, retinoblastoma, Li–Fraumeni syndrome, and Turcot syndrome. Other than these well-described syndromes, genetic etiologies of brain tumors remain uncertain. Studies suggest a role for multifactorial inheritance, polymorphisms, and genetic susceptibility. Disease association studies and familial linkage studies, such as the Gliogene study

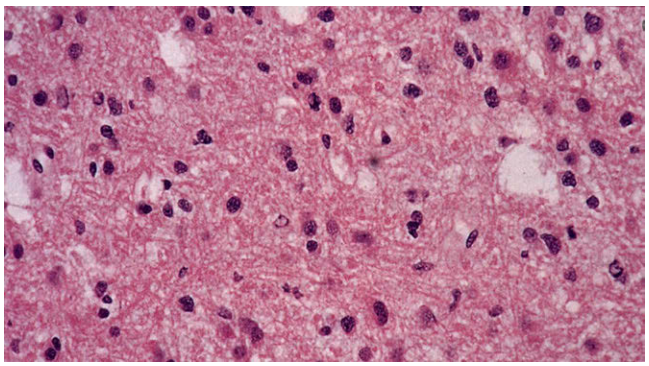


Figure 70.1 Histologic features of grade II astrocytoma, including increased astrocytic cellularity ("hypercellularity"). (Color Plate 70.1)

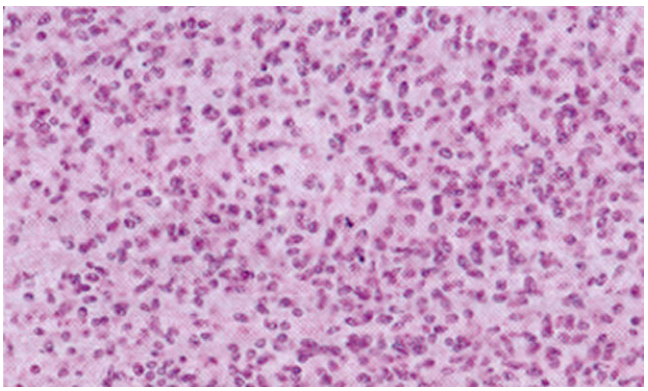


Figure 70.2 Histologic features of grade III anaplastic astrocytoma, including hypercellularity, atypical nuclei, and mitoses (not shown). (Color Plate 70.2)

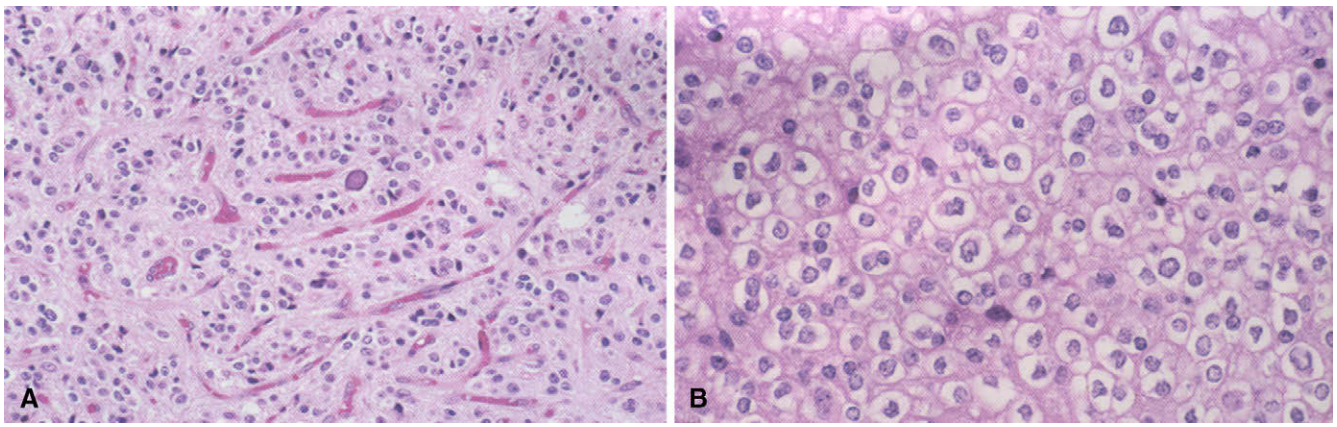


Figure 70.3 Histologic appearance of oligodendroglioma, with a dense network of branching capillaries ("chicken-wire vessels") (left) and clear cytoplasm with well-defined plasma membrane ("fried egg" artifact) (right). (Color Plate 70.3)

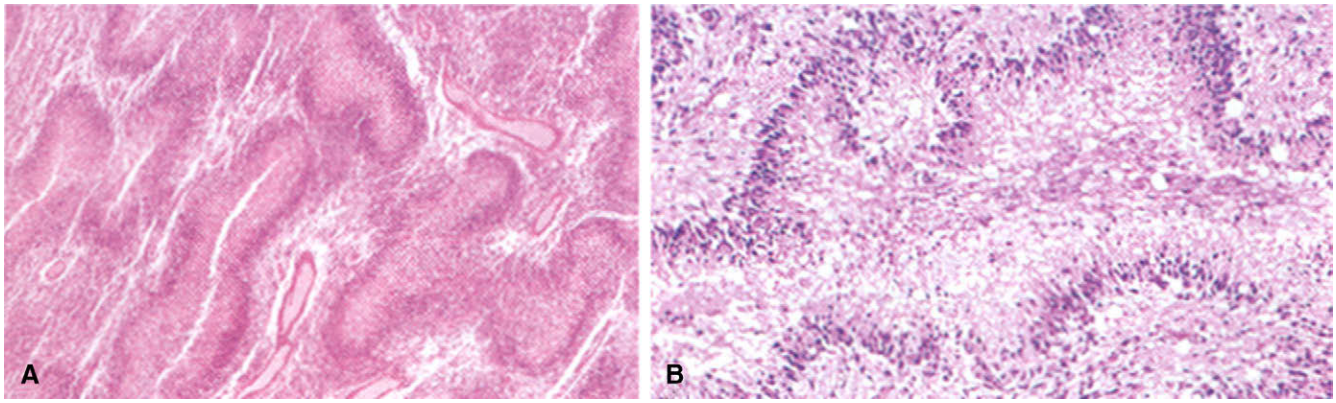


Figure 70.4 Histologic features of grade IV glioblastoma, including pseudopalisading necroses and endovascular proliferation (not shown). (Color Plate 70.4)

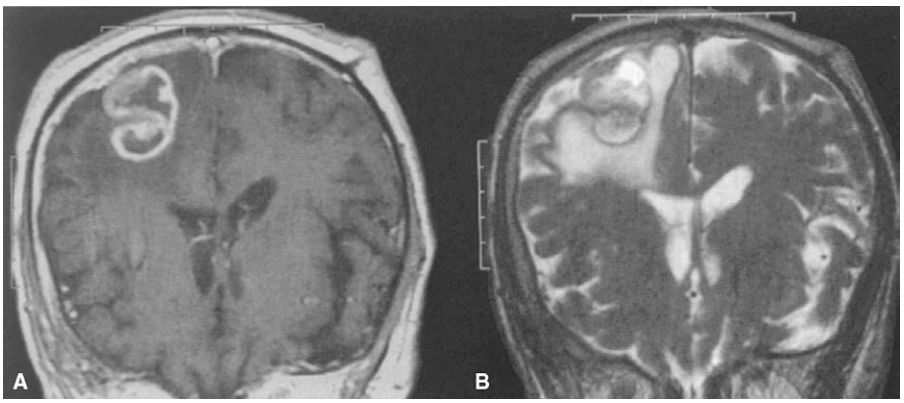


Figure 70.5 Typical glioblastoma MRI findings: T1-gadolinium contrast enhancement (left) and T2 hyperintensity (right).

(www.gliogene.org), are investigating inherited susceptibility to glioma.

5. What are the clinically relevant molecular markers, and what is the likely future role of molecular signatures in the diagnosis of malignant brain tumors?

Three prognostic molecular markers have emerged in the forefront of glioma research efforts and now play some role in clinical decision making: 1p/19q chromosomal deletion status, O-6-methylguanine DNA methyltransferase (MGMT) gene promoter methylation status, and isocitrate dehydrogenase1 (IDH1) mutation status. A recent approach to molecularly characterizing gliomas incorporates a combination of individual markers into a molecular signature. Incorporating biomarkers into clinical trials may better assess the benefit of a particular therapy by stratifying gliomas into prognostic and treatment groups. However, widespread molecular profiling is limited in community practice and is not necessarily cost-effective, and therefore most treatment decisions for glioblastoma are still based on age and performance status. In the future, the use of such markers may improve outcomes and move toward informing more personalized treatment decisions.

6. What are some emerging biomarkers in glioblastoma?

The Cancer Genome Atlas (TCGA) Research Network, a global genomic profiling project, was established to develop a comprehensive index of genomic abnormalities stimulating tumorigenesis, to further inform treatment planning. A multiplatform approach was used to analyze a large

number of glioblastoma samples, and these data continue to be interrogated. Some preliminary investigations using TCGA data have revealed that glioblastoma can be subclassified into four distinct groups on the basis of a gene expression profile. To date, these subtypes remain an interesting finding with no direct clinical application, although the "proneural" subtype of glioblastoma is associated with increased patient survival. Another study using data from TCGA found a distinct CpG island hypermethylator phenotype (G-CIMP) associated with significantly better outcomes. Other emerging biomarkers include the epidermal growth factor receptor–phosphatidylinositol 3-kinase–mammalian target of rapamycin (EGFR–PI3K–mTOR) and the p53–retinoblastoma gene (p53–Rb) pathways, and cancer stem cell markers.

7. What are the established prognostic factors for patients with glioblastoma?

For malignant gliomas, clinical prognostic factors include age, performance status, and extent of initial tumor resection. Tumor factors include MGMT gene promoter methylation, which is thought to be an important prognostic factor with possible predictive value in some patient populations, such as the elderly. IDH1 mutations, which among grade IV gliomas, are found almost exclusively in secondary glioblastoma (which arise from continued malignant transformation from lower-grade gliomas), and G-CIMP hypermethylator phenotype are positive prognostic factors. Recently, using the large tissue repository from MD Anderson Cancer Center and the Radiation Therapy Oncology Group (RTOG), a robust prognostic index combining four molecular tests (gene expression, hypermethylation, MGMT promoter methylation, and IDH1 mutation) and the RTOG recursive partitioning analysis (RPA) was developed, called the Molecular Clinical Prognostic Index. This index will help in clinical trial stratification and may ultimately yield predictive factors that may optimize individual patient treatment. Currently, despite the availability of these molecular and clinical prognostic factors, nearly all patients with glioblastoma deemed able to tolerate treatment require the same standard of care treatment regimen because, to date, no suitable alternative exists.

8. Are there prognostic and predictive factors for lower-grade gliomas?

In lower-grade glioma, in addition to astrocytoma histology and lack of 1p/19q co-deletion, several clinical factors negatively impact survival: age 40 years or older, tumor diameter (>4 cm), tumor crossing midline, neurologic deficit, poor performance status, and, perhaps, tumor involving "eloquent" brain. Mutation of IDH1 is associated with an improved prognosis. There is a confirmed survival benefit in patients with anaplastic oligodendroglioma and 1p/19q co-deletion treated with combined chemotherapy and radiation therapy; a similar benefit is suggested for grade II glioma with 1p/19q co-deletion.

Treatment questions

9. Is there a role for observation of a malignant brain tumor?

On occasion, low-grade gliomas (LGGs) may be discovered as incidental findings during brain imaging obtained for unrelated reasons, such as head injury or headache. Although the best management of incidentally detected asymptomatic LGGs remains controversial, we favor offering early, maximal, safe resection as soon as there is evidence of lesion growth on imaging. Delaying until symptom onset ("watch-and-wait" approach) likely increases the patient's risk of developing seizures, experiencing a decline in functional status, and presenting for resection with a larger tumor involving eloquent brain. Furthermore, incidental LGGs appear to progress at similar rates to symptomatic LGGs, further supporting the call for early intervention.

10. What is the optimal surgical approach to primary brain tumors?

Initially, patients with newly diagnosed glioblastoma should be treated with safe, maximal resection. Nonrandomized studies strongly suggest that gross total resection improves overall survival in glioblastoma, regardless of patient age or performance status. A similar survival benefit from extensive surgery is anticipated in anaplastic astrocytoma and possibly low-grade glioma, although this has not been fully established. For glioblastoma, the intraoperative placement of carmustine chemotherapy wafers is US Food and Drug Administration (FDA)-approved after tumor resection, but there is not widespread use as this treatment remains controversial.

11. Does maximal resection have a survival advantage over biopsy in PCNSL?

Except in the scenario of brain herniation due to mass effect, surgical resection offers no benefit, given the often deep brain location and the infiltrative, multifocal nature of lymphoma, and the not unusual involvement of leptomeninges and eyes. Furthermore, even when technically feasible, total resection offers no significant survival advantage, and therefore biopsy alone is recommended.

12. Can a trial of steroids be used to diagnose and treat suspected PCNSL?

Corticosteroids should be avoided, if possible, prior to stereotactic biopsy, as they have a direct lymphocytolytic

effect that can disrupt cellular morphology and lead to inaccurate tissue diagnosis. Rapid resolution of an intracranial process with corticosteroids has a differential diagnosis that includes PCNSL, sarcoidosis, CNS lupus, histiocytic syndromes, and multiple sclerosis. Corticosteroids as single therapy are not an optimal treatment option because, although they work quickly to cause tumor regression and decrease edema, PCNSL tends to recur within weeks to months of discontinuation.

13. For newly diagnosed glioblastoma, should adjuvant temozolomide be continued for 6 months, or longer?

The current standard of care for newly diagnosed glioblastoma, established by the landmark European Organization for Research and Treatment of Cancer–National Cancer Institute of Canada (EORTC–NCIC) study in 2005, consists of safe, maximal resection followed by external-beam radiation therapy with concurrent temozolomide (TMZ) chemotherapy for 6 weeks, followed by at least six cycles of adjuvant TMZ. Questions remain regarding the optimal use of TMZ. In practice, most neuro-oncologists in the United States treat with at least 12 cycles of adjuvant TMZ.

Key clinical trial: Stupp, *et al.* 2005.

14. Is there an advantage of dose-dense temozolomide over standard-dose TMZ?

As depletion of MGMT in tumor cells may enhance TMZ efficacy, and prolonged exposure to TMZ may decrease MGMT activity, the benefit of dose-dense TMZ was recently tested in RTOG 0525, a large, phase III study. The study found no significant improvement in progression-free survival or overall survival in patients treated with "dose-dense" TMZ ($75\,mg/m^2$ for 21 days every 28 days), regardless of methylation status. However, in another study, metronomic TMZ ($50\,mg/m^2$ daily) did have evidence of efficacy even in patients who had failed prior conventional TMZ dosing.

Key clinical trial: RT0G 0525

15. Is treatment with chemoradiation appropriate for elderly patients with glioblastoma?

The optimal management of glioblastoma in the elderly remains unresolved. Overall, survival of elderly patients with high-grade gliomas is significantly less than in younger patients. Because of concerns about tolerance and treatment toxicity, the elderly are less likely to undergo standard of care treatment, and, as expected, they experience more treatment toxicity. Although patient selection bias may skew results, there is a suggestion that extensive resection may modestly improve survival in the elderly, compared to stereotactic biopsy. There is a small but significant benefit of radiation therapy following resection. Hypofractionated radiation therapy is likely a more appropriate option than standard radiation therapy, given its seemingly similar effect but decreased toxicity. A recent study, NOA-8, demonstrated that TMZ alone was equivalent to radiation therapy alone in patients with MGMT promoter methylated tumors, but not in patients with MGMT unmethylated tumors. This trial, along with the prospective Nordic Trial, suggests a role for MGMT testing in elderly patients with glioblastoma, prior to treatment decisions. We advocate that patients ages 65–70 with good KPS and resection should receive standard of care treatment, or a short course of hypofractionated radiation therapy (with or without TMZ), and those older than age 70 with good KPS and resection should receive standard of care, short-course hypofractionated RT, or TMZ alone. Those with poor KPS should receive best supportive care or, if less affected, short-course hypofractionated RT, or TMZ alone. An ongoing randomized EORTC–NCIC study of hypofractionated radiation therapy with or without concurrent and adjuvant TMZ will further clarify optimal management in the elderly.

Key clinical trials: NOA-8 Trial and Nordic Trial.

16. What is the standard of care for patients with grade III anaplastic gliomas?

As a significant survival benefit is suggested following gross total resection, initial treatment of anaplastic gliomas consists of maximal safe resection. Recently reported data demonstrate significantly improved overall survival with upfront treatment with combined radiation therapy and procarbazine, lomustine, and vincristine (PCV) chemotherapy, over radiation therapy alone, in patients with 1p/19q co-deleted anaplastic gliomas. 1p/19q co-deletion is both prognostic and predictive of improved outcomes with this regimen. Neither timing (before, during, or following radiation treatment) nor dose intensity of PCV was found to be significant. In clinical practice, TMZ is often substituted for PCV. A phase III study (CATNON) is underway to examine the appropriate treatment of (non-co-deleted) tumors, but it will likely be years before results are known. Given the lack of better evidence, it is appropriate to treat 1p/19q intact anaplastic gliomas with safe maximal resection, followed by radiation therapy or combined radiation therapy and chemotherapy.

Key clinical trials: RTOG 9402 and EORTC 26951.

17. Is radiation therapy mandatory for all patients with grade III gliomas?

Considering the recent EORTC and RTOG findings, it is no longer appropriate to treat 1p/19q co-deleted tumors with radiation therapy alone. However, some subsets of patients may benefit from initiating treatment with chemotherapy

alone, delaying treatment with radiation therapy until progression. This select subset, typically young patients with good performance status and extensively resected co-deleted grade III gliomas, requires close observation and early implementation of combined radiation therapy and chemotherapy if the chemotherapy alone fails. The concept of this approach is to delay irradiation, thereby possibly delaying the onset of long-term cognitive side effects.

18. Can TMZ be substituted for PCV in patients with anaplastic glioma?

The recent publications of the EORTC and RTOG studies in anaplastic oligodendroglioma that demonstrated that the addition of PCV to radiation is superior to radiation therapy alone raise the question of whether, given this level 1 evidence, PCV should supplant the current widespread use of TMZ. The PCV regimen is far more toxic, and it is difficult to complete an entire course of six cycles, whereas most patients readily tolerate the TMZ. Recently, a survey demonstrated that many neuro-oncologists use TMZ rather than PCV. A retrospective analysis suggested that PCV may be superior to TMZ, although as a retrospective survey there are concerns about full extrapolation of the data.

19. How are patients with low-grade glioma best managed?

Low-grade gliomas (LGGs, WHO grade II) in adults include astrocytoma and oligodendroglioma. LGGs initially grow slowly, but often undergo malignant transformation to WHO grade III and IV tumors. There now appears to be a survival benefit to early and maximal surgical resection, which also allows for early and accurate histologic and molecular diagnosis. Radical resection may also improve symptoms, particularly seizures. For high-risk patients (age >40 years and/or partial tumor resection), we generally recommend radiation therapy following surgery. The role of chemotherapy in this setting has not been resolved. Low-dose radiation therapy (typically around 50 Gy) is preferable, as high-dose radiation provides no significant survival advantage and may be more toxic. After the initial surgery, low-risk patients (age younger than 40, and tumor less than 6 cm diameter and not crossing the midline) can undergo clinical observation using serial neurologic evaluations and serial magnetic resonance imaging (MRI). Although conventional analysis of the data was unrevealing, the addition of PCV to radiation in patients with LGG may confer a late survival benefit (beyond 2 years). The role for upfront chemotherapy (in clinical practice, TMZ is often substituted for PCV) without radiation therapy has not been clarified. Special consideration of radiation therapy plus chemotherapy is warranted in 1p–19q co-deleted tumors, given the survival benefit.

Key clinical trial: RTOG 9802.

20. What is the treatment for patients with recurrent glioblastoma?

Despite extensive efforts and a large number of clinical trials, there are no established treatments that significantly increase overall survival, although some have shown small improvements in progression-free survival. Bevacizumab, an anti-angiogenic agent that binds circulating vascular endothelial growth factor (VEGF), has been approved by the FDA for recurrent glioblastoma. There are no established alternatives; therefore, patients with recurrent glioblastoma should be considered for eligibility in clinical trials. Relief of mass effect and associated symptoms is a potential clinical benefit of repeat resection, and biopsy confirmation of true progression can be key in treatment decisions. Re-irradiation to the primary tumor region or distant spread may be a reasonable option; however, there are no rigorous prospective data on this approach. Stereotactic radiosurgery, given the very precise treatment field, has not proven to be beneficial for infiltrating gliomas. Recognizing the unmet need for patients with recurrent malignant glioma, a variety of new treatment regimens are under investigation, including combination chemotherapies, targeted biologic therapies, and direct injection of replication-competent vectors (i.e., Delta-24 adenovirus) containing gene therapies.

21. What is the role of "rechallenge" with TMZ at glioblastoma recurrence?

Several trials have considered various dosing schedules of single-agent TMZ for recurrent glioblastoma, as well as TMZ in combination with a multitude of other drugs. In general, no advantage has been found to any of these combinations or dosing schedules. Several poly(ADP-ribose) polymerase (PARP) inhibitors are in clinical trials in combination with various dosing schedules of TMZ, in an attempt to overcome TMZ resistance and therefore increase the drug's efficacy. An ongoing trial may help to clarify whether MGMT promoter methylated tumors are associated with better outcomes with TMZ at tumor recurrence.

22. What is the role of signal transduction modulators in gliomas?

Several growth factors, such as epidermal growth factor (EGF) and VEGF, and their receptors, are critical in the pathogenesis and survival of glioblastoma tumor cells. Activation of these tyrosine kinase receptors triggers four major downstream pathways: mitogen-activated protein kinase (MAPK), PI3K–Akt, phospholipase C gamma

(PLCγ), and protein kinase C (PKC). These signaling pathways are reasonable targets of glioblastoma treatment. Unfortunately, studies of single-agent signal transduction modulators have shown modest, if any, benefit, likely due to complex pathway mechanisms, such as redundancy and downstream effects. Combinations of targeted therapy may be more beneficial, but trials are complicated by toxicity concerns.

23. What is the role of anti-angiogenic agents in recurrent glioblastoma?

Angiogenesis is a key component in glioblastoma growth and invasion, and VEGF, a key regulator of angiogenesis, is often overexpressed in glioblastoma. In 2009, single-agent bevacizumab, a monoclonal antibody with anti-VEGF activity, received accelerated FDA approval for the treatment of recurrent glioblastoma, based on demonstration of significantly increased progression-free survival. The optimal timing, dosing, and duration of bevacizumab for glioblastoma had not been well defined. Bevacizumab has been tested in combination with other agents, including TMZ, without evidence of superiority to single-agent therapy. A variety of other anti-angiogenic agents, such as cilengitide, which targets integrins, are under investigation.

Key clinical trial: The "BRAIN" trial.

24. How do antiangiogenic agents such as bevacizumab affect interpretation of the treatment response?

Bevacizumab treatment typically results in improvement of contrast enhancement on MRI, likely secondary to its anti-angiogenic effect, and not necessarily corresponding to true tumor response with tumor cell death. Stable or improved contrast-enhancing tumor on MRI, but with increased non-enhancing tumor on T2–FLAIR-weighted MRI sequences, is a typical pattern of progression on bevacizumab treatment. This differs from the usual pattern of glioblastoma progression, which typically manifests as an increase in both enhancing and non-enhancing portions of tumor. MRI may not be sufficient to fully address treatment response, but there is no better alternative at this time.

25. Is there a benefit to delaying treatment with bevacizumab? Can it be given upfront?

Patients who progress while undergoing treatment with bevacizumab do not respond well to further salvage therapy and have limited eligibility for clinical trials. Therefore, it may be prudent to reserve bevacizumab as the final salvage option. Two randomized, phase III, placebo-controlled trials, AVAglio and RTOG 0825, evaluating bevacizumab as upfront treatment in newly-diagnosed glioblastoma, in combination with chemoradiation with TMZ, were recently published. Although both studies showed a 3–4 month increase in progression-free survival, neither found a benefit in overall survival. The studies showed conflicting results in terms of the effect of upfront bevacizumab on quality of life and other measures of clinical benefit.

26. Can bevacizumab be safely stopped? Does the use of antiangiogenic agents such as bevicizumab alter tumor biology, causing a more aggressive tumor?

It is unclear whether it is safe to discontinue bevacizumab, and when to do so. There is concern and speculation that discontinuing bevacizumab may lead to a significant rebound in the permeability of tumor vessels and accelerated vascular growth. Further, there is concern that antiangiogenic agents may result in distant spread by altering tumor biology and upregulating invasion-related genes.

27. How are primary brain tumors monitored on imaging?

Primary brain tumors are typically monitored using MRI scans with and without gadolinium contrast enhancement. The interval of monitoring varies by disease type and grade. For example, with ongoing treatment, patients with glioblastoma typically undergo MRI follow up evaluations every 2–3 months and at gradually longer intervals thereafter. Although tumor progression may be manifest on the clinical exam, progression can be clinically silent MRI findings, however, can be deceptive as evidenced by the relatively recent recognition of pseudo-progression and pseudo-response. Concern about the veracity of exclusively using MRT enhancement as a measure of response (as with the Macdonald criteria) led to the development of the Response Assessment in Neuro-oncology (RANO). The RANO criteria measure changes in apparent tumor size on both contrast-enhancing and T2–FLAIR-weighted MRI images, and incorporates timing, clinical status and steroid use into the decision-making process.

Key concept: Quant EC, Wen PY. Response assessment in neuro-oncology. Curr Oncol Rep. 2011;13(1):50–6.

28. How is pseudo-progression distinguished from true progression?

Discerning treatment-related changes from tumor recurrence is a central challenge in neuro-oncology, but is essential for appropriate treatment planning. The two entities often appear alike on MRI follow-up imaging, and may manifest with similar symptoms. Unfortunately, no imaging technique can reliably differentiate progression from pseudo-progression, and the diagnostic utility of advanced brain tumor imaging such as magnetic resonance spectroscopy and positron emission tomography (PET) is not yet clear.

Pseudo-progression reflects an early treatment effect, typically within 3 months of completing radiation treatment. Intratumoral viruses, vaccines, and carmustine chemotherapy wafers may also result in a transient increase in enhancement. Pseudo-progression is usually determined retrospectively on follow-up imaging, as it typically stabilizes or regresses without additional treatment, or by tissue diagnosis. In cases of suspected pseudo-progression, it is advised to continue treatment and reimage in 2–3 months, or sooner if symptoms arise or worsen. Glioblastoma progression is not diagnosed within 3 months of chemoradiation treatment completion, unless there is new enhancement beyond the radiation field, or biopsy-proven recurrence.

29. How is treatment-related necrosis distinguished from true tumor progression?

Treatment-related (radiation) necrosis, likely similar to pseudo-progression, reflects a delayed, severe degree of local tissue injury, typically occurring 3–24 months following chemoradiation, but it may occur even years later. Unlike pseudo-progression, which is often asymptomatic, is self-limited, and may be a positive prognostic indicator, radiation necrosis is often symptomatic and irreversible.

Selected reading

Anderson MD, Gilbert MR. Treatment recommendations for anaplastic oligodendrogliomas that are codeleted. Oncology (Williston Park). 2013;27(4):315–20, 322.

Brandes AA, Tosoni A, Spagnolli F, *et al*. Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: pitfalls in neurooncology. Neuro Oncol. 2008;10(3): 361–67. doi: 10.1215/15228517-2008-008

Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA. 2013:310(17):1842–50. doi: 10.1001/jama.2013.280319

Sanai N, Chang S, Berger MS. Low-grade gliomas in adults. J Neurosurg. 2011;115(5):948–65. doi: 10.3171/2011.7.JNS101238

Theeler BJ, Yung WK, Fuller GN, De Groot JF. Moving toward molecular classification of diffuse gliomas in adults. Neurology. 2012;79(18):1917–26. doi: 10.1212/WNL.0b013e318271f7cb

Wen PY, Kesari, S. Malignant gliomas in adults. N Engl J Med. 2008;359(5):492–507. doi: 10.1056/NEJMra0708126

CHAPTER 71

Secondary brain and spinal cord tumors

Rimas V. Lukas[1], Patrik Gabikian[2], and Steven J. Chmura[1]

[1]The University of Chicago, Chicago, IL, USA
[2]Kaiser Foundation Hospital, Los Angeles, CA, USA

Case study 71.1

A 70-year-old man with metastatic castration-resistant prostate cancer diagnosed 4 years ago presents to clinic with complaints of unsteady gait. His systemic disease burden had been stable for quite some time. He has received numerous prior lines of chemotherapy that have included neurotoxic agents. His medical history is also notable for hypertension and atrial fibrillation for which he is on anticoagulation with warfarin. He notes progressive difficulty walking over the past week. Examination reveals no reflexes in the upper or lower extremities. Babinski sign is present bilaterally. Imaging reveals an enhancing epidural lesion with frank compression of the spinal cord (Figure 71.1).

1. What would the optimal management of this patient involve?

A. High-dose steroids (dexamethasone 10–100 mg dose) alone
B. Surgical decompression alone
C. Stereotactic radiosurgery
D. Initiation of steroids followed by surgical decompression and radiation

High-dose steroids decrease edema within the spinal cord providing symptomatic improvement that may be associated with an improved long-term outcome. High-dose dexamethasone (96 mg followed by 24 mg QID for 3 days and then a taper) with radiation (28 Gy) has been compared in a randomized trial to radiation alone in patients with symptomatic acute cord compression. The steroid-treated group had a better ambulatory status at both the completion of therapy and 6 months later. This supports the rapid initiation of steroids when there is significant concern for metastatic disease causing spinal cord compression. Additional studies comparing doses of steroids have not revealed any obvious superiority of the very-high-dose (96 mg) dexamethasone as opposed to more moderate doses (10–16 mg).

Surgical decompression without additional radiation has not been studied in a randomized fashion. For symptomatic extra-axial metastatic lesions from solid tumors compressing the spinal cord, a single nonblinded randomized

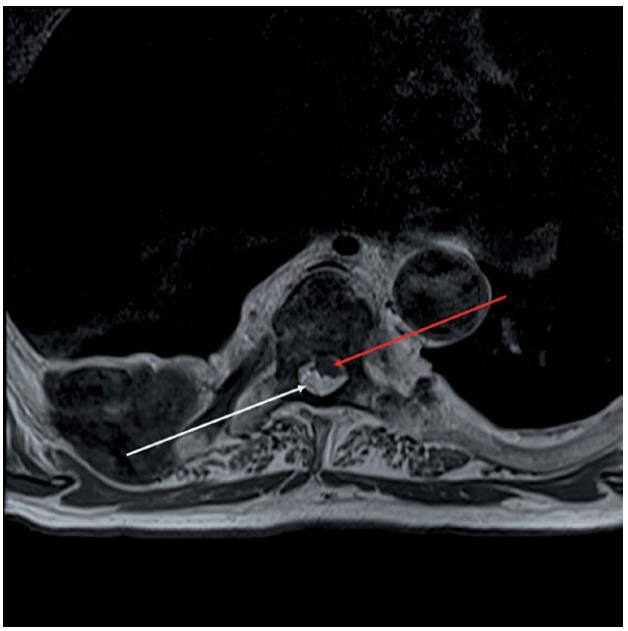


Figure 71.1 T1 postcontrast axial image of the thoracic spine. The red arrow indicates the spinal cord, which is being compressed by the extra-axial mass posteriorly (white arrow).

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

trial comparing surgery followed by focal fractionated radiation (30 Gy) versus radiation alone has demonstrated a higher ambulatory rate after completion of treatment (84% vs. 57%; $P = 0.001$), overall survival (OS) (126 days vs. 100 days; $P = 0.033$), maintenance of continence (156 days vs. 17 days; $P = 0.016$), and duration of retained ability to walk (122 days vs. 13 days; $P = 0.003$) in the combined treatment arm. The benefit of surgical intervention decreases with increasing age. Radiation therapy (RT) alone without surgery has been evaluated in a large, prospective nonrandomized study using a number of different dosing schedules. Long course (10–30 fractions, 30–40 Gy) compared to short course (1–5 fractions, 8–20 Gy) demonstrated superior local control (81% vs. 61% at 1 year; $P = 0.005$), but similar functional outcome and survival. In patients with expected favorable survival, surgical decompression followed by long-course radiation should be considered. In those with poor expected survival, short course is a reasonable option. In either scenario, realistic expectations regarding goals of care should be presented to the patient during the decision-making process. While there is some evidence supporting the benefit for stereotactic radiosurgery (SRS) for mechanically stable non-cord-compressing vertebral body lesions, evidence of benefit in acute cord compression is lacking, and ongoing randomized trials to assess tumor control and quality of life are being conducted by cooperative groups.

Case study 71.2

A 57-year-old male with no past medical history presents with new-onset complex partial seizures. Three enhancing lesions, each approximately 1 cm in size, are noted on magnetic resonance imaging (MRI) in the left anterior temporal, left posterior temporal, and right parietal lobes. The patient's neurological examination is unremarkable. A single lung lesion is noted as well. Biopsy of this lesion reveals adenocarcinoma consistent with non-small-cell lung cancer (NSCLC).

1. Which of the following statements regarding the prognostic category this patient falls into is correct?

A. Median overall survival (OS) is ~2 months.
B. Median OS is ~7–10 months.
C. Median OS is ~12 months.
D. Median OS is ~24 months.

Various prognostic classification systems exist for patients with solid tumor brain metastases. The Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) classification system is derived from data from three RTOG studies evaluating different whole-brain radiation therapy (WBRT) treatment regimens in patients with solid tumor brain metastases from varying histologies. A significant percentage (61%) of patients had lung cancer. Three prognostic classes were established with performance status having the greatest correlation with survival. Patients with Karnovsky performance score (KPS) <70% have a median OS of 2.3 months. For the younger patients with KPS ≥70 and controlled primary disease, median OS was 7.1 months. As our patient has a good performance status, is young, and does not have an uncontrolled primary, he would be categorized in prognostic group 1 (median OS: 7.1 months). A more nuanced brain metastases prognostic classification system, the Disease Specific Graded Prognostic Assessment (DS-GPA), has been described more recently. It is based on a multi-institutional retrospective database analysis and provides survival estimates for various histologies based on a number of potential factors that may include age, performance status, presence of extracranial metastases, and the number of brain metastases. Using this system, estimated median OS in patients with similar characteristics such as ours would be 9.43 months.

2. The optimal management for this patient's brain metastases involves which of the following?

A. Surgical resection of all three lesions followed by WBRT
B. Surgical resection of the anterior temporal lesion, which was the most likely focus of the seizure followed by WBRT
C. SRS to all three lesions either with or without WBRT
D. WBRT

We present the case of a patient with excellent performance status and three new brain metastases. There are no randomized studies evaluating the role of surgical resection in patients with three brain metastases. While it is possible that the anterior temporal lesion is the focus of seizure activity, it is likely that this could be well controlled with antiepileptic medications. Surgical resection for seizure control is typically employed in the setting of medically refractory seizures. While WBRT would treat the radiographically evident metastases as well as any micrometastatic disease, it is not without consequences. SRS has been studied in a number of trials, the majority of which involved patients with more than one central nervous system (CNS) metastasis. One study comparing SRS versus SRS plus WBRT in patients with one to four brain metastases revealed no significant difference in OS, but there was a significantly increased risk of recurrence outside of the SRS field in the SRS-alone group. Another similar study compared patients with one to three brain metastases treated initially with either surgery or SRS and subsequently randomized to observation versus WBRT. No improvement in OS was noted, although risk of CNS relapse and neurologic death

was significantly decreased in the WBRT arm. Comparison of WBRT versus WBRT plus SRS in patients with one to four brain metastases demonstrated superior local control with the addition of SRS but no significant improvement in OS. Additionally, WBRT was associated with a decrease in health-related quality-of-life (QOL) measures. However, more recent randomized trials examining memory with WBRT in the prophylactic cranial irradiation (PCI) setting (RTOG 02-14) demonstrated no significant declines in global cognitive function, evaluated via Mini-Mental Status Examination (MMSE), or QOL after PCI in the absence of tumor progression. *In our case, although one could reasonably argue for the use of WBRT or SRS alone, in this patient with an excellent performance status, brain metastases within the size parameters for SRS, reasonable likelihood for controlling his limited systemic disease burden, and a desire on the patient's part to follow an aggressive treatment path, it was decided to treat him with SRS and WBRT in order to maximize CNS tumor control.* In multivariate analysis by histology and treatment in the retrospective DS-GPA study, NSCLC patients treated with SRS and WBRT had an improved OS and decreased risk of death compared to those treated with WBRT alone.

Case study 71.3

A 58-year-old male with only a history of hypertension presents with only mild headache. As part of the work-up, an MRI of the brain with and without contrast reveals five enhancing lesions without any significant mass effect. Work-up for an underlying malignancy reveals moderately differentiated adenocarcinoma of the gastroesophageal junction.

1. In this patient with synchronous minimally symptomatic brain metastases, what would the optimal management involve?

A. WBRT
B. WBRT plus SRS boost
C. Surgical resection of all five lesions followed by WBRT
D. Close observation

This is a case of multiple brain metastases. There are no strong data supporting surgical resection in patients with multiple asymptomatic brain metastases. The randomized studies evaluating SRS, discussed in Question 2 in Case study 71.2, included patients with up to four brain metastases. Although in certain settings SRS to more than four lesions is performed, the data to support this approach are limited when compared to the data evaluating the role of SRS in four or fewer lesions. It is presumed that in patients with multiple radiographically evident brain metastases, there are additional micrometastases as is noted in other organ systems. In turn, WBRT is the modality most often employed in this clinical setting. As the incidence of metastases to the hippocampi is quite low, hippocampal-sparing techniques of WBRT in an effort to decrease potential neurologic toxicities were being investigated in an attempt to limit some of the neurocognitive effects of radiation (NCT01227954 and NCT01414738).

2. The optimal radiation dosing schedule in the patient described in Question 1 would involve:

A. 4 Gy over 5 fractions (20 Gy total)
B. 5 Gy over 4 fractions (20 Gy total)
C. 3 Gy over 10 fractions (30 Gy total)
D. 2.5 Gy over 15 fractions (37.5 Gy total)

The initial RTOG 6901 trial established 30 Gy total in 3 Gy fractions 5 days per week as the standard of care. Numerous other trials, such as RTOG 7361, have attempted hypofractioned techniques (choice A) in an attempt to finish patients more quickly but have failed to improve outcomes and may have a trend to worse neurocognitive performance. Increasing the total dose and time to 50Gy/2Gy fractions also failed to improve upon a shorter course in terms of brain control or OS (RTOG 7606). Attempts to increase the biologic effective dose (BED) through the use of hyperfractionated radiation therapy (1.6 Gy twice per day) to total doses of 54.4 Gy in KPS >70 patients have also failed to demonstrate control or OS improvement. Finally, choice D (2.5 Gy to 37.5 Gy) is the WBRT arm used in patients with three or fewer metastasis that are planned for immediate SRS per RTOG 95-08.

Case study 71.4

A 69-year-old female with a history of hypertension, poorly controlled diabetes, coronary artery disease, and chronic obstructive pulmonary disease (COPD) as well as NSCLC treated with chemoradiation develops a single right parietal brain metastasis measuring 2 cm approximately one year after her initial diagnosis. She is without evidence of systemic disease on restaging.

1. Management of her brain metastasis would optimally involve which of the following?

A. Surgical resection alone
B. SRS alone or with WBRT
C. WBRT alone
D. Close clinical and radiographic observation

In patients with single brain metastases and relatively stable systemic disease, focal interventions such as surgery or SRS should be considered over WBRT. Per the RPA prognostic classification system, the patient would fall into either class II (OS: 4.3 months) or class III (2.3 months) depending on her performance status. Using the more contemporary DS-GPA prognostic index, median OS would range from 5.49 to 9.43 months, also depending on performance status. An understanding of the overall prognosis in brain metastasis patients helps guide the management plan. In this case, her multiple medical comorbidities may make her a suboptimal surgical candidate. Although surgical resection may be a reasonable option, SRS may be the more appropriate choice in this patient. Additionally, a patient's preconceived notions regarding treatment options—both surgery and radiation—may influence their decision making during pretreatment counseling.

SRS alone has been compared to surgery followed by WBRT in patients with a single solid tumor brain metastasis. No significant difference in OS was noted; however, the study closed prior to reaching accrual goals due to poor enrollment. Other completed randomized trials demonstrate no significant effect on OS by omitting WBRT, although local control of the known lesion(s), progression-free survival (PFS), and neurologic death are compromised without WBRT. In another study, SRS plus WBRT have demonstrated improved OS when compared to WBRT alone in the subgroup of patients with a single brain metastasis. A nonrandomized trial specifically for NSCLC adds additional evidence for improved OS with the use of an SRS-containing regimen over WBRT. Choosing SRS alone due to concern for the potential cognitive side effects of the additional WBRT or using both modalities of RT upfront would be reasonable to consider.

Case study 71.5

The patient is a 57-year-old male with no additional medical history except for papillary thyroid cancer treated with surgery and radioactive iodine. With recurrence in the local lymph nodes, he received focal RT to the region. Approximately 3 years later, he developed new headaches that were concerning for increased intracranial pressure. Imaging revealed a large right frontal cystic mass approximately 4.5 cm in diameter with significant surrounding edema. Systemic restaging reveals no evidence of disease. His KPS is 100%.

1. What would management of the brain lesion include?

A. Surgical resection
B. SRS
C. WBRT
D. Close clinical and radiographic follow-up

Surgery in this case would serve both a diagnostic and therapeutic purpose. The long disease-free interval and lack of systemic recurrence lead one to broaden the differential diagnosis to include primary brain tumors, infections, and autoimmune processes. There are three randomized trials evaluating surgery followed by WBRT versus WBRT alone in the treatment of single brain metastases. Two of these studies demonstrated improved OS (~10 months vs. ~4–6 months), while the third did not. For patients who are deemed good surgical candidates from a medical perspective and who have a symptomatic metastasis for which surgery will likely improve symptomatology, surgery is often considered over SRS. In the case described here, the size of the lesion exceeds the typical 4 cm cutoff for SRS due to increased risk of radiation necrosis, edema, and poor local control.

2. What would the optimal management of this patient after complete radiographic resection involve?

A. WBRT shortly after surgery
B. WBRT if there is evidence for progressive disease in the CNS
C. SRS to the resection cavity
D. Systemic treatment with a small-molecule targeted therapy with reasonable CNS penetration

The randomized trials evaluating the role of surgical resection of a single metastasis followed surgery with WBRT. WBRT doses of 30 to 40 Gy were employed. The role of WBRT after complete surgical resection was investigated in a randomized trial in which patients either were observed

or received WBRT to 50.4 Gy in 1.8 Gy fractions. This dose is notably higher than the dose used in the prior surgical trials. WBRT decreased the recurrence of tumor in the brain (18% vs. 70%), recurrence at the site of resection (10% vs. 46%), recurrence elsewhere in the brain (14% vs. 37%), and likelihood of dying of neurologic causes (14% vs. 44%). There was, however, no improvement in OS. This evidence can be used to argue for a number of different management plans. Often, physicians' and patients' preferences will affect the decision-making process. As systemic therapies improve, both the ability to control disease in the brain as well as the long-term effects of WBRT will need to be carefully weighed. It is these concerns regarding the long-term effects of RT that lead some physicians to defer all radiation or to consider more limited fields. The use of more limited treatment fields is most reasonable in tumor histologies that are less likely to develop a pronounced number of metastases or in those tumors that may benefit from single larger fractions of radiation. In the case described here, it is uncertain to what size the resection cavity will collapse after complete radiographic resection of this large cystic tumor. The size of the residual resection cavity may influence which options other than WBRT are entertained, specifically single-fraction SRS versus a focal fractionated approach.

Case study 71.6

A 55-year-old female with metastatic NSCLC (adenocarcinoma) presents with new-onset seizures, and imaging reveals multiple (>10) small brain metastases. She receives WBRT to 30 Gy. Her systemic disease remains stable even when her brain metastases progress approximately 8 months after WBRT. The majority of small metastases have all increased in size, and a number of small new radiographically evident metastases are also present. Her neurological exam is unremarkable, and she continues to have good cognitive performance. Her overall performance status remains quite good.

1. What does the preferred management of progressive brain metastases in this case include?

A. Surgical resection of the largest brain metastases
B. Repeat WBRT
C. Stereotactic radiosurgery to the new metastases only
D. A chemotherapy regimen with reasonable CNS penetration

As discussed in this chapter, the role for surgical resection of brain metastases is most clearly defined in single brain metastases. Surgery may also be indicated when the relief of compressive mass effect on adjacent structures may benefit the patient symptomatically. This may be pursued in the setting of multiple brain metastases, but the role of surgical intervention within the broader context of the patient's overall disease needs to be carefully considered. Repeat WBRT is potentially a viable treatment modality. Lower doses and smaller fraction sizes are often employed with repeat WBRT in an attempt to decrease toxicity but also decreasing efficacy. With re-irradiation acute adverse reactions are common, but they are typically mild to moderate in severity. In our patient with no active systemic disease and good cognition, one would be concerned about the potential long-term neurologic deficits that the patient may be at risk for with re-irradiation. There are only limited data about these complications. Re-irradiation with SRS in patients with prior WBRT has demonstrated good response rates and local control rates. In our case, there are a significant number of progressive metastases. Randomized data for SRS to newly diagnosed brain metastases are limited to patients with between one and four lesions. There are currently no randomized data evaluating the specific role of SRS for recurrent brain metastases. In our patient, there were more progressive lesions than would be suitable for SRS.

While routine use of chemotherapy for newly diagnosed brain metastases is not recommended, for patients with good performance status who have exhausted reasonable surgical and radiation options, chemotherapy is worth considering. The choice of chemotherapeutic agent must weigh the likelihood of it reaching active concentrations within the CNS. This is influenced by the size of the molecule, its lipophilicity, and whether it is a substrate for transporters such as P glycoprotein. Additionally, the clinician needs to weigh the potential for efficacy in the histologic subtype of tumor being treated. In certain malignancies, such as NSCLC, the molecular diagnostic studies that guide the treatment of extra-CNS tumor should also play a role in the therapeutic decision making for CNS metastases. Unfortunately, for many newer agents, the published literature regarding CNS concentrations of drug in humans is scarce.

A work-up is pursued for this patient. MRI reveals some enhancement in the CSF space, most notable in the posterior fossa between the cerebellar folia. There is no evidence of bulky disease in the cerebrospinal fluid (CSF) space. Lumbar puncture is performed, revealing a mildly elevated opening pressure, a mild increase in protein, a mild decrease in glucose, a mild elevation in WBC count, and the presence of malignant cells on cytopathology. A diagnosis of leptomeningeal carcinomatosis is made. After discussing the

(*Continued*)

seriousness of the diagnosis, the patient is still interested in pursuing additional treatment with realistic expectations regarding potential risks and benefits.

2. Which of the following management options would not be appropriate to discuss?

A. WBRT
B. Intrathecal chemotherapy
C. SRS to the posterior fossa tumor burden
D. Hospice

While focal therapy such as SRS can be considered in patients with leptomeningeal carcinomatosis, it is not indicated when there is no distinct radiographic target. There is no single standard-of-care pathway for patients with leptomeningeal carcinomatosis. Due to the overall poor prognosis, it is our practice to discuss the role of hospice with all of our patients diagnosed with leptomeningeal carcinomatosis. In patients with favorable prognostic factors, we discuss consideration of various treatment modalities, setting out realistic expectations from the outset. In breast cancer patients with newly diagnosed leptomeningeal carcinomatosis, performance is the most clearly defined prognostic factor. Other factors that have also been shown to potentially influence prognosis include age, hormone receptor status, prior chemotherapy regimens, as well as CSF findings.

Radiation therapy is typically employed to treat any bulky disease in the CSF space. It also has a role in patients with nonbulky disease. WBRT is often chosen over craniospinal radiation due to the lower side effect profile. Intrathecal chemotherapy with a number of different agents has been employed in the treatment of leptomeningeal carcinomatosis. The majority of clinical trials evaluating the use of intrathecal chemotherapy are single-arm studies and include a number of different histologies. Breast cancer patients constitute a large percentage of patients in most of these studies.

In our experience, our preference is to administer intrathecal chemotherapy via an Ommaya reservoir. Each intrathecal chemotherapy administration is easier for the patient in comparison to delivery of chemotherapy via lumbar puncture. Accessing the Ommaya reservoir is not limited by thrombocytopenia, which would contraindicate performance of a lumber puncture. Finally, by delivering the chemotherapy directly into the ventricle, it is more likely to have a more adequate distribution throughout the CSF space. Intrathecal chemotherapy can potentially be administered in conjunction with systemic chemotherapies or after radiation therapy. Regarding postradiation intrathecal chemotherapy, the potential for neurologic toxicities such as leukoencephalopathy, particularly with methotrexate, should be noted.

Case study 71.7

A 54-year-old male with a known history of papillary thyroid cancer is referred after having received a significant amount of treatment for brain metastases. Approximately 3 years after his initial cancer diagnosis, he developed a single symptomatic left frontal metastasis that underwent a complete radiographic resection followed by WBRT to 37.5 Gy. Approximately one year later, he developed another distinct left frontal metastasis that was treated with SRS to 20 Gy. Seven months after SRS, he developed additional enhancement at the site of the second tumor. He underwent surgical resection of this, which exclusively revealed necrosis and reactive gliosis without any evidence of tumor. Follow-up MRI one month postoperatively revealed additional progression in the enhancement at the edge of the resection cavity (Figure 71.2). His vital signs are stable, and neurological examination remains unchanged.

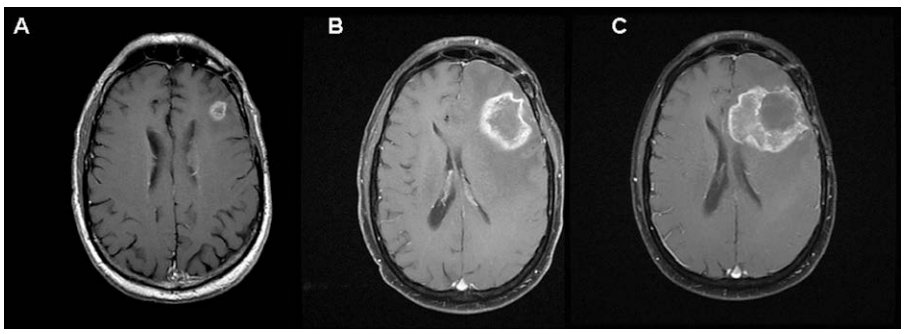


Figure 71.2 T1 postcontrast axial magnetic resonance imaging (MRI) images of the brain. (A) Stable enhancing pattern ~6 months after stereotactic radiosurgery. (B) Progressive enhancement is noted ~7 months after stereotactic radiosurgery. (C) Two months after resection revealing radiation necrosis, there is additional progression of enhancement.

1. What do these radiographic findings most likely represent?

A. Progressive papillary thyroid cancer metastases
B. Progressive radiation necrosis
C. Postoperative abscess
D. Postoperative infarction

Radiation necrosis, a type of late-delayed radiation injury, typically begins at least 3 months after the completion of RT and is dependent in part on the dose and size of the RT field. The patient lacks the typical systemic signs such as fever that are often seen with postoperative infections. The radiographic picture is not typical for infarction related to surgery. The likelihood of the rapid evolution of the radiographic findings as being consistent with tumor growth is low due to lack of evidence for viable tumor on the recent surgical resection. This patient has received a substantial dose of radiation to the area of radiographic changes. The onset of progressive enhancement 7 months after his most recent radiation is within the timeframe for the development of radiation necrosis.

2. Which management option for cerebral radiation necrosis has randomized data supporting its use?

A. High-dose steroids
B. Hyperbaric oxygen
C. Anticoagulation
D. Bevacizumab

Steroids, hyperbaric oxygen, anticoagulation, and bevacizumab have all been used in the treatment of symptomatic cerebral radiation necrosis. Asymptomatic radiation necrosis is often followed clinically and radiographically. In Question 2 in Case study 71.6, when the patient was referred after his second craniotomy, subsequent MRIs demonstrated a marked decrease in the enhancement over a period of months without any intervention (Figure 71.3). This does not occur in the majority of patients with late-delayed radiation injury.

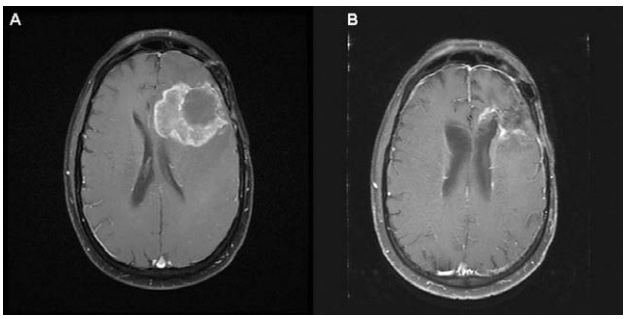


Figure 71.3 T1 postcontrast axial MRI images of the brain. (A) Two months after resection revealing radiation necrosis, there is additional progression of enhancement. (B) Interval decrease in the enhancement without intervention 15 months later.

Of the modalities described here, only bevacizumab has been investigated in a randomized fashion for the treatment of symptomatic radiation necrosis. A randomized double-blind placebo-controlled trial of 14 patients with head and neck carcinoma, meningioma, or low- to midgrade glioma was conducted. Bevacizumab was dosed at 7.5 mg/kg every 3 weeks for two to four treatments. All patients randomized to bevacizumab demonstrated improvement of neurologic symptoms, while the majority randomized to placebo demonstrated deterioration. At 6 weeks, all patients receiving bevacizumab had improvements on both T1 postcontrast as well as FLAIR MRI sequences, while those receiving placebo had radiographic progression. A quarter of patients who had received bevacizumab developed subsequent progression of radiation necrosis in long-term follow-up, requiring additional doses of bevacizumab.

Case study answers

Case study 71.1

Question 1: Answer D

Case study 71.2

Question 1: Answer B
Question 2: Answer C

Case study 71.3

Question 1: Answer A
Question 2: Answer C

Case study 71.4

Question 1: Answer B

Case study 71.5

Question 1: Answer A
Question 2: Answer A

Case study 71.6

Question 1: Answer D
Question 2: Answer C

Case study 71.7

Question 1: Answer B
Question 2: Answer D

Selected reading

Eichler AF, Chung E, Kodack DP, *et al*. The biology of brain metastases-translation to new therapies. Nat Rev Clin Oncol. 2011;8(6):344–56.

Patchell RA, Tibbs PA, Regine WF, *et al*. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005; 366(9486):643–8.

Patchell RA, Tibbs PA, Walsh JW, *et al*. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322(8):494–500.

Sperduto PW, Kased N, Roberge D, *et al*. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30(4):419–25.

PART 2

Head and Neck Cancers and Thoracic Malignancies

CHAPTER 72

Medical management of head and neck cancers

Tobenna Nwizu and David Adelstein

Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Case study 72.1

A 66-year-old male with significant tobacco and alcohol history presents with a 4 cm left neck node, which he noticed while shaving. There are no other findings on physical exam, and the patient feels well. A chest X-ray is of poor quality, but no clear neoplasm can be identified. A fine needle aspirate of the mass was not diagnostic.

1. What should the next diagnostic step be?

A. Reevaluation in 3 months
B. Bone marrow aspiration and biopsy
C. Referral to a head and neck surgeon
D. CT scans of the neck, and chest
E. Positron emission tomography (PET) scan

The presence of an enlarged cervical lymph node in a patient with significant smoking and alcohol history is highly suspicious for head and neck squamous cell carcinoma (HNSCC). This is the fifth most common cancer worldwide, with approximately 600,000 new cases diagnosed each year. Tobacco and alcohol consumption are the most important risk factors. Recently, the human papillomavirus (HPV) has been implicated in the pathogenesis of HNSCC, especially those arising in the oropharynx, and has been responsible for the recent rise in oropharyngeal HNSCC. HNSCC can arise from a wide variety of locations in the head and neck region, including the oral cavity, pharynx, larynx, nasal cavity, and paranasal sinuses.

The diagnosis of HNSCC starts with a detailed history and physical exam, as the clinical presentation of head and neck cancer typically depends on the location of the primary site. Typical presenting symptoms include nonhealing oral ulcers, loosening of teeth, dysphagia, odynophagia, oral bleeding, referred otalgia, and cervical lymphadenopathy in tumors arising from the oral cavity; hearing loss, frequent unilateral serous otitis media, and tinnitus in patients with nasopharyngeal carcinoma (NPC); obstructive sleep apnea, snoring, odynophagia, and dysphagia in patients with oropharyngeal cancers (OPCs); persistent hoarseness, stridor, chronic cough, hemoptysis, referred otalgia, and dysphagia in patients with laryngeal cancer; and unilateral nasal obstruction, epistaxis, and facial pain in patients with tumors arising from the paranasal sinuses. Enlargement of a cervical lymph node can be the only presenting symptom in a patient with HNSCC. Ninety percent of patients with nasopharyngeal cancer and 66% of patients with primary tongue lesions present with an enlarged cervical lymph node.

Referral to a head and neck surgeon for a careful office and endoscopic evaluation of the entire head and neck mucosa is the most important first step in establishing the diagnosis and identifying the primary site. As smoking is such an important risk factor for head and neck cancer, the examination should also search for synchronous second primary aerodigestive tract tumors. Fine needle aspiration (FNA) of an enlarged cervical lymph node is frequently used to make the diagnosis of head and neck cancer. Even though FNA is very sensitive and specific, a nondiagnostic aspiration may occur in 5–16% of cases.

Once the diagnosis is established, or at least strongly suspected, imaging studies such as a CT of the neck or a PET scan may be used to assess the degree of local invasion, the extent of regional lymph node involvement, and the possible presence of distant metastases.

Given this very suspicious presentation in a high-risk patient, an expectant approach for 3 months would not be appropriate. Although a patient with lymphoma may present in a very similar way, a bone marrow exam should await establishment of that diagnosis.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 72.2

A 60-year-old male Vietnam veteran consults you about his recently diagnosed tonsil cancer. The tumor has been staged as a T2N3M0 poorly differentiated squamous cell cancer (SCC) with basaloid features. Although both of his parents smoked tobacco, he has never smoked, and he does not drink alcohol. He works in a foundry, is exposed to fumes throughout the day, and does not wear any kind of protective mask. He is distressed about his diagnosis and wants to know how he developed this malignancy.

1. What do you tell him the most likely cause of his cancer is?

A. Secondhand smoke in the workplace
B. Secondhand smoke in the home
C. Agent Orange exposure while in Vietnam
D. Toxic fume exposure at work
E. HPV infection

Over the last 10 years, there has been the recognition of a change in the epidemiology of HNSCC, with a significant rise in the incidence of OPCs despite declining prevalence of smoking and a decreasing incidence of all other head and neck cancers. An epidemic of HPV-initiated OPC seems to account for this rise. Epidemiologic and molecular studies have identified the HPV-16 serotype as the main causative agent.

HPV-initiated HNSCC typically occurs in the oropharynx, especially in the tonsil and base of the tongue, and currently accounts for 70% or more of the cancers at this site in the United States. Patients with HPV-initiated HNSCC tend to be approximately 10 years younger than patients with HPV-negative disease, with many presenting in their late thirties or forties. They are also less likely to have a history of tobacco use and typically have a better performance status. HPV-initiated cancers often have a poorly differentiated histology, and patients tend to present with a smaller primary tumor (T1/T2) and more nodal involvement (N2/N3). These lymph nodes are often large and cystic.

The prognosis for patients with HPV-initiated cancer is distinctly better than for patients with HPV-negative disease, and this improvement in outcome is independent of the other favorable prognostic features of this patient population. Tobacco smoking is, however, associated with a worse prognosis in these patients.

Agent Orange exposure or exposure to toxic fumes has not been well established in the pathogenesis of HNSCC. Retrospective studies have suggested that secondhand tobacco smoke exposure is a risk factor for HNSCC, but it is far less likely in this patient than HPV infection.

Case study 72.3

A 62-year-old Caucasian male with a long history of cigarette smoking presents to his primary care physician with 4 weeks of hoarseness. He is referred to a head and neck surgeon, who notes a 1 cm lesion on the right true vocal cord with no impairment of vocal cord mobility. An examination under anesthesia confirms that the lesion is a squamous cell carcinoma (SCC) limited to the true cord and that there is no suggestion of regional lymphadenopathy. Chest X-ray is unremarkable.

1. Which treatment do you recommend option for this patient?

A. Definitive radiation therapy with concurrent cisplatin 100 mg/m^2 given every 3 weeks
B. Total laryngectomy
C. Definitive radiation therapy alone
D. Induction docetaxel, cisplatin, and 5-fluorouracil (5-FU) followed by definitive radiation therapy
E. Partial laryngectomy with right radical neck dissection

The clinical management of HNSCC requires a multidisciplinary approach. Treatment is determined by the stage of disease, location of primary site, patient's age, comorbidity, and performance status.

HNSCC is divided into three general clinical categories: early-stage disease (stage I–II), locally advanced disease (stages III–IV), and recurrent or metastatic disease. The majority of HNSCC patients present with locally advanced disease requiring a multidisciplinary approach involving surgery, radiation (RT), and/or chemotherapy. Patients who present with early-stage disease can generally be treated with single-modality therapy, either surgery or RT, and do not usually require chemotherapy. RT is preferred in cases where surgical resection would lead to loss of organ function.

This patient has a T1aN0M0 (stage I) cancer of the glottic larynx. Such tumors rarely spread to lymph nodes or elsewhere and are considered highly curable. Larynx preservation should be the expectation and can be accomplished either with limited larynx preservation surgery or with RT. The rarity of spread to the lymph nodes would make a neck dissection unnecessary.

Case study 72.4

A 50-year-old schoolteacher presents with a 2-month history of hoarseness. Evaluation reveals a SCC involving both vocal cords, with fixation on the right, and two 2 cm enlarged right level II cervical lymph nodes that are hypermetabolic on PET scan. She would prefer to avoid surgery.

1. What treatment do you recommend?

A. Palliative chemotherapy with cetuximab, 5-FU, and cisplatin
B. A total laryngectomy with right cervical lymph node dissection
C. Radiation therapy and concurrent cisplatin
D. Radiation therapy and concurrent cetuximab
E. Radiation therapy alone
F. Induction cisplatin and 5-FU followed by definitive radiation therapy

This patient presents with a loco-regionally advanced T3N2b, stage IVa tumor, for which concurrent chemoradiotherapy (CCRT) is an effective definitive treatment. Historically, locally advanced laryngeal cancer was managed with a laryngectomy and postoperative RT. Surgical resection led to loss of organ function and significant morbidity. Over the years, the integration of chemotherapy with radiation has led to similar survival as surgical resection, but with the possibility of larynx preservation.

The first trial to test a laryngeal preserving approach was the Veteran Affairs Laryngeal Cancer Study group. In this trial, patients with stage III or IV laryngeal SCC were randomized to either organ preservation with chemotherapy and RT or to laryngectomy and RT. Organ preservation consisted of two cycles of cisplatin and fluorouracil chemotherapy followed by an assessment for response. Patients with a response received a third chemotherapy cycle followed by definitive RT. Patients in whom there was no tumor response or who had locally recurrent cancer after chemotherapy and radiation therapy underwent salvage laryngectomy. After a median follow-up of 33 months, the 2-year survival was similar in both groups, with larynx preservation possible in 64% of the patients in the chemotherapy and RT group.

The Radiation Therapy Oncology Group (RTOG) subsequently conducted the RTOG 91-11 trial to determine the optimal treatment schema for larynx preservation. Patients with stage III–IV laryngeal SCC were randomized between induction chemotherapy with cisplatin + 5-FU (PF) followed by RT, CCRT with cisplatin, or RT alone.

With a median follow-up of 10.8 years, the trial showed that CCRT significantly improved the larynx preservation rate over induction PF followed by RT ($P = 0.005$), and over RT alone ($P < 0.001$), whereas induction PF followed by RT was not better than treatment with RT alone ($P = .35$). Overall survival did not differ significantly between the groups, in large part due to the success of surgical salvage.

However, not all patients with advanced larynx cancer were eligible for this study or appropriate for laryngeal preservation. Those with high-volume T4 primaries (invasion >1 cm into the base of the tongue or penetration through the thyroid cartilage) are usually better served by a laryngectomy, as there is little rationale in attempting to preserve a nonfunctional larynx.

As this patient has no evidence of metastatic disease, treatment should be curative in intent, and palliative chemotherapy is not indicated. Laryngectomy can likely be avoided by administering CCRT, and cisplatin-based CCRT results in better organ preservation than the induction schedules or RT alone. Cetuximab and radiation have not been well tested in this setting.

Case study 72.5

A 58-year-old male presents with a 3-month history of progressively worsening odynophagia and dysphagia. Clinical and radiographic staging demonstrates a 5 cm right base-of-tongue lesion crossing midline, three enlarged level II right cervical lymph nodes measuring up to 2 cm in diameter, and an enlarged left cervical lymph node. Biopsy of the base of tongue lesion reveals SCC. PET scan reveals no evidence of distant metastasis.

1. You recommend which treatment intervention?

A. Definitive RT alone
B. Surgical resection alone
C. Induction docetaxel, cisplatin, and 5-FU followed by definitive radiation therapy
D. Definitive radiation therapy with concurrent cisplatin 100 mg/m^2 given every 3 weeks
E. Systemic therapy with cisplatin, 5 FU, and cetuximab

This patient presents with a loco-regionally advanced T3N2c, stage IVa tumor, and would be an excellent candidate for treatment with CCRT with curative intent. The treatment of locally advanced HNC has evolved over the years to a multidisciplinary approach, with organ preservation and treatment morbidity being factored into all treatment decisions. Because of the many vital structures in the head

(*Continued*)

and neck region, and the difficulties obtaining adequate surgical exposure, surgical resection of locally advanced disease is often not an attractive treatment option.

Multiple phase III trials have now established that the use of CCRT can produce excellent results while avoiding the need for surgical resection. The landmark Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC) demonstrated that patients treated with CCRT had an overall 8% 5-year survival benefit when compared to patients treated with RT alone with no chemotherapy. The group analyzed the effect of chemotherapy on HNSCC using data from 63 randomized clinical trials conducted between 1965 and 1993. No survival benefit was identified when the chemotherapy was given in an induction, or an adjuvant schedule. A follow-up report, which included an additional 24 randomized trials completed by 2000, yielded similar results. The clinical benefit was found to be significantly higher for patients treated with platinum-based chemotherapy. However, there was no difference between single-agent chemotherapy and multi-agent chemotherapy.

Although there are no phase III trials that have identified the best concurrent chemoradiotherapeutic regimen, the most frequently administered standard is high-dose cisplatin 100 mg/m^2 administered every 3 weeks on days 1, 22, and 43 with concurrent standard fractionation radiation. Recently, the RTOG 0129 trial demonstrated that two doses of cisplatin given on days 1 and 22 with an accelerated fractionation concomitant boost RT schedule produced similar results.

Surgical resection alone would not be sufficient based on the extent of disease and would most likely require postoperative RT or CCRT. Chemotherapy alone is a palliative treatment approach and not appropriate in this setting.

Case study 72.6

You are asked to see a 59-year-old female with a recently diagnosed poorly differentiated SCC of the pyriform sinus. Examination under anesthesia reveals a 6 cm mass arising from the pyriform sinus and invading the prevertebral fascia. Also noted is massive ipsilateral cervical lymphadenopathy with carotid artery encasement. PET scan is negative for any distant metastatic disease.

1. What treatment option would you recommend?

A. Palliative chemotherapy with fluorouracil, cisplatin, and cetuximab
B. Palliative radiation therapy alone
C. Induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by definitive radiation therapy alone.
D. Definitive radiation therapy with concurrent cisplatin
E. Surgical resection

Because of the involvement of prevertebral fascia, this patient has unresectable T4b disease. Other reasons for unresectability include skull base involvement, encasement of the carotid arteries, and involvement of mediastinal structures or other distant metastases. Patients with unresectable HNSCC without distant metastasis can still be treated with curative intent. The Intergroup 0126 trial demonstrated a clear survival advantage for patients treated with radiation and concurrent single-agent cisplatin, and this approach represents the standard of care for this stage of disease.

Case study 72.7

You have been consulted about a 61-year-old man who is recovering after primary resection and neck dissection for a 3 cm mobile tongue SCC. One resection margin was found to have microscopic tumor involvement not appreciated on the frozen section, and three of 38 regional nodes contained cancer. Extracapsular nodal spread was found in one of these nodes.

1. What do you recommend?

A. Postoperative radiation therapy
B. Postoperative radiation therapy and concurrent single-agent cisplatin
C. Postoperative radiation therapy and concurrent cetuximab
D. Postoperative cisplatin-based chemotherapy
E. Brachytherapy to the site of the positive margin

Because of the positive margin and extracapsular nodal extension, this patient is at increased risk for loco-regional recurrence and distant metastasis. The role of adjuvant chemotherapy alone following surgical resection was first addressed by the landmark trial conducted by the Head and Neck Intergroup testing the efficacy of sequential chemotherapy as an adjuvant to surgery and postoperative RT for patients with locally advanced but operable HNSCC. In the

trial, patients with completely resected HNSCC were randomized to receive either three cycles of cisplatin + 5FU followed by postoperative RT or postoperative RT alone. The study demonstrated no statistically significant survival benefit from the addition of adjuvant chemotherapy, although distant metastases were reduced. Subset analysis did, however, reveal that high-risk patients (i.e., adverse pathologic features), close margins (<5 mm), and extracapsular spread (ECS) were more likely to benefit from the adjuvant chemotherapy.

Two large cooperative group randomized trials were subsequently initiated by the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) to compare postoperative CCRT with cisplatin at a dose of 100 mg/m^2 given every 3 weeks (days 1, 22 and 43) to RT alone. Both studies reported benefit from the CCRT. A retrospective pooled analysis using the combined data from the trials revealed that positive surgical margins and ECS were the most significant prognostic factors for a reduction in loco-regional control and survival in patients with locally advanced HNSCC. The addition of cisplatin to postoperative RT in these patients led to improved survival. Based on this data, the current standard of care for patients with locally advanced HNSCC with positive surgical margins or ECS is postoperative concurrent cisplatin-based CRT.

2. In squamous cell head and neck cancer, concurrent radiation and cetuximab:

A. Will increase laryngeal preservation when compared to radiation therapy alone
B. Will improve survival when compared to radiation therapy alone
C. Will improve loco-regional control when compared to radiation and concurrent single-agent cisplatin
D. Has become the standard of care for patients with unresectable, loco-regionally advanced disease
E. Has been of optimal benefit when also given with concurrent single-agent cisplatin

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), is the only monoclonal antibody that has been approved by the US Food and Drug Administration for the treatment of HNSCC. This is based on a phase III randomized multicentered study that compared RT plus cetuximab with RT alone in the treatment of stage III or IV nonmetastatic HNSCC. There was an improvement in loco-regional control, progression-free survival, and overall survival (median duration: 49 vs. 29.3 months; $P = 0.03$) from the addition of cetuximab to RT. With the exception of the characteristic cutaneous toxicity of cetuximab (acneiform rash), the incidence of grade 3 toxicities, particularly mucositis, was not significantly higher in the group treated with cetuximab.

Cetuximab has not, however, been demonstrated to be superior or even equivalent to concurrent radiation and cisplatin. The RTOG 1016 trial is an ongoing phase III randomized trial that will attempt to answer this question by comparing cetuximab with concurrent RT, to cisplatin with concurrent RT in HPV-positive patients. Cetuximab has not been well tested in an organ preservation protocol. It also cannot be considered a treatment standard for patients with unresectable disease in the absence of a direct comparative trial with radiation and cisplatin. When added to radiation and concurrent cisplatin, no apparent benefit was identified in the RTOG 0522 trial.

Case study 72.8

This 65-year-old male was treated with definitive radiation and concurrent single-agent cisplatin for a T3N0M0 SCC of the right true vocal cord. A complete remission was achieved. He now presents, 14 months later, with biopsy-proven evidence of an advanced local recurrence with multilevel ipsilateral regional lymphadenopathy. Chest radiograph is normal, with no evidence of distant metastases.

1. What is the optimal management?

A. Palliative chemotherapy with a taxane-based regimen
B. Palliative chemotherapy with cisplatin and cetuximab
C. Concurrent re-irradiation with cetuximab
D. Laryngectomy with ipsilateral neck dissection
E. Best supportive care

Patients who have received organ-sparing treatment with CCRT who then develop recurrent disease should undergo surgical resection. In this patient with recurrent vocal cord SCC, laryngectomy with ipsilateral neck dissection is indicated. As there is no evidence of distant metastatic disease, treatment should be considered curative in intent. Palliative chemotherapy or best supportive care alone is not appropriate. Although there are ongoing clinical trials evaluating the role of re-irradiation in patients with locally recurrent disease, this is still an area of active investigation, and it should not be considered the standard of care.

Case study 72.9

This 60-year-old male smoker completed definitive cisplatin-based chemoradiotherapy 2 years ago for a T4N1M0 SCC of the base of the tongue. Although he continues to have loco-regional disease control, he now presents with a new asymptomatic 1.5 cm right lung nodule. Percutaneous needle aspirate reveals SCC. His PET scan demonstrates this lesion to be hypermetabolic, but it is otherwise negative.

1. How should he be treated?

A. Definitive radiation therapy alone
B. Palliative chemotherapy with 5-fluorouracil and cisplatin
C. Palliative chemotherapy with 5-fluorouracil, cisplatin, and cetuximab
D. Palliative treatment with cetuximab alone
E. Surgical resection

As smoking is a major risk factor for HNSCC, these patients are also at risk for second primary, smoking-related malignancy. The most common sites of second primary malignancies are the head and neck, lungs, and esophagus. A new isolated lung lesion in a patient with a history of HNSCC should be considered to be a second primary lung cancer unless proven otherwise. Surgical resection, with cure being the goal, is the best treatment option.

In the absence of other evidence of systemic disease, treatment should not be considered palliative, and there is no role for palliative chemotherapy. RT alone might be indicated in an elderly patient who cannot tolerate surgery, but not in this patient who is asymptomatic with no contraindication to surgery.

Case study 72.10

A 56-year-old Caucasian male with a 50-pack-year smoking history presents with a 3-month history of progressively worsening odynophagia and dysphagia and with the recent development of trace hemoptysis that led him to seek medical attention. Office examination and CT scan of the neck revealed a 5 cm mass arising from the hypopharynx with bilateral cervical lymphadenopathy. PET scan reveals multiple hypermetabolic bilateral lung nodules. A CT-guided biopsy of one of the lung lesions reveals metastatic SCC. The patient is in good medical condition, walks 3 miles three times a week, and works full-time as a sales representative.

1. What treatment option would you recommend?

A. Surgical resection of the primary lesion
B. Hospice care
C. Palliative radiation to the primary lesion
D. Palliative chemotherapy with cetuximab, cisplatin, and infusional 5- FU
E. Palliative chemotherapy with cisplatin and 5-FU

Patients with HNSCC who are found to have distant metastasis are, with rare exceptions, considered incurable. Frequently, they are treated with chemotherapy with the goal being palliation of symptoms and prolongation of survival. The patient's performance status and previous therapies are generally factored into the choice of chemotherapy. Various chemotherapeutic agents have been found to be active in HNSCC, some of which include platinum compounds, such as cisplatin and carboplatin; taxanes, such as paclitaxel and docetaxel; methotrexate; 5-FU; and cetuximab. Other agents with activity in HNSCC but less studied include pemetrexed, gemcitabine, etoposide, gefitinib, and capecitabine.

In chemotherapy-naïve patients with excellent performance status, the EXTREME trial suggested that the most successful chemotherapy regimen in the metastatic setting consists of carboplatin or cisplatin with infusional 5-FU and cetuximab. This study randomized 442 eligible patients with untreated recurrent or metastatic HNSCC to receive cisplatin or carboplatin plus 5-FU every 3 weeks with or without weekly cetuximab for a maximum of six cycles. Patients with stable disease who had received chemotherapy plus cetuximab continued to receive cetuximab until disease progression or unacceptable toxic effects, whichever occurred first. The addition of cetuximab to the 5FU–platinum-based regimen was found to significantly prolong the median overall survival from 7.4 to 10.1 months (hazard ratio for death, 0.80; 95% confidence interval, 0.64 to 0.99; $P = 0.04$). This is the only chemotherapy combination that has ever produced a survival benefit in patients with recurrent or metastatic HNSCC, and it has become a standard of care in otherwise fit patients.

In patients with a borderline performance status, or with prior exposure to one or several of these agents, other chemotherapy treatment options can be considered. Patients with a poor performance status should be treated with best supportive care alone, as they will likely not benefit from chemotherapy.

Case study 72.11

A 42-year-old Asian woman presents with recurrent right-sided otitis media. Evaluation reveals a mass in the nasopharynx with parapharyngeal extension and multiple right-sided cervical lymphadenopathy, the largest measuring 6.3 cm. Biopsy of this lymph node reveals undifferentiated nasopharyngeal carcinoma. No evidence of distant metastases was identified on further staging.

1. What treatment do you recommend?

A. Surgical resection with postoperative concurrent chemoradiotherapy with cisplatin
B. Definitive radiation therapy alone
C. Induction docetaxel, cisplatin, and fluorouracil chemotherapy, followed by radiation therapy
D. Palliative chemotherapy with a platinum-based regimen
E. Concurrent chemoradiotherapy with cisplatin, followed by adjuvant fluorouracil and cisplatin chemotherapy

Nasopharyngeal carcinoma (NPC) differs from other head and neck cancers in its epidemiology, etiology, pathology, and treatment. NPC is classified into several distinct histopathologic types: keratinizing SCC (WHO Type I); nonkeratinizing carcinoma, differentiated (WHO Type II) and undifferentiated (WHO Type III); and basaloid SCC. Although NPC shows a wide geographic variation in its incidence, the disease is endemic in East Asia and rare in the United States. A strong etiologic association with the Epstein–Barr virus has been identified.

Because of the location in the nasopharynx and close proximity to vital neurovascular structures, these tumors are not easily amenable to surgery. As such, radiation is the mainstay of treatment for patients with early-stage disease. In patients with more loco-regionally advanced tumors, in the absence of distant metastasis, combined modality therapy with CCRT followed with postradiotherapy adjuvant chemotherapy is the treatment standard. This is based on the Intergroup 0099 study, which randomized patients to RT alone versus chemotherapy with cisplatin 100 mg/m^2 on days 1, 22, and 43 during radiotherapy, followed by postradiotherapy chemotherapy with cisplatin 80 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2/d on days 1 to 4 administered every 4 weeks for three cycles. Both the 3-year progression-free survival rate (24% vs. 69%; $P < .001$) and 3-year overall survival rate (47% vs. 78%; $P = .005$) were markedly better in the patients given the chemotherapy.

Some clinical trials have suggested that induction chemotherapy rather than adjuvant chemotherapy might be of similar benefit. This is still an area of investigation, however, and should not be considered the standard of care.

If this patient had metastatic disease, then a platinum-based regimen would have been indicated. Possible combinations include cisplatin and 5-FU (PF); paclitaxel and cisplatin (TP); gemcitabine and cisplain (GP); paclitaxel, cisplatin, and 5-fluororacil (TPF); or bleomycin, cisplatin, and 5-FU (BPF). All these regimens have similar progression-free and overall rates.

Case study 72.12

A 55-year-old female presents with a 3 cm left parotid mass, and left facial nerve weakness. A parotid fine needle aspirate had been obtained by an outside surgeon and demonstrated adenoid cystic carcinoma (ACC). There was no evidence of other disease spread.

1. What treatment do you recommend?

A. Cyclophosphamide, doxorubicin, and cisplatin chemotherapy
B. Total parotidectomy, with facial nerve sacrifice followed by radiation therapy
C. Parotidectomy with facial nerve preservation followed by doxorubicin, cyclophosphamide, and cisplatin therapy
D. Radiation alone
E. Radiation and concurrent cisplatin chemotherapy

Salivary gland tumors include a wide variety of histologic types and can be either benign or malignant. The most common tumor site is the parotid gland, but neoplasms of the submandibular and sublingual glands, as well as the minor salivary glands (located throughout the submucosa of the mouth and upper aerodigestive tract), are not infrequent. Surgery is the cornerstone of management when the tumor is resectable, and there is no evidence of distant metastatic disease. The extent of surgery and the need for adjuvant treatment are dependent on the histology, the salivary gland involved, and the location within the gland. Effort is made to preserve the facial nerve, unless it is nonfunctional or directly involved by the malignant tumor. Postoperative radiation is also recommended in patients with high-risk features, including high-grade and advanced-stage lesions, positive surgical margins, and skin or nerve invasion.

This patient presents with an ACC, a low-grade malignant tumor of the salivary gland, with involvement of the facial nerve as evidenced by facial nerve dysfunction. As such, a

(*Continued*)

total parotidectomy with facial nerve sacrifice followed by radiation therapy is the optimal treatment. Chemotherapy alone or chemoradiotherapy does not have an established role in the definitive management of this disease.

This same patient undergoes the recommended definitive treatment but is then lost to follow-up. She presents 10 years later and is found to have six 1–3 cm bilateral pulmonary nodules. Biopsy of one of these nodules is positive for metastatic ACC. She is asymptomatic, no other metastatic disease can be found, and she is otherwise healthy. Liver, renal, and bone marrow function appears to be normal.

2. Which treatment do you recommend for her?

A. Expectant management with no anti-neoplastic therapy
B. Chemotherapy with cisplatin, doxorubicin, and cyclophosphamide
C. Imatinib therapy
D. Surgical resection of these multiple nodules
E. Cetuximab therapy

The patient presents with metastatic ACC. The most common sites for metastases from salivary gland malignancies are the lung, liver, and bone.

Distant metastases of ACC of the salivary glands occur most often in the lungs, and these patients tend to have better survival than patients with metastasis in other organs.

The natural history of metastatic disease of the salivary gland is variable, with some patients having an indolent, nonprogressive course for months to years, while others have rapidly progressive disease. Resection of a solitary site might be curative in select patients. But patients with multiple metastases are treated with palliative intent.

In asymptomatic patients with a metastatic low-grade ACC, watchful waiting is appropriate until there is evidence of disease progression or development of symptoms. In patients with more aggressive histologies such as high-grade adenocarcinoma or mucoepidermoid, chemotherapy may be indicated for symptom palliation. There are few prospective clinical trials of chemotherapy in advanced ACC. The optimum regimen is unclear, but should chemotherapy be considered, the most frequently reported regimen is cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and cisplatin 50 mg/m^2 (CAP).

Although multiple molecular targets have been identified in salivary gland malignancies such as c-kit tyrosine kinase in patients with ACC and human epidermal growth factor receptor 2 (HER2) in patients with salivary duct cancers, clinical investigation of targeted therapies has been disappointing.

Case study answers

Case study 72.1

Question 1: Answer C

Case study 72.2

Question 1: Answer E

Case study 72.3

Question 1: Answer C

Case study 72.4

Question 1: Answer C

Case study 72.5

Question 1: Answer D

Case study 72.6

Question 1: Answer D

Case study 72.7

Question 1: Answer B
Question 2: Answer B

Case study 72.8

Question 1: Answer D

Case study 72.9

Question 1: Answer E

Case study 72.10

Question 1: Answer D

Case study 72.11

Question 1: Answer E

Case study 72.12

Question 1: Answer B
Question 2: Answer A

Selected reading

Al-Sarraf M, LeBlanc M, Giri PG, *et al*. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998;16(4):1310–7.

Ang KK, Harris J, Wheeler R, *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35.

Bonner JA, Harari PM, Giralt J, *et al*. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–78.

Forastiere AA, Zhang Q, Weber RS, *et al*. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845–52.

Pignon JP, *et al*. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4–14.

For further information on this area please also consult Chapters 107, 117, 127, 132, 137, and 138

CHAPTER 73

Endocrine malignancies

Ann W. Gramza
NIH/NCI Endocrine Oncology Branch, Bethesda, MD, USA

Case study 73.1

A 48-year-old female with MEN 2A and metastatic medullary thyroid cancer (MTC) is referred for consideration of systemic therapy. She is euthyroid and asymptomatic, and her calcitonin has been stable for the past year. Imaging studies reveal a 1.6 cm mediastinal lymph node and multiple subcentimeter pulmonary lesions. Her bone scan is negative. Several of the lesions have increased by 2–3 mm since imaging done 2 years prior.

1. What is the best course of management for this patient?

A. Perform an I-131 diagnostic scan to determine if I-131 is a treatment option.
B. Repeat imaging studies and calcitonin in 6 months.
C. Vandetanib
D. Cabozantinib
E. Increase levothyroxine for TSH suppression.

Given the overall stability of this patient's disease and lack of symptoms, the best course of management is to repeat her imaging and calcitonin in 6 months. If her disease has been stable for several years, it may be appropriate to image her yearly. Vandetanib and cabozantinib are both FDA approved for unresectable locally advanced or metastatic MTC that is progressing or symptomatic. I-131 and TSH suppression are treatment modalities for differentiated thyroid cancers such as papillary and follicular thyroid cancer.

2. Vandetanib, but not cabozantinib, improves overall survival for patients with metastatic medullary thyroid cancer?

A. Yes
B. No

Both of these tyrosine kinase inhibitors (TKIs) were approved for MTC based on improvements in progression-free survival. Neither drug has provided a complete response or improved overall survival. Both TKIs are associated with toxicities, which can be severe. Therefore, patients with metastatic MTC should be treated with a TKI only if they have progressive or symptomatic disease, such that the benefit of therapy has the potential to outweigh the risk. Cabozantinib and vandetanib have not been compared in a randomized trial; therefore, it is unknown which is the superior agent and which should be used as first-line therapy.

Case study 73.2

A 52-year-old man presents with Cushing's syndrome is found to have an adrenal mass. An adrenalectomy reveals a 4.7 cm low-grade adrenocortical carcinoma with capsular invasion but negative margins, no invasion of adjacent organs or vessels, and no positive lymph nodes. There are no distant metastases.

1. What should be done next?

A. Adjuvant mitotane alone
B. Adjuvant mitotane and external beam radiation to the adrenal fossa
C. Adjuvant mitotane and streptozotocin

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

D. External beam radiation to the adrenal fossa alone
E. Observation with imaging and biomarkers in 3 months

In this case, which presents a low-risk patient with stage I disease, most experts would recommend observation alone. There are several reports demonstrating the benefit of adjuvant mitotane for patients with resected stage I to III disease; however, none are prospective randomized clinical trials. The decision to treat with adjuvant mitotane is controversial, particularly for those with low-risk disease (low grade, small tumor, complete resection, etc.). Mitotane is associated with toxicities such as adrenal insufficiency, hypogonadism, and hypothyroidism, and the clear benefit for patients with low-risk disease is unknown. An international randomized phase III trial is currently underway for patients with low- and intermediate-risk disease to address this question.

Multiple choice questions

1. True or false? For patients with metastatic adrenocortical carcinoma (ACC) not amenable to radical surgical resection, systemic therapy with etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) improves overall survival when compared to treatment with streptozocin and mitotane (Sz-M).

A. True
B. False

This question refers to the results of the largest prospective, randomized trial of patients with ACC, in which 304 patients were randomized to EDP-M or Sz-M. For first-line therapy, patients in the EDP-M arm had a higher response rate than those in the Sz-M arm (23.2% vs. 9.2%; $P < 0.001$) and longer median progression-free survival (5.0 months vs. 2.1 months; $P < 0.001$), with similar rates of adverse events. However, there was no statistically significant improvement in overall survival. Patients with disease progression received the alternate regimen as second-line therapy. The response to EDP-M as second-line therapy could have affected the overall survival analysis.

Case study 73.3

A 37-year-old woman has a fine needle aspiration of both a thyroid mass and lung nodule, and she is diagnosed with metastatic papillary thyroid cancer. She has approximately 15 bilateral pulmonary nodules, the largest of which is 0.6 cm.

1. What should be the first step in her management?

A. Radioactive iodine (RAI) treatment
B. Diagnostic RAI whole-body scan to evaluate sites of disease
C. Total thyroidectomy and lymphadenectomy
D. Treat with sorafenib

Unlike most malignancies, resection of the primary tumor and lymph nodes should be performed in all patients with metastatic differentiated thyroid cancer. These patients are still potentially curable with total thyroidectomy, lymphadenectomy, and subsequent RAI treatment. Complete responses are seen in approximately 45% of patients. This is particularly true for young patients with multiple pulmonary metastases.

2. The patient undergoes a thyroidectomy and subsequent RAI treatment. Unfortunately, her posttreatment RAI scan shows no uptake in her pulmonary lesions. She is referred to medical oncology for treatment with a kinase inhibitor. The best recommendation is:

A. TSH suppression therapy, then restage in 3 months with CT scans
B. Doxorubicin-based systemic chemotherapy
C. Treat with sorafenib
D. Hospice

This patient received the appropriate initial therapy of thyroidectomy and adjuvant RAI for ablation of the thyroid remnant and treatment of her pulmonary metastases. After RAI, an uptake scan is performed to assess degree of uptake in the remnant and/or metastases. If the scan is negative, the lesions will not respond to RAI. Despite this, many patients with non-RAI avid disease will maintain stable or slowly progressive metastatic disease with TSH suppression alone. The kinase inhibitor sorafenib is now approved by the FDA for the treatment of locally recurrent or metastatic, progressive differentiated thyroid cancer that no longer responds to RAI therapy. This approval was based on improved progression-free survival when treated with sorafenib (10.8 months) compared to placebo (5.8 months). There is no known overall survival advantage. Therefore, patients should only be treated with sorafenib if they have progressive or symptomatic RAI-refractory disease. Given that this patient is newly diagnosed, we cannot yet assess the pace of her disease. Therefore, treatment with supratherapeutic doses of levothyroxine and restaging in 3 months are the correct answer. If this patient develops symptomatic disease or significant radiographic progression, treatment with sorafenib should be considered.

Case study 73.4

A 47-year-old male is admitted to the hospital with hypertensive urgency. His medical history is significant for a left adrenalectomy at age 35 for pheochromocytoma. Evaluation reveals a plasma metanephrine level of 950 nmol/L (normal: <0.5 nmol/L) and a CT scan showing two nodules in the right adrenal gland, periaortic and right iliac adenopathy, and multiple hepatic nodules. A biopsy confirms metastatic pheochromocytoma.

1. After controlling his hypertension, the next step in his management should be:

A. Sunitinib therapy
B. Cyclophosphamide, vincristine, and dacarbazine (CVD) chemotherapy
C. I-131 metaiodiobenzylguanidine (MIBG) uptake scan
D. Octreotide therapy

Malignant pheochromocytoma (pheo) is very rare, as 90% of pheos are benign. Patients can develop metastatic disease up to 20 years after the initial diagnosis. The presence of metastases defines the pheo as malignant, as no pathologic features can differentiate malignant from benign disease. Metastatic disease is ideally treated with surgery or local therapy. When this is not possible, a MIBG scan should be performed to assess for MIBG uptake. MIBG is structurally similar to noradrenaline and is taken up by chromaffin cells. Approximately 60% of tumors will take up MIBG, and can then be treated with radiolabeled I-131-MIBG. Patients treated with I-131-MIBG can achieve objective responses or stable disease in approximately 75% of cases. CVD has produced objective responses of 25–56% in retrospective series, but is typically reserved for patients who have failed or are not candidates for MIBG therapy, have rapidly progressive disease, or have predominately bone metastases. Bone lesions typically respond poorly to MIBG. Sunitinib has shown activity in case studies, and further evaluation is ongoing.

2. The primary cause of morbidity and mortality related to parathyroid carcinoma is:

A. Local invasion
B. Bone metastases
C. MEN2-related malignancies
D. Hypercalcemia
E. Hypocalcemia

Parathyroid carcinoma is extremely rare, with an estimated incidence of approximately 5 per 10 million according to 1988–2003 SEER data. Benign parathyroid hyperplasia is associated with MEN 2A, not parathyroid carcinoma. Parathyroid carcinoma is treated with surgical resection of the parathyroid mass and adjacent involved tissues. Most patients will recur, but disease is often indolent, with 10-year survival rates close to 70%. Recurrent or metastatic disease is treated with surgical resection when possible. There is no standard chemotherapy for this malignancy, and experience is limited to case reports. The mainstay of treatment is controlling the hypercalcemia. Therapy consists of aggressive intravenous hydration, bisphosphonates, and calcimimetics such as cinacalcet. Calcimimetics decrease PTH production, resulting in lower serum calcium concentrations.

Case study 73.5

A 72-year-old male presents with a rapidly enlarging neck mass. He notes hoarseness, dysphagia, and a 15-pound weight loss over the past month. Imaging reveals a heterogeneous mass of the left thyroid lobe measuring 5 cm with bilateral cervical lymphadenopathy, osseous lesions of the manubrium and right anterior first and second ribs, and two subcentimeter pulmonary nodules. His ECOG performance status is 1. A core needle biopsy is done, revealing anaplastic thyroid cancer.

1. What is the best next step in his management?

A. External beam radiation to the thyroid mass and sternum
B. External beam radiation to the thyroid mass and sternum with concurrent doxorubicin
C. Surgical debulking of thyroid mass
D. Carboplatin and paclitaxel chemotherapy

Anaplastic thyroid cancer is an aggressive malignancy with a nearly 100% disease-specific mortality and average survival of 3 to 6 months. If possible, the patient should be referred to a specialized center for discussion of treatment options and for evaluation of potential resectability. There are no prospective studies defining the optimal treatment for these patients. Retrospective series have shown that complete gross surgical resection for patients with resectable local disease or disease confined to the thyroid may improve outcomes. Some experts recommend adjuvant chemotherapy and radiation following a complete resection; however, there are no prospective data to support this. For patients

with unresectable and/or metastatic disease, external beam radiotherapy alone is the best treatment option. The addition of chemotherapy to radiation will add toxicity without providing a known benefit. The purpose of radiation in this instance is to delay local progression, relieve symptoms from the primary tumor, and delay or prevent asphyxiation as the cause of death. Regarding chemotherapy, paclitaxel is the most active single-agent chemotherapy, but patients should be referred to clinical trials when possible.

3. What is the most common genetic mutation found in papillary thyroid cancer (PTC)?

A. RET
B. NRAS
C. BRAF
D. APC
E. TP53

Somatic mutations of the *BRAF* gene resulting in $BRAF^{V600E}$ are found in approximately 45% of resected PTC. While several studies have correlated $BRAF^{V600E}$ with aggressive clinicopathologic criteria, it is unlikely to be the only factor to confer a poor prognosis in a small percentage of patients, as PTC has a 5-year survival of >95%. One large retrospective study of 1849 PTC patients found that $BRAF^{V600E}$ was strongly associated with thyroid cancer mortality. However, this association was no longer statistically significant after adjusting for known high-risk features such as distant metastases, lymph node involvement, and extrathyroidal extension. $BRAF^{V600E}$ testing is widely available, but there are no data supporting routine testing to determine a patient's prognosis or therapeutic course. Clinical trials for advanced PTC patients with BRAF-mutated tumors are currently underway and may help to provide information regarding the clinical significance of this mutation.

Case study answers

Case study 73.1

Question 1: Answer B
Question 2: Answer B

Case study 73.2

Question 1: Answer E

Case study 73.3

Question 1: Answer C
Question 2: Answer A

Case study 73.4

Question 1: Answer C

Case study 73.5

Question 1: Answer A

Multiple choice answers

Question 1: Answer B ("False")
Question 2: Answer D
Question 3: Answer C

Selected reading

Fassnacht M, Terzolo M, Allolio B, *et al*. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012;366(23):2189–97.

National Comprehensive Cancer Center Network (NCCN). NCCN clinical practice guidelines in oncology: thyroid cancer. Version 2.2014. Retrieved from: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

National Comprehensive Cancer Center Network (NCCN). NCCN clinical practice guidelines in oncology: neuroendocrine tumors. Version 1.2014. Retrieved from: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Wells SA, Jr., Robinson BG, Gagel RF, *et al*. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30(2):134–41.

Xing M, Alzahrani AS, Carson KA, *et al*. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013;309(14):1493–501.

CHAPTER 74

Methodological and practical challenges for personalized therapies in non-small-cell lung cancer

Ignacio I. Wistuba

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction

Lung tumors are the result of a multistep and complex process in which normal lung cells accumulate genetic and epigenetic abnormalities and evolve into cells with malignant biological capabilities. The identification of an oncogene, or other specific products required by the tumor cells for sustained growth (oncogene addiction), followed by administration of a specific inhibitor to the target are the basis of personalized cancer treatment. Recent advances in understanding the complex biology of lung cancer, particularly oncogene addictions, have provided new treatment targets and allowed the identification of subsets of tumors with unique molecular profiles that can predict response to therapy in this disease. The successful development of personalized therapy depends on the identification of a specific molecular target that drives cancer growth and the subsequent validation of a clinically applicable biomarker molecular test. In this process, the analysis of molecular changes is becoming increasingly important and poses multiple challenges to adequately integrate both routine histopathology analysis and molecular testing into the clinical pathology diagnosis for selection of therapy. In non-small-cell lung carcinomas (NSCLCs), this is best exemplified by treating patients with tyrosine kinase inhibitors (TKIs) when their tumors harbor activating epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements.

In this chapter, there is description and discussion of important methodological and practical issues that represent significant challenges for personalized therapy of NSCLC. Several of the recommendations discussed in this chapter have been obtained from the recently published evidence-based *Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors* by the College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (AMP).

1. Which molecular test should be performed in a lung tumor specimen?

In lung adenocarcinoma, *EGFR* mutation and *ALK* and *ROS1* fusions should be tested to select targeted therapy against these three targets. A similar recommendation is valid for mixed tumors with an adenocarcinoma component and for NSCLC not otherwise specified (NOS) (Figure 74.1). In squamous cell carcinoma, although there are some promising molecular targets (e.g., *DDR2* and *FGFR1*), there is no current validated molecular testing to be recommended.

NSCLC represents over 80% of lung cancers. Adenocarcinoma (40%) and squamous cell carcinoma (30%) are the most frequent histologies (Figure 74.1), but there are also less frequent types, including large-cell, adenosquamous (a mixture of adenocarcinoma and squamous cell carcinoma differentiations), and sarcomatoid carcinomas. NSCLC NOS corresponds to tumors in which adenocarcinoma, squamous cell carcinoma, and neuroendocrine differentiation are not detected by histology and immunohistochemical analyses.

Molecular targets in lung adenocarcinoma

At least two different major pathways have been identified in its pathogenesis, a smoking-associated activation of the *KRAS* signaling, and non-smoking-associated activation of the *EGFR* signaling (Table 74.1). Lung adenocarcinomas

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

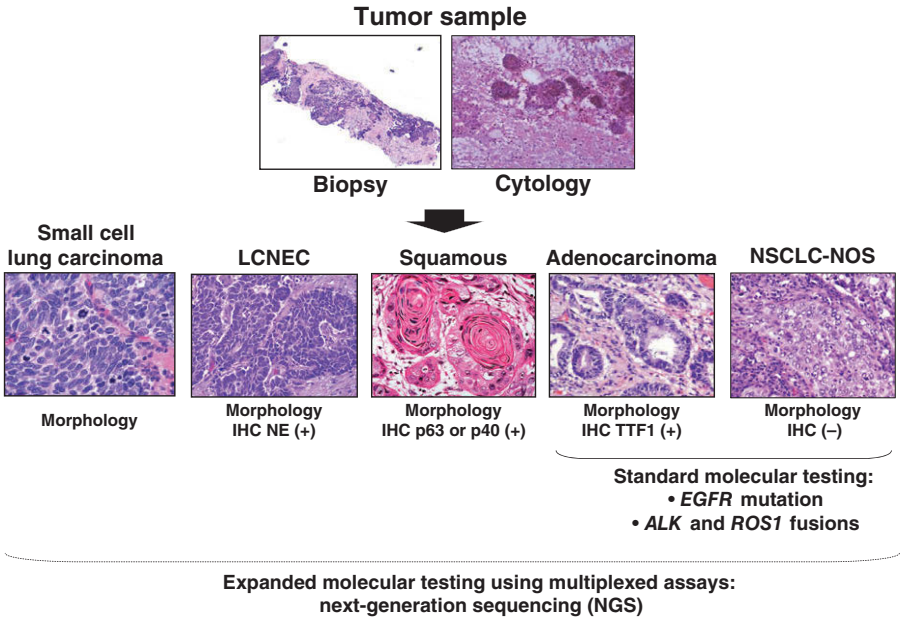


Figure 74.1 Microphotographs of representative examples of core needle biopsy (biopsy) and fine needle aspiration (cytology) specimens frequently available for histology diagnosis of advanced lung cancer. In lung tumors, the diagnosis of the histology is the first step. In tumors with poorly differentiated histology and with negative immunohistochemistry (IHC) markers, the diagnosis of NSCLC not otherwise specified (NOS) is performed. However, a more specific histology diagnosis should be reached by using a limited panel of IHC: neuroendocrine markers (NEs) are needed for the diagnosis of large cell neuroendocrine carcinoma (LCNEC) histology; TTF1 a is marker of adenocarcinoma histology; and p63 and p40 are markers of squamous cell carcinoma histology. After assessment of tissue quality for molecular testing, the sample should be submitted for a panel of molecular tests. In lung adenocarcinoma and NSCLC-NOS, the standard testing includes *EGFR* mutation, and *ALK* and *ROS1* fusions. When available, multiplexed assays can be applied to maximize the utilization of small-tissue and cytology samples, including the newer next-generation of sequencing methodologies. (Color plate 74.1)

Table 74.1 Summary of molecular abnormalities associated with lung adenocarcinoma and squamous cell carcinoma histologies.

Gene	Molecular change	Adenocarcinoma	Squamous cell carcinoma
EGFR	Mutation	10–40%	Very rare
HER2	Mutation	2–4%	Very rare
	Amplification	8%	2%
EML4–ALK	Fusion	5–15%	Very rare
KIF5B–RET	Fusion	2%	Not reported
ROS1	Fusion	<1%	Not reported
KRAS	Mutation	10–30%	Very rare
BRAF	Mutation	1–3%	Very rare
FGFR1	Amplification	Not reported	20%
DDR2	Mutation	Not reported	4%
PIK3CA	Amplification and CNG	2–6%	30%
	Mutation	2–6%	2–6%

CNG, copy number gain.

arising in never or light smokers are characterized by significantly higher frequencies of a series of targetable oncogene abnormalities, including *EGFR* tyrosine kinase (TK) domain activating mutations and *EML4–ALK* (2;5)(p23q35) translocation. Recently, two additional potentially targetable gene translocations, *ROS1* (6q22; *SLC34A2–ROS1* and *CD74–ROS1*) and *KIF5B–RET* (10p;11q)(p11.22; q11–21), have been identified in lung adenocarcinoma from never and ever smokers.

Mutations of *EGFR* occur in ~24% of adenocarcinomas and up to 60% in tumors from never smokers. The mutations are limited to the first four exons of the TK domain (exons 18–21). The most frequent mutations are in-frame deletions in exon 19 (44% of all mutations) and missense mutations in exon 21 (41% of all mutations). In addition, in-frame duplications and insertions occurring in exon 20 have been described in about 5% of the mutant cases, and rare missense mutations occur in multiple sites. *EGFR* mutations occur predominantly in adenocarcinoma (~20–48%; vs. other NSCLC histologies: ~2%), and are more frequent in never smokers (54%; vs. ever smokers: 16%) and female patients (49%; vs. male patients: 19%). *EGFR* mutations comprise the most important criterion to select patients for EGFR TKI therapy in lung cancer.

*A*berrant *ALK* expression has been identified in a subset (~6%) of lung adenocarcinomas, and this abnormality consists in the formation of a fusion transcript with cell-transforming activity, which is the product of a inverted translocation of the *EML4* gene located at chromosome 2p21 and the *ALK* gene located at 2p23. *EML4–ALK* translocations have multiple distinct isoforms (up to nine) with demonstrated transforming activity. *EML4–ALK* translocation has been detected, particularly in patients with never or light smoking history, and has been associated with young onset of tumor. Histologically, *EML4–ALK*-rearranged adenocarcinomas have been described to have a predominantly solid pattern with signet ring cells, but also combined acinar and cribiform patterns have been described in these tumors. *ALK* fusion is the criterion to select patients for ALK-targeted therapy (crizotinib) in lung cancer. In addition, tumors with *ROS1* fusion have also shown a higher response to therapy with crizotinib.

Molecular targets in squamous cell carcinoma

This tumor type has been histologically and molecularly less studied than the adenocarcinoma histology (Table 74.1). Squamous cell carcinoma also harbors genetic abnormalities resulting in activation of oncogenes, including *EGFR-vIII* (deletion of exons 2–7) and *DDR2* mutations, and *FGFR1* (8p12) gene amplification. However, these molecular targets are still under clinical investigation. Amplification of *FGFR1* (chromosome 8p11–12) is a driver event in NSCLC, predominantly in squamous cell carcinoma histology subtype (~20%) compared with adenocarcinomas (1–3%). Mutations of the TK *DDR2* have been described in 4% of lung squamous cell carcinomas. Tumors with *FGFR1* amplification and *DDR2* mutation have demonstrated some sensitivity to FGFR1 TKI and dasatinib, respectively.

2. When should a lung tumor specimen be tested for molecular markers?

Molecular testing should be performed in the tumor tissue specimen at the time of pathological diagnosis, particularly in patients with advanced metastatic (stage IV) tumors. In patients with chemorefractory tumors, a new tissue specimen is warranted for molecular testing to determine molecular markers associated to resistance to therapy.

It has been demonstrated that for patients with stage IV tumors, activating *EGFR* mutations, and *ALK* and *ROS1* fusions, timely diagnosis is critical and molecular testing should be initiated as soon as a histology diagnosis has been established. In some institutions, the test order is performed by the treating physician, but in others there is a reflex testing in place. The later is a testing policy that does not require a clinician order for each case and the testing is automatically ordered when the histological diagnosis is established.

In patients with localized NSCLC (stages I, II, and III) who are not initially treated with targeted therapies, the molecular testing of the surgical specimen could be beneficial since more tissue sample is available for the various testing. However, our growing understanding of cancer biology of NSCLC, particularly the molecular evolution of tumors during local progression and metastasis, and the identification of molecular abnormalities developed after resistance to TKI therapies, emphasizes the importance of characterizing the molecular abnormalities of the disease at every stage of its evolution, including recurrent tumors, chemorefractory disease, and tumors progressing at the time of receiving targeted therapy. Therefore, molecular testing of advanced metastatic NSCLC is important to sample and analyze the tumor specimen at each time point of clinical decision making.

3. What are the specimen requirements for molecular testing?

Although tissue specimens are preferable, both tissue (biopsy) and cell (cytology) specimens are suitable for molecular testing. The critical requirements are appropriate sample processing and the presence of an adequate amount of viable tumor cells. Tissue and cytology formalin-fixed and paraffin-embedded (FFPE) specimens, or fresh frozen or alcohol-fixed samples, are suitable for molecular testing. For testing of cytology specimens, cell blocks are preferred over smear samples.

The biopsy and cytology samples available for molecular testing in advanced metastatic tumors are likely to be small specimens, including core needle biopsies (CNBs) and/or fine needle aspiration (FNA), which may limit molecular and genomic analysis with currently available methodologies and technologies. There are several scientific and methodological challenges, as well as practical barriers, to widespread molecular testing using lung tumor biopsy and cytology specimens. The ideal specimens for molecular testing would be tumor tissues obtained fresh and followed by immediate snap freezing. However, these samples are usually available only for research purposes in academic centers and utilized for discovery purposes.

In pathology labs, the diagnostic clinical tumor tissue specimens (e.g., CNBs, bronchoscopy samples, and surgical resections) are fixed in formalin and embedded in paraffin for histology process. Both formalin fixation and paraffin embedding compromise the integrity of protein and nuclei acids (RNA and DNA) for molecular testing, particularly when nonbuffered formalin is utilized and the specimens are fixed in formalin for greater than 24 hours. The cytology specimens (e.g., bronchial brushes, bronchoalveolar lavages, pleural fluids, and FNAs) are usually fixed in alcohol, which is optimal for preservation of nucleic acids. When the cytology specimen has abundant material, the sample can be fixed in formalin and processed as a tissue specimen (cell block) to obtain histology sections. Although tissue specimens are preferable for molecular testing, cytology samples with abundant malignant cells can be successfully used for molecular testing.

The requirement of malignant cell content for adequacy for molecular testing varies between laboratories and testing platforms; however, a minimum of 50 viable cells per tissue section is required for *ALK* fluorescent in situ hybridization (FISH) testing, and at least 500 cells are needed for DNA extraction (~200 ng of DNA) and mutation analysis of *EGFR* mutations. For DNA extraction for mutation analysis, at least 20% of malignant cell content is needed for proper identification of mutations. In some laboratories, the utilization of laser capture microdissection (LCM) techniques is advocated; however, LCM is a time-consuming method that usually yields a low amount of DNA.

4. How do you integrate molecular testing into the tumor tissue histology diagnosis workout?

The handling of the biopsy and cytology specimens for histology and subsequent molecular testing requires thoughtful prioritization of the utilization of the sample to prevent the loss of tissue in less important analysis that the molecular testing requires for selection of therapy. A limited immunohistochemical (IHC) workout should be implemented in the histological diagnosis of lung cancer to preserve enough tissue for molecular testing.

In lung cancer, the use of IHC markers is currently used for histopathology diagnosis and classification of tumors, particularly when small tissue specimens are examined. IHC markers are frequently used by pathologists to subtype clinically NSCLC: cytokeratin 7 and TTF1 are positive in most adenocarcinomas, while p63, p40, and cytokeratines 5/6 are positive in most squamous cell carcinomas (Figure 74.1). There is consensus in the pathology community that a limited IHC workout (TTF-1, and p63 or p40) should be implemented in the histological diagnosis of lung cancer to preserve enough tissue for molecular testing. For molecular testing, it is crucial that a pathologist determines if the amount of malignant cells available in the specimen is adequate for nuclei acid extractions and also for histology section-based molecular tests (e.g., FISH).

5. What methods should be used for molecular testing?

Testing laboratories should use any validating testing method; however, multiplexed methodologies are preferred over individual (uniplex) assays.

The need for analysis of multiple molecular and genetic changes in small biopsy and cytology specimens is prompting the scientific community and the molecular pathology labs to develop multiplexed approaches for molecular testing of small tumor samples. These multiplexed assays can simultaneously determine the mutation, translocation, and expression status of many genes. These methodologies are useful to maximize the utilization of small diagnostic lung tumor tissue and cytology specimens (Figure 74.1).

Mutation testing

Direct nucleic acid sequencing previous polymerase chain reaction (PCR) amplification of extracted DNA is the most used technique for gene mutation analysis. There are several sequencing methods available for mutation analysis applied to DNA extracted from tumor tissue and cell specimens, especially for FFPE samples. The current PCR-based sequencing mutation analysis methods can be divided into uniplex (e.g., Sanger sequencing and pyrosequencing) and multiplexed (e.g., matrix-assisted laser desorption ionization time-off light mass spectrometry and primer extension assay) methodologies. While in the uniplex method, one hotspot sequence is examined at a time, in the multiplexed technique multiple hotspot mutations are examined simultaneously. Sanger sequencing is the most used sequencing method to detect *EGFR* mutations in lung cancer. The main disadvantage is the relatively low sensitivity of mutant alleles, estimated to be ~20% of mutant versus wild-type alleles. Currently, multiplexed methodologies, including next-generation

sequencing (NGS) platforms, are available in several testing laboratories. The analysis of EGFR normal or mutant protein by IHC is not currently recommended as a molecular test for the indication of EGFR-targeted therapies in lung cancer.

Fusion testing

The standard methodology to assess *EML4–ALK* fusion in lung cancer tumors is FISH using a "break-apart" probe. Samples are considered to be *EML4–ALK* fusion FISH-positive if more than 15% of scored tumor cells have split *ALK* 5′ and 3′ probe signals or have isolated 3′ signals. Also, a similar FISH assay has been developed for *ROS1* fusion detection. There are some reports suggesting that ALK protein expression assessment by IHC correlates with the presence of *EML4–ALK* fusion, and there are ongoing studies testing ALK protein expression as a screening method for gene fusions.

Next generation of sequencing (NGS) testing

The rapid development of technologies for large-scale sequencing has facilitated high-throughput molecular analysis holding various advantages over traditionally sequencing, including the ability to fully sequence large numbers of genes in a single test and simultaneously detect deletions, insertions, copy number alterations, translocations, and exome-wide base substitutions (including known hotspot mutations) in all known cancer-related genes. Currently, NGS platforms, including whole genome, whole exome, and targeted gene sequencing, represent emerging diagnostic methodologies for the detection of oncogene fusions and mutations in tumor tissue specimens, including FFPE samples.

6. How can you have test results in a timely fashion?

It has been recommended that molecular testing results (*EGFR* mutation and *ALK* and *ROS1* fusion) should be available in 2 weeks (10 working days).

A timely reporting of the molecular test results represents one of the most important challenges in targeted therapy in lung cancer. The recommendation of 2 weeks for reporting since the specimen is received in the testing laboratory was based on an expert opinion of members of the CAP–IASLC–AMP panel. This seems a very reasonable and achievable timeline for routine molecular testing, which includes *EGFR* mutation and *ALK* and *ROS1* fusions. However, when a larger of genetic alterations, mostly gene mutations, are examined by using multiplexed platforms, particularly the newer NGS platforms, the 2-week period becomes more difficult to achieve since they require exhaustive bioinformatics analysis.

However, the most challenging issues to report molecular tests in a timely fashion is the availability of the tumor tissue sample (e.g., FFPE tissue or cell block, and unstained histology sections) in the testing labs. In many instances, the tissue specimens are stored in different locations in the pathology labs, and retrieval of the specimen and review of the material by a pathologist take a long period of time.

7. How should molecular testing be reported?

The report should include the molecular test results and a brief interpretation that is readily understandable by clinicians and pathologists.

It has been recommended that the report should include at least the following information for adequate interpretation by clinicians: (i) the name of any clinically relevant mutation or gene fusion should be identified; (ii) incidental findings of uncertain significance should be clearly presented as such; (iii) for multiplexed assays, the results should be presented in a summary format; (iv) histopathological assessment of tissue adequacy (e.g., malignant cell content for mutation testing, and number of cells examined for FISH analysis); and (v) a brief technical section indicating the basic methodology utilized (e.g., for mutation analysis, the genes and exome sequenced). In cases of inconclusive results, the report should indicate an interpretation of the reason (e.g., limited tissue sample, poor tissue or cell fixation, and inadequate quality of the DNA) of why the test was inconclusive, and suggestions of the requirements (e.g., another tissue blocks from the same biopsy, or a new biopsy) that would yield a successful report.

Conclusion

The recent advances in NSCLC targeted therapy require the analysis of a panel of molecular abnormalities of tumor specimens, including gene mutations and fusions, by applying different methodologies to the samples. This new era of personalized therapy and increasing capabilities of examining the genome of tumor cells poses several methodological and practical challenges for the implementation of clinical molecular testing. In this new context, the routine utilization of advanced technologies and molecular information, including the application of the NGS tools, coupled with appropriate data management and analysis, may help us to better develop personalized therapies in lung cancer. As the price of whole-genome sequencing falls to reach the "$1000 genome" mark, and the capability of this technology to analyze small clinical tumor tissue specimens is proven and becomes widely accessible, it will be an invaluable tool to be utilized in clinical trials testing personalized therapies in cancer.

Selected reading

Bergethon K, Shaw AT, Ou SH, *et al*. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30:863–70.

Li T, Kung HJ, Mack PC, *et al*. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. J Clin Oncol. 2013;31:1039–49.

Lindeman NI, Cagle PT, Beasley MB, *et al*. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013;15(4):415–53.

Ross JS, Cronin M. Whole cancer genome sequencing by next-generation methods. Am J Clin Pathol. 2011;136:527–39.

Shaw AT, Engelman JA. ALK in lung cancer: past, present, and future. J Clin Oncol. 2013;31:1105–11.

CHAPTER 75

Screening, staging, and stage I non-small-cell lung cancer

Tarek M. Mekhail
Cancer Institute of Florida, Orlando, FL, USA

Case study 75.1

A 58-year-old man presents to your clinic accompanied by his wife. He has smoked one pack per day since age 19, and he has quit 5 years ago. He is concerned about lung cancer and is enquiring about screening.

1. Should you recommend a yearly low-dose computed tomography (CT) scan of the chest?

A. Yes
B. No

Lung cancer is the leading cause of cancer death in the United States. It is responsible for more cancer deaths than breast, prostate, and colon cancer combined. Because early-stage lung cancer is usually asymptomatic, most lung cancers are diagnosed at late symptomatic stages. Survival of patients diagnosed with locally advanced or metastatic stages is dismal with 5-year survival rates of 16%. Early detection of lung cancer provides the best chance of cure. Only 15% of patients with lung cancer in the United States are diagnosed with curable early-stage disease (stages I and II), and those are usually discovered incidentally, by imaging of the chest for other reasons.

Over the past 4 decades, a large amount of research has been performed to evaluate if conventional radiography or CT could be effective screening tests for lung cancer. Previous screening studies with chest radiographs and/or sputum cytology have failed to show any mortality reduction from lung cancer from those tests. The Prostate, Lung, Colorectal, and Ovarian cancer screening trial compared screening with chest radiograph to observation and detected no mortality reduction from lung cancer in the screened population. These earlier randomized controlled trials (RCTs) showed that chest radiographs detected slightly more lung cancers and more stage I tumors, but failed to demonstrate decreased mortality from lung cancer, or a stage shift, defined as follows: increase detection of early cancer and decreased incidence of late stages.

The advent of low-dose (radiation) computed tomography (LDCT) imaging created renewed interest in screening. In the past 10 to 15 years, there have been a large number of clinical trials evaluating the role of LDCT screening for asymptomatic lung cancer. Early studies demonstrated that when a chest X-ray was obtained within 30 days of an LDCT scan, the chest X-ray missed 70% to 80% of the LDCT-detected lung cancers. Many of these early lung cancers detected on these trials were curable by surgical resection. These nonrandomized trials, however, have many inherent limitations that hamper our ability to draw definitive conclusions. These limitations include the potential for overdiagnosis bias, lead-time bias, and disease-type bias.

Overdiagnosis bias occurs when a screening test identifies disease that never would have affected the patient's life in the absence of screening. This type of bias might occur if screening identifies indolent lesions that would have never caused clinical disease.

Lead-time bias occurs when screening results in earlier recognition of disease, but does not change the patient's

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

eventual lifespan, creating the illusion that the patient's survival time with the disease is longer.

Disease-type bias arises from the observation that any screening test that is applied intermittently is more likely to detect indolent tumors than aggressive, fast-growing tumors that would result in clinical symptoms.

Randomized controlled trials

Three randomized studies provided evidence on the effect of LDCT screening on lung cancer mortality, of which the National Lung Screening Trial (NLST) was the most informative.

The NLST

The NLST included 53,454 persons at high risk for lung cancer. Participants were randomly assigned to undergo three annual screenings with either low-dose CT or single-view postero-anterior chest radiography. These three annual rounds of screening (baseline and 1 and 2 years later) with LDCT resulted in a 20% relative decrease in deaths from lung cancer versus chest radiographs over a median of 6.5 years of follow-up ($P = 0.004$). In absolute terms, the chance of dying from lung cancer was 0.33% less over the study period in the LDCT group (87 avoided deaths over 26,722 screened participants).

It is important to know that the rate of positive screening tests was 24.2% with LDCT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the LDCT group and 94.5% in the radiography group were false-positive results. This emphasizes the need for careful and structured evaluation protocols for patients with positive screening findings to avoid unnecessary interventions.

Two other considerably smaller ongoing studies, DANTE and DLCST, each compared five annual rounds of LDCT screening to usual care; after a median of 34 and 58 months of follow-up, respectively, no statistically significant difference in lung cancer mortality was observed in either study (DANTE: relative risk (RR), 0.97; 95% CI, 0.71–1.32; $P = .84$; DLCST: RR, 1.15; 95% CI, 0.83–1.61; $P = .43$).

Since the publication of the NSLT results, many organizations, including the American Thoracic Society, American Society of Clinical Oncology, National Comprehensive Cancer Network, and American Cancer Society, have endorsed LDCT screening for high-risk populations, as defined on the NSLT. A substantial amount of data on LDCT screening should be reported in the near future, including numerous planned analyses of the NLST data both by its investigators and by the Cancer Intervention and Surveillance Modeling Network (CISNET) investigators. The ongoing RCTs in Europe will also be reporting estimates of both the magnitude of LDCT's mortality benefit and the extent of its harms soon. These data may help inform some of the important questions that still linger regarding LDCT screening.

Case study 75.2

The wife of the patient in Case study 75.1 is also concerned about lung cancer. She is 50 years old and never smoked. Her father developed lung cancer at age 75. She is worried that she was exposed to secondhand smoking through her father and husband.

1. Should you recommend yearly low-dose CT of the chest?

A. Yes

B. No

The NSLT found that three annual rounds of screening in high-risk individuals with LDCT resulted in a 20% relative decrease in deaths from lung cancer versus chest radiographs over a median of 6.5 years of follow-up ($P = 0.004$). This intervention, however, is not of proven benefit in population at lower risk of developing lung cancer than those included in the NLST. Physicians are occasional asked to order such a test by individuals who have a family member diagnosed with lung cancer, or those who are generally more concerned about their health. A US survey found that a high proportion of never-smokers would be willing to consider lung CT screening. Besides lack of evidence of benefit in this population, risks of screening should be considered. These risks include the discovery of benign pulmonary nodules (false-positive), resulting in unneeded intervention, and the risk of radiation-induced cancer.

False-positive results

LDCT identifies both cancerous and benign nodules; the latter are often called "false positives." Based on the study's own size cutoffs, the average nodule detection rate per round of screening was 20%. Most studies reported that more than 90% of nodules were benign.

The NSLT found that the rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false-positive results. The numbers of false-positive results are likely to be higher in

never-smokers, in whom the incidence of cancer is lower. In lower-risk populations, the incidence of false-positive results from screening would be expected to be even higher than that reported in the NSLT.

A detected nodule will likely trigger further imaging. The frequency of further CT imaging among screened individuals ranged from 1% to 44.6%. The frequency of further positron emission tomography (PET) imaging among screened individuals ranged from 2.5% to 5.5% in the NLST. Findings could also result in invasive evaluation. In the NLST, 1.2% of patients who were not found to have lung cancer underwent an invasive procedure such as needle biopsy or bronchoscopy, and 0.7% of patients who were not found to have lung cancer had a thoracoscopy, mediastinoscopy, or thoracotomy. Invasive nonsurgical procedures occurred in 73% of patients with benign lesions in the NLST. Anxiety and unnecessary interventions and complications from these procedures should all be weighed against the potential benefit of LDCT screening.

Table 75.1 Percentage reduction in lung cancer mortality needed to outweigh risk of radiation by smoking status, age, and gender (Source: Adapted from Berrington de Gonzalez *et al.* J Med Screen. 2008;15:153–158. Reproduced with permission of Sage).

Smoking status	Age (years)	% reduction in lung cancer mortality needed to outweigh risk of radiation (90% CI)	
		Male	Female
Never smoker	30–32	125 (40–300)	375 (200–800)
	40–42	70 (30–190)	170 (100–300)
	50–52	25 (10–70)	75 (30–130)
Current smoker	30–32	70 (20–120)	170 (100–500)
	40–42	10 (3–20)	30 (10–70)
	50–52	2 (1–4)	4 (2–10)

CI, confidence interval.

Radiation exposure

The risk of radiation-induced cancer from lung CT screening is small. Most relevant, however is the relative magnitude of the potential absolute benefit from screening compared to the risk of induced cancer. The effective dose of radiation of LDCT is estimated to be 1.5 mSv per examination, although there is substantial variation in actual clinical practice. Diagnostic chest CT (~8 mSv) or PET–CT (~14 mSv) to further investigate detected lesions accounts for most of the radiation exposure in screening studies. It is estimated that NLST participants received approximately 8 mSv per participant over 3 years, including both screening and diagnostic examinations (averaged over the entire screened population).

Estimates of harms from radiation come from several official bodies and commissioned studies, based on dose extrapolations from atomic bombings and also many studies of medical imaging. Brenner *et al*. previously estimated the risk of radiation-induced lung cancer mortality for smokers aged 50, and suggested that lung cancer mortality would need to be reduced by at least 5% to outweigh these risks. This figure is likely to be higher for screening at younger ages because the radiation risks will be higher, due to the longer time available to develop a radiation-induced cancer, while the absolute benefit will be lower because lung cancer incidence rates are lower.

Using the NLST data, these models predict that approximately one cancer death may be caused by radiation from imaging per 2500 persons screened, compared to a benefit of prevention of one cancer death per 320 persons screened reported by the NSLT investigators. The benefit, therefore, in preventing lung cancer deaths in NLST is greater than the radiation risk—which only becomes manifest 10 to 20 years later.

Younger individuals or those with lower risk of developing lung cancer have less favorable trade-offs. Radiation-induced cancer risk estimates from lung CT screening are not currently available for never smokers, or for screening before age 50. Preliminary modeling studies suggest that potential risks may vastly outweigh benefits in nonsmokers or those aged 42 years or younger.

Berrington de Gonzalez *et al*. conducted a study to estimate the potential risk of radiation-induced lung cancer from three annual lung CT screens for asymptomatic individuals starting at age 30, 40, and 50 years. They estimated the level of screening efficacy that would be required to outweigh these risks of radiation exposure (Table 75.1). The risk estimates were developed for never smokers and current smokers. For women, they also estimated the risk of radiation-induced breast cancer. They used the Cancer Prevention Study II to estimate the lung cancer rates for never smokers. For current smokers, they used the Bach lung cancer risk model, assuming a 40-cigarettes-per-day smoking history, which has been recently validated using data from the Alpha-Tocopherol, Beta-Carotene trial.

Table 75.1 summarizes the mortality reduction required to outweigh the radiation risks for each man and woman depending on their age and smoking status. As illustrated in Table 75.1, for a woman who is 50 years old and a never smoker, screening has to have a benefit of approximately 75% reduction of mortality to justify the risk of radiation exposure. This is clearly unlikely given the results of the NSLT that demonstrated only a 20% reduction in mortality in the higher-risk screened population.

Case study 75.3

Stage I lung cancer

A 60-year-old man presented to his primary care physician with persistent cough. A chest X-ray revealed a right upper lobe lung 4 cm nodule. Staging work-up revealed no evidence to suggest metastasis. He underwent mediastinoscopy and video-assisted thoracotomy (VATS), and right upper lobe lobectomy. The surgical pathology report revealed a 4.5 cm tumor. All margins of resection were negative, and all lymph nodes sampled were negative.

1. Surgical staging was *yp*T2a, NO, MO (Stage IB). You now recommend:

A. Four cycles of adjuvant cisplatin-based chemotherapy
B. Adjuvant radiation therapy
C. No adjuvant therapy is recommended

Before 2003, several phase III studies failed to show a significant benefit with adjuvant chemotherapy. Adjuvant chemotherapy after resection of stage II–IIIA non-small-cell lung cancer then became the standard of care based on the results of three phase III studies using cisplatin-based regimens, IALT (International Adjuvant Lung Trial), National Cancer Institute of Canada JBR.10, and ANITA (Adjuvant Navelbine International Trialist Association). The role of adjuvant chemotherapy for stage IB (T2 (tumors >3 cm and involvement of the visceral pleura)/N0) disease remains controversial.

The IALT (International Adjuvant Lung Trial) reported in 2004 was the first study to prove a benefit from adjuvant chemotherapy. A statistically significant 4% survival advantage at 5 years (hazard ratio [HR]: 0.86) with the addition of four cycles of cisplatin-based chemotherapy after complete resection of stage I–III NSCLC was demonstrated. This trial included 1867 stage I–III patients who were randomized to receive cisplatin-based chemotherapy versus observation. The study was not stratified to evaluate results by stage, but a trend toward increased benefit in patients with stage II–III disease was identified. This study was later updated with 7-year follow-up showing disappearance of the survival benefit with longer-term follow-up.

In 2004, the National Cancer Institute of Canada JBR.10 trial randomized 482 patients with completely resected stage IB–IIB NSCLC to receive four cycles of cisplatin–vinorelbine versus observation. A 15% survival advantage was reported at 5 years (HR: 0.7) with the addition of chemotherapy. This trial was stratified by stage. In subset analysis, no benefit was noted for patients with stage IB disease.

Confirmation of the overall beneficial role of adjuvant therapy was demonstrated in 2005 with the results of the ANITA (Adjuvant Navelbine International Trialist Association) trial. This study of 840 patients with resected NSCLC, stages IB–IIIA, found a 9% survival advantage at 5 years (HR: 0.79) with four cycles of adjuvant cisplatin–vinorelbine. Once more, however, no benefit was found for the patients with stage IB disease on subset analysis. The CALGB (Cancer and Leukemia Group B) trial 9633 was the only study to focus exclusively on stage IB. Three hundred and thirty-four patients with resected stage IB NSCLC were randomized to receive either four cycles of paclitaxel–carboplatin or observation. At an initial report, the CALGB 9633 showed a survival advantage for those receiving adjuvant chemotherapy versus observation. This was the only adjuvant trial to use a carboplatin-based regimen. CALGB 9633 was closed early when the first interim analysis demonstrated a 12% survival advantage at 4 years (HR: 0.62).

With the results of these positive trials, adjuvant chemotherapy was established as the standard of care for completely resected stage II–IIIA NSCLC. The initial positive results of CALGB 9633 were the basis of recommendation of adjuvant chemotherapy for stage IB, despite the negative results from the subset analyses of the other trials.

An update of CALGB 9633, presented at the 2006 annual meeting of the American Society of Clinical Oncology, has further clouded the issue of adjuvant chemotherapy in stage IB disease. The update this year is based on 137 events, now with an HR for overall survival (OS) of 0.8 ($P = 0.1$). The statistically significant survival advantage was lost by 5 years follow-up. Failure-free survival still favors the chemotherapy arm (HR: 0.74; $P = 0.03$).

The CALGB 9633 had many shortcomings, however. First, the study was underpowered to detect survival advantage with an HR of 0.8, which would need more than 1000 patients. It is worth mentioning that the initial accrual target for the study was 500 patients. This was reduced to 384 patients in 2000 secondary to slow accrual and further reduced with early closure of the trial because of the initial positive results at interim analysis. Besides being underpowered, other possible explanations for the negative results of the CALGB 9633 include a true lack of benefit from adjuvant therapy in patients with stage IB disease, or the use of carboplatin-based (as opposed to cisplatin-based) adjuvant chemotherapy.

A recent individual patient meta-analysis of the large adjuvant trials conducted since the 1995 meta-analysis (excluding CALGB 9633) was reported by Pignon *et al.* (2008) A 5.5% survival advantage at 5 years (HR: 0.84; $P < 0.001$) for adjuvant cisplatin therapy was reported. Stage IB subset analysis showed a trend toward benefit (HR: 0.92)

(*Continued*)

Table 75.2 Recent phase III studies and meta-analyses of adjuvant chemotherapy for early-stage NSCLC.

Trial	Stage	Number of patients	Chemotherapy regimen	Hazard ratio	*P*-value
IALT	I–III	1867	Cisplatin/vinca alkaloid or VP16	0.86	<0.03
IALT (2010)	I–III	1867	Cisplatin/vinca alkaloid or VP16	0.91	0.1
NCIC JBR.10	IB–IIB	482	Cisplatin/vinorelbine	0.7	0.012
CALGB 9633 (2004)	IB	344	Carboplatin/paclitaxel	0.62	0.028
ANITA	IB–IIIA	840	Cisplatin/vinorelbine	0.79	0.013
CALGB 9633 (2008)	IB	344	Carboplatin/paclitaxel	0.8	0.1
LACE[a]	I–III	4584	Platinum doublets	0.89	0.0004

LACE, Lung Adjuvant Cisplatin Evaluation; MVd, mitomycin C/vindestine; NCIC, National Cancer Institute of Canada; VP16, etoposide.
[a]Meta-analyses.

but failed to reach statistical significance (95% CI: 0.73–0.95). Stage IA patients had worse outcomes with adjuvant chemotherapy. This meta-analysis emphasizes that the benefit of platinum agent–based adjuvant chemotherapy, if it exists, in stage IB is small and would require a large trial to be detected.

Table 75.2 summarizes the result of some of the recent adjuvant clinical trials and the most recent meta-analyses.

Tumor size

Previously, stage IB included T2 (tumor >3 cm, or involvement of visceral pleura) and N0 (no lymphadenopathy). In the new TNM, 7th edition classification, the T classification has been redefined:

T1 has been subclassified into T1a: ≤2 cm; and T1b: >2–3 cm.
T2 has been subclassified into T2a: >3–5 cm; and T2b: >5–7 cm.
T2 (tumor >7 cm) has been reclassified as T3.

Stage IB would now only include patients with tumors T2a N0. Patients with T2b N0 tumors are now reclassified into stage IIA, and patients with T3 (T tumors > 7 cm) N0 tumors are now subclassified into stage IIB.

All the relevant adjuvant clinical trials mentioned here had applied the old TNM classification, 6th edition. Thus the findings now apply to patients with T2a/N0 (stage IB), T2b/N0 (stage IIA), and T3/N0 (stage IIB), according to the new subclassification (see Table 75.3).

The tumor size has been a factor in trying to identify patients who might benefit from adjuvant chemotherapy within the stage IB subgroup. In an unplanned subset analysis, patients on CALGB 9633 with tumors >4 cm (approximately 100 patients on each arm) did have an OS advantage, with an HR of 0.66 ($P = 0.04$). The importance of tumor size in stage IB disease was also supported by a long-term follow-up update of the JBR-10. In this report, the OS and disease-specific survival (DSS) data showed persistence of the benefit of adjuvant chemotherapy that was confined to N1 patients. Within stage IB, however, patients with tumors 4 cm or larger in size derived clinically meaningful benefit from chemotherapy (HR: 0.66; 95% CI, 0.39 to 1.14; $P = 0.13$), while those with tumors smaller than 4 cm did not (HR: 1.73; 95% CI, 0.98 to 3.04; $P = 0.06$). The 5-year survival for patients with tumors 4 cm or larger was 59% on observation versus 79% with chemotherapy.

Table 75.3 Summary of changes to TNM staging system.

6th edition	7th edition
T1 (0–3 cm)	T1a (0–2 cm) T1b (>2–3 cm)
T2 (>3 cm)	T2a (3–5 cm) T2b (>5–7 cm) T3 (>7 cm)
T4 (multiple nodules in the same lobe)	T 3
T4 (Malignant pleural effusion)	M1a
M1 (ipsilateral nodule in a different lobe	T4
M1 (systemic metastases)	M1a (Nodules in contralateral lobes, malignant pleural effusion) M1b (distant metastases)

Both of the subgroup analyses of the CLAGB 9633 and the JBR 10 provide support that a subpopulation of patients with stage IB (i.e., tumors larger than 4 cm) may derive benefit from adjuvant chemotherapy. These patients are included in the current ongoing randomized phase III clinical trial ECOG-1505, which is examining the role of bevacizumab in addition to cisplatin-based chemotherapy in the adjuvant setting.

Further risk assessment of lung cancer patients, beyond TNM staging alone, has been the focus of recent studies. Moving forward, it is unlikely that large randomized trials will be designed based on TNM classification alone. Rather,

future clinical trials must take into account the prognostic value of other factors, including molecular markers as well as genomic profiling. ERCC1 is one such molecular marker. Patients enrolled on the IALT with completely resected non-small-cell lung cancer and ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors do not.

A 14-gene expression assay that uses quantitative polymerase chain reactiom, runs on formalin-fixed paraffin-embedded tissue samples, and differentiates patients with heterogeneous statistical prognoses was developed in a cohort of 361 patients with nonsquamous NSCLC resected at the University of California, San Francisco. The assay was then independently validated by the Kaiser Permanente Division of Research in a masked cohort of 433 patients with stage I nonsquamous NSCLC resected at Kaiser Permanente Northern California hospitals, and on a cohort of 1006 patients with stage I–III nonsquamous NSCLC resected in several leading Chinese cancer centers that are part of the China Clinical Trials Consortium (CCTC). The Kaplan–Meier analysis of the Kaiser validation cohort showed 5-year overall survival of 71.4% (95% CI: 60.5–80.0) in low-risk, 58.3% (48.9–66.6) in intermediate-risk, and 49.2% (42.2–55.8) in high-risk patients (P(trend) = 0.0003). Similar analysis of the CCTC cohort indicated 5-year overall survivals of 74.1% (66.0–80.6) in low-risk, 57.4% (48.3–65.5) in intermediate-risk, and 44.6% (40.2–48.9) in high-risk patients (P(trend) $<$ 0.0001). Multivariate analysis in both cohorts indicated that no standard clinical risk factors could account for, or provide, the prognostic information derived from tumor gene expression. The assay improved prognostic accuracy beyond National Comprehensive Cancer Network criteria for stage I high-risk tumors ($P < 0.0001$), and differentiated low-risk, intermediate-risk, and high-risk patients within all disease stages.

Zhu *et al*. (2010) on further analysis of the JBR.10 trial hypothesized that gene expression profiling may identify stage-independent subgroups who might benefit from adjuvant chemotherapy. A 15-gene expression signature was found to be an independent prognostic marker in early-stage, completely resected NSCLC. Furthermore, it has demonstrated the potential to select patients with stage IB–II NSCLC most likely to benefit from adjuvant chemotherapy. This signature separated observation patients into high-risk and low-risk subgroups with significantly different survival (HR: 15.02; 95% CI: 5.12–44.04; $P < .001$; stage I HR: 13.31; $P < .001$; stage II HR: 13.47; $P < .001$). The signature was also predictive of improved survival after adjuvant chemotherapy in JBR.10 high-risk patients (HR: 0.33; 95% CI: 0.17 to 0.63; $P < .0005$), but not in low-risk patients (HR: 3.67; 95% CI: 1.22 to 11.06; $P = .0133$; interaction $P < .001$). Genomic profiling awaits confirmation in prospectively designed clinical trials.

In our practice, we generally recommend adjuvant chemotherapy to fit patients with tumors >4 cm. We have not yet adopted any of the genomic profiling models pending further validation.

Conclusion

Screening a population of individuals at a substantially elevated risk of lung cancer most likely could be performed in a manner such that the benefits outweigh the harms. The fear and anxiety that patients can experience once there is even a slight suspicion of lung cancer highlight the need for careful education of LDCT participants and the need for carefully worded scan interpretations, as well as a structured work-up, evaluation, and follow-up program.

In the setting of increasing healthcare costs, the relative cost-effectiveness of LDCT screening compared with other interventions will be a topic of concern. For patients at low risk of cancer, the harm of screening could outweigh the potential benefit, and these tests should not be offered outside a clinical trial context.

Case study answers

Case study 75.1

Question 1: Answer A ("Yes")

Case study 75.2

Question 1: Answer B ("No")

Case study 75.3

Question 1: Answer A

Selected reading

Arriagada R, Dunant A, Pignon JP, *et al*. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol. 2010;28(1):35–42.

Bach PB, Mirkin JN, Oliver TK, *et al*. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307(22):2418–29.

Butts CA, Ding K, Seymour L, *et al*. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol. 2010; 28(1):29–34.

Douillard JY, Rosell R, De Lena M, *et al*. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7(9):719–27.

Zhu CQ, Ding K, Strumpf D, *et al*. Prognostic and predictive gene signature for adjuvant chemotherapy in resected non-small-cell lung cancer. J Clin Oncol. 2010;28(29):4417–24.

For further information on this area please also consult Chapters 108, 120, 131, and 136

CHAPTER 76

Stage II and III non-small-cell lung cancer

Grzegorz Korpanty and Natasha B. Leighl

Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Case study 76.1

A 55-year-old woman, a lifetime nonsmoker, was diagnosed with a 6 cm spiculated right upper lobe lung nodule. Staging showed no evidence of distant metastatic disease. She underwent a right upper lobectomy. The surgical pathology report indicated a T2bN0M0 well-differentiated lung adenocarcinoma (stage IIA, AJCC version 7). Surgical resection margins were negative, and there was no evidence of lymphovascular space invasion. Molecular analysis revealed an activating epidermal growth factor receptor (EGFR) mutation (exon 19 deletion).

1. How should she be managed after surgery?

A. She should receive adjuvant cisplatin-based chemotherapy for four cycles followed by chest radiotherapy

B. She should complete four cycles of cisplatin-based chemotherapy followed by two years of an EGFR tyrosine kinase inhibitor (TKI)

C. She should only receive an EGFR TKI for 2 years

D. She should receive four cycles of adjuvant cisplatin-based chemotherapy

E. She should be scheduled for ongoing surveillance only

After surgical excision with curative intent, the 5-year survival for pathological stage IIA non-small-cell lung cancer (NSCLC) is 46%. Adjuvant chemotherapy prolongs survival in patients with resected stage II and III NSCLC based on long-term follow-up results of two phase III clinical trials and a recent meta-analysis. While there is clear evidence to recommend adjuvant cisplatin-based chemotherapy for those with resected N1 or N2 disease, the value of adjuvant chemotherapy, in the absence of pathological evidence of lymph node metastasis (N0), remains the subject of debate.

The Cancer and Leukemia Group B (CALGB) 9633 randomized trial investigated the role of adjuvant chemotherapy in completely resected T2N0 tumors (Stage IB; *AJCC cancer staging manual*, 6th ed.). Upon final analysis, while there was no statistically significant difference between the observation and chemotherapy arms in this small trial, exploratory analysis suggested that patients with tumors $\geq$4.0 cm may benefit from adjuvant carboplatin and paclitaxel chemotherapy ($P = 0.043$). A similar exploratory analysis of the NCIC Clinical Trials Group JBR.10 randomized trial demonstrated that the subgroup of patients with node-negative tumors $\geq$4 cm derived clinically meaningful benefit from cisplatin-based adjuvant chemotherapy (hazard ratio (HR): 0.66). Thus, many clinicians do offer adjuvant cisplatin-based therapy to fit patients with completely resected lymph node negative NSCLC if the tumor size is $\geq$4 cm.

The role of *EGFR*-activating mutations as predictors of EGFR TKI response in patients with metastatic NSCLC is well established. Five randomized phase III trials have prospectively compared the efficacy of initial EGFR TKI therapy to standard platinum-based chemotherapy in patients with *EGFR* mutation–positive advanced NSCLC: the West Japanese WJTOG3405, North-East Japan Study Group (NEJ002), OPTIMAL-CTONG-0802, EURTAC, and LUX-LUNG3 studies. In all trials, patients treated with EGFR TKI had significantly better progression-free survival (PFS), response rate (RR), symptom relief, or quality of life than patients treated with platinum-based chemotherapy. However, the prognostic and predictive value of the *EGFR* mutation in resected early-stage NSCLC remains less clear. At least three retrospective analyses demonstrated that patients with resected *EGFR* mutation–positive NSCLC had a better prognosis compared to those with *EGFR* wild-type tumors. In the NCIC Clinical Trials Group BR.19 adjuvant intergroup trial, patients with completely resected stage IB–IIIA, otherwise unselected, NSCLC were

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

randomized to receive gefitinib or placebo for up to 2 years. The study was later amended to allow adjuvant cisplatin-based chemotherapy (stratified) as appropriate prior to a gefitinib or placebo start. Unfortunately, this trial was prematurely closed after 503 patients had been randomized because of the negative SWOG S0023 trial, where maintenance gefitinib after chemoradiation in locally advanced NSCLC yielded worse survival than placebo. Analysis of the underpowered NCIC CTG BR.19 trial did not show any difference between adjuvant gefitinib and placebo. In addition, neither *KRAS* mutation status nor *EGFR* copy number by fluorescence in situ hybridization (FISH) or *EGFR* mutation status had prognostic or predictive value. Of 503 patients, 357 had *EGFR* genotyping performed, and 21% had *EGFR* mutation–positive tumors. The HR for survival in the gefitinib arm was 1.58 (95% confidence interval (CI): 0.83 to 3.00; log-rank *P*-value = 0.160). Median survival in the *EGFR* mutation–positive subgroup receiving adjuvant gefitinib was 3.7 years, and it was 5.1 years for those receiving placebo. Interestingly, multivariate analysis indicated that never smokers, a group with a high incidence of sensitizing *EGFR* mutations, had longer survival with gefitinib in this study ($P = 0.02$). A retrospective cohort analysis at a single institution suggested that survival outcomes of early-stage *EGFR* mutation–positive NSCLC patients were longer if they received adjuvant EGFR TKI than if they did not. Interestingly, a subgroup analysis of the NCIC CTG JBR.10 study suggested longer survival and greater chemotherapy benefit in those with exon 19 and 21 *EGFR* mutations compared to *EGFR* wild type, although these differences were not statistically significant.

The hypothesis that patients with *EGFR* mutant NSCLC derive clinically significant benefit from adjuvant treatment with EGFR TKI therapy remains compelling, and the existing data does not support routine use of EGFR TKI as adjuvant treatment outside a clinical trial at this time. The RADIANT trial of adjuvant erlotinib versus placebo in resected stage IB–IIIA NSCLC has completed accrual. While initial results are pending, a preliminary assessment indicates that 14% of participants have *EGFR* mutant tumors. In the WJTOG6410L study, which is led by Japanese investigators, patients with resected *EGFR* mutation-positive NSCLC are randomized to four cycles of vinorelbine–cisplatin versus gefitinib. Those with classic *EGFR* exon 19 deletion or L858R exon 21 insertion mutations are eligible; those with tumors harboring T790M mutations conferring resistance to EGFR TKIs are excluded. Results of this randomized study will shed more light on the role of adjuvant EGFR TKI therapy in patients with *EGFR*-sensitizing mutations.

In summary, patients with completely resected stage II and III NSCLC should be offered adjuvant cisplatin-based chemotherapy. This recommendation extends to those with node-negative tumors where the primary tumor size is ≥4 cm. At present, there is insufficient data to recommend adjuvant EGFR TKI therapy in those with resected NSCLC harboring *EGFR* mutations. These patients should be considered for adjuvant chemotherapy if appropriate.

Case study 76.2

A 65-year-old man with a 50-pack-year smoking history was diagnosed with a 6.5 cm right upper lobe lung adenocarcinoma. Staging computed tomography (CT) scan showed enlarged (3.5 cm) mediastinal lymph nodes. Mediastinal staging by endobronchial ultrasound (EBUS) demonstrated metastatic disease in ipsilateral mediastinal lymph nodes at stations 4R and 7. Staging positron emission tomography (PET) scan showed no evidence of extrathoracic metastatic disease (T2N2M0; stage IIIA; AJCC version 7). His case was discussed at a multidisciplinary tumor board, and bimodality treatment with chemotherapy and radical radiotherapy was recommended. He received two cycles of combined-modality treatment with cisplatin–etoposide chemotherapy concurrently with radiotherapy (66 Gy). His posttreatment restaging CT thorax and abdomen scan demonstrated partial response to treatment: his tumor is now 2.5 cm, and mediastinal lymphadenopathy decreased to 1.2 cm.

- **Is there a role for surgery in this patient?**

Patients with stage IIIA(N2) NSCLC represent a very heterogeneous group; the extent of lymph node involvement ranges from single-station microscopic disease to multilevel bulky lymphadenopathy. Patients with microscopic N2 involvement have 34% 5-year survival when compared with 3% for those with extensive multilevel involvement.

The management of locally advanced NSCLC (T1-3 N2M0; stage IIIA) has two major goals—to eradicate local tumor burden and micrometastatic disease. The management of N2 disease, regardless of tumor size, remains one of the most controversial issues in NSCLC therapy. Despite the fact that stage III tumors may be technically resectable, once mediastinal lymph nodes are involved, outcomes, after surgical resection, are poor. Surgical resection in selected patients results in 5-year survival rates of 7% to 24%, with improvement to 17% to 36% after neo-adjuvant chemotherapy.

Bimodality therapy with radiation and chemotherapy yields 5-year survival rates of 15% to 20% in patients with stage III NSCLC. Based on the results of phase III randomized trials and a recent meta-analysis, concurrent administration of chemotherapy and radiotherapy is superior to sequential administration, and concurrent chemo-

radiotherapy is regarded now as a standard of care for patients with stage IIIA(N2) NSCLC.

Trimodality (or bimodality) therapy with surgical resection after induction treatment with chemotherapy or chemoradiotherapy has been investigated in phase II and phase III clinical trials. The European Organization for Research and Treatment of Cancer—Lung Cancer Group (EORTC-LCG) clinical trial investigated the role of surgery versus radiotherapy in patients with stage IIIA(N2) NSCLC after neoadjuvant platinum-based chemotherapy. Stage IIIA(N2) patients deemed initially inoperable (defined as any N2 involvement by a nonsquamous carcinoma, or, if squamous carcinoma, any N2 nodal involvement exceeding level 4R for a right-sided tumor and levels 5 and 6 for a left-sided tumor) received three cycles of platinum-based chemotherapy. Patients without disease progression were randomly assigned to surgical excision versus radiotherapy (60–62.5 Gy). Induction chemotherapy resulted in an overall response rate of 61%, with 87% of patients receiving all three cycles of chemotherapy. The majority randomized to the surgical arm underwent surgery (92%); however, only 50% of patients had complete (R0) resection and 40% received radiotherapy postoperatively. There was no significant difference in overall survival (OS) and PFS between the two study arms. Median OS and 5-year survival for patients treated by surgery was 16.4 months and 15.7% compared to 17.5 months and 14% in the radiotherapy arm, respectively (HR: 1.06, 95% CI: 0.84 to 1.35).

The North American Intergroup 0139 trial included patients with technically resectable stage IIIA(N2) NSCLC who were treated with two cycles of cisplatin and etoposide chemotherapy combined with concurrent thoracic radiation (45 Gy). Patients without disease progression were then randomized to surgical resection or completion of radiotherapy to a total dose of 61 Gy. Patients in both arms received two further cycles of cisplatin and etoposide consolidation chemotherapy, and the primary endpoint of the study was overall survival. The addition of surgery did not improve survival, with a median survival of 23.6 months with trimodality therapy compared to 22.2 months with chemoradiation alone. Median PFS, however, was significantly better in the surgical arm (12.8 versus 10.5 months; $P = 0.017$). A hypothesis-generating retrospective subset analysis looked at patients who underwent lobectomy versus pneumonectomy and compared the survival data with that of matched patients from the chemoradiation arm. It showed better median OS for those undergoing lobectomy (33.6 months) compared to pneumonectomy (21.7 months).

In summary, concurrent chemoradiotherapy remains the standard of care in management of stage III NSCLC. Patients who respond to chemoradiotherapy may derive clinical benefit from surgical resection if they are suitable resection candidates or can undergo limited surgery such as lobectomy.

Case study 76.3

A 66-year-old man diagnosed with stage IIIA lung adenocarcinoma was treated with combined-modality treatment with two cycles of cisplatin and etoposide chemotherapy combined with a radical (66 Gy) dose of radiotherapy, with excellent response.

- **What is the role of consolidation chemotherapy in this patient?**

The role of combined-modality treatment in unresectable stage III NSCLC is well established and is the treatment of choice in good-performance-status patients based on phase III clinical trials. Concurrent administration of chemotherapy and radiotherapy is superior in terms of survival benefit to a sequential approach but at the cost of a greater toxicity, such as esophagitis.

The role of consolidation chemotherapy in patients with unresectable stage III NSCLC after radical chemoradiation remains controversial. In the SWOG 9109 phase II study, patients with stage IIIB NSCLC received two cycles of etoposide–cisplatin concurrently with once-daily thoracic radiation (45 Gy), which was then increased to a total dose of 61 Gy with two cycles of consolidation etoposide–cisplatin. At a median follow-up of 52 months, the median OS was 15 months. The 3- and 5-year survival rates were 17% and 15%, respectively. This regimen has been used in other landmark studies, such as the INT0139 trial.

A subsequent phase II study, SWOG 9504, evaluated the role of docetaxel as consolidation chemotherapy after concurrent etoposide–cisplatin and radical radiation in stage IIIB NSCLC. Median OS in SWOG 9504 was significantly better (26 months) when compared with 15 months in SWOG 9019, which translated into a 37% 3-year survival rate, compared with 17%. However, phase II trials cannot replace the value of a phase III comparison to test differences between treatment regimens. A phase III trial from the Hoosier Oncology Group (HOG LUN-01-24) randomized patients with unresectable stage IIIA or IIIB NSCLC treated with definitive chemoradiotherapy to either observation or consolidation chemotherapy with single-agent docetaxel. This trial was terminated for futility after initial analysis of

(*Continued*)

203 patients. The median OS of all patients enrolled ($n = 203$) was 21.7 months, and the 3-year overall survival rate was 30.2%. There was no statistically significant difference in survival between the two study arms, with a median OS time of 23.2 months in the observation arm and 21.2 months in the docetaxel arm (3-year OS: 26.1% and 27.1%, respectively). There was also no difference in PFS between the two arms. Patients who received docetaxel had a higher incidence of hospitalization, infections, pneumonitis, and treatment-related death.

Recently, the results of meta-analysis of 45 phase II–III trials ($n = 3447$) examining survival of locally advanced NSCLC patients treated with concurrent platinum-based chemoradiotherapy between 1995 and 2011 were presented. Trial arms were divided into two groups, depending on the presence of consolidation chemotherapy. There was no statistical difference in pooled median OS data between studies with and without consolidation chemotherapy—18.5 months versus 18.1 months, respectively. The caveat of using a meta-analysis to definitively answer the question about the role of consolidation chemotherapy lies in the dependence of treatment response on both patient and tumor characteristics. It is important to identify subgroups of patients within stage III NSCLC that may benefit from consolidation chemotherapy after radical chemoradiotherapy.

In summary, while fit patients who have tolerated chemoradiation well may be offered consolidation chemotherapy, the clear demonstration of benefit from consolidation therapy remains to be proven.

• What is the role of neo-adjuvant chemotherapy and chemoradiotherapy in stage I or II resectable NSCLC?

Preoperative or neo-adjuvant therapy has several theoretical advantages. It may downstage tumors and improve surgical resection rates, provide earlier control or prevention of micrometastatic disease, yield information about chemosensitivity and/or radiosensitivity, and be better tolerated than postoperative therapy.

In a meta-analysis in 2006, seven trials of neo-adjuvant chemotherapy in patients with resectable NSCLC demonstrated a 6% overall survival benefit ($P = 0.02$) for the induction chemotherapy group compared with surgery alone.

In 2007, adjuvant chemotherapy became an accepted standard in resected stage II and III NSCLC, resulting in premature closure of the phase III SWOG 9900 study of surgery with or without preoperative paclitaxel–carboplatin in stage IB–IIIA (excluding N2 disease and superior sulcus tumors) resected NSCLC. The response rate to induction chemotherapy was 41%, and median PFS (62 vs. 41 months PFS; HR: 0.79; $P = 0.11$) and OS (33 vs. 20 months OS; HR: 0.80; $P = 0.10$) favored the preoperative chemotherapy arm. Although OS and PFS was higher with preoperative chemotherapy instead surgery alone, these results were not statistically significant, and stronger evidence existed for postoperative chemotherapy in resected NSCLC.

In 2007, the results of MRC LU22–NVALT 2–EORTC 08012 trial were published. Patients (N = 519) with resected stage I-III NSCLC were randomized to surgery alone or three cycles of platinum-based chemotherapy followed by surgery. Surprisingly, despite the fact that 75% of patients in this trial received all three cycles of chemotherapy, there was no survival benefit in the neo-adjuvant chemotherapy arm when compared with the control arm. Stage imbalances within the trial may explain the negative results—61% of patients in this trial had stage I disease, for which several trials have failed to demonstrate benefit from adjuvant chemotherapy (31% had stage II, and only 7% resected stage III NSCLC). The Spanish NATCH trial randomized 624 patients with stage IA ($T > 2$ cm), IB, II or T3N1 NSCLC to surgery, three cycles of preoperative paclitaxel–carboplatin, followed by surgery, or to surgery followed by three cycles of postoperative paclitaxel–carboplatin. Although 97% of patients received chemotherapy in the preoperative arm compared to only 66% of those randomized to receive it as adjuvant therapy, no difference in outcome was observed. Again, there was a predominance of stage I patients (more than 75% of all patients). A more recent meta-analysis of 13 randomized trials demonstrated significant improvement in survival with preoperative chemotherapy compared to surgery alone (HR: 0.84; $P = 0.0001$). This effect appeared to be derived from those with stage III disease, and insufficient data was available for stage I and II patients, although, on balance, data did not support an effect in earlier-stage disease.

One of the greatest limitations of neo-adjuvant trials in resectable NSCLC is the accuracy of preoperative staging, upon which appropriate treatment depends. Trials in this area include heterogeneous patient populations and varying treatment regimens. The question of whether neo-adjuvant or adjuvant chemotherapy is better in patients with resectable NSCLC remains unanswered, and adjuvant chemotherapy is the standard of care for eligible patients who undergo surgical resection.

Case study 76.4

A 64-year-old woman, a lifetime nonsmoker, was found to have a right middle lobe 4 cm mass on chest X-ray during follow-up of a nonresolving pneumonia. PET–CT scan confirmed a metabolically active right middle lobe mass, along with a 2.5 cm metabolically active right upper lobe nodule. She had no evidence of extrathoracic metastatic disease, including normal magnetic resonance imaging of the brain. Biopsy revealed well-differentiated lung adenocarcinoma in both tumors, and genotyping results confirmed the tumors were *EGFR* wild type and *ALK* fusion negative. Mediastinal lymph node stations 2R and L, 4R and L, and 7 were negative for metastatic disease by EBUS fine needle aspirate biopsy. She is fit, with excellent pulmonary and cardiac function and no comorbidities. After pathology review, it was deemed that this was the same cancer rather than two primaries.

• Should she go for radical surgery (T4N0), or should she be considered to have metastatic disease?

The most important prognostic factor for survival in NSCLC is the TNM (tumor, node, and metastasis) stage. In the presence of multiple lung lesions, it may be difficult to distinguish multiple synchronous tumors from metastatic lesions. Synchronous lung tumors remain a therapeutic challenge often with ongoing debate about whether they are distinct primaries or metastatic lesions. Antakli *et al*. (1995) suggest that tumors of differing or the same histology, in the absence of metastatic spread to mediastinal lymph nodes, can be classified as synchronous primaries rather than metastatic. Based on the population studies and retrospective analyses, the 7th edition of TNM staging for lung cancer has downstaged nodules in the ipsilateral lung from M1 to T4. Resection of these nodules may yield comparable survival to patients with stage I and II NSCLC. In the setting of intrapulmonary metastatic NSCLC, selected patients (e.g., with bronchioloalveolar adenocarcinoma (BAC)) may have up to 60% 5-year survival after resection. However, it is impossible to separate the indolent natural history of BAC from any potential benefit from surgical resection without a randomized trial. Lung transplantation in highly selected patients with unresectable multifocal BAC has a documented 5-year survival rate of 51%, but recurrence occurred in nearly 50% of patients.

Whenever two primary lung cancer tumors are diagnosed without evidence of distant metastases, surgical resection should be recommended in fit patients. There are multiple factors that should be considered before surgery, including the clinical stage of both tumors, the extent of resection required, and the patient's pulmonary function, as well as the role of systemic therapy prior to resection. It is unlikely that randomized trials of surgery versus a palliative approach will be conducted; in retrospective single-institution reports, even the survival of patients with bilateral synchronous lung cancers, when treated aggressively with surgery and adjuvant treatment, exceeded that of patients with metastatic NSCLC treated with systemic treatments. Without surgical excision, long-term survival is unlikely. While we do not have the data to suggest that the outcome of surgical management of synchronous lung cancer tumors is different from that of tumors that may represent metastatic lesions, these cases should be reviewed by a larger multidisciplinary tumor board. The role of adjuvant therapy in patients with resected multifocal NSCLC without nodal involvement remains controversial, but adjuvant chemotherapy should be discussed with patients with evidence of lymph node metastases.

Case study 76.5

A 62-year-old man, an ex-smoker with a 20-pack-year smoking history, was diagnosed with T4 lung adenocarcinoma invading the carina. His PET–CT scan showed no evidence of distant metastases, and mediastinal staging by EBUS revealed no mediastinal or regional lymph node involvement. His final clinical stage is deemed to be T4N0M0 (IIIA). He is fit, and his comorbidities include well-controlled hypertension and hypercholesterolemia, with no weight loss and excellent pulmonary function. His case was discussed at the local multidisciplinary tumor board meeting. In the opinion of thoracic surgeons, the lesion was technically resectable, and the patient was a surgical candidate. The radiation and medical oncologists recommended bimodality therapy with radical radiation (66 Gy) combined with concurrent cisplatin and etoposide chemotherapy.

• Given the patient's young age and the absence of medical conditions that would impose significant risk for surgery, should he be treated with surgical excision or with combined chemoradiation alone?

Stage III NSCLC is a heterogeneous disease, comprising both technically resectable and unresectable cancer. While

(*Continued*)

concurrent chemoradiation is accepted as a standard treatment of unresectable disease, surgical advances are rendering a larger number of stage III tumors potentially resectable, particularly T4 tumors. Many T4 tumors are deemed unresectable; even if resected, studies suggest a poor survival rate but often include patients with multilevel mediastinal node involvement, rather than those who have only T4N0 or N1 tumors.

Because T4 tumors invade major mediastinal structures, including the trachea, esophagus, thoracic spine, great vessels, and heart, they are still considered a relative contraindication for surgery because of poor outcomes after surgical excision, and because of the complexity and technical challenge of such resections. However, carefully selected patients with T4 tumors may achieve long-term survival after surgical resection based on multiple, retrospective, single institution–based reports with resectability rates from 40% to 90%.

Specific subgroups (i.e., those with superior sulcus tumors, carinal invasion, and mediastinal invasion) have different surgical outcomes that depend on the extent of surgical resection and the nature of loco-regional complications. Trimodality therapy is often considered standard in fit patients with superior sulcus tumors (T4N0 or N1) able to withstand chemoradiation and surgical resection. A phase II Intergroup Trial (INT0160) enrolled patients with T3–4 N0–1 superior sulcus NSCLC, treating them with two cycles of etoposide–cisplatin and 45 Gy of concurrent radiation, thoracotomy in those with stable or responding disease, and two further cycles of consolidation chemotherapy. Of 110 patients enrolled, 95% completed induction chemoradiation. Eighty percent of those eligible for surgery underwent thoracotomy, with a complete resection rate of 76%. Complete pathologic or major response was seen in 56% of patients, 5-year survival was 44% in all patients, and it was 54% after complete resection. Distant metastasis was the main site of failure.

Unfavorable outcomes are associated with tumors invading spine, esophagus, and mediastinal cardiovascular structures such as the great vessels and the heart. Limited data on the use of cardiopulmonary bypass techniques, to facilitate surgical resection of T4 lesions invading mainly mediastinal great-vascular structures, report no adverse events during this procedure and suggest cardiopulmonary bypass as helpful and feasible in these complex surgeries requiring vascular mediastinal reconstruction. Shiraishi *et al*. (2005) reported their experience with surgical resection of T4 NSCLC tumors invading the thoracic aorta and analyzed the outcome of 16 patients who underwent surgical resection. Half underwent pneumonectomy, and the rest lobectomy, with a 50% rate of complete resection. Cardiopulmonary bypass technique was used in seven patients. The overall cumulative survival at 3 and 5 years was 34.7% and 17.4%, respectively, and patients who underwent complete surgical resection achieved a 5-year survival rate of 36.5%.

Retrospective, single institution–based experience with preoperative induction chemotherapy and radiotherapy in the management of T4N0 tumors is encouraging. The administration of induction chemoradiotherapy increased resectability, and pathological response to chemoradiotherapy has significant prognostic value in those patients, including patients with T4 tumors invading the spine. An analysis of 23 patients revealed that complete resection after induction chemoradiation or chemotherapy was achieved in 83% of cases. The 3-year survival was 58%, with pathologic response predicting better outcome.

Although controversy persists for patients with T4 tumors and optimal management, highly selected groups of patients with T4N0 NSCLC may benefit from surgical resection, usually as part of multimodal therapy. Patients with complete resection, with no evidence of mediastinal nodal metastases, and without need for pneumonectomy, based on nonrandomized, retrospective data, may achieve long-term survival with this approach. These cases should be discussed at multidisciplinary tumor boards, treated at high-volume centers with significant experience, and considered in T4N0/1 NSCLC whenever a complete resection is technically feasible and the patient's condition allows for complex and extensive surgery.

Case study answer

Case study 76.1

Question 1: Answer D

Selected reading

Albain KS, Swann RS, Rusch VW, *et al*. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379–86.

Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol. 2006;1(7):611–21.

D'Angelo SP, Janjigian YY, Ahye N, *et al*. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol. 2012;7(12):1815–22.

Fischer S, Darling G, Pierre AF, *et al*. Induction chemoradiation therapy followed by surgical resection for non-small cell lung cancer (NSCLC) invading the thoracic inlet. Eur J Cardiothorac Surg. 2008;33(6):1129–34.

Pignon JP, Tribodet H, Scagliotti GV, *et al*. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–9.

Tsao MS, Sakurada A, Ding K, *et al*. Prognostic and predictive value of epidermal growth factor receptor tyrosine kinase domain mutation status and gene copy number for adjuvant chemotherapy in non-small cell lung cancer. J Thorac Oncol. 2011;6(1):139–47.

For further information on this area please also consult Chapters 108, 120, 131, and 136

CHAPTER 77

Recurrent and metastatic non-small-cell lung cancer and novel targets

Evan Pisick[1] and Ravi Salgia[2]

[1]Cancer Treatment Centers of America, Zion, IL, USA
[2]The University of Chicago Medicine, Chicago, IL, USA

Case study 77.1

A 64-year-old man, with a 40-pack-year history, presents with chest pain and dyspnea. During his work-up, a chest X-ray reveals a right lower lobe mass. He undergoes a bronchoscopy and biopsy that reveals non-small-cell lung cancer (NSCLC), adenocarcinoma histology. Computed tomography (CT) and positron emission tomography (PET) scans reveal a right lower lobe mass, mediastinal and hilar adenopathy, and hepatic metastases. Magnetic resonance imaging (MRI) of the brain is negative for metastases.

1. What molecular testing on his cancer is appropriate for this patient?

A. Epidermal growth factor receptor (EGFR) mutation
B. K-ras mutation
C. EML4–ALK translocation
D. ROS1 translocation
E. All of the above

EGFR mutations are found in 15% of patients, EML4–ALK translocations are found in 4–5% of patients, and ROS1 translocations are found in 1–2% of patients. K-ras mutations are found in 20–25% of patients and may be associated with a poorer prognosis. As new molecular (genomic or proteomic) tests are available, the relevance of other molecular diagnostic tests will expand. There are a number of companies (as well as academic sites) that offer these tests, and it is important to have expert analysis of these markers.

2. This patient tests negative for an EGFR mutation and for EML4–ALK and ROS1 translocations. What would be an appropriate initial treatment regimen?

A. Carboplatin, paclitaxel, and bevacizumab
B. Cisplatin and pemetrexed
C. Carboplatin and paclitaxel
D. Cisplatin and gemcitabine
E. A and B
F. All of the above

All of the above regimens are appropriate for this patient, but A is a regimen that should be used as long as patients do not have a contraindication for use of bevacizumab. Eastern Cooperative Oncology Group (ECOG) trial E459 randomized patients to carboplatin and paclitaxel versus the same chemotherapy with bevacizumab, followed by maintenance therapy with bevacizumab until disease progression. The data revealed a significant increase in median overall survival, progression-free survival, objective response, and 1- and 2-year survivals in the group that received bevacizumab. However, in clinical practice, decision making has to be based on how the patient can tolerate the therapy.

3. After completing 4–6 cycles, this patient has a partial response to therapy. Which of the following would be the best options for this patient?

A. Maintenance therapy with single-agent bevacizumab
B. Maintenance therapy with pemetrexed
C. No further therapy, but restart therapy when he progresses.
D. All of the above

If the patient is started on carboplatin, paclitaxel, and bevacizumab, then bevacizumab should be continued after an initial 4–6 cycles until disease progression as it has shown superior efficacy in ECOG trial E459. If the patient were started on cisplatin and pemetrexed, then pemetrexed should be continued after an initial 4–6 cycles until disease progression.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 77.2

A 58-year-old woman, with a 20-pack-year history of smoking, presents to her primary care physician with a 2-week history of hemoptysis. A chest X-ray reveals a left hilar mass. She undergoes a bronchoscopy with biopsy of the mass, which reveals a squamous NSCLC. CT and PET scans reveal metastases to bone and liver. MRI of the brain is negative for metastases.

1. EGFR mutation testing should be performed in this patient?

A. Yes
B. No

Patients with squamous histology have been shown to have an EGFR mutation in less than 4% of cases, but patients with a positive mutation may respond to therapy with erlotinib. K-ras mutation testing can also be done, as this mutation may confer a poorer prognosis and a lesser response to erlotinib therapy.

2. Which of the following would be an appropriate treatment regimen?

A. Carboplatin and paclitaxel
B. Cisplatin and pemetrexed
C. Cisplatin and gemcitabine
D. Cisplatin and docetaxel
E. A, C, and D
F. All of the above

A, C, and D are all acceptable regimens for patients with squamous cell histology. A randomized clinical trial revealed that cisplatin and gemcitabine were superior to cisplatin and pemetrexed in patients with squamous cell histology.

Case study 77.3

A 56-year-old woman who is a nonsmoker presents to her local emergency room after suffering a seizure. MRI of the brain reveals multiple brain metastases. CT scans of the chest, abdomen, and pelvis reveal a left lower lobe mass, a left pleural effusion, and a right adrenal metastasis. She undergoes a CT-guided biopsy of the left lower lobe pulmonary mass, and it reveals NSCLC, adenocarcinoma histology. She receives whole-brain radiation therapy (WBRT) for the metastatic disease to the brain.

1. What molecular testing would be appropriate for this patient?

A. EGFR mutation
B. EML4–ALK translocation
C. ROS1 translocation
D. All of the above

All of the above tests are appropriate for patients with NSCLC, adenocarcinoma histology. EGFR mutations are found in 15% of patients, EML4–ALK translocations are found in 4–5% of patients, and ROS1 translocations are found in 1–2% of patients.

2. This patient tests positive for an EGFR mutation. Which of the following would be the *BEST* option for this patient?

A. Carboplatin, paclitaxel, and bevacizumab
B. Erlotinib
C. Cisplatin and pemetrexed
D. Crizotinib

The Optimal and EURTAC trials both showed increased progression-free survival when given in the first-line setting over cytotoxic chemotherapeutic regimens.

3. This patient tests positive for the EML4–ALK gene rearrangement. Which of the following would be the *BEST* option for this patient?

A. Carboplatin, paclitaxel, and bevacizumab
B. Erlotinib
C. Cisplatin and pemetrexed
D. Crizotinib
E. All of the above

A phase I trial revealed increased 1- and 2-year survivals over historical controls, and a randomized phase II trial revealed increased progression-free survival over cytotoxic chemotherapy. Both trials were in patients who had been pretreated with chemotherapy, but based on these results, any patient with a known EML4–ALK translocation should be given crizotinib, as first-line therapy trials are being conducted. It is also important to note that if clinical trials are available, they should be considered.

Case study 77.4

A 68-year-old man is undergoing a preoperative work-up for a right total knee replacement. Chest X-ray reveals a left upper lobe spiculated mass. CT scan reveals a 3 cm left upper lobe mass with no hilar or mediastinal adenopathy. PET scan reveals hypermetabolic uptake in the left upper lobe mass but nowhere else. He undergoes a left upper lobectomy; pathology reveals a 3.2 cm NSCLC with adenocarcinoma histology, and all lymph nodes are negative for metastases. He receives no adjuvant therapy. He is being followed with serial exams and CT scans. Three years after surgery, he presents with 2 weeks of headaches with no other neurologic symptoms. MRI of the brain reveals a solitary mass in the right frontal lobe. CT and PET scans reveal no other systemic disease.

1. What would be the appropriate next step for this patient?

A. Craniotomy with resection of the mass
B. Biopsy of the mass
C. WBRT
D. Stereotactic radiation therapy (SRS)
E. Chemotherapy
F. A and B

As the patient is 3 years out from his surgery and primary diagnosis, the pathology of the brain tumor needs to be determined. A primary central nervous system malignancy and metastatic disease from another primary have to be ruled out prior to determining treatment options.

2. If this patient undergoes a craniotomy and it reveals metastatic adenocarcinoma consistent with his lung primary, what would be the next *BEST* option for this patient?

A. WBRT
B. SRS
C. No further therapy
D. Chemotherapy

Three randomized trials have shown increased local control, and two have shown overall survival benefits from WBRT after craniotomy. SRS has been shown to improve local control but not affect overall survival. Another option for this patient would be to use SRS and WBRT in conjunction after biopsy of the tumor confirms metastatic disease from a lung primary, and this has been shown to be as effective as craniotomy followed by WBRT.

Case study answers

Case study 77.1

Question 1: Answer E
Question 2: Answer F
Question 3: Answer D

Case study 77.2

Question 1: Answer A
Question 2: Answer E

Case study 77.3

Question 1: Answer D
Question 2: Answer B
Question 3: Answer D

Case study 77.4

Question 1: Answer F
Question 2: Answer A

Suggested reading

Kwak EL, Bang YJ, Camidge DR, *et al*. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. New Engl J Med. 2010;363(18):1693.

Lopez-Chavez A, Young T, Fages S, *et al*. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the Eastern Cooperative Oncology Group 4599 Study: results of an exploratory analysis. J Thorac Oncol. 2012;7(11):1707.

Scagliotti GV, Parikh P, von Pawel J, *et al*. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543.

Vecht CJ, Haaxma-Reiche H, Noordijk EM, *et al*. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Annals Neurol. 1993;33(6):583.

Zhou C, Wu YL, Chen G, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735.

For further information on this area please also consult Chapters 71, 108, 120, 131, and 136

CHAPTER 78

Small-cell lung cancer

Stephen V. Liu[1] and Glen J. Weiss[2]

[1]University of Southern California School of Medicine, Los Angeles, CA, USA
[2]Cancer Treatment Centers of America, Goodyear, AZ *and* Translational Genomics Research Institute (TGen), Phoenix, AZ *and* University of Arizona College of Medicine, Phoenix, AZ, USA

Multiple choice questions

1. What is the leading risk factor for developing small-cell lung cancer (SCLC)?

A. Exposure to radon
B. Exposure to asbestos
C. Smoking cigarettes
D. Air pollution

Smoking cigarettes is the leading cause of SCLC, and it is not uncommon to diagnose this type of lung cancer in current smokers. Radon is a distant, second most common cause for lung cancer. Asbestos and air pollution are risk factors, but they are minimal when compared to cigarette smoking.

2. Should surgery ever be considered for a patient with limited-stage SCLC?

A. Yes
B. Yes, but only in a select group of patients
C. No

While many consider SCLC a systemic disease at diagnosis, there is a small subset of patients with limited disease who appear to benefit from surgery. Several retrospective analyses report 5-year survival rates approaching 50% for patients with pathologic stage I SCLC treated with resection. Of note, these data also demonstrate a significant discordance between clinical and pathologic staging. While surgical resection should be considered for patients with stage I SCLC, an exhaustive staging work-up, including positron emission tomography–computed tomography (PET–CT) and mediastinoscopy, must be completed prior to resection.

Case study 78.1

A 50-year-old woman is found to have a large lung mass on a preoperative chest X-ray. Work-up reveals a T2N1, limited-stage SCLC, and you recommend concurrent cisplatin plus etoposide with thoracic radiation.

- **What radiation schedule do you recommend?**

Twice daily ×30 treatments (15 days). While the ideal schedule is not known, hyperfractionation of radiation has been shown to improve survival in patients with limited-stage SCLC receiving concurrent chemotherapy. In this study, patients on the twice-daily schedule had a 5-year survival of 26%, compared to 16% for those treated once daily. There is increased toxicity, specifically a higher rate of acute esophagitis. Of note, a recent meta-analysis did not show a statistically significant difference in survival, but a trend toward better outcomes was noted. For patients able to comply with a twice-daily schedule, I would select a hyperfractionation approach. An ongoing RTOG trial is exploring a boost approach that delivers 70 Gy in 7 weeks.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 78.2

A 67-year-old man with limited-stage SCLC just completed six cycles of cisplatin and etoposide. A restaging CT scan shows a partial response.

1. Would you offer this patient prophylactic cranial irradiation (PCI)?

A. Yes
B. No

The brain has been an important site of late relapse for patients with SCLC, and the use of PCI has been shown to decrease the risk of future brain metastases and improve overall survival. Initial studies were conducted in patients with limited-stage SCLC who had achieved a complete response. Subsequent studies demonstrated similar benefit for patients with extensive-stage SCLC who achieved any response. While there are less prospective data for patients with limited-stage SCLC who achieve a partial response, PCI is a reasonable treatment strategy that is supported by current National Comprehensive Cancer Network guidelines.

Case study 78.3

A 62-year-old Asian man presents with shoulder pain and is found to have multiple osseous metastases and a large, central lung mass. Biopsies demonstrate SCLC. Brain magnetic resonance imaging shows no metastases.

• **What first-line regimen is best suited for this patient?**

Either cisplatin or carboplatin with etoposide. Platinum plus etoposide has been the standard for nearly 3 decades and remains so today. While cisplatin is the agent of choice in limited-stage SCLC, carboplatin appears to be an acceptable substitute in extensive-stage SCLC. The COSIS meta-analysis compared cisplatin and carboplatin in the first-line setting for SCLC and showed no significant difference in overall survival, progression-free survival, or response rate. The role of irinotecan remains unclear. Randomized trials in Japan demonstrated improved survival with cisplatin plus irinotecan compared to cisplatin plus etoposide. Two randomized trials in the United States failed to confirm this benefit. Until these discrepancies can be explained, the use of platinum plus etoposide is still considered standard of care. A triplet of cisplatin, etoposide, and ifosfamide was associated with a survival benefit over cisplatin and etoposide alone, but the toxicity was unacceptable. We await results of the ongoing phase III trial of carboplatin plus etoposide with and without palifosfamide, an active metabolite of ifosfamide with a more favorable toxicity profile.

Case study 78.4

A 50-year-old male former smoker is diagnosed with extensive-stage SCLC after presenting with progressive dyspnea and weight loss. Staging studies reveal a large, central lung mass with bulky mediastinal adenopathy, diffuse liver metastases, and 3 subcentimeter brain metastases. He has no neurologic symptoms but has significant dyspnea at rest.

1. What is the most appropriate treatment option?

A. Whole-brain radiation followed by cisplatin plus etoposide
B. Whole-brain radiation and concurrent cisplatin plus etoposide
C. Stereotactic radiosurgery to the brain metastases followed by cisplatin plus etoposide
D. Cisplatin plus etoposide
E. Surgical resection of the brain metastases followed by cisplatin plus etoposide

Brain metastases are very common in SCLC. When MRI is used as a screening study, the incidence of brain metastases at diagnosis is 24%, and approximately half of these patients are asymptomatic. In the absence of neurologic symptoms, initiation of systemic chemotherapy is reasonable, particularly when the primary lung lesion is causing symptoms. Systemic chemotherapy may also treat these brain metastases. In an analysis of patients with asymptomatic brain metastases, 27% demonstrated radiographic response after systemic chemotherapy. There is also a reported response to systemic chemotherapy in patients with symptomatic brain metastases, although the optimal sequence of therapy remains controversial.

Case study 78.5

A 55-year-old man recently diagnosed with extensive-stage SCLC has not yet started chemotherapy. He now presents with confusion and disorientation. Brain imaging does not reveal any abnormalities. He is euvolemic and has a serum sodium of 115 mEq/L and normal renal function.

- **How should he be managed?**

He should be treated with intravenous hypertonic saline, ideally in an intensive-care setting, and then systemic chemotherapy should be initiated. The patient has the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This paraneoplastic syndrome is often associated with SCLC. Treatment should be directed toward the underlying cause (i.e., SCLC). Correction of sodium in symptomatic individuals with SIADH using hypertonic saline should be performed in monitored settings to avoid complications such as central pontine myelinolysis. Patients with SCLC can also have other paraneoplastic syndromes. including Cushing's syndrome, Lambert–Eaton myasthenia syndrome, and limbic encephalitis.

Case study 78.6

A 68-year-old woman with extensive-stage SCLC has disease progression 4 months after six cycles of cisplatin and etoposide.

- **What is the best evidence-based treatment for her?**

Clinical trial or topotecan. When feasible, a clinical trial for SCLC that has progressed after first-line therapy is preferred. When a clinical trial is not feasible, then topotecan is the recommended US Food and Drug Administration–approved treatment, although outcomes are relatively poor.

3. What molecular testing is commonly used for treatment decision making for patients with SCLC?

None. There are currently no evidence-based molecular tests with proven benefit for patients with SCLC at the time of this printing. Recent reports of whole-exome sequencing provide promise that novel druggable molecular targets can be identified. Until those compounds become commercially available, coupled with data supporting molecular screening of SCLC for these targets, use of molecular testing in SCLC remains exploratory.

Multiple choice answers

Question 1: Answer C

Question 2: Answer B ("Yes, but only in a select group of patients")

Case study answers

Case study 78.2

Question 1: Answer A ("Yes")

Case study 78.4

Question 1: Answer D

Selected reading

Noda K, Nishiwaki Y, Kawahara M, *et al*. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med. 2002;346:85–91.

O'Brien ME, Ciuleanu TE, Tsekov H, *et al*. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006;24:5441–47.

Peifer M, Fernández-Cuesta L, Sos ML, *et al*. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012;44:1104–10.

Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010;85:838–54. Erratum in Mayo Clin Proc. 2011;86:364.

Rudin CM, Durinck S, Stawiski EW, *et al*. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet. 2012;44:1111–16.

For further information on this area please also consult Chapters 71, 108, 120, 131, 133, and 136

CHAPTER 79

Mesothelioma

Christopher W. Towe and Harvey I. Pass
NYU Langone Medical Center, New York University, New York, NY, USA

Case study 79.1

You are asked to see a 67-year-old female after an abnormal chest X-ray shows a unilateral pleural effusion and pleural-based mass. She is an otherwise healthy woman who is a nonsmoker, and she works from home selling pottery and taking care of her family. Her husband retired 5 years ago after working 40 years as an insulator. She reports right-sided chest pain and weight loss, but no cough, hemoptysis, or other symptoms. How would you approach making a diagnosis of malignant pleural mesothelioma (MPM) in this patient?

1. What is the relative importance of different environmental exposures?

The link between asbestos exposure and malignant pleural mesothelioma has been well documented in both human studies and animal models, and it is estimated that up to 5% of asbestos miners will develop MPM. The mechanism of asbestos-induced mesothelioma is thought to involve inhalation of insoluble fibers, which lead to chronic inflammation, genetic changes, and subsequent cellular oncogenic dysregulation. The incidence of MPM is ~2500 cases per year in the United States, and reflects a 25- to 40-year latency between exposure and tumor development. Outside of the United States, death rates from mesothelioma mirror national asbestos exposure, with high rates seen in Australian, New Zealand, Western Europe, and the United Kingdom. Although a dose–response relationship exists with all types of asbestos fibers in animal models of carcinogenicity, epidemiologic studies in humans suggest that amosite and crocidolite carry a higher risk that chrysotile fibers. Other nonasbestos mineral fibers, such as erionite (found in high levels in areas of Turkey as well as in regions of the western United States), also show a strong relationship to MPM prevalence.

The threshold exposure level below which MPM will not develop remains unclear. Professions other than miners with lower level exposure, such as plumbers, insulators, and carpenters, may also develop mesothelioma from asbestos exposure that is higher than that of the general population, but still much lower than that experienced by miners. As in our hypothetical patient, reports have shown that even wives of insulators have developed mesothelioma, presumably through exposure to their contaminated clothing. Other professions with cases of documented asbestos exposure include aircraft mechanics, aerospace workers, electricians, shipyard workers, auto mechanics, pipe fitters, construction workers, boilermakers, railway workers, mining, asbestos removal, and sheet metal workers. While the relationship between asbestos exposure and the development of MPM is incontrovertible, the level and type of exposure that lead to mesothelioma formation are unclear and remain a topic of intense research.

Although over 80% of MPM is attributable to asbestos exposure by patient histories, other factors may also predispose people to mesothelioma formation. Simian virus 40 (SV40) is a DNA tumor virus that has been associated with the formation of mesothelioma. Although animal studies show that pleurally injected SV40 alone can lead to MPM formation, controversial human studies suggest that SV40 may act as a co-carcinogen in asbestos-exposed individuals. Tobacco exposure's role in mesothelioma formation remains controversial, but it is generally not considered a strong risk factor for MPM formation, unless there is a history of consumption of Kent cigarettes, whose micronite

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

filter was constructed with asbestiform fibers. Other factors that may lead to malignant transformation are radiation and chronic inflammation of the pleura, such as tuberculosis, collagen vascular disease, and empyema thoracis. Genetics also clearly plays a key role in cancer formation, with implicated genetic predisposition through mutations in the neurofibromatosis gene, among others, and the recent observations of familial mesothelioma and uveal melanomas in individuals with germline mutations of the *BAP1* gene.

2. How is the diagnosis of mesothelioma made?

Diagnosis of MPM is suggested by risk factors, clinical presentation, physical exam, and radiographic imaging, but it ultimately depends on tissue diagnosis. The most common presenting symptoms are nonpleuritic chest pain (60%) and dyspnea (50–70%). Patients typically report several months of symptoms before seeking attention, with as many as 25% reporting more than 6 months of symptoms. On physical exam, evidence of effusion is common, and digital clubbing may reflect poor respiratory function secondary to entrapped lung. Weight loss (cachexia) is common in late-stage disease.

Mesothelioma can have a diverse radiographic appearance and may be confused with benign entities, such as pleural plaques or parenchymal pulmonary fibrosis. Chest radiograph classically shows pleural effusion, diffuse pleural thickening, and nodularity and more commonly affects the right side (60%). Often the lower chest demonstrates a loculated effusion, which may encase and trap the lung. Chest computed tomography (CT) can more clearly demonstrate the nature of the pleural thickening and effusion. CT accurately visualizes the involvement of the pericardium, diaphragm, and extrathoracic organs, such as the liver and stomach, but is poor in other regards. While certain radiographic "patterns" suggest malignant disease, CT radiographic criteria are insensitive and prevent the use of CT as the sole method of diagnosis. Positron emission tomography (PET) and the radionuclide imaging agent [^{18}F] fluoro-deoxyglucose (FDG) can be used to identify pleural malignancies and predict prognosis in patients with mesothelioma. However, studies of FDG-PET have shown poor sensitivity in identifying lymph node metastases, and therefore FDG-avid lesions should be pathologically confirmed before proceeding with a stage-defined treatment algorithm.

Soluble markers for mesothelioma are a promising new strategy for screening patients at risk for mesothelioma and improving diagnostic accuracy in patients with unclear diagnoses. The Mesomark assay (Fujirebio, Malvern, PA) is a commercially available assay that measures soluble mesothelin-related proteins (SMPRs); it has a high specificity (95%) but low sensitivity (32%), limiting its use as a screening test. Fibulin-3 has recently been identified as a specific (>95%) and sensitive (>90%) serum and pleural fluid marker of MPM, and it can accurately distinguish healthy persons with asbestos exposure from patients with mesothelioma. Although not commercially available, Fibulin-3 is a promising screening tool for mesothelioma.

Pathologic confirmation ultimately establishes the diagnosis of MPM, but it also carries a risk of equivocation. Patients with unexplained pleural effusions should undergo thoracentesis and closed pleural biopsy. Modern cell-block techniques have improved the diagnostic accuracy of pleural fluid analysis, but they remain imperfect with a reported sensitivity of only 70–80%. Patients who have negative pleural fluid and biopsy (or whose effusions recur after initial drainage) should undergo thoracoscopic evaluation. Video-assisted thoracoscopic surgery (VATS) is invaluable in providing diagnostic information and is the method of choice in acquiring tissue for analysis. VATS is also useful prognostically in that patients with more widespread disease on thoracoscopic evaluation showed consistently worse outcomes. In patients whose disease precludes the use of VATS due to obliteration of the pleural space, open (but limited) pleural biopsy is necessary, preferably in line with a potential cytoreductive incision for later removal.

Given the phenotypic heterogeneity of MPM, pathologic evaluation of pleural specimens is complex and outside the scope of this review. In general, evidence of stromal invasion remains the gold standard in diagnosis. However, the number of proliferating cells, their distribution, inflammation, and the presence of necrosis are important factors to consider. While significant controversy exists over the use of antibody panels, immunohistochemistry, and fluorescence in situ hybridization (FISH), the use of these adjunctive stains can facilitate diagnosis in certain cases, and usually reveals tumor cells that stain for cytokeratins, calretinin, and Wilms tumor 1.

3. How is MPM staged, and what are the prognostic implications of staging?

Multiple staging systems have existed for MPM, which reflects the controversial nature of the diagnosis and treatment of this disease. The initial system proposed by Buchart was nonquantitative and was intended to identify surgical candidates. It accurately prognosticates good outcomes for patients with stage I disease, but not those with later-stage disease. The Brigham system takes a more pathologic approach and emphasizes the importance of mediastinal lymph node involvement. The American Joint Committee on Cancer (AJCC) staging system for mesothelioma (see Table 79.1) is the most common staging system used in the United States. It was proposed by the International Mesothelioma Interest Group in 1995 based on the known

Table 79.1 American Joint Commission on Cancer–International Union Against Cancer international staging system for malignant pleural mesothelioma (Source: Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY. Springer, 2010. Reproduced with permission of Springer.)

Primary tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
T1	Tumor involves ipsilateral parietal pleura, with or without focal involvement of the visceral pleura.
T1a	Tumor involves ipsilateral parietal pleura (mediastinal, diaphragmatic), with no involvement of the visceral pleura.
T1b	Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura.
T2	Tumor involves any of the ipsilateral pleural surfaces with at least one of the following: • Confluent visceral pleural tumor (including fissure); • Invasion of diaphragmatic muscle; and/or • Invasion of lung parenchyma.
T3	Describes locally advanced but potentially resectable tumor Tumor involves any of the ipsilateral pleural surfaces with at least one of the following: • Invasion of the endothoracic fascia; • Invasion into mediastinal fat; • Solitary focus of tumor invading the soft tissues of the chest wall; and/or • Nontransmural involvement of the pericardium.
T4	Describes locally advanced, technically unresectable tumor Tumor involves any of the ipsilateral pleural surfaces with at least one of the following: • Diffuse or multifocal invasion of soft tissues of the chest wall; • Any involvement of rib; • Invasion through the diaphragm to the peritoneum; • Direct extension of any mediastinal organs; • Direct extension to the contralateral pleura; • Invasion into the spine; • Extension to the internal surface of the pericardium; • Pericardial effusion with positive cytology; • Invasion of the myocardium; and/or • Invasion of the brachial plexus.

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary and/or hilar lymph nodes
N2	Metastases in the subcarinal lymph nodes and/or the ipsilateral internal mammary or mediastinal lymph nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, or hilar lymph nodes, and/or the ipsilateral or contralateral supraclavicular or scalene lymph nodes

Distant metastasis (M)	
MX	Distant metastases cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis is present.

Stage grouping			
Stage I	T1	N0	M0
Stage Ia	T1a	N0	M0
Stage Ib	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T1, T2	N2	
	T3	N0, N1, N2	
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Ant T	Any N	M1

prognostic importance of tumor size (T) and the involvement of lymph node stations (N) in the chest. A revision to the AJCC staging system is currently underway using a registry of 3101 patients, with hopes to improve the accuracy of the current system given shortcomings in its ability to differentiate the survival of patients by stage. In that study, a cohort from 15 centers and 4 continents, median survival times by both clinical TNM (tumor, node, and metastasis) and pathological TNM staging were similar: stage I, 21 months; stage II, 19 months; stage III, 16 months; and stage IV, 12 months. The study specifically faulted the current system for its inability to differentiate the prognosis of stage T2 versus T1, N1 versus N2, and stage II versus I. The study also reemphasized several factors associated with good prognosis: epithelioid histology (vs. sarcomatoid), whether the patient underwent a procedure "with curative intent" (vs. palliation; median survival 18 vs. 12 months; $P < 0.0001$), and, among patients who received surgery, whether they received multimodal treatment (vs. surgery alone; median survival 20 vs. 11 months; $P < 0.0001$). Further analysis of other factors, including platelet count, white blood cell count, hemoglobin, and use of adjuvant therapy, is ongoing.

A more controversial question exists as to the importance of pathologic confirmation of nodal involvement in providing accurate staging. While studies have shown that PET–CT can identify MPM with high sensitivity and specificity, PET–CT has a low sensitivity for N2 and T4 disease. Therefore, many have advocated for "invasive" staging of patients suspected of having advanced disease by mediastinoscopy, thoracoscopic evaluation of resectability, and laparoscopic examination for occult abdominal disease. It should be noted, however, that mediastinoscopy may underestimate the presence of N2 disease given the predilection of MPM to metastasize to lymph nodes below the subcarinal level. Ultimately, the decision for "invasive" staging should be individualized based on clinical and radiographic parameters.

The patient in Case study 79.1 returns to your office with core needle biopsy–confirmed MPM and radiographic evidence of diaphragmatic involvement. She is otherwise in excellent physical health and has a good performance status. How should you approach her treatment?

4. What is the role for surgery in treatment of MPM?

Surgical therapy for treatment of mesothelioma remains controversial as there are insufficient randomized trials to guide decision making with regard to surgical intervention. The MARS randomized trial was an attempt to compare multimodality therapy for MPM with and without extrapleural pneumonectomy, but it failed to reach the expected number of accrued patients for meaningful power measurements, and was faulted for lack of prerandomization criteria, patient crossover, and a higher-than-expected surgical mortality. Therefore, while it is clear that patients with widespread disease do not benefit from surgical intervention, it is less clear which patients with nonmetastatic disease benefit from surgical resection and even less clear which surgery they should receive.

Unfortunately, the growth patterns of MPM can make complete surgical excision difficult. Unlike other solid tumors, nodular invasion and the irregular anatomy of the thoracic cavity often prevent surgical resection from removal of all microscopic disease (R0 resection). Instead, surgery is an integral part of a "multimodal" treatment approach, which, when correctly applied, can rapidly reduce the bulk of the tumor to microscopic levels that are then treated with adjuvant therapy. Two operations are routinely used in this cytoreductive tactic in an attempt to provide complete "macroscopic" resection: extrapleural pneumonectomy (EPP) and pleurectomy decortication (PD). A recent consensus statement has been published in order to standardize the nomenclature for mesothelioma operations.

EPP involves complete resection of the visceral and parietal pleurae, underlying lung, and often ipsilateral diaphragm and pericardium (which must be then surgically reconstructed at the time of the procedure). Surgical morbidity is considerable, but it has improved from unacceptably high mortality (>30%) in the 1970s to 3–8% mortality and 20–40% morbidity in modern series, which is comparable to other major oncologic surgeries (esophagectomy, hepatectomy, and pancreatic duodenectomy). The surgical results of EPP have been generally disappointing and overall offer limited benefit in survival relative to nonsurgical therapies. Median survival after surgery ranges from 9 to 17 months in most series. The longest survival is generally found among patients with early-stage (stage I or II) disease and among patients with epithelioid histology, where median survival of greater than 17 months is possible. There are also functional consequences to EPP, as pneumonectomy limits a patient's ability to receive treatment upon tumor progression, leading to a median time to death of 3 months once there is recurrence after EPP. The difficulty in widespread application of EPP to mesothelioma, therefore, has been reconciling the high morbidity of surgery with its marginal benefit and long-term sequelae.

PD is a "lung-conserving" approach to surgery for MPM, and it has been repopularized as a potential therapeutic cytoreductive modality. The goal of PD is to achieve an equivalent surgical resection while avoiding the high morbidities associated with EPP that are discussed in this chapter. Although controversial, it gained acceptance after

a retrospective study of 663 patients from three institutions demonstrated that patients undergoing PD had a survival that was at least equivalent to those who received EPP. Given the lack of appropriate prospective surgical trials, there are no consensus recommendations for the timing and extent of surgical therapy except that any patient who is considered a surgical candidate must be able to undergo a maximal cytoreduction of the disease. Nonetheless, physicians who encounter patients who *may* have a surgical option for MPM should consider referring the patient to an experienced mesothelioma surgeon at a known mesothelioma center, where the surgical procedure will reflect surgeon experience, patient characteristics, and emerging evidence of surgical benefit.

As mentioned, surgery is only part of a multimodal approach. Radiation has been used as an adjuvant therapy after surgery as mesothelioma is relatively radiosensitive. Radiation doses higher than 45 Gy have been successful at reducing the risk of local recurrence after EPP among selected patients. High-dose radiation therapy (RT) after PD has, in the past, been limited by radiation injury to the ipsilateral lung, which prevents its widespread application to these patients. Newer-intensity modulated RT protocols at selected centers are examining the use of RT not only after PD but also as a preoperative induction therapy in an attempt to limit collateral radiation injury.

Although MPM was previously considered to be chemoresistant, newer platinum-based therapy has shown promise as an adjuvant therapy for MPM. The efficacy of platinum and pemetrexed (antifolate agent) was established in 2003 in a multicenter randomized trial of patients with unresectable disease, which demonstrated improved median survival time (12.1 vs. 9.3 months; $P = 0.012$) and longer median time to disease progression (5.7 vs. 3.9 months; $P = 0.001$) in the combination therapy group compared with cisplatin alone. Although trials of chemotherapy have shown improved survival and that patients can be expected to achieve a partial response or stabilization of disease, chemotherapy alone is not considered a curative option.

Current trials are focusing on the use of "trimodality" therapy, and early results suggest that these therapies improve survival. In a multicenter trial of induction pemetrexed and cisplatin, followed by EPP and radiation (54 Gy), patients who completed all three stages of therapy showed a median survival of 29.1 months. In that study, complete or partial response to chemotherapy was associated with dramatically improved median survival (26 vs. 13.9 months; $P = 0.05$).

Overall, no "best" treatment algorithm has been established, and all patients with MPM should be considered for referral to clinical trials. The use of new agents, dose schedules, radiation techniques, and timing these therapies relative to surgery will be the key to improving outcomes.

5. What is the treatment approach to patients with unresectable disease?

Patients with unresectable disease have poor prognoses, and use of nonsurgical therapy is not curative. As mentioned in this chapter, cisplatin- and pemetrexed-based chemotherapy can improve median survival in unresectable patients. Prospective studies have also examined the use of pemetrexed and carboplatin with similar results. Small studies have shown good response rates with the use of gemcitabine in combination with platinum agents, but small sample sizes have limited the applicability of these results. Radiation can also be used in the palliative setting to reduce chest wall pain, with side effects of fatigue, nausea, and skin irritation. Surgery has been used in the palliative setting to control pleural effusions either through talc pleurodesis or by indwelling pleural drainage catheters with good effect. Palliation of ascites can be accomplished with a valved intraperitoneal catheter in order to help the patient be more functional for second-line therapy.

Three years after undergoing extended PD (with no radiographic evidence of disease), the patient in Case study 79.1 returns to your office with new-onset ascites and a new contralateral pleural effusion. What are her treatment options now?

6. What is the best "second-line" therapy for recurrent MPM?

Sites of recurrence after surgery are unfortunately quite predictable. The abdomen is the most common site of recurrence overall, and after EPP, diaphragmatic and pericardial margins are often involved.

There is no standard therapy for recurrent MPM, and patients who recur should be considered for enrollment in a clinical trial. Combination or single-agent therapies of gemcitabine, vinorelbine, paclitaxel, and docetaxel have been used with limited success. Single-agent vinorelbine and pemetrexed have both been studied specifically among patients who have received prior therapies and had disappointing results. In the pemetrexed study, relative to best supportive care (BSC), chemotherapy improved disease control rate (59.3% vs. 19.2%) but was not associated with improved survival (8.4 months for pemetrexed + BSC vs. 9.7 months for BSC alone; $P = 0.74$).

Palliative surgical options include chest wall debulking (controversial), and insertion of valved pleural and abdominal drainage catheters, which have been used with success.

7. What novel therapies and targeted molecular agents are being used?

Several targeted molecular agents have been used in the treatment of MPM with disappointing results. MPM expresses high levels of epidermal growth factor receptor (EGFR), but targeted therapies with erlotinib and gefinitib used in a phase II clinical trial have not shown promise. A phase II, multicenter, placebo-controlled, randomized trial of an anti-VEGF (vascular endothelial growth factor) monoclonal antibody, bevacizumab, or placebo in combination with gemcitabine–cisplatin did not improve progression-free or overall survival relative to placebo. Most recently, a large international study demonstrated no efficacy for the use of deacytylating agents (i.e., Vorinostat). Phase I and II trials of various agents are underway, including antimesothelin monoclonal antibodies, peptide vaccination against Wilms tumor, and recombinant antimesothelin immunotoxins.

Selected reading

Janne PA, Baldini EH. Patterns of failure following surgical resection for malignant pleural mesothelioma. Thoracic Surg Clin. 2004;14:567–73.

Pass HI, Levin SM, Harbut MR, *et al*. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. New Engl J Med. 2012;367:1417–27.

Rice D, Rusch V, Pass H, *et al*. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. J Thorac Oncol. 2011;6:1304–12.

Sugarbaker DJ, Wolf AS. Surgery for malignant pleural mesothelioma. Exp Rev Resp Med. 2010;4:363–72.

Zahid I, Sharif S, Routledge T, *et al*. What is the best way to diagnose and stage malignant pleural mesothelioma? Inter Cardio Thorac Surg. 2011;12:254–9.

PART 3

Breast Cancer

CHAPTER 80

Immunohistochemistry testing and beyond in breast cancer

Alejandro A. Gru[1] and D. Craig Allred[2]

[1]Ohio State University Wexner Medical Center, Columbus, OH, USA
[2]Washington University School of Medicine, St. Louis, MO, USA

Case study 80.1

A biopsy taken from a 68-year-old postmenopausal woman shows an invasive ductal carcinoma of no special type. Additional biomarkers show the tumor is positive for estrogen receptor (ER) and progesterone receptor (PgR). The report reads: ER positive (Allred score = 5 + 2 = 7 / 8) and PgR positive (Allred score = 3 + 2 = 5 / 8).

1. How is ER expression measured?

Immunohistochemistry (IHC) has proven to be more sensitive, specific, and cost-effective compared to previously performed biochemical ligand-binding assays (LBAs). Adherence to the most current recommendations by the College of American Pathologists (CAP) is very important to achieve similar results across different labs and for the purpose of standardization of the methods and results. Several quantitative scores have been created, such as the Allred score. There are advantages to using IHC over LBAs, especially its ability to measure ERα on routine formalin-fixed paraffin-embedded tissue (FFPET) samples, eliminating the need for fresh-frozen samples and the burdensome infrastructure required to provide it. Several head-to-head comparisons have demonstrated that assessing ERα by IHC can be equivalent to or better than LBAs in predicting response to endocrine therapy, which is comforting because IHC replaced LBA before such proof was available.

2. What are some of the limitations in ER expression testing?

Following CAP and American Society of Clinical Oncology (ASCO) approval for IHC-related testing, there were significant problems with the technical and clinical validation of IHC that persist today, resulting in inaccurate interpretations (i.e., positive vs. negative) in approximately 20% or more of cases. In the Eastern Cooperative Oncology Group (ECOG) 2197 trial, 11% of local ER tests were scored positive on central testing, with an overall concordance rate of 90%. In the ALTTO trial (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation; 5000 patients from countries worldwide), so far, 4.3% of tumors that tested ER+ in local laboratories were found to be negative (false positive) on central review. More than 20% of tumors exhibited at least some expression of ER (false negative) on central review. There are many causes for discrepancies and no easy solutions. There are useful guidelines and recommendations from ASCO and CAP. A strategy published by Harvey and colleagues was among the first to be well validated and is based on a highly specific and sensitive primary antibody to ERα (mouse monoclonal 6F11), a quantitative and reproducible method of scoring results (the so-called Allred score), and a definition of "positive" that is calibrated to clinical outcome in several large studies, including randomized clinical trials. The latter involved patients with all stages of breast cancer treated with tamoxifen or aromatase inhibitors in adjuvant, neoadjuvant, and advanced-disease settings. It is extremely difficult to standardize and validate IHC assays for ERα and PgR in a comprehensive manner, but any laboratory can utilize assays that have already been validated.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Noteworthy, all tumor areas of the tissue section on the slide should be evaluated. This can be achieved manually by counting cells or through image analysis.

3. How is positive ER or PgR defined?

A positive result is defined as follows: at least 1% or more of the tumor cells express ER by IHC. Studies evaluating ERα by IHC in breast cancer collectively demonstrate that about 75% express ERα, that it is almost entirely nuclear in location, and that there is tremendous variation of expression on a continuum ranging from 0% to nearly 100% positive cells. The term "equivocal" must not be used or reported. Importantly, the gradient is skewed such that tumors expressing even very low levels show a significant benefit far above that of entirely ERα-negative tumors, which are essentially unresponsive. Negative ER and PgR interpretations in tumors that characteristically have an ER+ phenotype (e.g., lobular, tubular, and mucinous carcinomas) should be confirmed by retesting. "Not interpretable" receptor results refer to samples that did not conform to pre-analytic specifications of the guidelines, they were processed using procedures that did not conform to guideline specifications of the lab operating procedures, or the assay used to analyze the specimen was not validated and controlled as specified in the guideline. Examples of circumstances leading to uninterpretable results include testing of needle biopsies or cytology samples fixed in alcohol, use of fixatives other than 10% NBF, biopsies fixed for intervals shorter than 6 hours or longer than 72 hours, samples where fixation was delayed more than 1 hour, samples with prior decalcification, and samples without internal or external controls. Recurrences should also always be tested to exclude prior false negatives and to document changes in biologic behavior.

Case study 80.2

A 56-year-old woman's breast biopsy is read as invasive lobular carcinoma. ER determination is read as negative, but the pathologist made a comment that the internal control (normal epithelial cells) also does not stain with ER.

- **What will be the next best step?**

Repeat the IHC. An apparently negative lobular breast cancer (IBC) in a sample where all the normal epithelial cells are also all negative should be repeated and confirmed because a significant proportion of normal cells are usually positive in most (>90%) samples.

4. What are some of the molecular tools to assess for ER expression?

Several strategies based on newer technologies than IHC have been developed to assess multiple prognostic and predictive biomarkers simultaneously. The OncoType DX® Assay measures RNA expression of 21 genes to determine a recurrence score (RS); ER and PgR are among the genes in the signature. Comparison between measures of ER and PgR protein expression by IHC and of mRNA by reverse transcription polymerase chain reaction (RT-PCR) showed a discordance rate of 9% and 12%, respectively. There are no published correlations of the individual measures of ER and PgR mRNA from the 21-gene signature with clinical outcome. Another strategy uses microarray technology to determine an RNA expression profile of estrogen-induced genes in IBCs, which appears to be very powerful in predicting response to endocrine therapy. The expression ratio of the *HOXB13* and *IL18B* genes, determined by quantitative reverse transcription PCR (qRT-PCR), also appears to be highly predictive of endocrine response. Eventually, multifactorial molecular approaches will replace IHC for determining prognostic and predictive factors in IBCs, including responsiveness to endocrine therapy. There are new immunofluorescence strategies that can simultaneously measure multiple proteins in a highly quantitative manner, which may revitalize the usefulness of IHC-like methods for the in situ assessment of prognostic biomarkers, which has advantages over assays evaluating homogenates of tumor tissue.

5. Why is it important to test for PgR expression?

PgR expression usually indicates an intact axis of the ER receptor. Patients with ER+ and PgR+ have a lower rate of tumor recurrence after tamoxifen compared to those who are ER+ and PgR−. Compared to ERα, there are fewer studies in the medical literature standardizing and validating IHC assays for PgR. There is a direct correlation between PgR levels and response to hormonal therapies, and tumors with even very low levels of PgR+ cells (≥1%) have a significant chance of responding. Thus, the ASCO–CAP guidelines recommend a cut point of ≥1% IHC-positive cells to define PgR positivity. PgR expression is also associated with reduced local recurrence in patients with ductal carcinoma in situ treated with lumpectomy and radiation followed by endocrine therapy.

6. What implications exist clinically when combining different results of ER and PgR status?

The four possible phenotypes (ER/PR: +/+, −/−, +/−, and −/+) show different rates of response to hormonal

therapy. In a recent comparison of patients receiving adjuvant tamoxifen, the relative risk of disease recurrence was 28% higher in patients with ER+ and PR− tumors than ER+ and PgR+ ones. It appears that ERα may also reside on the outer cell membrane in a subset of IBCs. A majority of these tumors are negative for PgR, but positive for HER2 and nuclear ERα, and the latter is thought to be nonfunctional in many of these tumors, consistent with their PgR− status. However, membrane ERα appears to be functional and promotes tumor cell proliferation in cooperation with overexpressed HER2. To further complicate matters, there is also evidence that tamoxifen has a stimulatory or agonist effect on membrane ERα, leading to the speculation that aromatase inhibitors may remain effective in this setting because they inhibit the upstream production of estrogen, which is the ligand for both nuclear and membrane ERα. If these preliminary studies are confirmed, then the quantitative assessment of PgR may have added importance, especially in the ERα and erbB2+ subset of IBCs.

Case study 80.3

A 72-year-old woman has an invasive ductal carcinoma of the breast. ER and PgR are reported as negative. A HER2 immunohistochemistry assay reveals 2+ positive staining. What will be the next approach?

• What are the implications of a positive or negative HER2 assay?

Perform *HER2* analysis by fluorescent in situ hybridization (FISH) in the patient described. *HER2* is a proto-oncogene located on chromosome 17. It encodes a tyrosine kinase receptor residing in the surface membrane of breast epithelial cells. It forms complexes with similar proteins (erbB1, erbB3, and erbB4) and acts as receptors for several ligands, such as epidermal growth factor (EGF), heregulin, and amphiregulin. It regulates many normal cell functions, including proliferation, survival, and apoptosis. The overall relationship between HER2 and clinical outcome is complex and varies with the clinical setting. A weak but significant association between poor outcome and a positive HER2 (overexpression or amplification) in patients receiving no additional therapy after initial surgery is seen. But this only represents a small fraction of patients. The majority of patients typically receive some form of adjuvant treatment. Some studies have shown that HER2+ breast cancers are resistant to certain types of cytotoxic chemotherapy (e.g., the combination of cyclophosphamide, methotrexate, and 5-fluorouracil) but sensitive to others (e.g., anthracyclines and taxanes). In general, it is accepted that HER2+ cancers appear to be associated with relative, but not absolute, resistance to endocrine therapies in general. However, this issue remains controversial. The most promising and useful findings are based on recent studies showing that HER2+ cancers respond favorably to new antibody-based therapies targeting specifically the HER2 protein, such as trastuzumab. Although this therapy was originally demonstrated effective in patients with metastatic disease, more recent clinical trials have shown significant benefits in the adjuvant setting for patients with less advanced disease. The NSABP-B31 clinical trial, which randomized patients with HER2+ cancer to adjuvant chemotherapy +/− trastuzumab, showed a 52% improvement in disease-free survival with the monoclonal antibody.

7. What is the best method to assess for HER2, and what do equivocal and negative results imply with regard to IHC and FISH testing?

HER2 amplification can be tested by IHC, as strong expression of the protein is directly related to gene amplification (3+ expression by IHC). FISH is indicated in cases where the protein is weakly positive (2+). Owens *et al*. (2004) observed a similar frequency of HER2-amplified cases by IHC (20%) among 116,736 specimens and by FISH (22%) among 6556 specimens. A positive HER2 test is defined as a result of 3+ surface protein expression (formed as uniform intense membrane staining of >30% of invasive tumor cells) or a FISH result of amplified *HER2* gene copy number (an average of >6 copies per nucleus for test systems without an internal control probe) or a *HER2–CEP17* ratio of more than 2.2, where *CEP17* is a centromeric probe for chromosome 17 on which the *HER2* gene resides.

Originally, FISH testing results were reported as either positive or negative, but an intermediate range (referred as an "equivocal range") has since been described and its clinical significance remains unclear. Much of the confusion in using this term comes from the need to define the need for trastuzumab treatment. There is also significant

variation in the intermediate (equivocal) ranges for both the IHC and FISH assays. The equivocal range for IHC consists of samples scored 2+, which includes up to 15% of samples. An equivocal result (2+) is complete membrane staining that is either nonuniform or weak in intensity but with obvious circumferential distribution in at least 10% of cells. Some, but not all, of these samples may have *HER2* gene amplification and require additional testing to define the true HER2 status. The equivocal range for FISH assays is defined as *HER2–CEP17* ratios from 1.8 to 2.2 or average gene copy numbers between 4.0 and 6.0 for systems without an internal control probe. About 3% of patients have ratios of 2.0 to 2.2 and were previously included in treatment arms with trastuzumab. Discordant results (IHC3+ and FISH−; or IHC <3+ and FISH+) have been documented in approximately 4% of cases. The significance of this is unclear. Equivocal results of a single test require additional action, which should be specified in the report. Equivocal results by IHC should follow confirmatory FISH analysis. Counting additional cells or repeating the test confirms equivocal FISH results. If the results remain indeterminate, confirmatory IHC is recommended. A negative HER2 test is defined as either an IHC result of 0 or 1+ for cellular membrane protein expression (no staining or weak, incomplete membrane staining in any proportion of tumor cells) or a FISH result showing a *HER2–CEP17* ratio of less than 1.8 or an average of fewer than four copies of the *HER2* gene per nucleus for systems without an internal control probe.

8. Are there alternative methods to measure HER2 amplification?

The bright-field in situ hybridization (ISH) techniques such as chromogenic in situ hybridization (CISH) and silver-enhanced in situ hybridization (SISH), which combine features of immunohistochemical analysis and ISH, have been introduced for the determination of HER2 status. The use of CISH in the evaluation of HER2 amplification appears to be equally effective when compared to the current gold standard, FISH. These new techniques allow results to be visualized by standard bright-field microscopy, and signals do not decay over time.

9. Are there other potentially helpful biomarkers that are not mandatory in the routine evaluation of breast carcinomas?

The Ki67 proliferation index testing appears to have a significant role for prognostic determination in early breast cancer. However, its role in breast cancer management is still unclear, and most of the time it is used in research studies and not in the routine assessment of breast tumors in clinical practice. About 17 of 18 studies that included more than 200 patients showed a statistically significant association between Ki67 and prog¬nosis, providing compelling evidence for a biological relationship, but the cutoffs to distinguish "Ki67 high" from "Ki67 low" varied from 1% to 28.6%. Perhaps one of the most attractive studies evaluating the role of Ki67 in the management of breast cancer has been the P024 study, where the authors observed that after 4 months of treatment with either letrozole or tamoxifen, there was a significant association between Ki67, ER status, tumor size, and node status with recurrence-free survival and OS. This mainstay publication served the basis for the determination of the Preoperative Endocrine Prognostic Index (PEPI) score. The PEPI score identifies a group of patients at the end of neo-adjuvant endocrine therapy with such an extremely low risk of recurrence on endocrine therapy alone that they might be spared additional chemotherapy. These authors have suggested that high PEPI scores identify those who most likely should receive chemotherapy, given that their tumors are relatively resistant to endocrine treatment. A separate study also advocated a possible role for Ki67 during neo-adjuvant treatment. They have shown that in patients who did not achieve a pathologic complete response, the Ki67 levels in the residual tumor were strongly associated with survival. This approach is therefore attractive for identifying patients for trials of additional adjuvant therapy after neo-adjuvant chemo¬therapy; such patients stand to benefit most from added therapy, and the *high event rate* should provide a rapid result.

10. What cutoff values are "most definitively accepted" when using Ki67 for high-proliferative or low-proliferative tumors?

Methods to develop cut points to distinguish positive from negative or high from low tumor marker results have been widely discussed in the literature. Using the IHC method for Ki67, many cutoffs have been used, although staining levels of 10–20% have been the most common to dichotomize populations.

11. What is Oncotype DX®?

Oncotype DX® is a prognostic test measuring the RNA expression of 21 genes, which provides a recurrence score (RS; range: 0 to 100) using FFPET tumor samples. The genes include proliferation markers (Ki67, survivin, and cyclin D1), invasion-related genes (*MMP11* and cathepsin), HER2, hormone receptors (HRs; ER and PgR), and others (*GSTM1*, *CD68*, and *BCL2*), as well as five housekeeping genes used to normalize expression overall. The RS quantifies the likelihood of disease recurrence based on studies in women with early-stage ER-positive-only breast cancer, and assesses the likely benefit from certain types of chemotherapy. Scores are reported as low (<18), intermediate (18–31), or high (>31) relative to risk of recurrence. Typically, patients in the high-risk group receive chemo-

therapy, and those in the low-risk group do not. Studies have demonstrated that treatment is modified in 31% of patients who are tested by Oncotype DX®, including omission of presumed unnecessary chemotherapy in 22%. Recently, the test has also shown similar prognostic and predictive significance in women with receptor-positive node-positive who received adjuvant treatment with the aromatase inhibitor anastrozole, and in cancer patients receiving neo-adjuvant hormonal therapy and chemotherapy. There is an important ongoing phase III clinical trial, referred to as the TAILORx study, designed to help optimize the use of adjuvant endocrine and chemotherapy in patients with receptor-positive breast cancer. The study is primarily designed to evaluate the effect of chemotherapy on those with a recurrence score of 11 to 25.

12. What type of molecular assay is MammaPrint®, and what is its clinical utility?

MammaPrint is a 70-gene prognostic index that was validated as clinically useful in studies of younger women with node-negative breast cancer by classifying them into low risk and high risk for disease recurrence. It requires frozen tumor samples. Genes involved in the regulation of cell cycle, invasion, and angiogenesis heavily weight it. Genes of interest do not include known prognostic markers such as ER, PgR, and HER2. The prospective validation of the MammaPrint® signature's prognostic value is currently ongoing through the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial. This trial opened in February 2007 and has enrolled over 6000 patients from five European countries. It assesses all patients by the standard clinicopathologic prognostic factors included in adjuvant settings and by the 70-gene signature assay. If both traditional and molecular assays predict a high-risk status, the patient receives adjuvant cytotoxic chemotherapy and also hormonal therapy if ER positive. If both assays indicate a low risk, no chemotherapy is given and ER-positive patients are given adjuvant hormonal therapy only. When there is discordance between the traditional clinicopathologic prognostic factor prediction of risk and the 70-gene signature prediction of risk, the patients are randomized to receive treatment based on either the genomic or the clinical prediction results. The primary goal of the study is to confirm that breast cancer patients with a "low-risk" molecular prognosis by MammaPrint and "high-risk" clinical prognosis can be safely spared chemotherapy without affecting distant metastasis-free survival (DMFS).

13. What type of molecular test is the PAM50? What is it used for?

The PAM50 was developed to efficiently determine intrinsic molecular subtypes based on evaluating 50 carefully selected genes using next-generation sequencing and FFPET samples. It is currently performed in a commercial reference laboratory, but an instrument dedicated to perform this will be available to pathology laboratories. The PAM50 test provides a risk-of-relapse (ROR) score initially based on studies of patients with node-negative breast cancer who did not receive adjuvant systemic therapy. The ability of ROR to predict prognosis has recently been confirmed as useful in an independent set of 786 patients with ER+ treated only with tamoxifen. In these studies, ROR was a better predictor than standard clinicopathologic variables, including Ki67, PgR, and histological grade. Most recently, PAM50 outperformed OncotypeDX® for predicting response to endocrine therapy in a large prospective clinical trial of receptor-positive node-negative patients.

Case study 80.4

A 42-year-old woman undergoes a resection of an invasive ductal carcinoma of no special type. The tumor is ER+, PgR+, and HER2−. She has no evidence of axillary lymph node or systemic metastases.

- **The margins are negative. Further molecular studies reveal a Luminal A intrinsic subtype. What are the molecular intrinsic subtypes?**

Four molecular subtypes were originally described: luminal, normal breast-like, HER2, and basal-like. Subsequently, luminal subtypes were further subdivided into Luminal A (Lum A) and Luminal B (Lum B). Luminal tumors are reminiscent of "normal luminal epithelial cells," including CK8/18+. Lum A are ER+ and enriched with genes associated with an active ER pathway, low levels of proliferation related-genes, low histological grade, and generally good prognosis. The Lum B tumors are typically higher grade, with high proliferation indexes and worse outcome, and a significant proportion are HER2+. Recent data show no good separation between Lum A and Lum B based on proliferation. The normal breast-like subtype has gene expression profiles similar to fibro-adenomas and normal breast enriched in adipose tissue genes. They are relatively poorly characterized, and their prognostic significance is unclear. Recent studies suggest that the normal breast-like group may be an artifact caused by contamination of samples with normal tissue. The HER2+ subtype shows amplification or 3+ reactivity by IHC, and expresses many other genes

(*Continued*)

associated with the HER2 pathway. However, a good number of *HER2*-amplified, ER+ cancers fall into the Lum B category. The basal subtype expresses genes found in normal basal or mammary epithelial cells (MECs) of the breast, such as *CK5*, *CK14*, p-cadherin, caveolins 1–2, nestin, *CD44*, and *EGFR*. A minority has *EGFR* amplification. However, unlike MECs, they also express certain proteins characteristic of luminal epithelial cells, such as CK8, CK18, and KIT. Basal-like carcinomas are usually high-histological-grade tumors with high proliferation, necrosis, pushing borders, and lymphocytic infiltrate. Histological subtypes commonly seen in this category include medullary or metaplastic carcinomas. The basal-like subtype more commonly occurs in younger individuals, often of African American or Hispanic descent. The tumors usually show high initial response to cytotoxic chemotherapy, although the majority relapse and overall prognosis is very poor. These features are similar to those seen in tumors of patients with *BRCA1* mutation, and the *BRCA1* pathway is dysfunctional in basal-like cancers.

14. Can molecular intrinsic subtypes be determined on the basis of IHC?

Yes, but no definitive validation studies using IHC have been performed in the clinical practice. Therefore, if intrinsic subtyping is needed, a clinically validated gene-array platform is necessary.

The use of IHC has recently been advocated as a surrogate to microarray analysis to define the intrinsic molecular subtypes: expression by IHC of ER, PgR, and luminal cytokeratins (CKs) (CK8 and CK18); lack of HER2 overexpression; and low Ki67 are typical of Lum A. Expression of ER, PgR, and luminal CKs and HER2 overexpression are seen in Lum B. Absence of ER, PgR, and HER2 and expression of basal CKs (CK5/6) define basal-like tumors.

15. What is the pathologist's approach to sentinel lymph node biopsy (SLNB)?

The lymph node is carefully cut at 1 mm cross-sections. Each one will get three different levels (and the tissue in between IS spared). The current standard of practice does not include a routine CK stain if there is no histologic evidence of tumor cells by routine hematoxylin and eosin examination. SLNB has been developed and accepted in breast cancer management in recent years, although the involvement of non-SLNs and limited long-term data on those treated by SLNB alone have raised concern. More recently, a single study has shown that additional axillary lymph node dissection versus plain sentinel biopsy has not been proven to reduce the rate of loco-regional recurrence in breast cancer. This study might determine that the role of SLNB might be of capital importance in the management of breast cancer. Patients with SLNB positive undergo axillary dissection, which reduces the risk of loco-regional disease. However, this statement has been questioned recently.

16. How are lymph node metastases defined in the most recent World Health Organization (WHO) classification?

The sixth edition of the WHO staging guidelines for breast cancer introduces a semiquantitative assessment of nodal burden categorized as individual tumor cells or groups of cells <0.2 mm (ITC), micrometastasis between 0.2 and 2 mm diameter (Mi), and macrometastasis >2 mm. The chances of finding ITC in a 4 um section is on the order of 0.4%. Therefore, there will be a need for approximately 300 sections in order to find ITC with better accuracy in a 10 mm lymph node. A survey of 240 labs in Europe revealed that only 4% of labs use additional molecular tools in the evaluation of sentinel lymph nodes. The most problematic reason in the question "What tool is better for SLN evaluation?" is that it is not clear what the prognostic significance of ITC or micrometastasis is, using the WHO criteria. A meta-analysis by Cserni *et al*. (2004) has shown a 20% probability of non-SLNs being positive if the SLN contains low-volume disease (Mi or ITC) and 9% if the SLN metastasis is found by IHC alone. The risk of higher-echelon metastases has been related to SLN metastasis size and shown to be 2.24 times higher if the SLN metastasis is >1 mm, whereas with smaller SLN Mi, the risk is no greater than with ITC. Are these metastases in non-SLNs of prognostic significance in these patients? They may not be viable or capable of further growth because of their inability to induce angiogenesis or stromal support. Should these patients with ITC or micrometastatic disease in the axillary lymph nodes be offered adjuvant chemotherapy? As the biological and prognostic significance of these findings is unknown and there are no mature clinical trials to guide management, these questions are currently unanswerable. Current guidelines suggest that routine use of IHC to find occult micrometastatic disease or ITC is not justified, as the prognostic significance of this level of tumor metastasis is not established. Some pathologists would argue that routine use of IHC is justified to save time highlighting metastatic cells more efficiently. In addition, the sensitivity of frozen sections and imprint cytology for the histopathologic identification of node metastases in breast cancer is known to be limited. The most recent guidelines recommend that specimens be divided into pieces no more than 2 or 3 mm thick and that a single section be obtained from each to ensure a high probability of detecting all macrometastases.

17. What are some novel tools in the evaluation of SLNB?

One method, the one-step nucleic acid amplification assay (OSNA) allows automated detection of CK19 mRNA in samples of homogenized lymph node tissue. On the basis of cutoff values for CK19 mRNA, the method allows micrometastases and macrometastases to be distinguished along with low expression levels (which may correspond to ITCs), and numerous studies have shown a high level of specificity for the detection of lymph node metastases in patients with breast cancer. A recent study has shown significant discordant results between OSNA and histopathology in up to 42% of patients. Nearly 47% of patients with negative histopathologic studies on SLNB show a positive result on OSNA. In addition, OSNA was able to upgrade histologic micrometastases into macrometastases by molecular methods. No false-negative results were seen with the use of OSNA. Strikingly, >80% of nodes found to be positive for metastasis by OSNA assay were not identified as such by conventional histology. In the case of SLNB, up to 40% of metastases can be missed if a single 10 mm slice is done histopathologically.

18. What is the prognostic significance of circulating tumor cells (CTCs), and what is the role of their detection for clinical management for oncologists in general?

CTCs are strong predictors of survival in patients with metastatic breast cancer, and possibly in patients with less advanced disease. A recent meta-analysis indicated that the detection of CTCs was a stable prognosticator in patients with early-stage and metastatic breast cancer. The DETECT study has shown that the prognostic relevance of CTC detection in metastatic breast cancer patients depends on the test method. The study results indicated that the CellSearch system was superior to the AdnaTest Breast Cancer in predicting clinical outcome in advanced breast cancer.

In addition, a recent study by Lucci *et al*. (2012) identified one or more circulating tumor cells in 73 (24%) of 302 patients with no evidence of metastatic disease. Detection of one or more circulating tumor cells predicted both decreased progression-free survival (log-*rank* $P = 0.005$; hazard ratio (HR): 4.62; 95% CI: 1.79–11.9) and overall survival (log-rank $P = 0.01$; HR: 4.04; 95% CI: 1.28–12.8). The presence of one or more circulating tumor cells predicted early recurrence and decreased OS in chemotherapy-naïve patients with nonmetastatic breast cancer. These results suggest that assessment of circulating tumor cells might provide important prognostic information in these patients.

Conclusion

The use of high-throughput methods for the analysis of cancers has provided new opportunities for understanding the diversity and heterogeneity of cancers and to devise classification systems that better recapitulate the biology and clinical behavior of human tumors. Microarray-based gene expression profiling has highlighted the existence of breast cancer subtypes with distinct biology and clin¬ical behavior. One fundamental aspect of microarray-based class discovery studies, which has not been sys¬tematically analyzed, is the subjectivity involved in assigning the molecular subtypes through the analysis of dendrograms generated with hierarchical clustering methods. It is believed that the molecular intrinsic-subtype classification follows to some extent (Lum A and B, Her2, and basal-like) the clinical subgroups of breast cancer identified in the clinical practice (tamoxifen-sensitive ER+, tamoxifen-resistant ER+, trastuzumab-sensitive, and other).

A recent study by Reis-Filho *et al*. (2011) has provided direct evidence that the identification of subgroups of luminal cancers and normal breast-like cancers by visual inspection of dendrograms obtained from hierar¬chical cluster analysis showed suboptimal levels of interobserver agreement, even when the molecular subtypes are known a priori and guidelines for the identification of these subtypes are provided. The identification of basal-like and HER2 showed excellent scores in terms of interobserver agreement.

The reproducibility of the interpretation of histopathologic and immunohistochemical findings has been heavily criticized because of the "heavy subjectivity" involved in the human eye, which describes the routine work of pathologists. The need for more objective methods to guide breast cancer therapy in decision making is, therefore, justified. Hierarchical cluster analysis is undoubtedly a powerful tool for class discovery, and the work of Perou *et al*. (2000) represented one of the main publications in the next-step molecular identification of breast cancers in the twentieth century. However, hierarchical clustering, and all commercial available tests, which are based on this method, may not be ideal for breast cancer classification because they are neither objective nor entirely reproducible. In fact, the current molecular classification systems for breast cancer are similar to histopathology: descriptive and prognostic.

Based on the available data and the limitations of our knowledge on the heterogeneity of breast cancers, it is still not possible to determine with absolute certainty how many molecular cancers exist. It is, therefore, very important to stand back, look at the future of our specialty, and clarify that all our systems are complementary and not substitutable. The growing expansion of different molecular techniques will enrich the future of molecular pathology, and pathologists will be part of a practice that combines the traditional routine histology with advanced molecular analysis. But, the histopathologic evaluation and immunohistochemical interpretation in breast cancer will still remain a mainstay tool in the evaluation of breast cancers.

Selected reading

Allred DC. Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Mod Pathol. 2010;23(Suppl. 2):S52–9.

Gru AA, Allred DC. Molecular pathology of breast cancer. In: Cheng L, Eble JN, editors. Molecular surgical pathology. Berlin: Springer; 2013. p. 95–128.

Hammond ME, Hayes DF, *et al*. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med. 2010;134(6):907–22.

Wolff AC, Hammond ME, *et al*. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25(1):118–45.

CHAPTER 81

Prevention and adjuvant therapy in breast cancer

Faithlore P. Gardner and Edith A. Perez
Mayo Clinic, Jacksonville, FL, USA

• What are the best strategies for breast cancer prevention in postmenopausal women?

There are essentially two approaches to optimize breast cancer prevention in postmenopausal women. The first strategy consists of lifestyle modifications, such as exercising regularly, decreasing alcohol use, and minimizing exposure to combined estrogen and progesterone exogenous hormones. Regarding exercise, at least 60 cohort and case studies have examined the relationship between exercise and primary breast cancer prevention. Although the evidence has not all been consistent, most findings suggest a 15% to 20% risk reduction for women who exercise regularly compared to those who remain sedentary. The second strategy consists of chemoprevention. Currently, two selective estrogen receptor modulators (SERMS), tamoxifen and raloxifene, have been approved by the US Food and Drug Administration (FDA) for breast cancer prevention. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial, tamoxifen significantly deceased the number of invasive breast cancers by 49% ($P < 0.001$) compared to placebo. Similar risk reductions were found with raloxifene. However, both raloxifene and tamoxifen have increased risk of venous thromboembolism, and tamoxifen is associated with an increased risk of endometrial cancer. Given the toxicity profiles of these two drugs, and their perhaps lower-than-anticipated patient acceptance, they have failed to gain full adoption for primary breast cancer prevention.

Aromatase inhibitors (AIs) do suppress estrogen levels in postmenopausal women and are part of standard therapy for patients with early- or advanced-stage estrogen and/or progesterone receptor–positive breast cancer. Moreover, both nonsteroidal and steroidal AIs have been demonstrated to reduce contralateral primary breast cancers compared to tamoxifen or placebo in patients with early breast cancer, with an arguably better tolerability profile. These observations led to the MAP.3 study, a phase III, randomized, double-blind trial of exemestane (a steroidal AI) versus placebo for primary breast cancer prevention in postmenopausal women. A total of 4560 postmenopausal women with a median Gail risk score of 2.3% received exemestane at 25 mg daily for 5 years. After a median follow-up of 35 months, exemestane significantly reduced the relative incidence of invasive breast cancers by 65% in postmenopausal women compared to placebo, with an annual incidence of invasive breast cancer of 0.55% with placebo compared to 0.19% in the exemestane group (hazard ratio (HR): 0.35; $P = 0.002$). Additionally, exemestane reduced the risk of known breast cancer precursor lesions such as ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia, and atypical lobular hyperplasia. In terms of tolerability, there were no significant differences between the two groups in terms of skeletal fractures, cardiovascular deaths, other cancers, treatment-related deaths, or quality of life. Although not currently FDA approved for primary breast cancer prevention, exemestane or anastrozole administered for 5 years is a reasonable option for primary breast cancer prevention in postmenopausal women. Ongoing trials will further improve our understanding of the long-term efficacy and toxicity of AIs, as well as the optimal duration of therapy.

• What is the role of CYP2D6 in the efficacy and tolerability of tamoxifen in the chemoprevention setting?

There are currently two SERMs that are approved by the FDA for the chemoprevention of breast cancer, tamoxifen and raloxifene. Tamoxifen, a weak anti-estrogen, is metabolized in vivo to potent anti-estrogens, 4-hydroxy tamoxifen

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

and 4-hydroxy *N*-desmethyl tamoxifen (also known as endoxifen, felt to be the most abundant and active metabolite of tamoxifen). The metabolism of tamoxifen is mediated by several of the cytochrome P450 enzymes, including the CYP2D6-mediated oxidation of endoxifen.

Controversy exists regarding the association between CYP2D6 phenotype and the effectiveness of tamoxifen in the adjuvant and metastatic settings for invasive breast cancer. Depending on race, it has been estimated that 50% of women are thought to be extensive metabolizers (EMs), 43% are intermediate metabolizers (IMs) with reduced activity of CYP2D6, and 7% are poor metabolizers (PMs) with essentially negligible CYP2D6 enzyme activity. These genotypic variations of CYP2D6 have been showed to affect endoxifen concentration. Both IMs and PMs are likely to have decreased concentrations of endoxifen, which has been hypothesized to reduce the effectiveness of tamoxifen.

Numerous retrospective studies have shown conflicting results (i.e., both positive and negative associations of the CYP2D6 genotype and inhibition with tamoxifen efficacy). This heterogeneity of data was also seen in three large adjuvant clinical trials. Both the Breast International Group (BIG) I-98 clinical trial and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial found no statistically significant associations between the CYP2D6 genotype and breast cancer recurrence in tamoxifen-treated postmenopausal women. These two clinical trials are in contrast to the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8 clinical trial, in which PMs of CYP2D6 treated with 5 years of tamoxifen were shown to have a statistically significant increased risk of breast cancer recurrence compared to EMs. However, for patients who were randomized to 2 years of tamoxifen followed by 3 years of anastrozole, the CYP2D6 genotype was not associated with increased disease recurrence. However, there was a trend toward nonsignificant higher odds of a disease event among PMs of CYP2D6 relative to EMs in the first 2 years of tamoxifen similar to those who received tamoxifen alone, but no such trend was seen during the 3 years of anastrozole treatment, suggesting that the use of AIs after tamoxifen negates the trend toward disease recurrence. Overall, the data regarding the role of tamoxifen metabolism and clinical outcomes are inconsistent and remain controversial. There are currently prospective studies designed to test whether measured activity of CYP2D6 and other metabolizing enzymes significantly affects clinical adjuvant outcome to warrant routine testing.

Studies in the primary prevention setting are also worthy of mention. In a subgroup analysis of a small number of patients in the Italian Tamoxifen Prevention Trial, PMs of CYP2D6, of which there were only eight patients, had a higher risk of developing breast cancer compared to women who were EMs or IMs. This result suggested that a pharmacogenetic work-up for CYP2D6 may help to tailor tamoxifen therapy for breast cancer prevention to those who are most likely to benefit. Indeed, Irvin and his colleagues (2011) did demonstrate that it was feasible to have genotype-driven dosing of tamoxifen. Doubling the dose of tamoxifen did increase the endoxifen concentration for IMs and PMs. Interestingly, only with IMs did the endoxifen concentration reach the level found in EMs. However, in a nested case–control study using data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 and P2 prevention clinical trials, Goetz and colleagues (2011) sought to analyze the association between CYP2D6 genotype, CYP2D6 inhibitor use, and the combination of both with breast cancer events in women who received tamoxifen or raloxifene for the prevention of breast cancer. No association was found between the CYP2D6 genotype and the development of breast cancer in either the tamoxifen or raloxifene arms. Additionally, no association between the odds of developing breast cancer and the use of either a potent or weak CYP2D6 inhibitor with tamoxifen or raloxifene was found.

At this time CYP2D6 genotyping is not considered part of clinical standard of care for decisions related to the use of tamoxifen.

- **What are some of the genetic assays used to predict the risk of breast cancer recurrence, and how do they differ?**

Since the early 2000s, genetic assays have emerged as useful tools for assessing the risk of recurrence in patients with early-stage breast cancer. Several commercially available multiple-gene assays have been validated in node-negative breast cancer patients, including Oncotype DX™ (Genomic Health), MammaPrint™ (Agendia), Mammostrat™ (Clarient), and IHC4™. Both MammaPrint and Oncotype DX are based on gene expression profiling, whereas Mammostrat and IHC4 are based on immunohistochemistry (IHC) or protein expression profiling (see Table 81.1).

MammaPrint was developed in the Netherlands as a tool to help clinicians determine which patients with early breast cancer will develop metastases after curative surgery and radiotherapy (without systemic therapy). Using a 70-gene microarray, it stratifies women with hormone receptor–positive or –negative, lymph node–negative or –positive breast cancer to either a "low risk" or "high risk" of distant recurrence. Those women with low risk have a ~10% risk of developing distant metastases in the next 10 years without any adjuvant hormonal or chemotherapy. Those who are "high risk" have a 30% risk of distant recurrence and are thought to benefit from both neo-adjuvant and adjuvant chemotherapy. MammaPrint is currently the only FDA-approved prognostic and predictive assay, although its predictive ability for benefit to standard therapies needs to be better defined.

Table 81.1 Comparison of Oncotype DX™, MammaPrint™, Mammostrat™, and IHC4™.

Tests	Test methodology	ER status	LN	Results
Oncotype DX™	Quantifies the expression of 21 genes (16 target and 5 reference) in breast cancer by reverse transcriptase PCR	ER+, *tamoxifen treated*	LN− or LN+ (up to 3 positive LNs)	Low risk (RS $<$ 18), intermediate risk (18 $\leq$ RS $\leq$ 30), high risk (RS $>$ 31) ER, PR, HER2 status
MammaPrint™	Microarray technology that uses an expression profile of 70 genes	ER+ or ER−	LN− or LN+ (up to 3 positive LNs)	"Low risk" or "high risk" ER, PR, HER2 status Tumor type: luminal, basal, or ERBB2 (HER2) type
Mammostrat™	Uses 5 IHC biomarkers (SLC7A5, HTF9C, P53, NDRG1, and CEACAM5) to stratify patients into risk groups	ER+, *tamoxifen treated*	LN−	Low risk, moderate risk, or high risk
IHC4™	Prognostic score based on 4 standard IHC assays: ER, PR, HER2, and Ki67	ER+, tamoxifen treated	LN−	Score calculated using a mathematical algorithm (Cuzick *et al.*, 2011)

ER, estrogen receptor; HER2, human epidermal growth hormone 2; IHC, immunohistochemistry; LN, lymph node; PCR, polymerase chain reaction; PI, prognostic index; PR, progesterone receptor; RS, recurrence score.

Mammostrat, as opposed to MammaPrint or Oncotype DX, stratifies patients into low-, moderate-, and high-risk groups by measuring the protein-level expression of five biomarkers (SLC7A5, HTF9C, P53, NDRG1, and CEACAM5) in tumor tissue. It provides a score that predicts the 10-year risk of distant recurrence for ER+, node-negative breast cancer after 5 years of adjuvant endocrine therapy. In validation studies using archived samples from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials, it was found that women with "low risk" had a 7.6% chance of distant recurrence in 10 years, while those with "moderate risk" and "high risk" had a 16.3% and 20.9% chance of distant recurrence in 10 years, respectively. This platform has also been recently reported to be a good prognostic classifier in the adjuvant hormonal setting of breast cancer, in the context of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study.

IHC4 is a protein expression-profiling prognostic tool based on quantitative values of four standard laboratory assays (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67). IHC4 is combined with clinicopathologic parameters of tumor grade, size, nodal burden, and treatment with an AI or tamoxifen (IHC4 + clinical score (IHC4 +C)). The IHC4 score gives prediction of distant recurrence at 9 years for postmenopausal women with node-negative, hormone receptor–positive cancer treated with 5 years of adjuvant endocrine therapy. The IHC4 +C was found to have comparable prognostic information similar to that of Oncotype DX using the TransATAC data set and was also validated in an independent data set. A major advantage of IHC4 +C is its cost-effectiveness, as it is considerably less expensive than gene expression profiling tools. Another advantage is that it uses existing laboratory assays and in theory could be performed in the majority of clinical laboratories. However, lack of standardization of these assays may make implementation of this prognostic tool difficult.

The best-known and most utilized test is Oncotype DX. Oncotype DX is a 21-gene assay that uses a panel of 16 cancer-related genes and 5 reference genes to predict the likelihood of developing distant recurrence in estrogen receptor (ER)-positive, early-stage breast cancer. This recurrence score (RS) predicts a 10-year risk of distant recurrence after 5 years of adjuvant hormonal therapy. Ranging from 0 to 100, the RS can be subdivided into three risk categories: low (<18), intermediate (18–30), and high (>31) scores. This 21-gene assay has been shown to quantify the likelihood of breast cancer recurrence in several validation studies. In a validation study using paraffin-embedded tissue blocks from the NSABP B-14 tamoxifen-treated cohort, Kaplan–Meier estimates of the rates of distant recurrence at 10 years in the low-risk, intermediate-risk, and high-risk categories were 6.8%, 14.3%, and 30.5%, respectively. There are many other panels reported to play

a role in determination of prognosis, most recently expanded with the availability of the PAM50 assay. Further studies will be required to optimize the utilization of all of these panels in clinical practice.

- **Is molecular profiling needed for every patient diagnosis with invasive breast cancer?**

No, not every diagnosis. For many years, hormonal therapy with tamoxifen was the gold standard for patients with node-negative, ER-positive breast cancer. Then, in 1997, the NSABP-20 trial showed a significant benefit in adding chemotherapy to tamoxifen, although the absolute benefit was relatively modest. As a result of this clinical trial and others, many women with ER-positive, node-negative breast cancer receive combination chemotherapy and hormonal therapies, with the understanding that not all benefit from that approach.

A series of pivotal trials incorporating genomic profiles will help figure out who should routinely undergo the available tests, to determine whether there is significant benefit to adding chemotherapy for relevant subsets for which the retrospective studies done are not clear. The Microarray in Node Negative Disease May Avoid Chemotherapy (MINDACT) trial is an ongoing prospective, randomized clinical trial that will compare risk assessment using MammaPrint profile with risk assessment using the clinicopathological criteria of Adjuvant! Online. The results of the MINDACT trial should be available in 2014. The rationale for this study is strong. MammaPrint is currently the only FDA-approved multigene prognostic and predictive assay for early-stage breast cancers irrespective of hormone receptor or nodal status. MammaPrint was found to provide prognostic information beyond what was determined by the patient's age, tumor grade, tumor size, and ER status in a population of node-negative patients who did not receive adjuvant hormonal therapy or chemotherapy. It also performed better than outcome assessments derived from Adjuvant! Online. Indeed, there was 28–35% discordance between MammaPrint and Adjuvant! Online.

The Trial Assigning Individualized Options for Therapy (TAILORx) Trial is the second prospective trial eagerly awaiting analyses. In this trial, patients with an RS of 25 or higher will receive chemotherapy plus hormonal therapy, and patients will an RS lower than 11 will receive only hormonal therapy. Those with an RS between 11 and 25 will be randomly assigned to receive chemotherapy and hormonal therapy or hormonal therapy alone. It is noted that the intermediate group of TAILORx (women with an RS between 11 and 25) is different from the definition of "intermediate" in commercially available tests, where the score is between 18 and 31. This has prompted some physicians to offer chemotherapy to patients with a recurrence score greater than 26, to coincide with the study. The TAILORx study completed accrual, with data expected in 2017.

According to 2007 American Society of Clinical Oncology (ASCO) guidelines, in newly diagnosed patients with node-negative, estrogen receptor–positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are likely to benefit from tamoxifen therapy alone and may not require adjuvant chemotherapy. These 2007 guidelines were limited only to women treated with tamoxifen; however, a later study showed that the 21-gene recurrence score can also be applied to postmenopausal women treated with anastrozole as well. Combining the ASCO guidelines with National Comprehensive Cancer (NCCN) guidelines, molecular profiling based on tumor size may be the most cost-effective option. For node-negative or micrometastatic ($\leq$2 mm axillary node metastases) tumors that are less than 0.5 cm, molecular profiling is not needed as adjuvant chemotherapy is usually not recommended. For patients with node-negative tumors between 0.6 and 1.0 cm, molecular profiling can help guide therapy. For tumors larger than 1.0 cm, adjuvant chemotherapy is usually recommended. Adjuvant chemotherapy is also recommended for lymph node–positive breast cancer regardless of tumor size, although there is some evidence that gene profiling expression can also be used for women with three or fewer positive lymph nodes. The results of the MINDACT and TAILORx trials will further help clarify the role of molecular profiling for many patients.

- **How accurate is HER2 testing in breast cancer?**

Overall, there are three relevant areas that influence the accuracy of HER2 testing: (i) preparation of the specimen, (ii) the type of test performed, and (iii) the definition of HER2 positivity. To address these issues, ASCO and the College of American Pathologists (CAP) released joint consensus guidelines in 2007 with the overall purpose of improving the accuracy of HER2 testing in invasive breast cancer. Preparation of the specimen remains a crucial aspect in determining the accuracy of HER2 testing, and is sometimes referred to as the pre-analytical part of testing. The length of time to tissue fixation is the most important step in preparing the specimen for analysis. According to the ASCO–CAP recommendations, all breast tissue samples should be fixed in 10% neutral buffered formalin. Optimal fixation times are 6 to 48 hours, which should be documented in the pathology report.

There are currently two FDA-approved methods to assess for HER2 positivity. IHC analysis examines the overexpression of the HER2 protein on the cell surface, while fluorescent in situ hybridization (FISH) looks at gene amplification. Some have argued that the subjective decisions in IHC staining can lead to variability in HER2 testing by IHC, whereas counting copies of genes as done in the FISH methodology is a more objective process. However,

newer data and the ASCO–CAP 2007 guidelines state that when carefully validated testing is performed, neither IHC nor FISH is superior as a predictor of which patients with invasive breast cancer will benefit from anti-HER2 therapy. There are currently other methodologies such as HER2 mRNA testing, AQUA™ technology of automated quantitative analysis, and HERmark™, which are under further investigation to determine their role in the clinical setting.

The original and still-current FDA definition of HER2 positivity is considered a HER2 gene–to–chromosome 17 (HER2:CEP 17) ratio of at least 2.0 by FISH and/or an IHC score of 3+ high-intensity staining in 10% of the tumor cells. This was also the definition used for HER2 positivity for patients enrolled in clinical trials, including the pivotal adjuvant trastuzumab trials. The 2007 ASCO–CAP guidelines modified the definition of HER2 positivity, causing some confusion and uncertainty among clinicians and research investigators. According to the 2007 guidelines, HER2 positivity was defined as an IHC score of 3+ with more than 30% of the cell membranes staining intensely, and gene amplification of more than six gene copies per nucleus or a HER2–CEP17 ratio greater than 2.2. However, in N9831, it was found that using the new 2007 ASCO–CAP criteria for HER2 positivity would create a small but meaningful group of patients who may potentially benefit from life-saving trastuzumab therapy. Therefore, patients with a FISH ratio of 2.0 should be treated with anti-HER2 therapy. This new information, as well as others, was used to update the ASCO–CAP HER2 testing guidelines in 2013. An important factor that also needs attention is what patients should undergo a second test if the first test is negative for HER2, a situation that may be very important to avoid undertreatment and has already been demonstrated to be a cost-effective strategy.

• What is the best adjuvant endocrine therapy for patients with hormone-positive invasive breast cancer?

The use of adjuvant endocrine therapy is recommended for essentially all women with hormone receptor–positive breast cancer regardless of menopausal status, age, or HER2 status. Tamoxifen is the best established adjuvant endocrine therapy for both premenopausal and postmenopausal women. Adjuvant tamoxifen at a dose of 20 mg/daily decreases the annual risk of breast cancer recurrence by 39% and breast cancer mortality by 31%, irrespective of age, menopausal status, or the use of chemotherapy, for women with hormone receptor–positive breast cancer. Daily tamoxifen use is also associated with a decreased incidence in contralateral primary breast cancer. For those women who are receiving both adjuvant chemotherapy and endocrine therapy, chemotherapy should be given first, followed by endocrine therapy. Prospective clinical trials had established that the optimal duration of tamoxifen therapy is 5 years. Recently, the Adjuvant Tamoxifen, Longer Against Shorter (ATLAS) clinical trial has challenged that notion. In this study, 6846 women with ER-positive breast cancer who had remained disease-free after 5 years of tamoxifen therapy were randomized either to another 5 years of tamoxifen or to stop therapy. After a median follow-up of 7.6 years, continuing tamoxifen for 10 years reduced the risk of breast cancer recurrence ($P = 0.002$), decreased breast cancer mortality ($P = 0.01$), and reduced overall mortality ($P = 0.01$). Five years of adjuvant tamoxifen with or without ovarian ablation or suppression is recommended for premenopausal women with hormone receptor–positive early-stage breast cancer. More information related to ovarian ablation or AIs for premenopausal women is discussed in this chapter.

For postmenopausal women, adjuvant endocrine therapy with nonsteroidal (anastrozole or letrozole) or steroidal (exemestane) AIs has become the standard of care, whether it is given as a single therapy sequentially following 5 years of tamoxifen, or as initial endocrine therapy followed by 2–3 years of tamoxifen.

The ATAC trial showed that anastrozole was superior to tamoxifen alone or the combination of tamoxifen and anastrozole. For 5216 women with hormone receptor–positive early-stage breast cancer, anastrozole had fewer breast recurrences (HR: 0.85; $P = 0.003$) compared to tamoxifen, although there is no difference in overall survival. The Breast International Group (BIG) I-98 Study was a randomized trial testing tamoxifen alone for 5 years, letrozole alone for 5 years, tamoxifen for 2 years sequentially followed by letrozole for 3 years, or letrozole for 2 years followed by 3 years of tamoxifen therapy. Letrozole was associated with decreased risk of breast cancer recurrence (HR: 0.81; $P = 0.003$), especially distant recurrence (HR: 0.73; $P = 0.003$), although there was no difference in overall survival.

Overall, the results of these studies suggest that adjuvant endocrine therapy with AIs is statistically superior to tamoxifen therapy. However, it is not known whether initial, sequential, or extended use of adjuvant AIs is the optimal strategy. Also, what is not known is the optimal

Table 81.2 Selected ongoing studies for adjuvant endocrine therapy with aromatase inhibitors in postmenopausal women.

Study name	Study purpose
MA17R	5 versus 10 years of letrozole therapy
SALSA	2 versus 5 years of adjuvant arimidex therapy
SOLE	Intermittent versus continuous letrozole therapy after 4 to 6 years of prior adjuvant hormonal therapy
NSABP B-42	5 versus 10 years of adjuvant letrozole therapy

duration of adjuvant AI therapy. There are currently ongoing clinical studies to determine the optimal duration (i.e., intermittent versus continuous use) of AI therapy (see Table 81.2). The results of these studies will help determine guidelines for optimal adjuvant endocrine therapy in postmenopausal women.

Currently, AI therapy in premenopausal women is not recommended except in the confines of a clinical trial. Ongoing clinical trials are evaluating the strategy of ovarian suppression in combination with AIs. The Suppression of Ovarian Function (SOFT) trial is a phase III trial evaluating the role of ovarian function suppression with exemestane as adjuvant therapies for premenopausal women with hormone receptor–positive breast cancer. The Tamoxifen and Exemestane Trial (TEXT) is another ongoing phase III study examining disease-free and overall survival of premenopausal women with hormone-positive breast cancer when treated with triptorelin (a GnRH agonist) and exemestane versus triptorelin and tamoxifen. Data from these studies are expected in 2014. For now, premenopausal women should be treated with tamoxifen. For those women who become amenorrheic during therapy or after chemotherapy, serial assessments of circulating luteinizing hormone, follicle-stimulating hormone, and estradiol (in spite of caveats) could be considered to establish postmenopausal status before the initiation of therapy with an AI.

• What is the state-of-the-art adjuvant approach for triple-negative breast cancer (TNBC)?

TNBC is clinically characterized by the lack of expression of ER, PR, as well as HER2. They account for 15–20% of all newly diagnosed breast cancers. TNBC is associated with African American ethnicity, younger age, and advanced stage at the time of diagnosis. TNBC also tends to have higher recurrence, metastatic, and mortality rates.

Histologically, TNBC tends to be a heterogeneous group of cancers consisting of various histologic subtypes such as secretory or adenoid cystic tumors, which are generally less aggressive than high-grade tumors such as invasive ductal carcinoma, medullary breast cancer, and metaplastic breast cancer. An important phenotypic overlap is present with BRCA1-associated tumors and TNBC, as IHC-based studies have shown 80% to 90% of BRCA1-associated tumors as TNBC and/or basal-like breast cancer.

There are no specific molecular targets for TNBC. Current targets that have been studied include epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), Src kinase, the mammalian target of rapamycin (mTOR) pathway, androgen receptor, PDGFR, and c-KIT, to name a few. Although EGFR inhibition with cetuximab had shown some promise in preclinical data, the results of the TBCRC 001 clinical trial combining carboplatin with cetuximab in metastatic TNBC showed only an 18% overall response rate. Similarly, most other potential targets have been incompletely validated in TNBC, although there is some evidence that the new poly(ADP-ribose) polymerase (PARP) inhibitors may have an effect on the BRCA1/2 subgroup of TNBC. A molecular approach to TNBC is still being investigated.

There are no unique guidelines addressing targeted management of patients with TNBC. The NCCN includes TNBC in its overall guidelines, but they are nondirective on the management of this unique class of breast cancer. There are a variety of ongoing prospective clinical trials exploring therapeutic options for TNBC. For example, the BEATRICE study evaluated the benefit of adding a biologic such as bevacizumab to conventional chemotherapy in the adjuvant setting. However, according to results presented at the 35th annual San Antonio Breast Cancer Symposium in December 2012, adding bevacizumab to chemotherapy for the treatment of TNBC after surgery did not improve disease-free survival. After a median follow-up of 31.5 months in the chemotherapy-alone arm and 32 months in the bevacizumab arm, the 3-year invasive disease-free survival (IDFS) rate was 83.7% in the bevacizumab arm compared to 82.7% in the chemotherapy arm (HR: 0.87; $P = .1810$). Interim analysis of overall survival also was not statistically significantly different (HR: 0.84; $P = .2318$), although there were fewer deaths in the bevacizumab arm compared to chemotherapy (93 vs. 107, respectively). However, at the time of the analysis, only 59% of the required number of events had occurred. Further follow-up was needed to determine if the addition of bevacizumab improves overall survival, and the results were made available in 2013.

Until the results of all these various studies are published, the best approach for adjuvant chemotherapy in TNBC remains an anthracycline (A)- and taxane (T)-based regimen. There is increasing interest in the use of platinum agents as adjuvant therapy in TNBC, especially now that there are significant data of improved pathological complete response when carboplatin is added to A T regimens in the neoadjuvant setting. Trials including potential predictive biomarkers are in development.

• Is there a role in for mTOR inhibition in early breast cancer?

Not yet. The phosphatidylinositol 3 kinase (PI3K)–Akt–mTOR signaling pathway has emerged as a mechanism of endocrine resistance. There is a growing body of evidence supporting a close interaction between the mTOR pathway and ER signaling. Blockades of both pathways with everolimus, an mTOR inhibitor, and an AI have resulted in enhanced antitumor activity in preclinical models. This has led to several clinical trials assessing the efficacy of everolimus in conjunction with an AI in various clinical stages of breast cancer.

Baselga and colleagues (2009) conducted a phase II randomized controlled trial in which 270 postmenopausal women with operable ER-positive breast cancer were randomized to receive 4 months of neoadjuvant therapy with letrozole at 2.5 mg daily and everolimus at 10 mg daily or placebo. The results of this study showed that everolimus increased the efficacy of letrozole in the neo-adjuvant settings for ER-positive breast cancer. Additionally, the GINECO study showed that adding everolimus to tamoxifen increased time to progression and overall survival compared to tamoxifen alone in postmenopausal women with aromatase-resistant metastatic breast cancer.

The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study evaluated the efficacy and safety of the combination of everolimus and exemestane in patients with HR-positive breast cancer refractory to nonsteroidal AIs. The median progression-free survival (PFS) was 6.9 months for those patients who received everolimus and exemestane versus 2.8 months for those who received exemestane and placebo, corresponding to an HR of 57%. This result was consistent with the results found by Bachelot and colleagues (2012), who showed in a randomized phase II trial of 111 postmenopausal women with HR-positive, HER2-negative metastatic breast cancer that the combination of everolimus and tamoxifen was associated with significantly improved PFS relative to tamoxifen alone (8.6 months vs. 4.5 months) as well as significantly improved overall survival. However, results of BOLERO-2 were updated in 2014: no improvement in overall survival was observed.

Adverse events of everolimus, including stomatitis, fatigue, asthenia, diarrhea, cough, pyrexia, and hyperglycemia, were also observed in the BOLERO-2 study. Indeed, a high percentage (19% vs. 4%) of patients discontinued treatment in the everolimus group due to these adverse events. The long treatment duration in the combination therapy group might have contributed to the high discontinuation rate.

Temsirolimus, another inhibitor of mTOR, was recently studied in a randomized phase III placebo-controlled trial in combination with letrozole as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. However, this study showed no improvement in PFS when temsirolimus is added to letrozole in AI-naïve postmenopausal women. Additionally, more grade 3 to 4 toxicities were observed in the group that received letrozole and temsirolimus. However, in a planned subset analysis, women $\leq$65 years of age treated with the combination of letrozole–temsirolimus did have improved PFS (9.0 versus 5.0 months; $P = 0.009$), suggesting that younger postmenopausal women are the most likely to benefit from this combination of treatment.

These studies suggest that mTOR inhibition adds to the anticancer activity of anti-estrogen therapy in a variety of clinical settings for breast cancer. However, further studies are needed to evaluate women with early breast cancer who are most likely to benefit from the combination therapy. One such study is the SWOG S1207, which is a phase III, randomized, placebo-controlled clinical study examining the benefit of adjuvant endocrine therapy with or without one year of everolimus in patients with high-risk, hormone receptor–positive, HER2-negative breast cancer. Patients will be stratified according to risk level according to tumor size and nodal involvement: (i) node-negative and recurrence score (RS) >25; (ii) a tumor measuring $\geq$2 cm in greatest diameter treated with adjuvant therapy; (iii) a primary tumor with 1–3 positive lymph nodes and RS >25 treated with adjuvant therapy; (iv) a primary tumor with $\geq$4 positive lymph nodes regardless of RS score treated with adjuvant therapy; and (v) primary tumor with $\geq$4 positive lymph nodes and any RS score prior to or after neoadjuvant chemotherapy. Patients will be randomized to receive endocrine therapy for 2–5 years with either a placebo or everolimus for one year. The primary endpoint for this study will be IDFS with secondary endpoints of overall survival and distant recurrence–free survival (DRFS). The estimated completion date of the study is March 2016.

- **What is the real cardiovascular risk of anthracyclines used for the treatment of breast cancer?**

Anthracyclines are very active drugs against breast cancer. However, there is concern that treatment with anthracyclines can cause early or late cardiotoxic effects in a dose-dependent manner. Early effects may manifest as arrhythmias, usually within hours or days after administration of the drug, although rare cases of pericarditis, myocarditis, or sudden onset of left ventricular failure have also been observed. Late cardiac effects involve loss of left ventricular ejection fraction (LVEF), presenting as congestive heart failure and/or cardiomyopathy. The rate of severe toxicities is currently much lower than it was 20 years ago, as cumulative doses of doxorubicin higher than 360 mg/m^2 are hardly ever used in current practice.

Data from clinical trials suggest that anthracycline use is associated with a 0.45–2.00% increase in incidence in heart failure (HF) and/or cardiomyopathy (CM). When anthracycline use is followed by trastuzumab, the incidence of symptomatic congestive heart failure (CHF) has been reported to be from 0.6% to 4.0%. Of note is that most of these effects appear to occur early during treatment and appear to be reversible in the majority of patients. Other risk factors for anthracycline-induced cardiotoxicity include age, race, hypertension, diabetes, and/or underlying coronary artery disease, which are the same risk factors for CHF in the general population. A hugely relevant issue in comparative trials is the fact that women receiving anthracycline-based adjuvant therapies have higher

survival than those in non-anthracycline arms, which skews the data. Specifically, those receiving anthracycline have a longer time to potentially develop side effects that are from therapy or associated with aging.

There have been several observational studies using Surveillance, Epidemiology, and End Results (SEER) Medicare data that have evaluated HF and CM incidence following treatment with anthracyclines. Although these studies did show that women who received anthracyclines in the adjuvant setting had a significant increase in incidence of CHF and/or CM, they were limited to women age 65 or older. Another population-based, retrospective cohort study consisting of women diagnosed with invasive breast cancer from January 1, 1999, through December 31, 2007, was recently published. Unlikely the other SEER database studies, the average age of the 12,500 women included in this cohort was 60 years, with a range of 20–99 years. In this study, women who received anthracycline alone or anthracycline plus trastuzumab were younger, were diagnosed at later stages, and had fewer comorbidities than women who received other chemotherapy. Results of this study showed that the use of anthracycline is associated with a 1-year cumulative incidence of HF and CM of 1.2% and a 5-year cumulative incidence of 4.3%. The incidence of HF and CM is higher for women who received an anthracycline-based therapy compared to those women who did not receive chemotherapy (1-year cumulative incidence of 0.9%). However, the incidence of anthracycline-induced toxicity was similar to that of recipients of other chemotherapy, with 1-year and 5-year cumulative incidences of 1.3% and 4.5%, respectively. The 5-year cumulative incidences for HF and CM associated with other chemotherapy use were greatest among the two oldest groups (8.7% for women aged 65–74 years and 18.7% for women 75 and older). Similarly, the risk of HF and CM associated with anthracycline increases with increasing age. For women <55 years of age, the 5-year cumulative incidence was 1.2%, compared to 2.9% for women aged 55–64, 6.2% for women aged 65–74, and 10.6% for women 75 years and older. Although limited by being observational in nature, this study shows that although there is indeed an increased risk of HF and CM associated with the use of anthracyclines, the incidence is similar for women who receive non-anthracycline chemotherapy.

Further studies are planned to improve understanding of risk, predisposing factors, and potential preventative interventions; all balanced with optimizing overall antitumor efficacy of anthracyclines.

• What is the optimal adjuvant approach for patients with resected HER2-positive invasive breast cancer?

Prior to the development of HER2-directed therapies, patients with HER2-positive breast cancer had a worse prognosis that those with HER2-negative tumors. Trastuzumab is a humanized, monoclonal antibody with specificity for the extracellular domain of HER2. In 1998, trastuzumab was approved as a first-line therapy in combination with paclitaxel for HER2-positive metastatic breast cancer. The benefit of HER2-directed therapy in the metastatic setting led the National Cancer Institute (NCI) to sponsor two studies examining trastuzumab in the adjuvant setting, added to other trials conducted in other countries.

In the National Surgical Adjuvant and Bowel Project (NSABP) B-31 clinical trial, patients with node-positive, HER2-positive breast cancer were randomly assigned to four cycles of doxorubicin and cyclophosphamide followed by paclitaxel (group 1) compared to the same chemotherapy plus 52 weeks of trastuzumab beginning on day 1 of paclitaxel therapy (group 2). In the North Central Cancer Treatment Group (NCCTG) trial N9883, three regimens were studied: four cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel for 12 weeks, four cycles of doxorubicin and cyclophosphamide followed by 52 weeks of trastuzumab after the completion of paclitaxel therapy, and four cycles of doxorubicin and cyclophosphamide followed by 52 weeks of trastuzumab beginning on day 1 of paclitaxel therapy.

The B-31 and N9831 trials were jointly analyzed using the control arms for both trials and compared to the merged arms that used trastuzumab that began concurrently with paclitaxel. In the initial report, the addition of adjuvant trastuzumab to chemotherapy decreased the risk of breast cancer recurrence by 52% (HR: 0.48; $P < 0.001$) with a relative reduction in the death rate of 35% (HR: 0.65; $P < 0.001$) at 2.9 years of follow-up. In the 4-year follow-up, the addition of adjuvant trastuzumab to chemotherapy still continued to have a significant increase in disease-free survival and overall survival benefit (HR: 0.52; $P < 0.001$; and HR: 0.61; $P < 0.001$, respectively).

For patients with early-stage, HER2-positive breast cancer, the benefit of trastuzumab and chemotherapy in the adjuvant setting has been evaluated in seven randomized clinical trials with over 10,000 patients (NSABP B-31, NCCTG N9831, HERA (Herceptin Adjuvant), FinHER (Finland Herceptin), NOAH (Neo-adjuvant Herceptin), FNCLCC-PACS (Fédération Nationale des Centres de Lutte Contre le Cancer-Programmes d'Actions Concertées Sein) 04, and BCIRG (Breast Cancer International Research Group) 006). These include different modes of administration (concurrent versus sequential), duration of therapy (1 year, 2 years, or 9 weeks), and chemotherapy regimens. The last study, BCIRG 006, compared two different chemotherapy–trastuzumab combinations—one was anthracycline based (doxorubicin and cyclophosphamide followed by docetaxel (ACT) with 52 weeks of trastuzumab (ACTH)), and the other was not (docetaxel and carboplatin with trastuzumab (TCH))—against a chemotherapy (ACT)

control. This study showed no statistically significant difference between the two trastuzumab-containing arms, but the anthracycline-containing arm had higher rates of cardiac dysfunction and CHF, leading the authors of the study to favor the TCH arm over the ACTH arm. After the presentation of the BCIRG 006, the TCH regimen was approved by the FDA and may arguably account for a majority of adjuvant trastuzumab-containing regimens in the United States.

There are several limitations to the BCIRG 006, which brings us to question the assertion of TCH as the better regimen. Most importantly, the BCIRG 006 was not powered to show either equivalence or even non-inferiority between the two trastuzumab-containing arms. The data showed that after 5 years of follow-up, the disease-free interval was actually superior for those who received the ACTH regimen compared to the TCH regimen (84% versus 81%, respectively) in both node-negative and node-positive patients. Similarly, the HR was superior for ACTH (HR: 0.64; $P < 0.001$) compared to TCH (HR: 0.75; $P = 0.04$). As the BCRIG 006 was underpowered, it is quite plausible that superiority of ACTH over TCH could have been missed. Other than the BCIRG 006, no other study has directly compared ACTH to TCH. However, a retrospective, single-institution study shows higher rates of complete pathologic response and longer relapse-free survival for those women with HER2-positive breast cancer who receive a neo-adjuvant regimen consisting of an anthracycline with a weekly taxane combined with trastuzumab compared to those who receive TCH. Taken together, as reported by Burstein *et al*. (2012), the data suggest the superiority of ACTH to TCH in the adjuvant setting for operable HER2-positive breast cancer, although TCH remains another option for select patients.

Other HER2-directed therapies such as lapatinib, an oral tyrosine kinase inhibitor, and pertuzumab, a monoclonal antibody that binds to the HER2 dimerization domain, and the novel drug antibody conjugated T-DM1, are currently being considered in the adjuvant setting. In the metastatic setting, the addition of pertuzumab to trastuzumab with docetaxel resulted in longer progression-free survival (18.5 months vs. 12.4 months with trastuzumab alone), showing a benefit to dual-targeted anti-HER2 therapy. Similarly, in the metastatic setting, the addition of trastuzumab to pertuzumab resulted in increased progression-free survival compared to monotherapy with pertuzumab alone (17.4 vs. 7.1 weeks, respectively). There are currently several studies looking at combinations of anti-HER2 therapies in the adjuvant setting. The ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study is an international phase III study evaluating the addition of lapatinib (sequential or concomitantly) with trastuzumab in the adjuvant setting. The APHINITY Study, is a randomized, multicenter phase III study examining the addition of pertuzumab to standard chemotherapy and trastuzumab in the adjuvant setting for HER2-positive breast cancer. T-DM1 is being evaluated as a substitute of additional anti-HER2 therapy.

Selected reading

Baselga J, Cortes J, Kim SB, *et al*. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–19.

Goetz MP, Schaid DJ, Wickerham DL, *et al*. Evaluation of CYP2D6 and efficacy of tamoxifen and raloxifene in women treated for breast cancer chemoprevention: results from the NSABP P1 and P2 clinical trials. Clin Cancer Res. 2011;17:6944–51.

Goss PE, Ingle JN, Ales-Martinez JE, *et al*. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381–91.

National Comprehensive Cancer Center Network (NCCN). Available from: http://www.nccn.org

Perez EA, Romond EH, Suman VJ, *et al*. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011 Sep 1;29(25):3366–73. Epub 2011 Jul 18. PMID:21768458. PMCID:3164242. DOI:10.1200/JCO.2011.35.0868.

CHAPTER 82

Preoperative systemic therapy for breast cancer

Virginia Kaklamani and William J. Gradishar

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Case study 82.1

A 67-year-old female presents with a right breast mass clinically measuring ~4 cm without nodal involvement. There is no skin involvement, the tumor is freely moveable, and the remainder of the exam is unremarkable. A mammogram confirms the same, and a biopsy reveals an estrogen receptor–positive (ER+) (90%), progesterone receptor–positive (PR+) (10%), human epidermal growth factor receptor 2–negative (HER2−), infiltrating duct carcinoma. The surgeon suggests that she be considered for preoperative chemotherapy, but the patient is reluctant to receive chemotherapy.

1. Is a preoperative endocrine approach reasonable in this patient?

The use of preoperative endocrine therapy has been evaluated in small clinical trials as well as more recent rigorously conducted randomized clinical trials. Because of the favorable toxicity profile of endocrine agents, the first experiences were reported in elderly patients who were considered unfit to receive chemotherapy. Tamoxifen therapy was shown to produce a response rate of >30% in several small studies. One of the key lessons learned from this approach is that a clinical response may require a greater interval of time to achieve compared to chemotherapy. Whereas with chemotherapy some evidence of a response may be evident following 1–2 cycles of therapy, endocrine therapy may require many months of therapy to see clear evidence of tumor shrinkage. A more patient mindset is therefore required for both the patient and clinician. Subsequent studies with preoperative tamoxifen compared to postoperative tamoxifen showed similar overall survival rates. This observation confirmed that even in patients in whom a surgical approach could be considered initially, there was no detriment in patient outcome with preoperative tamoxifen therapy.

More recently, third-generation aromatase inhibitors (AIs) have been evaluated in the preoperative setting for postmenopausal women. This class of endocrine agents is potentially more attractive than tamoxifen because of superior efficacy demonstrated in the metastatic disease setting in postmenopausal women. In a randomized phase II trial (P024), 4 months of preoperative letrozole was compared to tamoxifen in 337 postmenopausal women with clinical stage II or III, ER+ and/or PR+ breast cancer. None of the patients were considered breast conservation candidates at the outset. Patients receiving letrozole were more likely to attain a clinical response (55% vs. 36%; $P = 0.001$), an ultrasound response (35% vs. 25%; $P = 0.042$), a mammographic response (34% vs. 16%; $P = 0.001$) and breast conservation (45% vs. 35%; $P = 0.022$) compared to those receiving tamoxifen. Letrozole also more clearly reduced the proliferative index of tumor cells (Ki67) compared to tamoxifen. The Pre-Operative Arimidex Compared to Tamoxifen (PROACT) study studied postmenopausal patients with large (T2/T3, N0-2) operable, or potentially operable (T4b, N0-2), breast cancer, who received either tamoxifen or anastrozole. Ultrasound response (39.5% vs. 35.4%), clinical response (50% vs. 46.2%) and operability (43% vs.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

30.8%) were all greater in patients receiving anastrozole compared to tamoxifen.

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial compared treatment arms of anastrozole, tamoxifen, or the combination of these agents administered preoperatively to patients with locally advanced breast cancer. No difference in clinical response was demonstrated between tamoxifen and anastrozole, and, as predicted by the much larger postoperative Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, the combination of agents did confer additional clinical benefit or evidence of a greater biologic effect on Ki67. The IMPACT trial evaluated tissue samples at 2 and 12 weeks of therapy, and Ki67 was reduced to a greater degree at both time points in those receiving anastrozole compared to tamoxifen ($P = 0.013$ and $P = 0.0006$, respectively). The ACOGSOG Z1031 recruited 374 postmenopausal patients with clinical stage II or III, ER+ breast cancer to be randomly assigned to 16–18 weeks of preoperative anastrozole, letrozole, or exemestane. Clinical response rates or reductions in Ki67 were not statistically different between the three treatment arms.

The P024 and IMPACT studies were also the genesis of the preoperative endocrine prognostic index (PEPI) score, which incorporates tumor size, nodal status, Ki67 level, and ER score. In the P024 study, no patients with T1N0 tumor and a PEPI score of 0 developed disease relapse. In the ACOCOSOG Z1031 study, patients with a Ki67 $\leq$10% and the Luminal A subtype of breast cancer were both associated with a very high probability of a PEPI score of 0.

The anastrozole-based IMPACT and PROACT trials also showed a trend favoring the AI arm, although the results in comparison with tamoxifen were not statistically significant. A meta-analysis of these trials supported the notion that an AI was more effective than tamoxifen for promoting breast conservation. A promising 76% rate of breast conservation was also observed in a single-arm phase II study of neo-adjuvant exemestane in postmenopausal patients with hormone receptor–positive tumors, 3 cm or greater, after 12 weeks of therapy.

2. How does the pathologic complete response (pCR) rate compare with chemotherapy in ER+ disease?

One of the concerns most often cited by clinicians is the notion that endocrine therapy is less effective than chemotherapy when administered in the preoperative setting. This mindset is difficult to dislodge unless a critical evaluation of available data is undertaken. Although neo-adjuvant chemotherapy with or without trastuzumab is increasingly more effective in producing pCRs, the effect is seen largely in ER− and HER2+ tumors. A report by Guarneri *et al*. (2006) evaluated the effect of preoperative chemotherapy in 1731 patients, of whom 1163 had ER+ tumors. The pCR rate was 24% for ER− tumors and only 8% for ER+ tumors ($P < 0.001$). In the GeparTrio study involving 2071 patients receiving different durations of chemotherapy or compositions of chemotherapy depending on the response, a pCR was defined as no invasive cancer in the breast or axilla. There was a striking difference in the rate of pCR favoring the effect of chemotherapy in patients with hormone receptor–negative tumors versus those with hormone receptor–positive tumors, in both patients <40 years (48% vs. 15%) and those $\geq$40 years (32% vs. 9%). In the recent NeoSphere trial evaluating different anti-HER2 therapy combinations in a preoperative setting, 417 chemo-naïve patients with HER2+ operable or locally advanced breast cancer were randomized to docetaxel–trastuzumab, docetaxel–trastuzumab–pertuzumab, docetaxel–pertuzumab, or pertuzumab–trastuzumab. Interestingly, in the absence of chemotherapy (pertuzumab–trastuzumab), the patients with ER− or PR+ disease had the lowest pCR rate (5.9%) compared to 29.1% in patients with ER− and PR− disease.

Another important observation is that pCR is not as important in predicting outcome in ER+ tumors. Ring *et al*. (2004) reported on 435 patients who received neo-adjuvant chemotherapy and found that those attaining a pCR had a significant improvement in overall survival compared to those with less than a pCR. However, in those patients with ER+ disease, there was no difference in disease-free survival (DFS) in those with a pCR or not.

Direct comparisons of chemotherapy to endocrine therapy in the preoperative setting are sparse, yet equally revealing. Semiglazov *et al*. (2007) reported on 121 postmenopausal women with ER+, large operable tumors or locally advanced disease, who received either primary chemotherapy with an anthracycline and paclitaxel or endocrine therapy with anastrozole or exemestane for 3 months. Clinical and mammographic assessment showed equivalent antitumor effects between treatment modalities. The pCR rate was also essentially the same between the groups, but, as might be expected, fewer side effects were seen in patients receiving endocrine therapy. In a similar study by Alba *et al*. (2012), in 95 premenopausal patients who received either primary chemotherapy or primary endocrine therapy with a combination of exemestane and goserelin, there was no statistical difference between either treatment arm with respect to response rate or mastectomy rate.

3. How long should endocrine therapy be continued in a preoperative setting prior to surgery?

Whereas neo-adjuvant chemotherapy has been administered for durations as short as 3 months prior to

surgery, neo-adjuvant endocrine therapy is optimally administered for longer durations. Of 182 consecutive patients treated in Edinburgh with neo-adjuvant letrozole for 3 months or longer, 63 patients have continued on letrozole beyond 3 months. Of the 63 patients who continued on letrozole, 38 patients took letrozole for more than 1 year and 23 took letrozole for more than 24 months. The median reduction in clinical volume in the first 3 months in these 63 patients was 52%. Similar reductions in median clinical volume were seen at 3–6 months, 6–12 months, and 12–24 months (medians 50%, 37%, and 33%, respectively). At 3 months, 69.8% of the 182 patients had a partial or complete response. The response rate increased to 83.5% with prolonged letrozole treatment. Continuing letrozole beyond 3 months increased the number of women who had initially required mastectomy or had locally advanced breast cancer who were subsequently suitable for breast-conserving surgery from 60% (81/134) at 3 months to 72% (96/134).

4. Are there any genomic tests that can predict benefit from preoperative endocrine therapy over chemotherapy?

Several reports have suggested that the 21-gene recurrence score (RS) assay (Oncotype DX™, Genomic Health) may be useful in distinguishing tumors more likely to benefit from endocrine therapy compared with chemotherapy. Gianni *et al*. (2005) examined the 21-gene Oncotype DX assay in 89 women with locally advanced breast cancer. Reverse transcription polymerase chain reaction (RT-PCR) analysis was performed on core biopsy specimens. Following neo-adjuvant anthracyline–taxane treatment, assessment of the surgical specimens for pCR was performed. The likelihood of pCR increased with higher RS. There were no pCRs in tumors with an RS less than 25, all of which were ER+. Chang *et al*. (2008) evaluated the utility of RS to predict pCR in 97 patients with locally advanced breast cancer undergoing four preoperative cycles of docetaxel. They found that none of the eight patients with a low RS had a complete response, compared to nine of the 42 patients with a high RS. All 44 patients with an RS <44 were ER+. Akashi-Tanaka *et al*. (2009) evaluated 87 patients with ER- and PR-positive operable breast cancer who received either tamoxifen or anastrozole for 4 months. A pretreatment core biopsy was performed to assess RS. They found that tumors with low RS tended to have better clinical response compared to those tumors with an intermediate or high RS. Additionally, RS tended to predict clinical response in patients receiving tamoxifen or anastrozole. A low RS tended to have better relapse-free survival (RFS) than intermediate and high RS (5-year RFS: 100% vs. 84% vs. 73%, respectively).

Case study 82.2

A 45-year-old woman presents with an abnormal left mammogram showing a ~2 cm spiculated lesion in a relatively small breast. Physical exam reveals a 1–2 cm area of induration and nodularity without skin changes or immobility; no axillary adenopathy was present. The remainder of the exam was normal. Biopsy of the lesion reveals an infiltrating ductal carcinoma that is ER/PR-poor and HER2−. The patient has no other comorbidities. The surgeon requests a consultation to consider preoperative chemotherapy.

5. What are the advantages of preoperative systemic therapy compared to postoperative adjuvant therapy?

Insights into the biology of breast cancer and the benefit of novel therapeutic strategies have increasingly come into the preoperative or neo-adjuvant setting, where sequential tissue samples are available for interrogation and clinical endpoints can more immediately be reached. At first blush, the advantage of the neo-adjuvant setting as a "laboratory" appears obvious, but challenges have been previously articulated. Neo-adjuvant therapy in breast cancer has resulted in a fraction of patients who were destined to undergo mastectomy ultimately becoming candidates for breast conservation. There has been no compromise in survival for patients whether they receive pre- or postoperative therapy. Administering systemic therapy when clinically detectable disease is present also gives an "early read" as to the sensitivity, or lack thereof, to a particular regimen. There is also a significant literature suggesting that those able to attain a pCR to neo-adjuvant therapy will have the best overall clinical outcome compared to those attaining anything less than a pCR. Unfortunately, there are numerous empirical definitions of pCR throughout the medical literature, making a coherent interpretation of the relationship between pCR and clinical outcome challenging. Some definitions of pCR require no viable tumor cells in the breast only, or in the breast *and* axilla, while some definitions of pCR allow even minimal residual cancer cells to be present in the pathological specimen.

Von Minckwitz and colleagues (2012) attempted to bring some clarity to this issue by analyzing a series of seven prospectively conducted clinical trials of neo-adjuvant anthracycline–taxane (+/− trastuzumab)–based therapy in over 6300 patients. The main eligibility criteria to participate in these trials were largely similar. The first aim of the pooled analysis was to compare different definitions of pCR currently in use with the ability to predict recurrence

or death. They found that a definition of pCR that was most restrictive—allowing for absolutely no evidence of residual cancer, including in situ, invasive, or axillary involvement—was associated with the best prognosis. Any evidence of disease, invasive or in situ, following neo-adjuvant therapy was associated with a poorer prognosis.

The second, and arguably more important, analysis focused on the implication of pCR (best definition) and prognosis in different intrinsic subtypes of breast cancer. They found that a pCR in the Luminal A subtype (ER+ and/or PgR+; HER2−) had no prognostic value. The pCR rate was low (6.7%) in the Luminal A subtype, a finding corroborated in many studies of neo-adjuvant chemotherapy in a largely ER+ and HER2− population. Systemic therapy in Luminal B tumors (ER+ and/or PgR+; HER2+) performed only modestly better, with pCR rates of 11–22%, even in those patients who received trastuzumab. In contrast, the patients with nonluminal, HER2+ tumors and those with triple-negative disease (ER, PgR, AND HER2−), who are frequently thought to have a much more guarded prognosis, appeared to have an excellent prognosis and were most likely to attain a pCR (28–32%).

6. What is the role of neo-adjuvant or primary chemotherapy for patients to achieve lumpectomy or breast conservation eligibility?

Neo-adjuvant chemotherapy for patients with large tumors, locally advanced disease, or inflammatory breast cancer (IBC) is considered a standard approach. In certain patients with larger tumors or locally advanced breast cancer, neo-adjuvant chemotherapy can effectively downstage the tumor, making the patient a candidate for breast conservation when at the outset they would have been definite mastectomy candidates. The MD Anderson Cancer Center published one of the first experiences showing the ability of neo-adjuvant chemotherapy to convert a fraction of patients with stage IIb–IV breast cancer to breast conservation therapy (BCT). After receiving chemotherapy, all patients were treated with mastectomy and axillary lymph node dissection. The investigators applied retrospectively strict selection criteria: complete resolution of skin edema, residual tumor diameter less than 5 cm, and absence of known multicentric disease or extensive lymphatic invasion. They determined that 23% of patients would have been candidates for BCT after receiving primary chemotherapy.

Many other experiences have been reported that clearly show that the rate of breast conservation will increase with the use of neo-adjuvant chemotherapy in patients with operable breast cancer. In a meta-analysis of clinical trials, investigators reported that the mastectomy rate was decreased by 17% in patients receiving neo-adjuvant chemotherapy. It is likely that this is an underestimation of the rate of downstaging as many of the women in these studies were likely BCT candidates before they received neo-adjuvant chemotherapy. In the NSABP B-18 trial, patients with operable breast cancer were randomized to four cycles of doxorubicin and cyclophosphamide (AC) administered either prior to surgery or after surgery. In patients with tumors 5 cm or larger, the population thought not to be candidates for BCT, that administration of neo-adjuvant chemotherapy resulted in a BCT rate that went from 3% proposed to 22% performed. Similarly, in the European Organization for Research and Treatment of Cancer (EORTC) 10902 trial, which was a European trial that randomized patients with primary operable breast cancer to neo-adjuvant versus adjuvant chemotherapy with 5-FU, epirubicin, and cyclophosphamide (FEC), the surgical plan prior to starting chemotherapy in the group randomized to neo-adjuvant chemotherapy was evaluated. Prior to starting chemotherapy, 23% of patients who were thought to require mastectomy were ultimately able to undergo BCT.

7. Is there a preferred chemotherapy regimen that should be used?

A variety of regimens of chemotherapy have been utilized in neo-adjuvant trials. Those that are viewed as most active and subjected to evaluation through well-conducted clinical trials are acceptable and listed as such in the 2013 National Comprehensive Cancer Network (NCCN) guidelines.

8. If the tumor were ER−, PR−, and HER2− ("triple-negative" breast cancer, or TNBC), is neo-adjuvant therapy always the preferred approach, even in operable breast cancer?

No. There is no standard systemic therapy for patients with TNBC. Several clinical trials have hinted of activity of one regimen over another in subsets of patients with TNBC, but at present, in the absence of a clinical trial, standard neo-adjuvant chemotherapy programs are recommended. The preoperative setting does provide a unique setting to obtain serial tumor samples (diagnostic biopsy and surgery at a minimum) where the effect of an investigational approach can be assessed clinically and by interrogating pertubations in signaling pathways or proliferative indices.

9. Would genetic testing be indicated, and, if so, would it change your clinical management?

Although family history in not available in this patient, the NCCN guidelines indicate that she would be eligible for genetic testing for BRCA1/2 mutations. Although the

results of the testing would not be used to make clinical decisions on the type of chemotherapy recommended to this patient, it may impact her decision on the type of surgery she would like to have performed. Individuals who are BRCA+ have up to an 87% lifetime risk of breast cancer and up to a 50% lifetime risk of a second breast cancer. Furthermore, she would have up to a 50% risk of ovarian cancer. Her surgical options would include bilateral mastectomies and bilateral salpingo-oophorectomy (BSO). If she elected to not proceed with a bilateral mastectomy, then yearly breast magnetic resonance imaging would be added to her surveillance.

Case study 82.3

A 57-year-old woman with a large right breast mass presents for consideration of preoperative therapy. The breast mass has been present for the last year (per the patient) and has progressively distorted the upper outer quadrant with a noticeable bulge present. There is no erythema, peau d'orange, or changes in the nipple areolar complex. The mass remains freely moveable and measures ~5–6 cm. There is no skin breakdown. A palpable mass is present in the right axilla measuring ~2 cm. A core biopsy of the breast mass reveals a grade 3, infiltrating ductal carcinoma that is ER−, PR−, and HER2+ by FISH (ratio: 4).

- **A fine needle aspirate (FNA) of the lymph node confirms the presence of breast cancer cells similar to the primary. Is there an indication for staging scans?**

At the present time, the NCCN guidelines state that routine screening is not indicated in patients with early-stage breast cancer in the absence of symptoms or abnormal laboratory values. However, for clinical stage IIIA disease, staging scans can be considered, including computed tomography (CT) scans, a bone scan, and/or a positron emission tomography (PET)–CT scan. Therefore, in this case of palpable axillary lymphadenopathy, the use of staging imaging studies should be considered.

10. What is the optimal way to approach someone with HER2+ breast cancer requiring preoperative therapy?

In general, when treating patients prior to surgery, the same principles apply as when treating someone in the postoperative, adjuvant setting. Standard regimens such as TCH (docetaxel, carboplatin, and trastuzumab) and ACTH (doxorubicin and cyclophosphamide, followed by paclitaxel and trastuzumab) can be used in the neo-adjuvant setting. However, several clinical trials have been performed in the neo-adjuvant setting that provide further guidance as to acceptable regimens. A neo-adjuvant clinical trial performed by the MD Anderson Cancer Center group incorporated trastuzumab added to an epirubicin-based regimen. A total of 64 patients were included in the trial, which was conducted in two phases. Patients were randomized to receive four cycles of paclitaxel, followed by four cycles of FEC therapy. Patients were randomized to receive trastuzumab concurrently with chemotherapy, or not. pCR for patients receiving trastuzumab was 60% and 26.3% in the nontrastuzumab group. Cardiac safety data suggested that even though trastuzumab was given concurrently with epirubicin, there was no cardiac dysfunction. This study, although relatively small, compared with other neo-adjuvant and adjuvant clinical trials, confirmed the efficacy of the trastuzumab arm and an apparent lack of cardiac toxicity.

11. Can dual targeting of HER2 be employed?

Emerging data from neo-adjuvant trials have suggested activity of various anti-HER2 combination regimens when given alone or with chemotherapy. The phase III NeoALTTO trial evaluated neo-adjuvant lapatinib–trastuzumab–paclitaxel, trastuzumab–paclitaxel, and lapatinib–paclitaxel in patients with HER2-positive breast cancer ($N = 455$). The pCR rate (defined as the absence of invasive tumor cells in the breast at surgery) was 29.5% with trastuzumab alone, 24.7% with lapatinib alone, and 51.3% with lapatinib–trastuzumab (odds ratio relative to trastuzumab alone: 2.6; $P = 0.0001$). Lapatinib recipients experienced more grade 3–4 toxicity, primarily grade 3 diarrhea (23.4% and 21.1% with lapatinib and lapatinib–trastuzumab, respectively, vs. 2.0% with trastuzumab), grade 3 liver enzyme elevations (17.5% and 9.9%, respectively, vs. 7.4%), and grade 3 neutropenia (14.3% and 7.2%, respectively, vs. 1.3%).

The phase II NeoSphere trial evaluated neo-adjuvant trastuzumab–docetaxel, pertuzumab–trastuzumab–docetaxel, pertuzumab–trastuzumab, and docetaxel–pertuzumab in HER2+ stage II or III breast cancer ($N = 417$). The pCR (defined as the absence of invasive tumor cells in the breast at surgery) rate was 45.8% with pertuzumab–trastuzumab–docetaxel, significantly higher than the 29.0% rate with trastuzumab–docetaxel alone ($P = 0.0141$); conversely, the 16.8% pCR rate with pertuzumab–trastuzumab was significantly lower than that with trastuzumab–docetaxel ($P = 0.0198$). Pertuzumab–trastuzumab–docetaxel was associated with a grade ≥3 toxicity profile primarily consisting of neutropenia, febrile neutropenia, leukopenia, and diarrhea (in 45%, 8%, 5%, and 6% of patients, respectively); with trastuzumab–docetaxel alone, these were observed in 57%, 7%, 12%, and 4%, respectively. Grade ≥3 toxicity with pertuzumab–trastuzumab was limited to neutropenia and drug hypersensitivity (1% and 2%, respectively).

In the phase II CHER-LOB trial of neo-adjuvant anthracycline–taxane chemotherapy plus lapatinib, trastuzumab, or both in HER2+ breast cancer ($N = 121$), the pCR (defined as the absence of invasive tumor cells in the breast and axillary nodes at surgery) rate was 48% with the lapatinib–trastuzumab combination versus 28% with trastuzumab alone and 32% with lapatinib alone. The mean left ventricular ejection fraction remained stable during the study (62%, 61%, and 61% at baseline, after 12 to 13 weeks, and at treatment end, respectively), with no symptomatic cardiac events. In the phase II TBCRC 006 trial that evaluated neo-adjuvant lapatinib plus trastuzumab for large HER2+ breast tumors ($N = 66$), the pCR rate was 28% among 64 response-evaluable patients. Most toxicities were of grade 1–2 severity; however, there were reports of grade 3 metabolic, gastrointestinal, and liver toxicity ($n = 12$) and grade 4 liver toxicity ($n = 1$).

The phase III NSABP B-41 trial evaluated the efficacy and safety of neo-adjuvant combination chemotherapy (doxorubicin–cyclophosphamide) followed by paclitaxel plus lapatinib, trastuzumab, or both in HER2+, operable breast cancer ($N = 529$). The pCR (in the breast) rate was 52.5%, 53.2%, and 62% for the trastuzumab, lapatinib, and trastuzumab–lapatinib arms, respectively. Grade $\geq$3 toxicities included diarrhea (2%, 20%, and 27% with lapatinib, trastuzumab, and lapatinib–trastuzumab, respectively) and symptomatic left ventricular systolic dysfunction (4%, 4%, and 2%, respectively).

The phase II TRYPHAENA study of neo-adjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing chemotherapy or concurrent with an anthracycline-free chemotherapy regimen in locally advanced or inflammatory HER2+ breast cancer ($N = 225$) is ongoing (NCT00976989). The primary endpoint is tolerability; secondary endpoints include pCR (defined as the absence of invasive tumor cells in the breast at surgery), safety, time to response, clinical response rate, DFS, progression-free survival (PFS), and overall survival (OS).

Although these clinical trials suggest a distinct advantage to combining anti-HER2 therapies based on improvement in pCR, we should still await for the completion of adjuvant clinical trials (such as the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial) to confirm that this also translates to an improvement in PFS and, most importantly, OS. In the meantime, a combination of chemotherapy and trastuzumab should be considered standard therapy in the treatment of HER2+ breast cancer in the neo-adjuvant or adjuvant setting.

12. Should trastuzumab be continued following surgery if the patient has a complete response?

In order to answer this question, clinical trials conducted in the adjuvant setting with the purpose of determining the optimal duration of trastuzumab therapy need to be considered. The Protocol of Herceptin Adjuvant with Reduced Exposure (PHARE) trial evaluated the efficacy of 6 months of adjuvant trastuzumab compared with 1 year of therapy. This trial had a non-inferiority design, and a total of 3381 patients were randomized. In 2010, the trial was suspended after the data-monitoring committee concluded that the 6-month arm had more DFS events than the 1-year arm. Although this difference was not statistically significant (HR: 1.28; $P = 0.29$), there was a trend showing that the 6-month arm was inferior to the 1-year arm.

The HERA trial, a phase III, international, multicenter trial conducted by the Breast International Group (BIG), sequenced trastuzumab after primary surgery and a minimum of four cycles of adjuvant or neo-adjuvant chemotherapy. A total of 5102 HER2+ patients with early-stage breast cancer were randomized to receive trastuzumab for 1 or 2 years or to observation alone.

An analysis comparing the two trastuzumab-containing arms did not show any additional benefit with 2 years of trastuzumab compared with 1 year. The DFS in the 2-year arm was 75.8% compared with 76.0% in the 1-year arm (HR: 0.99; $P = 0.86$). The lack of benefit was seen in both the HR+ and HR− subgroups. Similarly, there was no benefit in OS (86.4% in the 2-year arm vs. 87.6% in the 1-year arm; HR: 1.05; $P = 0.63$). The incidence of cardiac toxicity was increased with the use of trastuzumab and was even higher in the 2-year arm. More specifically, the incidence of a significant decrease in the ejection fraction (EF) was 0.9% in the observation arm, 4.1% in the 1-year trastuzumab arm, and 7.2% in the 2-year trastuzumab arm.

These results suggest that 1 year of trastuzumab therapy is optimal. Therefore, when treating patients prior to surgery, trastuzumab should be continued after surgery to complete a year of therapy.

13. Is there a benefit to performing a sentinel lymph node biopsy (SLNB) prior to surgery?

Knowing the status of the axilla may influence treatment recommendations. Patients with negative axillary lymph nodes may be treated with shorter durations of therapy compared with patients with positive axillary lymph nodes (LNs). In general, a clinically positive axillary LN at presentation should be followed by an axillary LN dissection at the time of definitive surgery. The false-negative rate (FNR) of SLNB after neo-adjuvant chemotherapy is over 10% and may be as high as 14%. In previous studies, the FNR of SLNBs during primary surgery ranges from 7% to 9.8%. The decision on timing of SLNB should be made after consultation between the breast surgeon and breast medical oncologist.

Case study 82.4

A 35-year-old African American female presents with a history of a rapidly changing erythematous rash over her left breast. The patient had been nursing a baby born 2 months ago, and initially the area of erythema around the nipple area was thought to represent mastitis. Antibiotics failed to improve the appearance of the breast, and actually the entire breast became more swollen, erythematous, and tender. The patient was evaluated with a mammogram that showed skin thickening but no dominant mass. A surgical evaluation suggested a clinical diagnosis of IBC with diffuse erythema, peau d'orange, and nipple inversion. The right breast was normal. No adenopathy was appreciated, and the remainder of the exam was normal. A biopsy of the left breast confirmed dermal lymphatic occlusion by tumor cells and diffuse infiltrating ductal carcinoma that was weakly ER+, PR−, and HER2−. A PET–CT demonstrated significant activity throughout the left breast. No other evidence of metastatic disease was present.

14. What is the optimal chemotherapy regimen for inflammatory breast cancer?

IBC accounts for ~5% of all newly diagnosed breast cancer. Not uncommonly, it is confused with, or initially misdiagnosed as, a more benign breast disorder. The diagnosis can be established with clinical features (i.e., erythema of the breast, peau d'orange of the skin, and nipple inversion) and/or specific pathologic findings (e.g., cancer cells in the dermal lymphatics). The tempo of the disease progression can be rapid and the overall outcome poor, so it is imperative to confirm the diagnosis and to proceed with a multimodality approach to treatment. Since it is not uncommon for IBC to metastasize early, a staging evaluation is standard. Assuming the disease is not present in distant organs, the optimal approach is to proceed initially with standard systemic chemotherapy. If an acceptable clinical response has been achieved, surgery with a mastectomy followed by local-regional radiation therapy is recommended.

15. How do you judge whether systemic therapy is effective?

With the administration of neo-adjuvant chemotherapy, the appearance of the breast should progressively improve with each cycle of chemotherapy. Specifically, skin erythema, peau d'orange, and changes in the nipple–areola complex should begin to appear more normal. Although a distinct underlying tumor mass is not always present, if it is present, tumor size by clinical exam and imaging should decrease.

16. How long should systemic treatment be continued?

In the absence of a clinical trial, patients with IBC should receive neo-adjuvant chemotherapy consisting of a standard adjuvant regimen (see NCCN Guidelines), generally administered over a 3–4-month period. In concert with the surgeon, a decision will be made whether the improvement in the appearance of the breast is sufficient to proceed with surgery. The hazard of proceeding to surgery without an adequate response to chemotherapy is viable tumor cells remaining in the skin, heightening the risk for rapid clinical recurrence.

17. Are there circumstances where breast conservation can be considered?

The standard of care is that a mastectomy be performed. Additionally, the use of SLNB alone is not recommended for IBC. An axillary dissection should be performed.

18. Is radiation therapy necessary if a mastectomy is performed?

Yes. The evolution of multimodality care for patients with IBC has clearly demonstrated that there is an additive effect to improving outcome (reducing local recurrences and improving survival) when all modalities are included in the care of patients with IBC. Even with a mastectomy completed, there remains a concern that residual viable tumor cells may remain in the skin and place the patient at an elevated risk for disease recurrence. Chest wall and regional nodal radiation reduces the risk of a local-regional recurrence in the future. Additionally, if the tumor expresses ER, PR, or HER2, treatment with endocrine therapy and/or anti-HER2 therapy is indicated as with any other non-IBC patient.

Selected reading

Carlson RW, Anderson BO, *et al*. NCCN clinical practice guidelines in oncology: breast cancer. Version 2, 2013. Available from: http://www.NCCN.org

Chakrabarti J, Kenny FS, Syed BM, *et al*. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up. Crit Rev Oncol Hematol. 2011;78(3):260–4.

Rimawi MF, Mayer IA, Forero A, *et al*. Multicenter phase ii study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human

epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol. 2013;31(14):1726–1731.
von Minckwitz G, Untch M, Blohmer JU, *et al*. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30(15):1796–804.
Yamauchi H, Woodward WA, Valero V, *et al*. Inflammatory breast cancer: what we know and what we need to learn. Oncologist. 2012;17(7):891–9.

For further information on this area please also consult Chapters 118, 119, 123, 124, 131, 136, and 141

CHAPTER 83

Recurrent and metastatic breast cancer

Dennis L. Citrin

Cancer Treatment Centers of America, Zion, IL, USA

Case study 83.1

Brain metastases

A 35-year-old African American woman presented with a 5 cm mass in the right breast. Biopsy revealed high-grade triple-negative invasive ductal carcinoma. There were multiple lung and liver metastases documented on positron emission tomography (PET) scan. She was BRCA negative.

She was treated with six cycles of taxotere, adriamycin, and cytoxan and achieved a complete remission clinically and radiologically, and was then maintained for an additional six cycles of taxotere and cytoxan. Approximately 12 months after starting chemotherapy, she developed severe headaches. Magnetic resonance imaging (MRI) showed a single 2 cm mass in the right frontal cortex. Computed tomography (CT) scans revealed no evidence of liver and lung metastases.

1. How would you treat her?

A. Recommend surgical resection
B. Surgical resection followed by radiation
C. Radiation therapy (whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS))
D. Intrathecal methotrexate

Approximately 10–15% of patients with metastatic breast cancer will develop clinical evidence of central nervous system (CNS) recurrence, usually late in the course of the disease. The incidence appears to have increased in recent years, because of better control of systemic disease resulting in a higher incidence of metastases in sanctuary sites such as the CNS.

Brain metastases are most commonly seen in patients with biologically aggressive breast cancer, particularly triple-negative or Her2neu-positive disease. Several studies of patients with Her2-positive metastatic breast cancer treated with trastuzumab-based regimens have reported an incidence of CNS metastases ranging from 28% to 43%.

Median time to brain metastases was shorter for estrogen receptor (ER)-negative and HER2-positive compared with ER-positive disease. Over one-half of the patients who develop CNS metastases do so when their systemic disease was stable or responding to systemic treatment.

Treatment of CNS metastases is generally irradiation and surgery. Although most patients have multiple metastases, patients with a single resectable metastasis should be referred for surgery, as the median survival of such patients is significantly longer.

Several radiation techniques have been used; these include WBRT and SRS.

The place of drug treatment following radiation therapy is limited in most patients; because of the blood–brain barrier, few chemotherapy drugs attain high levels in the CNS. One exception is the small-molecule tyrosine kinase inhibitor lapatinib, which has shown modest efficacy in Her2-positive brain metastases. Current research attempts are focused on methods to disrupt the blood–brain barrier and increase chemotherapy penetration of the CNS. Herceptin can be given intrathecally where indicated.

Prognosis is best in patients <50 years of age, with good performance status, good control of systemic disease, and ER- or Her2-positive disease, and in patients who have surgical resection of CNS disease.

In this case, where there was an isolated brain metastasis in a surgically resectable area, an aggressive approach was warranted.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 83.2

"Adjuvant" therapy of locally recurrent disease after resection

A 60-year-old woman presented with several subcentimeter nodules in the left mastectomy scar, 7 years after mastectomy, adjuvant chemotherapy (AC; four cycles of AC followed by four cycles of Taxol), and radiation, and 5 years of adjuvant anastrazole for a T2N1M0 ER- and PR-positive invasive ductal carcinoma. Metastatic evaluation revealed no evident nodal, visceral, or bone metastases.

The recurrent tumor was surgically excised. Pathology was consistent with the original tumor.

1. What treatment would you recommend?

A. Restart aromatase inhibitor
B. Observation only
C. Radiation
D. Course of postresection chemotherapy followed by chemotherapy and endocrine therapy

Overall 10–20% of patients with stage 1–3 breast cancer will develop a loco-regional recurrence during the first 10 years after diagnosis. Most of these patients will have local chest wall or axillary recurrence without systemic metastases.

Surgical resection and radiation (if feasible) are the initial treatment of choice for such patients. Second local recurrences are seen in 60–70% of patients treated by surgical excision alone.

Re-irradiation following postmastectomy radiation carries an unacceptable risk of toxicity.

Until recently, there were only limited data to support the use of systemic treatment after surgical removal of locally recurrent disease. A randomized Swiss study published in 2003 demonstrated increased recurrence-free survival when tamoxifen was compared with observation after surgery.

The CALOR study, reported at the 2012 San Antonio Breast Cancer Symposium, demonstrated significant reduction in both 5-year disease-free and overall survival. These results were seen in patients with both ER-positive and ER-negative disease.

Case study 83.3

How to choose appropriate systemic therapy for the patient with newly diagnosed metastatic disease

Two years after lumpectomy and radiation therapy for a T1N1M0 ER-positive, PR-positive, and Her2-negative cancer of the left breast, a 45-year-old woman presented with abdominal bloating. Following her original surgery she had declined adjuvant chemotherapy and endocrine therapy, but received postlumpectomy radiation. She is known to be BRCA negative.

CT scan showed numerous liver lesions. Remainder of metastatic evaluation was negative. Biopsy of liver confirmed the clinical diagnosis of metastatic ER-positive breast cancer.

1. Which would be the best choice of treatment for this patient? (Choose all that apply.)

A. Endocrine therapy
B. Single-agent chemotherapy
C. Combination chemotherapy
D. Entry on a clinical trial

The goals of treatment for a patient with metastatic disease are to provide palliation, improve quality of life, and prolong survival.

Treatment options include combination and sequential single-agent chemotherapy. Additionally, in patients with ER-positive disease, there are numerous options for endocrine therapy, and there are also now available several drugs that target the Her2 pathway in patients with Her2-positive disease.

What factors help the oncologist decide which treatment is most appropriate? Broadly speaking, the most important factors are the biology of the tumor and relevant prognostic factors, which include disease-free interval, sites of metastatic disease (visceral vs. nonvisceral sites), prior (adjuvant) systemic therapy, and extent of organ dysfunction and comorbidities.

Endocrine therapy versus chemotherapy

In general, endocrine therapy is usually the first option for most women with metastatic ER-positive disease. Endocrine therapy, designed to minimize estrogen stimulation of the tumor, is less toxic than chemotherapy and often produces responses of long duration.

This patient has received no prior therapy, and has a high probability of response to whatever drug treatment is used. She does have numerous liver lesions, however, and this represents a life-threatening clinical scenario. Median duration of survival for the patient with liver metastases who does not achieve clinical remission is generally less than 12 months. Endocrine therapy would therefore not be recommended as initial treatment here.

(*Continued*)

Single-agent chemotherapy versus combination chemotherapy

In general, combination chemotherapy produces higher overall response rates, longer time to progression, and longer overall survival when compared with single-agent chemotherapy, at a cost of higher toxicity.

Sequential single-agent chemotherapy is generally used in patients with less dire clinical scenarios, where there may be a longer disease-free interval from initial treatment until first recurrence, a lesser body burden of metastatic disease, and an absence of disease in dire visceral sites (liver, lymphangitic lung, and CNS).

This patient has several poor prognostic factors, which include the relatively short disease-free interval and, most importantly, the presence of numerous liver metastases, which are symptomatic.

In such a clinical scenario, the use of aggressive combination chemotherapy would be most appropriate. Given the fact that she is chemotherapy naïve, there is a high probability (approximately 60%) that combination chemotherapy would achieve a partial remission with a relatively low probability of complete remission (approximately 20%).

Most patients can expect relief of symptoms from shrinkage of the liver metastases. In general, remissions from any one treatment regimen tend to be of relatively short duration (median length approximately 9 months). Second remissions from subsequent treatment are common, however.

There are a large number of agents active against metastatic breast cancer. Most physicians would choose first-line treatment with an anthracycline- or taxane-containing regimen, which have shown an overall survival benefit in randomized studies.

The patient may be offered entry on an appropriate clinical trial if one is available.

Case study 83.4

Role of surgery in patients presenting with stage 4 disease

A 46-year-old premenopausal woman presented with an indurated area measuring at least 5 cm in mass in the right breast, which had been present for at least 6 months. She complained of back pain.

Biopsy reveals a grade 2 ER- and PR-positive Her2neu-negative invasive lobular carcinoma. Bone scan revealed multiple lesions throughout the axial skeleton; plain radiographs confirmed osteoblastic metastases. CT scan of chest, abdomen, and pelvis showed no evidence of visceral metastases, but numerous enlarged right axillary nodes.

There was no family history of breast cancer, and the patient was BRCA negative.

She was treated initially with tamoxifen and intermittent injections of Xgeva. With this regimen her back pain resolved and the breast mass became less distinct, but was still palpable 12 months later.

1. What treatment would you recommend at that time?

A. Continue tamoxifen and Xgeva

B. Surgical resection of primary tumor and radiation, followed by continued tamoxifen and Xgeva

C. Bilateral mastectomy, and continued tamoxifen and Xgeva

Approximately 5% of patients have metastatic disease at the time of initial diagnosis (stage 4). The major focus of treatment of these patients is to control their systemic disease with appropriate drug treatment.

Historically, local treatment for the primary tumor and nodes has been reserved for those patients with locally advanced disease, to control local complications such as ulceration, bleeding, and infection.

With improvement in systemic treatment, however, many patients who present with metastatic disease are experiencing longer survival. In such patients, the question arises: do they benefit from resection of the primary tumor? And, if so, when?

There are numerous retrospective studies that have addressed the issue. Overall these studies suggest an approximately 40% improvement in short-term (3-year) survival in those patients who underwent surgery. Currently there are ongoing randomized prospective trials (in India, in Turkey, and ECOG 2108 in the United States) that will hopefully provide more definitive guidelines.

At present, surgical resection of the primary tumor appears most appropriate for younger patients, those who have a favorable response to systemic therapy, and patients who have bone and soft tissue, as opposed to visceral metastases.

Many patients with invasive lobular carcinoma have metastatic disease in bone at the time of first presentation, and this disease is often highly responsive to primary endocrine therapy. Such patients are, therefore, often ideal candidates for surgical treatment of the primary tumor once their systemic disease is in remission.

In the absence of BRCA gene mutation, and with the presence of metastatic disease, bilateral mastectomy is not indicated.

Case study 83.5

Locally advanced and inflammatory cancer

A 55-year-old woman presented with a 4-week history of swelling and redness of the right breast, which was unresponsive to two courses of antibiotics from her family doctor. Biopsy of the affected breast revealed a high-grade invasive cancer involving dermal lymphatics. ER and PR were negative, and Her2neu was 3+ by immunohistochemistry. Staging studies revealed multiple enlarged right axillary nodes, and several lung and liver metastases.

1. What would be your choice of initial treatment?

A. Four cycles of adriamycin and cytoxan followed by paclitaxel

B. Four cycles of adriamycin and cytoxan followed by paclitaxel with trastuzumab

C. Taxotere, carboplatin, and trastuzamab

The principles of treatment of the patient with locally advanced or inflammatory breast cancer are now well established: the primary treatment modality is systemic chemotherapy (with Her2-targeted therapy if indicated), followed by surgery when optimal tumor debulking has been achieved. Surgery is then followed promptly by radiation. With this approach, 5-year disease-free survivals of >50% can be achieved.

The NOAH trial, published in 2010, demonstrated that the addition of trastuzamab to neo-adjuvant chemotherapy significantly improved event-free survival of patients with locally advanced and inflammatory Her2-positive breast cancer.

Similar benefits were seen when postoperative adjuvant trastuzumab-containing combination chemotherapy was evaluated in numerous randomized studies, including BIG, HERA NSABP B-31, and FinHer.

The question of optimal drug combination for initial treatment of the patient with Her2-positive disease has to be considered. Numerous studies have shown that sequential use of anthracycline and trastuzamab is associated with increased cardiac toxicity. Attempts have therefore been made to identify alternative regimens.

In BCIRG 006, where over 3000 patients with stage 1 and 2 Her2-positive breast cancer were studied, the addition of adjuvant trastuzamab to postoperative adriamycin and cytoxan followed by paclitaxel improved relapse-free survival, consistent with other studies cited above.

An additional treatment arm in BCIRG 006 compared an anthracycline-free combination, taxotere, carboplatin, and trastuzamab (TCH) with adriamycin and cytoxan, followed by paclitaxel and one year of trastuzamab (AC-TH).

At the second interim analysis, the TCH arm was just as effective in producing relapse-free survival as AC-TH, but was significantly less likely to produce serious long-term toxicity (grade 3 and 4 cardiac events, and leukemia). Based on these data, we favor treatment regimen C.

Maintenance therapy versus no maintenance therapy

When patients achieve complete response or a (very good) partial response, what comes next? This patient with metastatic inflammatory Her2-positive breast cancer was treated with eight cycles of combination chemotherapy (taxotere and carboplatin) with trastuzamab, and achieved a complete clinical and radiological response.

2. What treatment would you then recommend?

A. No further systemic treatment; observation only

B. Maintenance trastuzamab

C. Right mastectomy and radiation therapy

D. Switch to lapatinib and capecitabine

Complete remissions can be anticipated in approximately 20% of patients with metastatic disease treated with systemic therapy, and they are more likely to occur in patients with Her2-positive disease, so the clinical scenario presented here is not at all uncommon.

This patient raises several interesting questions.

First, in a patient who presents with metastatic disease de novo, is there a survival advantage to continuing drug treatment to maintain remission?

Clinical data from 11 randomized prospective trials confirm that longer first-line chemotherapy produces significantly improved overall survival and progression-free survival. Practically speaking, however, prolonged chemotherapy is difficult to tolerate because of toxicity associated with long-term use, particularly neurotoxicity.

Most clinicians would anticipate that this patient would probably relapse within 12 months of discontinuing therapy, in view of the fact that she had documented visceral metastases in several sites, and her disease is biologically aggressive (Her2-positive).

Although prolonging trastuzamab beyond one year does not appear to be more effective when used in the postoperative *adjuvant* setting, there may be value to using trastuzamab as a single agent for maintenance therapy in patients with metastatic disease.

The second question has already been addressed in question #1, namely, is there a benefit to surgically removing the site of the original tumor?

In patients who present de novo with stage IV disease, there may well be a survival benefit to surgically removing the primary tumor site, particularly if there is evidence of residual disease after neo-adjuvant chemotherapy. In this

(*Continued*)

case, there was absolutely no evidence of residual disease in the breast and axilla.

Given that the original presentation was of an inflammatory cancer with nodal involvement, the only surgical option would be a total mastectomy and axillary node dissection with postoperative radiation. This treatment option is certainly a reasonable one, but would not remove the need for additional (maintenance) drug therapy.

After discussion with the patient it was elected to defer surgery, while recognizing the need for careful observation to detect early evidence of loco-regional relapse.

The third question is: if a decision is made to continue systemic treatment in an attempt to maintain a remission, what drug regimen should be chosen?

When used as a single agent, trastuzumab has significant activity, producing objective responses in approximately 30% of patients with measurable disease. Its long-term use is also much less likely to cause severe toxicity than chemotherapy.

We are fortunate that there are now available numerous drugs with significant activity against Her2-positive disease. These include pertusamab, a complex of trastuzamab with maytansine, and several small-molecule compounds that are inhibitors of tyrosine kinase pathways, namely, lapatinib and neratinib.

These drugs are used in patients who have demonstrated resistance to trastuzamab.

It is important to recognize that it is clinical scenarios like this that demonstrate how importantly the biology of each breast cancer directs treatment choice, and how individualized the treatment of breast cancer has become.

Case study 83.6

Triple-negative breast cancer

A 39-year-old premenopausal African American woman presented with a large mass in the right breast, together with a large right axillary node. She stated that she first noticed a lump in the breast 6 months earlier, but was too frightened to seek medical advice. The mass had increased significantly in size.

On examination, the mass measured 6 × 6 cm, and the right axillary node was approximately 3 × 3 cm. Core needle biopsy revealed a grade 3 triple-negative invasive ductal carcinoma. There was a history of breast cancer in her maternal grandmother, but the patient was negative for BRCA mutation.

1. The patient expressed a desire for breast conservation if possible. What would be the best treatment option for this patient?

A. Partial mastectomy and axillary node dissection
B. Total mastectomy and sentinel lymph node biopsy (SLNB)
C. Bilateral mastectomy
D. Neo-adjuvant chemotherapy

Triple-negative breast cancer is most commonly seen in patients with the BRCA1 gene mutation, women younger than 40 years of age, and African American women. Most, but not all, triple-negative tumors have a basal-like genomic profile.

Women with triple-negative breast cancer are more likely to develop early disease recurrence, including CNS involvement.

The initial treatment of this patient should be chemotherapy.

Partial mastectomy is relatively contraindicated by the size of the primary tumor (T3), unless the patient has an extremely large breast. The presence of enlarged axillary nodes precludes SLNB, as an axillary dissection is clearly required.

In the absence of BRCA gene mutation, the lifetime risk of a second tumor in the contralateral breast is relatively small, and prophylactic left mastectomy is not indicated.

Triple-negative tumors (and also Her2-positive disease) are generally highly responsive to primary (neo-adjuvant) chemotherapy, and significant tumor shrinkage can be anticipated. Reported objective response rates of >75% have been reported, with pathological complete response rates of >20%.

Those patients who achieve a pathologic complete response with neo-adjuvant chemotherapy have an excellent prognosis.

Prospective randomized trials of surgery followed by adjuvant chemotherapy compared with neo-adjuvant chemotherapy followed by surgery show equivalent results, in terms of relapse-free survival.

Advantages of neo-adjuvant chemotherapy include the opportunity to observe antitumor effect in vivo, and breast conservation in otherwise marginal cases.

2. In this patient, the decision was made to use neo-adjuvant (preoperative) chemotherapy. What regimen would you use?

A. Taxotere, adriamycin, and cytoxan (TAC)
B. Dose-dense adriamycin and cytoxan, followed by paclitaxel
C. Carboplatin and gemzar
D. Xeloda

Triple-negative breast cancer is seen most commonly in women younger than 40, patients with BRCA mutations, and African Americans. In the absence of any defined cel-

lular targets (like ER or Her2), we must rely on chemotherapy. Triple-negative disease is, however, highly sensitive to combination chemotherapy, including platinum-containing agents, such as cisplatin and carboplatin.

At the present time, there are insufficient data to recommend any one combination of drugs; however, single-agent Xeloda would not be considered adequate therapy.

The patient received four cycles of TAC, with significant improvement in the clinical findings in the breast and axilla. She then underwent right partial mastectomy and limited axillary dissection. Pathology of resected tissue showed extensive scarring (chemotherapy effect) with no visible residual tumor.

She received two additional cycles of Taxotere and cytoxan (without adriamycin), and postoperative radiation was then planned.

Case study answers

Case study 83.1

Question 1: Answer B

Case study 83.2

Question 1: Answer D

Case study 83.3

Question 1: Answer B and D

Case study 83.4

Question 1: Answer B

Case study 83.5

Question 1: Answer C
Question 2: Answer A

Case study 83.6

Question 1: Answer D
Question 2: Answer A

Suggested reading

Chia S, Swain SM, Byrd DR, *et al*. Locally advanced and inflammatory breast cancer. J Clin Oncol. 2008;26:786–90.

Gennari A, Stockler M, Puntoni M, *et al*. Duration of chemotherapy for metastatic breast cancer: a systemic review and meta-analysis of randomized clinical trials. J Clin Oncol. 2011;29:2144–9.

Melisko ME, Moore DH, Sneed PK, *et al*. Brain metastases in breast cancer: clinical and pathologic characteristics associated with improvements in survival. J Neuro-Oncol. 2008;88: 359–65.

Perez CB, Khan SA. Local therapy for the primary breast tumor in women with metastatic disease. Clin Adv Hematol Oncol. 2011;9:112–19.

Third consensus on medical treatment of metastatic breast cancer. Annals Oncol. 2009;20:1771–85.

For further information on this area please also consult Chapters 71, 118, 119, 123, 124, 131, 136, and 141

CHAPTER 84

Special issues in the young and pregnant patient with breast cancer

Hatem A. Azim Jr.[1] and Fedro A. Peccatori[2]

[1]Université Libre de Bruxelles, Brussels, Belgium
[2]European Institute of Oncology, Milan, Italy

Case study 84.1

A 33-year-old woman was recently diagnosed with a pT_{1c} (1.8 cm) pN_0 left breast cancer for which she was subjected to lumpectomy and sentinel lymph node sampling. Pathology revealed invasive ductal carcinoma grade II, estrogen receptor (ER) 30%, progesterone receptor (PgR) 0%, Ki67 14%, and HER2 score +1 by immunohistochemistry.

1. Would genomic testing by Oncotype DX™ or MammaPrint® be helpful in managing this patient?

A. Yes
B. No

Oncotype DX and MammaPrint are the most widely available genomic tests that are used to determine the risk of relapse in patients with ER-positive breast cancer. They have been shown to add prognostic information to classic clinicopathological prognostic factors; however, their value in young populations has not been widely explored. The fact that breast cancer arising in young women (below 35 or 40 years) has poorer prognosis compared to that in older women, poses a question of whether these tests could be of value in young populations. A large gene expression analysis has tried to address this question and found that genomic tests were able to add significant prognostic information to Adjuvant Online. This was observed in patients 40 years or younger as well as in other age groups with no interaction according to age.

This patient was diagnosed with an ER-positive tumor, with features suggesting incomplete endocrine sensitivity, manifested by the relatively low expression of ER (30%) and the lack of PgR expression (0%). Ki67 was 14%, which is rather borderline in defining highly proliferative ER-positive breast cancer. Hence, genomic tests could provide more accurate information on the absolute risk of relapse, which could aid the decision-making process. While these tools were not developed as predictive tools, preliminary evidence suggests that patients with high Oncotype Dx™ scores derive high benefit from adjuvant chemotherapy, while no benefit was observed in those with low scores. Nevertheless, the exact clinical utility of these tests has yet to be determined in two large prospective phase III trials (TailorX and MINDACT), which have already completed accrual and are expected to report in the coming few years.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 84.2

A nulliparous 36-year-old patient was diagnosed with a pT_{1c} pN_{1a} infiltrating ductal carcinoma that is ER- and PgR-negative and HER2-positive (+3 by immunohistochemistry). She was offered adjuvant treatment with FEC100 (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) ×3 followed by Docetaxel (100 mg/ m^2) ×3 cycles. The patient will also receive trastuzumab starting with docetaxel to complete a total duration of 1 year.

1. In your opinion, which of the following factors are the most important in determining the risk of chemotherapy-induced amenorrhea (CIA) in this patient? (Choose all that apply.)

A. Age
B. The dose of anthracycline
C. The sequential use of docetaxel
D. The dose of cyclophosphamide
E. Concomitant administration of trastuzumab with chemotherapy

The possible impact of chemotherapy on the ovarian function is a frequent concern, particularly for young women who have not started or completed their families.

Age remains the most important determinant of CIA irrespective of the regimen used. At the ages of 37–39, there is physiologically accelerated atresia of the oocytes. Hence, CIA rates have been largely variable according to the patient age being above or below 40, which coincides with the physiological decline in ovarian reserve. Table 84.1 summarizes the risk of CIA with different regimens according to age.

Alkylating agents are the most gonadotoxic chemotherapeutic agents. Cyclophosphamide has been shown to induce apoptosis of the primordial follicles. The incorporation of taxanes in the adjuvant setting has not been shown to increase the risk of CIA associated with classic anthracycline-based regimens. On the contrary, regimens in which 3–4 cycles of a taxane are given in sequence to 3–4 cycles of an anthracycline-based therapy appeared to be less gonadotoxic compared to 6–8 cycles of anthracycline- and cyclophosphamide-based regimens. This is believed to be largely related to the lower cyclophosphamide dose administered in the sequential regimens. Current available evidence on trastuzumab is limited; however, it does not appear to increase the risk associated with CIA.

Table 84.1 Risk of chemotherapy-induced amenorrhea with different regimens according to age.

Chemotherapy regimen	Age <30 years (%)	Age 30–40 years (%)	Age >40 years (%)
AC ×4		13	57–63
CMF ×6	19	31–38	76–96
CAF/CEF ×6	23–47	23–47	80–90
FEC 100 ×6		76.3	
FEC 100 ×3—docetaxel ×3		63.5	

AC, adriamycin and cyclophosphamide;
CAF, cyclophosphamide, adriamycin, and 5FU;
CEF, cyclophosphamide, epirubicin, and 5FU;
CMF, cyclophosphamide, methotrexate, and 5FU;
FEC, 5FU, epirubicin, and cyclophosphamide.

Case study 84.3

A 39-year-old breast cancer patient, who completed 5 years of adjuvant tamoxifen 6 months ago, presented to your office pregnant at week 8 of gestation. She was worried following her visit to her obstetrician, who recommended an abortion for fear that pregnancy could stimulate breast cancer recurrence. The patient would like to keep her pregnancy, but would like to understand whether taking this decision would have a detrimental effect on breast cancer outcome.

1. What would you advise her?

A. Pregnancy after ER-positive breast cancer increases the risk of recurrence, but abortion is not recommended as it is not clear that it improves prognosis.
B. Pregnancy after ER-positive breast cancer increases the risk of recurrence, and hence abortion is preferred as it could reduce such risk.
C. Pregnancy following breast cancer does not appear to be detrimental irrespective of ER status.
D. Pregnancy following breast cancer is protective and should be encouraged.

Pregnancy following breast cancer, particularly ER-positive breast cancer, represents one of the most controversial issues in managing young breast cancer patients. Despite several studies that have been reported for more than 3 decades showing that pregnancy after breast cancer is safe, these studies suffered major flaws regarding patient selection, low statistical power, and the lack of information on outcome according to endocrine receptor status. This has resulted in

(*Continued*)

more breast cancer survivors being advised against pregnancy, with induced abortion rates reaching up to 30%. This reflects a conception that pregnancy is detrimental and that abortion might reduce such risks.

Recently, a multicenter, prospectively powered study was reported that aimed to address many of the limitations highlighted here. This study included more than 1200 patients, of whom 333 patients became pregnant after breast cancer diagnosis. Importantly, all patients had known ER status. This study showed that pregnancy after ER-positive breast cancer does not increase the risk of breast cancer recurrence at least during the first 5 years following conception. In the same study, patients who underwent abortion did not appear to have a superior outcome compared to those who continued their pregnancy to term. Hence, women who completed their adjuvant therapy should not be denied the opportunity to become pregnant. Promotion of abortion in these patients for therapeutic reasons remains unjustified in the absence of supporting evidence.

Case study 84.4

A 35-year-old breast cancer patient, who is ER-negative and HER2-positive, was treated with adjuvant chemotherapy (AC) ×4 followed by four cycles of docetaxel along with one year of adjuvant trastuzumab. Three years later, she is disease-free and considering becoming pregnant for the first time.

1. Would you be concerned that the treatment she received could have adverse effects on the fetal outcome?

A. No, no significant increase in fetal adverse effects is foreseen.
B. Yes, prior exposure to chemotherapy could increase the risk of fetal anomalies.
C. Yes, prior exposure to trastuzumab could increase the risk of fetal anomalies.
D. Yes, prior exposure to both chemotherapy and trastuzumab could increase the risk of fetal anomalies.

There is no evidence that pregnancy in breast cancer survivors is associated with a significant increase in fetal or infant risk of malformations. Data from two large population-based cohort studies from Sweden and Denmark are rather reassuring in this regard. However, in the Swedish cohort, increased risks of delivery complications, caesarean section, very preterm birth (<32 weeks), and low birth weight (<1500 g) were reported compared to healthy controls. These findings have potential implications for vigilant pregnancy surveillance. Of note, these pregnancies should be regarded as high risk, considering that the average maternal age is usually higher compared to the general population. Taking into account the time of oocyte maturation, it is recommended to wait for 6–12 months from the end of chemotherapy before becoming pregnant.

A 6-month period should be allowed before becoming pregnant after cessation of trastuzumab. Based on available data, prior maternal exposure has not been shown to affect fetal outcome, at least in the short term. This is based on data from the Herceptin Adjuvant (HERA) trial, in which patients who became pregnant >3 months after stopping trastuzumab did not experience a high rate of spontaneous abortions or fetal adverse events at delivery.

2. How would you counsel a patient who became accidentally pregnant on maintenance therapy with trastuzumab or tamoxifen? (Choose all that apply.)

A. Abortion should be always considered in such cases.
B. Risk of miscarriage is high.
C. Risk of fetal anomalies appears high with trastuzumab exposure during the first trimester.
D. Risk of fetal anomalies appears high with tamoxifen exposure during the first trimester.

This is a very delicate situation that is increasingly encountered nowadays in breast cancer clinics. Patients commonly develop temporary amenorrhea secondary to chemotherapy, and hence advising them to use adequate contraceptive measures prior to starting tamoxifen or trastuzumab is frequently overlooked.

The fact that the patient became accidentally pregnant on trastuzumab or tamoxifen raises the concern of the possible in utero fetal toxicity. In utero exposure during the first 2 weeks of gestation is associated with a high probability of miscarriage. This is the case with almost any administered agent during this phase. Patients who had a pregnancy while on trastuzumab appear to have a relatively high rate of miscarriage, although this is based on a relatively small number of patients.

The situation is even more complex when evaluating the risk of fetal malformations. In utero exposure to tamoxifen during the first trimester (particularly weeks 3–12) is associated with a high risk of malformations, being the period of organogenesis. Anecdotal evidence and a recent review of the Astra Zeneca safety files have pointed out what appears to be a high risk of fetal malformation secondary to tamoxifen exposure during the first trimester. Out of 68 women with first-trimester exposure to tamoxifen and known pregnancy

outcome reported to Astra Zeneca, 15 (22%) fetal malformations were reported. On the contrary, no malformations were reported in 85 women who became pregnant on tamoxifen within a chemo-prevention trial with tamoxifen. Hence, it is difficult to provide an accurate estimate of the absolute risk of malformations associated with tamoxifen exposure during the first trimester. However, patients should be made aware of the possible risk of congenital malformations associated with accidental exposure to tamoxifen early in pregnancy.

The situation is somehow different with trastuzumab, which is—unlike tamoxifen—a large molecule that requires an active transport mechanism to cross the placental barrier. Such a mechanism is only activated starting week 14 of gestation. Hence, it is unlikely that brief exposure during the first trimester would be associated with a high risk of congenital malformation. Out of 16 patients who accidentally became pregnant on trastuzumab in the HERA trial, none developed a congenital anomaly. The same was observed in sporadic case reports. The risk remains, though, in patients who continue trastuzumab administration during the second and third trimesters. These patients have a high risk of developing oligohydramnios, which predisposes to preterm delivery, fetal morbidity and mortality. Hence, patients who become pregnant on trastuzumab should immediately stop the drug in case they are willing to proceed with the pregnancy. Unlike tamoxifen, such approach does not appear to carry a considerable risk of fetal congenital malformations.

Case study 84.5

A 39-year-old old female is diagnosed with a pT_2 N_{1b} ER-positive breast cancer. She is planned to start adjuvant chemotherapy. She expressed her concerns regarding the chances for future fertility following chemotherapy.

1. Which of the following options could be offered to preserve fertility? (Choose all that apply.)

A. Administration of LHRH analogs with chemotherapy
B. Embryo or oocyte cryopreservation
C. Ovarian tissue cryopreservation

The administration of chemotherapy is associated with a risk of permanent amenorrhea, which appears to be age dependent. Although the absolute effect of chemotherapy on ovarian function remains unknown, current evidence points out that patients who resume menstruation following chemotherapy administration have poor ovarian reserve. This suggests that the detrimental effect of chemotherapy on ovarian function could be even larger than that on menstrual function. This patient is 39 years old, and thus her chances of spontaneous recovery of adequate ovarian function following chemotherapy are limited. Hence, she should be counseled upfront on possible strategies to preserve her chances of conceiving.

Embryo cryopreservation has been an established and widely available method in treating infertility since the early 1980s. In the United States, the delivery rate is approximately 30% and 16% per embryo thaw in patients younger than 35 years and older than 40 years of age, respectively. As patients undergoing in vitro fertilization with embryo cryopreservation are generally not infertile, pregnancy rates might well be higher than those achieved by couples who potentially have poor oocytes and sperm quality. However, the main concern in breast cancer patients remains in applying ovarian stimulation regimens, which result in a significant increase in estradiol levels. In addition, this could result in a relative delay in initiating therapy, which could have a detrimental effect on breast cancer outcome. However, a series of studies were conducted using letrozole and follicle-stimulating hormone that showed high embryo yield and low peak estradiol levels with no apparent effect on breast cancer outcome, at least during the first 2 years.

Ethical and social considerations of embryo cryopreservation also exist. This procedure requires a partner, and the fate of the cryopreserved embryo, if available, remains a problem in case the patient dies before implantation. These latter two disadvantages to embryo preservation could therefore represent a potential advantage for oocyte cryopreservation and ovarian tissue freezing, although the latter currently remains highly experimental.

The role of luteinizing hormone–releasing hormone (LHRH) agonists in preserving fertility is debatable. At least four randomized trials have evaluated the effect of adding LHRH agonists to chemotherapy on menstrual function. These trials showed contradictory results. Importantly, none of the trials have evaluated the effect of LHRH agonists on ovarian function or shown long-term data on pregnancy rates. Hence, to date, LHRH agonists should not be considered as a reliable means to preserve fertility.

Case study 84.6

A 15 weeks' pregnant patient presented to you with locally advanced breast cancer along with liver metastasis. A core biopsy showed grade III invasive duct carcinoma, negative for ER and PgR expression but positive for HER2 (+3 by immunohistochemistry). The patient was 40 year old, and this was her first pregnancy after several years of receiving treatment for infertility.

1. The patient came for a second opinion as her doctor believes that she should proceed for an abortion, an option that she completely refuses. What would you advise her?

A. Close observation and proceed for delivery once the fetus is viable.
B. Initiate chemotherapy and trastuzumab, aiming at delivery once the fetus is viable.
C. Initiate chemotherapy and trastuzumab, aiming at delivery as close to term as possible.
D. Initiate chemotherapy and hold trastuzumab, aiming at delivery as close to term as possible.

This case addresses three key points: the therapeutic role of elective abortion, the safety of chemotherapy and trastuzumab during pregnancy, and the optimal timing of delivery.

Current evidence points out that induction of abortion in patients diagnosed with breast cancer during pregnancy has no effect on patient outcome. Hence, abortion should not be promoted for therapeutic reasons.

Delay of therapy could be sometimes considered in case diagnosis is made relatively late during gestation and/or the tumor has favorable features (e.g., grade 1, node negative, and Luminal A). However, in this patient, treatment should be initiated. The administration of chemotherapy starting in the second trimester is considered safe. Data from large registries suggest that treatment with chemotherapy slightly increases the risk of pregnancy-related complications and premature delivery. However, no increases in malformations or fetal mortality have been observed. Accordingly, chemotherapy should not be denied to patients who require active treatment during pregnancy.

Unlike chemotherapy, trastuzumab administration during pregnancy, particularly starting in the second trimester, has been associated with a high risk of oligohydramnios, resulting in a relatively high rate of fetal prematurity and fetal death (Table 84.2). This is believed to be secondary to the inhibitory effect of trastuzumab on HER2, which is expressed on the fetal kidney that is responsible for the amniotic fluid production. Based on the limited available data on trastuzumab administration during pregnancy, it looks clear that trastuzumab should be avoided during the course of gestation.

It is currently recommended to aim for full-term or near-full-term delivery in these patients. Early induction of labor does not improve patient outcome. Standard therapies could be offered to pregnant patients in the majority of cases until week 34 of gestation. More importantly, data from a large prospective study have shown that the long-term intellectual abilities of newborns exposed to chemotherapy in utero and delivered at term are significantly better than those of newborns delivered preterm. Hence, every effort should be made to deliver after the 36th week of pregnancy, whenever possible.

Table 84.2 Trastuzumab exposure during the second ± third trimesters of pregnancy.

	N	Oligohydramnios (*n*)	Fetal complications (*n*)	Fetal death (*n*)
Trastuzumab	7	5	Renal failure (1) Respiratory failure (2)	2
Trastuzumab + chemotherapy	5	4	Renal and respiratory failure (1)	0
Trastuzumab + hormonal	2	2	Respiratory failure (3)[a]	2

[a]One twin pregnancy.

Multiple choice questions

1. Is there a role for sentinel lymph node biopsy (SLNB) in patients diagnosed with breast cancer during pregnancy?

A. Yes
B. No

To date, limited clinical data are available on SLNB in patients diagnosed with breast cancer during pregnancy. An earlier simulation study from the European Institute of Oncology in Milan showed that the dose of radiation that the fetus could be exposed to is minimal. Later on, the same group published the first series of patients who were managed with SLNB during the course of pregnancy. A

total of 12 patients were included in this report, and all were exposed to low-dose (10 MBq) lymphoscintigraphy using ^{99m}Tc human serum albumin nanocolloids without blue dye injection. The SLN was detected in all patients, of whom 10 had pathologically negative nodes and hence were spared axillary dissection. None of these patients had evidence of axillary relapse at a median time of nearly 3 years. Importantly, all pregnancies resulted in healthy babies, except for one case of ventral septal defect, which was diagnosed on an ultrasound before the SLNB and was surgically corrected postpartum. While more data are required to confirm the reliability and safety of SLNB during pregnancy, several groups have recently endorsed this approach in pregnant breast cancer patients, given the apparent reduced fetal risk.

2. Which of the following chemotherapy regimens and agents should be avoided during pregnancy? (Check all that apply.)

A. AC (adriamycin and cyclophosphamide) or FAC (5-fluorouracil ("5FU"), adriamycin, and cyclophosphamide)
B. Epirubicin-based regimens (e.g., FEC)
C. CMF (cyclophosphamide, methotrexate, and 5FU)
D. Taxanes (docetaxel or paclitaxel)
E. Platinum salts

In breast cancer, considerable clinical evidence currently exists on the safety of anthracyclines during pregnancy, both doxorubicin and epirubicin. Transplacental animal models have further confirmed that they cross the placenta at low rates, particularly epirubicin, in which no more than 4% of the total maternal dose could be detectable in the fetal circulation. It is unknown whether such a low fetal exposure is clinically relevant or not; however, data on long-term follow-up further support that both doxorubicin and epirubicin could be safely used starting in the second trimester of pregnancy. Weekly fractionation of the anthracycline dose has been promoted to reduce peak plasma levels, which would possibly reduce the transplacental transfer. In addition, it would allow close monitoring of the pregnancy.

Data on taxanes are reassuring, although they remain more limited compared to data on anthracyclines. While we lack sufficient data on the long-term follow-up of babies exposed to taxanes in utero, transplacental studies point out that taxanes are seldom detected in the fetal circulation at all, which is rather reassuring. This could be due to the high expression of p-glycoprotein in the placenta, which is responsible for metabolizing taxanes.

Platinum salts cross the placenta at considerable rates compared to other agents. However, clinical data suggest an acceptable safety profile on the short term, although some minor anomalies were observed. Hence, in patients who require *urgent* treatment with platinum salts during pregnancy, treatment could be commenced acknowledging the lack of robust data as in the case of anthracyclines and taxanes. Further data are required to confirm their short- and long-term safety.

CMF should not be promoted during pregnancy for several reasons. Methotrexate is an abortive agent, and major malformations have been observed following first-trimester exposure. This regimen also includes the administration of high doses of cyclophosphamide, in which >50% of it has been detected in fetal circulation in animal transplacental models. Given the inferiority of CMF to the safer anthracycline- and taxane-based regimens, and its potential teratogenicity, there is no reason to consider CMF for pregnant breast cancer patients, and hence it should be avoided.

Case study 84.7

A 38-year-old woman recently noticed a right breast lump while breastfeeding her newborn. An ultrasound was quite suspicious, and accordingly a biopsy was performed revealing an invasive duct carcinoma. Further pathological evaluation and staging work-up are still pending.

1. Based on the available information, the prognosis of this patient is:

A. Favorable
B. Unfavorable

Compelling evidence suggests that the short period following pregnancy is associated with a high incidence of developing breast cancer, aggressive breast cancer biology, and poor prognosis. Women who develop breast cancer within 2 years following pregnancy are more likely to have grade 3 and triple-negative tumors. A large meta-analysis has shown that their prognosis in terms of disease-free and overall survival is significantly poorer compared to other breast cancer patients of the same age and stage.

Preclinical evidence points out that postpartum involution could be a main driving force for tumor progression mediated by collagen and high cyclooxygenase-2 (COX2) expression. However, we lack any data on the potential benefit of COX2 inhibitors in managing these patients.

Hence, this patient appears to have a guarded prognosis independent of stage and classic pathologic features. This should be taken into account when planning her management strategy.

Case study answers

Case study 84.1

Question 1: Answer A ("Yes")

Case study 84.2

Question 1: Answer A and D

Case study 84.3

Question 1: Answer C

Case study 84.4

Question 1: Answer A
Question 2: Answer B and D

Case study 84.5

Question 1: Answer B and C

Case study 84.6

Question 1: Answer D

Case study 84.7

Question 1: Answer B

Multiple choice answers

Question 1: Answer A ("Yes")
Question 2: Answer C

Selected reading

Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol. 2008;26:2630–5.

Azim HA Jr, Kroman N, Paesmans M, *et al*. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol. 2013;31:73–99.

Azim HA Jr, Michiels S, Bedard PL, *et al*. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res. 2012;18:1341–51.

Loibl S, Han SN, von Minckwitz G, *et al*. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012;13:887–96.

Peccatori FA, Azim HA Jr, Orecchia R, *et al*. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl. 6):vi60–70.

For further information on this area please also consult Chapters 118, 119, 123, 124, 131, 136, and 141

PART 4

Gastrointestinal Oncology

CHAPTER 85

Early-stage esophageal and stomach cancers

M. Naomi Horiba and Yixing Jiang
University of Maryland, Baltimore, MD, USA

Case study 85.1

A 65-year-old male presented with progressive dysphagia to solid food. He was evaluated with esphagogastroduodenoscopy (EGD) by his gastroenterologist. The EGD showed a mass protruding into the lumen of the esophagus at 39 cm from the incisors. At the same time, an endoscopic ultrasound (EUS) was performed, which showed that the mass invaded into the muscularis propria of the esophagus, and no suspicious lymph nodes were identified (T2N0). Biopsy of the mass showed adenocarcinoma of the esophagus. The patient underwent esophagectomy with lymph nodes dissection. The final pathology showed T2N1 disease. The patient is now referred to medical oncology for consideration of adjuvant therapy.

Adjuvant therapy for resected esophageal cancer (both adenocarcinoma and squamous cell carcinoma (SCC)) is not well established. There are relatively few studies evaluating adjuvant treatment of esophageal cancer. Several international studies have been unable to document an overall survival benefit. The Japanese Clinical Oncology Group Study (JCOG9024) enrolled a total of 242 patients that were randomized to either surgery alone or surgery plus adjuvant chemotherapy with two cycles of cisplatin (80 mg/m^2) and 5-fluorouracil (5FU) (800 mg/m^2/day on days 1–5). They demonstrated a 5-year disease-free survival (DFS) advantage of adjuvant chemotherapy over surgery alone (55% vs. 45%; $P = 0.037$), but no overall survival (OS) benefit (61% vs. 52%; $P = 0.13$). Of note, this trial accrued only patients with squamous cell esophageal cancer.

Eastern Cooperative Oncology Group trial ECOG 8296 was a single-arm phase II study evaluating the safety, feasibility, and survival benefit of four cycles of cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2) in the adjuvant setting. The study accrued 55 patients with adenocarcinoma of the esophagus, gastroesophageal (GE) junction, and gastric cardia. Compared to historical controls, there was a small benefit in survival; however, the value of a small single-arm phase II study is too limited to guide clinical practice. Thus, prospective randomized phase III studies are needed to clarify the benefit of adjuvant chemotherapy in esophageal cancer

The benefit of perioperative chemotherapy in esophageal cancer has also been evaluated. In the INT113 study by the US Intergroup in 1998 (RTOG9811), patients with operable cancers were randomly assigned to receive perioperative chemotherapy (213 patients) consisting of three cycles of pre- and postoperative cisplatin and 5FU, versus surgery alone (227 patients). Notably, only 38% of patients were able to complete postoperative chemotherapy. Kelsen *et al*. (2007) published the long-term results of this study in 2007. After 55.4 months of follow-up, no difference in the median OS was detected (14.9 months for the perioperative chemotherapy group vs. 16.1 months for the surgery-alone group; $P = 0.53$). Recently, Ychou *et al*. (2011) reported a phase III study comparing perioperative cisplatin and 5FU with surgery alone in patients with adenocarcinoma of the lower esophagus or GE junction, or gastric cancer. All study patients in the chemotherapy group received 2–3 cycles of preoperative chemotherapy and 3–4 cycles of postoperative chemotherapy. Approximately 50% of patients completed postoperative chemotherapy. The study demonstrated a

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

benefit in favor of the chemotherapy arm in terms of both OS (difference is HR: 0.69; $P = 0.021$) and DFS (difference is HR: 0.65; $P = 0.0033$) after 5 years of follow-up. Of note, the R0 resection rate was significantly higher in the preoperative chemotherapy group ($P = 0.04$). While chemotherapy has a role in resectable patients, given the design of the trial, it is difficult to know whether the benefit can be attributed to preoperative chemotherapy, postoperative chemotherapy, or both.

The role of adjuvant radiation alone has not been assessed systematically. Multiple studies demonstrated no significant benefit in OS or local control. However, most studies primarily included squamous cell histology. Adjuvant chemoradiation with 5FU was established as the standard care for gastric cancer by Macdonald and his colleagues (2001). Although INT116, a similar study to INT113, is primarily a gastric cancer study, the study included about 20% GE junction and distal esophageal adenocarcinoma cases. Hence, this approach is widely adopted for patients with distal esophageal cancer post resection.

In sum, adjuvant therapy for resected esophageal cancer is still an ongoing debate. The current National Comprehensive Cancer Network (NCCN) guidelines do not recommend adjuvant chemotherapy or chemoradiation for resected SCC or adenocarcinoma located in the middle or upper one-third of the thorax. For adenocarcinoma of the distal esophagus or GE junction (any TN+, T3N0, or T2N0 with poorly differentiated histology and lymphovascular invasion), adjuvant chemoradiation with 5FU-based chemotherapy is currently recommended. Continuous infusion of 5FU is preferred over bolus 5FU. Thus, the chemoradiation on the traditional Macdonald regimen is typically modified to include infusional 5FU or oral capecitabine.

Case study 85.2

A 65-year-old male with a history of hypertension and diabetes that are well controlled with medications presented with progressive dysphagia to solid food. He was evaluated with EGD by his gastroenterologist. EGD showed a mass protruding into the lumen of the esophagus at 39 cm from the incisors. At the same time, an EUS was performed that showed that the mass invaded the adventitia of the esophagus, and two suspicious lymph nodes were identified (T3N1). Pathology from the mass showed adenocarcinoma of the esophagus. A positron emission tomography–computed tomography (PET–CT) was performed that showed no evidence of distant metastatic disease. After discussing the case in a multidisciplinary conference, a consensus was reached that the patient should be treated with preoperative chemoradiation. Which chemoradiation regimen should be considered?

The goal of preoperative chemoradiation therapy is to prevent local and distant recurrence after surgery. In an attempt to eliminate micrometastases and sterilize the operative field, several neo-adjuvant regimens have been studied. One benefit of neo-adjuvant therapy is that it offers better radiation field design and tolerability. Combined-modality treatment has been explored for over 2 decades in several randomized phase III trials with somewhat inconsistent results. Several chemotherapy regimens have been evaluated for tolerability, safety, short-term or long-term toxicities, and efficacy.

Urba *et al*. (2001), Walsh *et al*. (1996), and Tepper *et al*. (2008) have each published well-known randomized trials comparing chemoradiation followed by surgery versus surgery alone in patients with primarily adenocarcinoma histology that showed a benefit in favor of neo-adjuvant chemoradiation. Urba's group demonstrated an increase in 3-year survival in the combined-modality group (30% vs. 16%). The difference was not statistically significant due to the small sample size. Walsh and colleagues demonstrated a significant benefit in the combined-modality treatment arm with a 32% 3-year survival vs. 6% in the surgery-alone arm ($P = 0.01$), although this trial has been criticized due to the unusually poor 3-year survival in the surgery-alone arm (6%). Tepper *et al*. also reported a statistically significant benefit in median survival (4.48 vs. 1.79 years; $P = 0.002$) in favor of the combined-modality group, but they studied only 56 patients as the trial closed early for poor accrual. All these trials used cisplatin and 5FU as radiosensitizing chemotherapy.

The cisplatin-based regimen was also evaluated in SCC of the esophagus. Bosset and colleagues (1997) randomized 257 patients with SCC of the esophagus to either surgery alone or cisplatin ($80\,mg/m^2$) with radiotherapy followed by surgical resection. The results are rather disappointing. The preoperative chemoradiation did not improve OS. However, the DFS and local control were better in the combined-modality arm. These results could be due to the fact that the study mainly enrolled early-stage disease (stages I and II). Burmeister *et al*. (2005) also used a cisplatin and 5FU regimen in their randomized phase III study. A total of 257 patients were randomized to receive neo-

adjuvant chemoradiation or surgery alone. No survival benefit was demonstrated in the study. Subgroup analysis showed potential benefit in squamous cell histology. Several meta-analyses suggest that chemoradiotherapy is of benefit. Most notably, Gebski and colleagues (2007) demonstrated a 13% absolute survival difference at 2 years for both adenocarcinoma and squamous histology (HR: 0.81; 95% CI: 0.70–0.93; $P = 0.02$).

Other chemotherapy drugs have been studied as radiosensitizers in the neo-adjuvant setting. Weekly cisplatin and irinotecan with radiation were developed by Ilson and colleagues (2012) at Memorial Sloan Kettering Cancer Center. The combination therapy is well tolerated and led to a pathologic complete response (pCR) of 16% in a small single-institution study. Other agents such as oxaliplatin and 5FU concurrent with radiation have demonstrated a pCR of 28% in a single-arm phase II study.

Most recently, Van Hagen *et al*. (2012) published the largest randomized neo-adjuvant chemoradiation study in esophageal cancer. The study enrolled a total of 386 patients who were randomized to either surgery alone or preoperative chemoradiation followed by surgery. All the patients in the experimental arm received weekly carboplatin (area under the curve: 2) and paclitaxel (50 mg/m^2) concurrent with radiation. The study showed a significant improvement in OS in the multimodality group (49.4 months vs. 24 months in the surgery-alone group; HR: 0.657; 95% CI: 0.495–0.871; $P < 0.003$). pCRs of 23% in adenocarcinoma and 49% in SCC were achieved. In the subgroup analysis, a significant improvement in survival was observed in both adenocarcinoma and squamous histology.

For a long time, there has been a lack of consensus on the ideal preoperative chemoradiation regimen. This is partly attributed to similar pCRs seen among various regimens. Cisplatin and 5FU have historically been accepted as the standard of care by many oncologists largely due to the large number of published studies using this regimen despite serious toxicity. Although the NCCN Guidelines include several preoperative chemoradiation regimens based on level of evidence, weekly carboplatin and paclitaxel should be considered as the new standard regimen in the neo-adjuvant setting for both adenocarcinoma and squamous cell histology as this combination has demonstrated efficacy and is well tolerated.

Case study 85.3

A 65-year-old male with a history of hypertension and diabetes that are well controlled with medications presented with progressive dysphagia to solid food. He was evaluated with EGD by his gastroenterologist. EGD showed a mass protruding into the lumen of the esophagus at 39 cm from the incisors. At the same time, an EUS was performed that showed the mass invaded the adventitia of the esophagus, and two suspicious lymph nodes were identified (T3N1). A biopsy of the mass showed adenocarcinoma of the esophagus. A PET–CT was performed showing no evidence of distant metastatic disease. He was treated with weekly carboplatin and paclitaxel concurrent with radiotherapy in the preoperative setting. Subsequently, he underwent esophagectomy. The final pathology showed a significant amount of persistent disease, T2N1. He was referred to you for discussion of further therapy.

In general, contemporary neo-adjuvant chemoradiation achieves a 25–30% pCR, which has been demonstrated in a number of studies. It has been noted that patients with pCR have better survival. Stahl and colleagues (2007) compared preoperative chemotherapy to preoperative chemoradiation and found a beneficial trend in overall survival ($P = 0.07$) and DFS ($P = 0.06$) in favor of the chemoradiation group. In spite of equivocal results, the use of preoperative chemoradiation has been embraced by the United States and some European countries. Unfortunately, even with most updated chemoradiation techniques, the majority of patients still do not achieve pCR. How to further manage those with significant residual disease after trimodality therapy is an ongoing debate in daily practice. The current NCCN Guidelines do not encourage more chemotherapy or other treatment modalities in this group of patients. There is no randomized study to support adjuvant chemotherapy versus no adjuvant therapy. For patients with minimal residual disease, the long-term outcome is probably comparable with those who achieved pCR, as shown by Koshy *et al*. (2011) from the University of Maryland. A recent retrospective study published by Harvin and coworkers (2012) also suggested that even a microscopic positive circumferential margin did not negatively impact survival in those patients treated with preoperative chemoradiation. Hence, close observation seems appropriate for patients with pCR or minimal residual disease. Nonetheless, for those with significant residual disease, the likelihood for recurrence is extremely high. A strategy to improve survival in this particular group of patients is urgently needed.

Case study 85.4

A 65-year-old male with a history of hypertension and diabetes that are well controlled with medications presented with progressive dysphagia to solid food. He also has a history of heavy alcohol use and cigarette smoking. He was evaluated with EGD by his gastroenterologist. EGD showed a mass protruding into the lumen of the midesophagus. At the same time, an EUS was performed that showed that the mass invaded the adventitia of the esophagus, and two suspicious lymph nodes were identified (T3N1). A PET scan showed a hypermetabolic lesion in the mid-esophagus without distant metastasis. A biopsy of the mass showed SCC of the esophagus. He was treated with weekly cisplatin and 5FU concurrent with radiotherapy in the preoperative setting. A repeat PET–CT scan prior to surgical resection showed complete resolution of the fluoro-deoxyglucose (FDG)-avid lesion. Endoscopy showed only erythematous mucosa consistent with radiation changes, and both random biopsies at the previous tumor site and washings showed no malignancy. His case is being discussed in the multidisciplinary tumor board. The necessity of surgical resection was debated.

The etiology of SCC of the esophagus is quite different from that of esophageal adenocarcinoma. Biologically, these are probably two different diseases. However, the current management of SCC of the esophagus is essentially the same as that of adenocarcinoma. Surgical resection remains the cornerstone of treatment for SCC. An organ preservation approach has been adopted in SCC of the head and neck or anal canal. Surgical resection remains as a salvage modality for recurrent disease. This approach still needs to be validated in SCC of the esophagus. RTOG 85-01 is a randomized study comparing chemoradiation (5FU and cisplatin) to radiation alone in locally advanced esophageal cancer. Although the study enrolled both patients with adenocarcinoma and those with SCC, the majority of patients (107 out of a total of 130) treated on the protocol had SCC histology. After 5 year of follow-up, the OS for the chemoradiation group was 26%, whereas the OS for the radiation-alone group was 0%. 25% patients had persistent disease, and over 40% patients experienced local recurrence after chemoradiation. This provides the rationale for surgical resection of esophageal SCC treated with chemoradiation. On the other hand, some experts have argued the futility of surgical resection as the overall prognosis of SCC is poor. The argument was not settled until the publication of a recent phase III study from France, FFCD 9102, by Bedenne *et al*. (2007). The study randomized 259 patients to either chemoradiation followed by surgery or chemoradiation alone. Two-year survivals were similar (34% for surgery arm vs. 40% for chemoradiation; $P = 0.44$). The local control was better in the surgery group (66.4% in the surgery arm vs. 57% in the chemoradiation arm). The chemoradiation group also needed more stent placements for dysphagia. The study concluded that surgery did not provide further benefit for those with locally advanced SCC of the esophagus who had responded to chemoradiation. Presently, the NCCN Guidelines do not support different treatment paradigms for SCC of esophagus versus adenocarcinoma of the esophagus, and it is reasonable to consider these patients for resection.

Case study 85.5

A 65-year-old male with a history of hypertension and diabetes that are well controlled with medications presented with progressive early satiety, weight loss, and epigastric discomfort. He was evaluated with EGD by his gastroenterologist. EGD showed a mass at the body of the stomach. At the same time, an EUS was performed, which showed that the mass invaded the muscularis propria of the stomach wall. No lymph node was seen. He has a clinical stage of T3N0. PET scan showed no distance metastasis. He had subtotal gastrectomy with lymph node dissection. A total of 30 lymph nodes were assessed. The final pathology stage is T3N1. He was referred to you for a discussion of adjuvant therapy.

The majority of gastric cancer patients suffer from loco-regional and distant recurrences after definitive resection. Gunnderson and Sosin (1982) retrospectively examined the patterns of recurrence in a re-operative series at the University of Minnesota, and showed that 87.8% of the patients experienced loco-regional failure and 29.3% of the patients had distant metastasis. Hence, systemic chemotherapy and radiation for both distance and local control are rationally sound. The adjuvant chemoradiation trial reported by the GI Intergroup (INT0116) is considered an important advance in treating resected gastric cancer. In this trial, a high-risk group (85% with node-positive cancer) of the patients was enrolled. In the initial analysis after a median follow-up of 5 years, the OS rates (50% vs. 41%; $P = 0.005$), hazard ratio for death (HR: 1.35; 95% CI: 1.09–1.66), and median OS (36 months vs. 27 months; $P = 0.0005$) were also significantly improved in the chemoradiation group. Outcome data of this trial were updated most recently after a median follow-up of more than 10 years. The trial has been criticized for its surgically undertreated patients. The majority of the patients (54%) in the trial had D0 resections, and only 10% of patients had received D2 dissections. Nowadays, extended lymphadenectomy with pancreas and spleen preservation (known as "over-D1") is generally practiced at major centers in the United States. Nevertheless, postoperative chemoradiation became the standard care in the United States since the early 2000s.

Adjuvant chemotherapy has been disappointing, and the results from early trials are inconsistent. In 2007, Sakuramoto and colleagues (2007) published a phase III study demonstrating that adjuvant therapy with S1, an oral fluoropyrimidine, for 1 year significantly increases 3-year overall survival in Asian patients with gastric cancer who underwent D2 lymph node dissection (80.1% for the S1 group vs. 70.1% for the surgery-alone group; $P = 0.003$). Most recently, Paoletti *et al*. (2010) reported a meta-analysis study to assess the role of adjuvant chemotherapy in resected gastric cancer. The study identified 31 randomized trials. A total of 3781 patients were included in the analysis. The median follow-up was more than 7 years. The results showed that adjuvant chemotherapy significantly improved both OS (hazard ratio (HR): 0.82; 95% confidence interval (CI): 0.76–0.90; $P < .001$) and DSF (HR: 0.82; 95% CI: 0.75–0.90; $P < .001$). The 5-year OS was improved from 49.6% to 55.3%. The regimens used in those trials were 5FU and its derivatives, mitomycin, anthracyclines, and cisplatin.

Although there is evidence to support using adjuvant chemotherapy in resected gastric cancer, adjuvant chemoradiation remains the standard of care at this point in time.

Case study 85.6

A 65-year-old male with a history of hypertension and diabetes well controlled with medications presented with progressive early satiety, weight loss, and epigastric discomfort. He was evaluated with EGD by his gastroenterologist. EGD showed a mass at the body of the stomach. At the same time, an EUS was performed, which showed the mass penetrating through the subserosa. Two lymph nodes were seen. He has a clinical stage of T3N1. PET scan showed no distance metastasis. He was treated with preoperative ECF (epirubicin, cisplatin, and 5FU) chemotherapy for three cycles. Subsequently, he had subtotal gastrectomy. Pathology showed some response to the therapy. The pathological staging is T2N1. Postoperatively, he is doing very well. Now he returned to your office for adjuvant therapy.

Several early studies showed that preoperative chemotherapy is feasible. Ajani *et al*. reported that three cycles of etoposide, adriamycin, and cisplatin (EAP) were given preoperatively in a total of 48 patients. Responders continued to receive two additional cycles of chemotherapy. No pathological complete response was achieved. Overall survival was not improved significantly. Kelsen and colleagues (1996) from Memorial Sloan Kettering Cancer Center reported a phase II study using three cycles of FAMTX (fluorouracil, doxorubicin, and methotrexate) preoperatively followed by intraperitoneal cisplatin. A median survival of 30.3 months was observed.

The most compelling evidence for perioperative chemotherapy is the phase III UK Medical Research Council Adjuvant Gastric (MAGIC) trial. In this trial, 503 patients with potentially resectable gastric cancer were randomized to receive preoperative and postoperative ECF or surgery alone. The perioperative chemotherapy group demonstrated a significantly better OS (HR: 0.75; 95% CI: 0.60–0.93; $P = 0.009$; 5-year survival rate of 36% vs. 23%) and progression-free survival (HR: 0.66; 95% CI: 0.53–0.81; $P < 0.001$). In addition, there is a trend of tumor downstaging in the perioperative chemotherapy group. The trial was criticized for its nonstandardized surgery, inaccurate preoperative staging, and poor outcome in the surgery-alone group.

The role of adjuvant radiation has been a constant debate for the INT116 study as the majority of patients were treated with insufficient lymphadenectomy. Lee *et al*. (2012) further explored the benefit of adjuvant

radiotherapy in patients treated with D2 lymph node dissection in a recent Korean study, the ARTIST study. This is a phase III study randomizing patients to receive postoperative chemotherapy or chemoradiation. The primary endpoint was DFS. The results from the study showed that there is a trend of benefit for adjuvant chemoradiation. However, this modest benefit did not reach statistical significance. Further analysis of the nodal-positive group revealed that adjuvant radiation offered a significant DFS in this group after multivariate analysis (HR: 0.6865; 95% CI: 0.4735–0.9952; $P = 0.0471$). Interestingly, there was no difference in local recurrence between the chemotherapy and chemoradiation groups. The ARTIST study suggested that it is reasonable to offer postoperative chemoradiation in patients with positive lymph nodes. The ongoing Dutch study, the CRITICS study, will further address the role of adjuvant chemoradiation in gastric cancer. All patients in the CRITICS study will be randomized to an observation arm and experimental arm. All patients will be treated with three cycles of preoperative ECC (epirubicin, cisplatin, and capecitabine) followed by over-D1 resection. Patients in the observation arm will continue three cycles of adjuvant ECC, while the patients in the experimental arm will receive chemoradiation with cisplatin and capecitabine. The primary endpoint is OS. The outcome of the CRITICS study will provide guidance in the adoption of adjuvant chemoradiation in the era of better surgical techniques.

Case study 85.7

A 65-year-old male with a history of hypertension and diabetes well controlled with medications presented with progressive early satiety, weight loss, and epigastric discomfort. He was evaluated with EGD by his gastroenterologist. EGD showed a mass at the body of the stomach. Biopsy revealed adenocarcinoma of the stomach. Further evaluation with PET scan showed multiple FDG-avid lesions in the liver. Immunohistochemistry staining of Her2–Neu in a tumor specimen showed 2+. This was confirmed with a fluorescent in situ hybridization (FISH) study as well. The patient was diagnosed with stage IV metastatic gastric cancer. The patient has an ECOG performance status of 1. He is now referred to you for palliative chemotherapy.

Based on the MAGIC study, our patient in Case study 85.6 should continue to receive three more cycles of postoperative ECF. Given that the patient has positive-nodal disease, adjuvant chemoradiation can potentially be considered.

The purpose of palliative chemotherapy is to relieve symptoms, improve quality of life, and extend survival time. To achieve these goals, palliative chemotherapy in patients with advanced gastric cancer should be individualized. Selection of systemic therapy is often determined by several factors: (i) the overall condition of a patient, which is usually reflected by ECOG performance status; (ii) comorbidity; (iii) cancer-related symptoms; (iv) extent of the disease; and (v) Her2–Neu status.

Both single-agent and combination chemotherapy have been used in advanced metastatic gastric cancer. Active agents have included 5FU, cisplatin, mitomycin C, doxorubicin, epirubicin, and etoposide, with response rates that vary from 10% to 20%. Wagner and colleagues (2006) performed a meta-analysis from randomized phase II and III trials and showed that (i) chemotherapy is better than best supportive care, (ii) combination chemotherapy with doublet is superior than a single agent, and (iii) the best survival is achieved with three agents at the cost of more toxicities. The studies discussed in this section were also included in the analysis published by Wagner *et al*. (2006).

In 1985, Cullinan *et al*. published a study comparing the efficacy of three regimens (5FU, FA (5FU and adriamycin), and FAM (5FU, adriamycin, and mitomycin C)) in advanced gastric patients. Surprisingly, FA and FAM did not increase palliative effects in response rate and survival. In contrast, FA and FAM added more toxicities to 5FU. Later, several different regimens, including FAMTX (5FU, doxorubicin, and methotrexate) and ELF (etoposide, leucovorin, and 5FU), were tested. No combination therapy has demonstrated superiority. In 1997, Webb *et al*. reported a randomized trial comparing ECF with FAMX and found that ECF has a better response (response rate (RR): 45% for ECF vs. 21% for FAMX; $P = 0.0002$) and survival (median survival: 8.9 months for ECF vs. 5.7 months for FAMX; $P = 0.0009$). These results were confirmed by studies reported from different groups. In Europe, ECF is considered as the standard of care for metastatic gastric caner.

The V-325 study is a large phase III trial comparing docetaxel–cisplatin–5FU (DCF) to cisplatin–5FU. The study showed that DCF had a 32% lower risk of disease progression (HR: 1.473; 95% CI: 1.189–1.825) and a 22.7% lower risk of death (HR: 1.293; 95% CI: 1.041–1.606). Grade 3–4 toxicities were more frequent in the DCF group than in the CF group (81% vs. 75%). Importantly, quality of life was maintained for a longer period of time with the DCF combination. Nonetheless, the DCF regimen was criticized for the

modest survival benefit at a cost of high toxicity, which could become a challenge in clinical practice. A phase II study reported by Roth *et al*. (2007) showed that ECF, DCF, and DC have similar response rates, with increasing hematological toxicities in ECF and DCF. In real-time practice, the modified DCF originally published by Shah *et al*. (2011) has become a popular regimen with excellent tolerability and good response.

Recently, new agents such as oxaliplatin, capecitabine, and S1 have been evaluated in treating advanced gastric cancer. Both phase II and phase III studies demonstrated that oxaliplatin and cisplatin have equivocal clinical efficacy. Oxaliplatin-based regimens have been evaluated in phase II clinical trials and had demonstrated RRs of 38–63% with a median OS of over 10 months. In addition, oxaliplatin-based regimens were extremely well tolerated with peripheral neuropathy being the main dose-limiting factor. Capecitabine has demonstrated a 19.4% RR as a single agent and up to a 60% RR in combination with other chemotherapies in small studies. Currently, a phase III study (REAL 2) is ongoing to compare the efficacy among four regimens: ECF, EOX (epirubicin, oxaliplatin, and capecitabine), EOF (epirubicin, oxaliplatin, and 5FU), and ECX (epirubicin, cisplatin, and capecitabine).

Perhaps the most promising of the newer agents is S1, which has demonstrated a single-agent efficacy of 30–49% in several phase II trials. Three large Japanese phase III studies using S1 either alone or in combination with other chemotherapy were reported. Boku *et al*. (2007) showed that S1 has at least the same efficacy as 5FU, with the survival trend toward the S1 group. A high RR was achieved when S1 was combined with cisplatin (54% vs. 31%). Furthermore, the 2-year OS was improved (23.6% in S1 + cisplatin and 15.3% in S1; HR: 0.774; $P = 0.0366$). At the same time, Chin and colleagues (2007) compared S1 plus irinotecan to S1 alone. A combination of S1 and irinotecan produced a significantly higher RR over S1 alone (41.5% for S1 + irinotecan vs. 26.9% for S1 alone; $P = 0.035$). The survival data are pending and should be available in the near future.

The results of targeted agents in gastroesophageal cancer were disappointing until a recent study with trastuzumab. The ToGA study randomized patients with advanced Her2–Neu+ gastric cancer to chemotherapy alone or chemotherapy with trastuzumab. The study demonstrated a significant OS benefit with the addition of trastuzumab (13.8 months in the trastuzumab group vs. 11.1 months in the chemotherapy-alone group; $P = 0.0046$). Trastuzumab is a first step forward toward personalized medicine for patients with gastric cancer.

For further information on this area please also consult Chapters 109, 121, 125, 131, 134, and 135

CHAPTER 86

Metastatic esophagogastric cancer: controversies, consensus, and new targets

Geoffrey Y. Ku and David H. Ilson

Memorial Sloan Kettering Cancer Center, New York, NY, USA

• What is the optimal first-line chemotherapy regimen for advanced esophagogastric cancer?

The combination of infusional 5FU and cisplatin has been studied extensively since the 1980s, and the doublet of a fluoropyrimidine with a platinum compound remains a reference regimen in many contemporary trials. This doublet is associated with response rates (RRs) of up to 40%, median progression-free survival (PFS) of about 6 months, and median overall survival (OS) of 10–12 months.

More contemporary trials have evaluated substitutions of both of these drugs with either an oral 5FU prodrug (capecitabine or S1) and/or the newer platinum compound oxaliplatin. Regimens such as S1–cisplatin, capecitabine–cisplatin, infusional 5FU–oxaliplatin, and capecitabine–oxaliplatin (along with the anthracycline epirubicin) appear to have at least comparable efficacy compared to 5FU–cisplatin and are also mostly associated with decreased toxicity and increased ease of administration. An individual patient data meta-analysis of two randomized trials that compared capecitabine-based with infusional 5FU-based regimens—the capecitabine–cisplatin versus 5FU–cisplatin trial and the REAL-2 (Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2) study discussed in this chapter—suggested that capecitabine-based treatments are associated with superior RRs and OS compared to infusional 5FU regimens.

A contemporary and commonly used regimen is the FOLFOX regimen (bolus and infusional 5FU–leucovorin–oxaliplatin), which is widely used for treating colorectal cancer. Support for the use of this regimen comes from a phase III trial that compared infusional 5FU–cisplatin with a similar infusional 5FU–oxaliplatin regimen (the German FLO regimen). This trial demonstrated reduced toxicity and comparable outcomes for the FLO regimen in the overall intention-to-treat population. In patients >65 years old, the FLO regimen was also associated with superior outcomes.

Outside of a clinical trial and in patients whose performance status does not permit for a triplet regimen (as discussed in this chapter), our standard treatment is FOLFOX chemotherapy. We generally prefer to avoid capecitabine-based therapy based on the often poor tolerance of this 5FU prodrug in US patients. However, in patients for whom placement of a central catheter or infusional 5FU is not an option, capecitabine is a reasonable alternative. However, its usage in the United States requires dose reductions in published protocol regimens conducted largely in Europe and Asia.

• Is there benefit for adding a third drug to this doublet?

The only trial that has shown a clear benefit for adding a third drug to the standard fluoropyrimidine–platinum doublet is the V325 study, which randomized patients with gastroesophageal (GE) junction and gastric adenocarcinomas to the DCF regimen (docetaxel–cisplatin–infusional 5FU) versus infusional 5FU–cisplatin. The addition of docetaxel improved RRs (37% vs. 25%; $P = 0.01$) and time to progression (5.6 vs. 3.7 months; $P < 0.001$), but OS was only slightly improved (median OS: 9.2 vs. 8.6 months; 2-year OS: 18% vs. 9%; $P = 0.02$). In addition, the three-drug regimen was associated with significantly more toxicity, including a grade 3/4 neutropenia rate of 82% (vs. 57%) and febrile neutropenia in 29% of patients (vs. 12%). Fifty percent of patients came off treatment due to either severe adverse events or consent withdrawal. Despite these significant toxicities, the authors reported a slower decrement in quality-of-life measurements in the DCF arm. On the basis of this study, docetaxel was approved by the US Food and Drug Administration in 2006 for use with 5FU–cisplatin in this context.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Several investigators have attempted to modify the regimen to increase tolerability. For example, our group performed a randomized phase II trial of a parent DCF (with prophylactic growth factor support) versus a modified DCF (mDCF) regimen (consisting of reduced doses of docetaxel and cisplatin administered with a bolus and 2-day infusional 5FU and leucovorin). mDCF was associated with decreased toxicity compared to parent DCF (neutropenic fever rate: 6% vs. 17%; grade 3–4 nausea and vomiting rate: 3% vs. 20%), while activity appeared comparable or even superior in the mDCF arm. Nevertheless, 30% of the patients receiving mDCF (who had a median age of 56 years) required hospitalization for treatment-related toxicities, reinforcing the notion that this remains a relatively difficult regimen to administer.

Many oncologists reserve three-drug therapy for younger, good-performance-status patients without comorbidities, who accept the risk of greater toxicity of therapy and who have frequent access to toxicity evaluation. A recent trial in patients $\geq$65 years old comparing 5FU–oxaliplatin to docetaxel–5FU–oxaliplatin found increased toxicity but no improvement in outcomes in the subgroup with metastatic disease.

In the United Kingdom, the reference regimen since the late 1990s has been the ECF (epirubicin–cisplatin–5FU) regimen. More recently, the REAL-2 study compared the ECF regimen to the ECX (which involves the substitution of 5FU with capecitabine), EOF (the substitution of oxaliplatin for cisplatin), and EOX regimens (a double substitution of both capecitabine and oxaliplatin) in patients with advanced esophagogastric adenocarcinomas or squamous cell carcinomas (SCCs). All the combinations had similar RRs (40–48%) and toxicities, and the EOX regimen was associated with improved median OS compared to the ECF regimen (11.2 vs. 9.9 months; $P = 0.02$), leading the authors to propose that the EOX regimen could replace ECF in future trials.

Despite the standard use of ECF or one of its derivatives in the United Kingdom, the clear superiority of this triplet over a fluoropyrimidine–platinum doublet has never been demonstrated in a randomized fashion. One piece of evidence frequently cited to support the incorporation of an anthracycline comes from a Cochrane meta-analysis, which analyzed three individually negative trials, including a negative evaluation of ECF versus MCF (mitomycin–cisplatin–5FU). Combining all three trials revealed a survival benefit for the addition of epirubicin (HR: 0.77; 95% CI: 0.62–0.91), which translates into an approximate 2-month survival advantage. However, this conclusion comes largely from the comparison of ECF versus MCF since that trial contributed two-thirds of the patients to the meta-analysis. Given the greater toxicity noted on the MCF arm and the fact that the comparison is not purely between an 5FU–cisplatin-only arm at identical doses and ECF, a determination of the relative merits of adding epirubicin remains difficult to make.

Continuing questions regarding the benefit of an anthracycline were raised by the results of the randomized phase II CALGB (Cancer and Leukemia Group B) 80403–ECOG (Eastern Cooperative Oncology Group) 1206 trial, which randomized 245 patients to one of three chemotherapy regimens—ECF, FOLFOX (biweekly bolus and infusional 5FU–leucovorin–oxaliplatin), or cisplatin and irinotecan—along with cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), for patients with advanced esophagogastric adenocarcinomas or SCCs. Both the ECF and FOLFOX regimens plus cetuximab produced RRs of >40% (58% and 51%, respectively), which met the primary objective of the trial. However, PFS and OS were nearly identical in both of these arms, and the FOLFOX–cetuximab regimen was associated with less overall grade 3–4 toxicity than the ECF–cetuximab regimen. Of course, the randomized phase II nature of this study was not designed to detect a survival difference between these regimens, and the contribution of cetuximab cannot be determined. Nevertheless, the results of this trial do support the contention that any benefit of an anthracycline, if there is any benefit at all, is likely to be small.

Based on these data, it is rarely our practice to use an anthracycline-containing regimen in the metastatic setting. For select patients who have good performance status, we do offer therapy with the mDCF regimen.

- **Should first-line chemotherapy be continued until progression or stopped after 4–6 months?**

This remains an area of uncertainty, and practice patterns vary widely by geography and physician. No randomized trial has addressed this question. In the United Kingdom, standard practice consists of up to 6 months of chemotherapy, followed by observation alone even in the absence of progression or serious toxicity. On the other hand, many oncologists in East Asia continue treatment indefinitely until progression or significant toxicity occurs. Similarly, most oncologists in the United States do continue chemotherapy indefinitely.

Our standard practice is to continue first-line chemotherapy until progression. This practice is based on the facts that esophagogastric cancers are moderately chemosensitive, the continuation of chemotherapy may delay tumor progression (radiographically and clinically), and also patients may experience rapid clinical deterioration at the time of radiographic progression that may preclude additional treatment. Because of cumulative toxicity with platinum compounds (especially with oxaliplatin, which is associated with a dose-limiting neuropathy), we do consider maintenance fluoropyrimidine alone after 3–4 months of chemotherapy. There are no data in esophagogastric cancers to support this, but we do base this strategy partly

on the validated strategy of maintenance infusional 5FU alone after initial FOLFOX chemotherapy in advanced colon cancer, as was shown in the OPTIMOX-1 study.

• Are there data for second-line chemotherapy?

Until very recently, there were no large randomized studies to support a survival benefit for second-line chemotherapy in esophagogastric cancers. However, the results of a 202-patient Korean trial were just published. These patients with advanced gastric cancer with an ECOG performance status of ≤ 1 who had previously received up to two prior regimens containing fluoropyrimidine and platinum agents were randomized in a 2:1 ratio to further treatment with either docetaxel or irinotecan versus best supportive care (BSC). The patients who received chemotherapy had a superior OS (5.3 vs. 3.8 months; HR: 0.66; $P = 0.007$) and therapy was well tolerated, with manageable hematologic toxicities and comparable rates of nonhematologic toxicities in both groups. There were no significant differences between either chemotherapy arm.

Another study of second-line therapy was recently presented in abstract form. The WJOG4007 study randomized 223 Japanese patients with progression on first-line fluoropyrimidine–platinum to either weekly paclitaxel or biweekly irinotecan. The study was designed to show superiority for irinotecan but instead revealed comparable outcomes (median OS: 8.4 months for irinotecan vs. 9.5 months for paclitaxel; $P = 0.38$). Toxicities appeared to be less on the paclitaxel arm, and more patients on this arm went on to receive third-line therapy. Finally, the recently presented COUGAR study from the United Kingdom confirmed a benefit for docetaxel versus BSC after progression on first-line fluoropyrimidine–platinum therapy (5.2 vs. 3.6 months; $P = 0.01$).

• What other chemotherapy drugs are active in esophagogastric cancer?

In addition to the taxanes and irinotecan (as discussed here), other agents that have activity in esophagogastric cancers include mitomycin, etoposide, and methotrexate. Many of these drugs were evaluated in trials performed in the 1970s and 1980s, and they are infrequently used in clinical practice. Drugs with no single-agent activity include gemcitabine and vinorelbine. As much as possible, patients who progress on established first- and second-line treatments should be offered participation on a clinical trial, if their performance status permits.

• Are esophageal and gastric tumors, adenocarcinomas, and SCCs treated alike?

One challenge in interpreting the results of clinical trials in esophagogastric cancers—especially smaller phase II studies—has been the fact that they have variously enrolled patients with esophageal, GE junction, and gastric tumors and patients with both adenocarcinoma and SCC histology. Increasingly, contemporary trials are restricting enrollment to patients with esophageal and GE junction tumors versus GE junction and gastric tumors, and they are further limiting enrollment to either adenocarcinoma or SCC histology.

Careful and consistent patient selection is necessary to ensure that the results of various trials are comparable, and it has been guided by the changing incidence of esophageal SCC and adenocarcinoma in Western countries and the recognition that GE junction and proximal gastric adenocarcinomas have a worse prognosis than distal gastric tumors. Nevertheless, enrollment of only one tumor histology does not always occur (e.g., about 10% of patients on the large and relatively recent REAL-2 study had SCCs). Nonetheless, RRs to systemic chemotherapy regimens appear largely similar for adenocarcinoma and squamous cancers, and the rarity of squamous cancers in the West makes specific trials in this histology difficult to conduct. More important may be the screening of targeted agents given the different epidemiology and likely different biology of these diseases. When both histologies are treated under one umbrella protocol, stratification of analysis by histology will need to be continued.

Because of these limitations, in practice, regimens validated at one site along the upper gastrointestinal tract in tumors with adenocarcinoma histology are commonly used in clinical practice to treat all esophagogastric adenocarcinomas.

• What targeted therapies are available?

The only targeted therapy approved for esophagogastric cancer is trastuzumab, a monoclonal antibody against Her2, which is overexpressed in approximately 20% of gastric cancers. In the pivotal ToGA trial, the addition of trastuzumab to fluoropyrimidine–cisplatin for patients with GE junction and gastric adenocarcinomas, whose tumors were Her2 positive by immunohistochemistry (IHC) (3+) or fluorescent in situ hybridization (FISH) (Her2–CEP17 ratio >2), improved outcomes. Response rates (47% vs. 35%; $P = 0.0017$) and median progression-free (6.7 vs. 5.5 months; $P = 0.0002$) and overall survival (13.8 vs. 11.1 months; $P = 0.0046$) were all improved with the addition of trastuzumab. Toxicities were consistent with the known side effects of this agent, and the incidence of heart failure was low in both arms (<1%). The greatest benefit seen for the addition of trastuzumab was in high Her2 overexpressors with IHC 3+ or in FISH-positive and IHC 2+ patients. Based on this differential benefit, trastuzumab is approved in the European Union only for this subgroup of high Her2 overexpressors; in the United States, it is approved for any patient who met the eligibility criteria for the ToGA study.

Unfortunately, evaluation of other targeted therapies has been negative or even suggested harm. The AVAGAST trial evaluated the addition of bevacizumab, a monoclonal anti-

body against vascular endothelial growth factor (VEGF), to capecitabine–cisplatin. While RRs and PFS were improved, the primary endpoint of an OS improvement was not met, although there was a nonstatistically significant trend toward benefit for the bevacizumab-containing arm (12.1 vs. 10.1 months; $P = 0.1002$). In a planned subset analysis, there did appear to be more benefit for European and Pan-American patients, leading the investigators to suggest in a subsequent abstract presentation that underlying biological differences in gastric cancers of patients from these regions may affect benefit from bevacizumab.

In contrast to the equivocal and debated results of this study, the REAL-3 study showed clear evidence of harm when panitumumab, a monoclonal antibody against EGFR, was added to EOX chemotherapy for patients with GE junction and gastric adenocarcinomas. Median OS was 11.3 versus 8.8 months ($P = 0.013$) in favor of the chemotherapy-only group. Similarly and equally unfortunately, EXPAND, a phase III trial of capecitabine–cisplatin with or without cetuximab, failed to show a benefit for adding this anti-EGFR antibody. Finally, gefitinib has been evaluated in the phase III COG (Cancer Oesophagus Gefitinib) trial performed in the United Kingdom, where 450 patients with progression on $\leq$2 prior regimens were randomized to gefitinib versus placebo. PFS was minimally improved in this study (49 vs. 35 days; HR: 0.795; $P = 0.017$), but there was no improvement in OS, which was the primary endpoint. Taken together, these three large trials have significantly dampened enthusiasm for further evaluation of anti-EGFR therapies in this disease.

- **What new targeted therapies are being evaluated?**

Building on the positive ToGA trial, other Her2-directed phase III trials have been reported or completed. In the second-line setting, activity has been suggested in the phase III TyTAN study, an evaluation of second-line paclitaxel with or without lapatinib that was recently presented in abstract form. This study enrolled 261 Asian gastric cancer patients with Her2-positive tumors by FISH. While median OS was not improved in the overall intention-to-treat population, a planned subset analysis of patients who were also 3+ by IHC revealed a benefit for adding lapatinib (14 vs. 7.6 months; $P = 0.0176$). The published abstract does not discuss what proportion of patients received first-line trastuzumab.

The LOGiC study (NCT00680901) is adding lapatininb, an oral tyrosine kinase inhibitor (TKI) against Her2 and EGFR, to chemotherapy and has completed accrual. A trial of T-DM1 (trastuzumab conjugated to a cytotoxic drug, mertansine)—which has been shown to have activity in trastuzumab-refractory Her2-positive breast cancer—added to chemotherapy is planned.

Similarly, anti-VEGF therapies continue to be investigated. Results of the phase III REGARD study were recently presented. This is a second-line study of ramucirumab, an antibody against VEGF receptor 2 (VEGFR2) , versus placebo in metastatic GE junction and gastric cancer. The study found an improvement in the primary endpoint of OS (5.2 vs. 3.8 months; $P = 0.0473$) for patients treated with ramucirumab. PFS was also improved in the ramucirumab group (2.1 vs. 1.3 months; $P < 0.0001$). More patients in the placebo arm went on to receive therapy at progression (39% vs. 32%), suggesting that the survival benefit was not solely because of a modest PFS benefit that permitted more patients to receive additional treatment at progression. In the first-line setting, the RAINBOW study (NCT01170663) is a randomized phase II trial of second-line paclitaxel with or without ramucirumab and has completed accrual.

We also completed a single-arm phase II study of sorafenib (NCT00917462), an oral TKI with activity against VEGFR and other targets, in patients with advanced chemorefractory esophageal cancer. In 34 evaluable patients, the median PFS was 3.6 months and median OS was 8.8 months. One patient experienced a durable complete response that is ongoing at 40+ months. Overall, 20 of 34 patients were progression-free at 2 months, which met the statistical endpoint for this study and suggests that further evaluation of this agent is warranted. In comparison, studies of sunitinib, another similar VEGFR TKI, have been negative.

One of the most exciting targets is c-MET, a receptor tyrosine kinase for hepatocyte growth factor (HGF). Activation of the c-MET–HGF pathway leads to downstream signaling that promotes the cancer phenotype in multiple solid tumors. In gastric cancer, c-MET overexpression occurs in about 40% of tumors and is associated with a worse prognosis. Results of a randomized phase II study of rilotumumab, a monoclonal antibody against HGF, added to chemotherapy were recently presented. In this study, patients were randomized to receive ECX chemotherapy alone or combined with one of two dose levels of rilotumumab. The trial met its primary endpoint of improving PFS in the rilotumumab-treated patients (5.6 vs. 4.2 months; HR: 0.64; 80% CI: 0.48–0.85). Subset analysis reviewed that patients whose tumors overexpressed c-MET (as determined by IHC) appeared to derive more benefit from rilotumumab therapy in terms of PFS (6.9 vs. 4.6 months; HR: 0.53; 80% CI: 0.25–1.13) and OS (11.1 vs. 5.7 months; $P = 0.012$). Based on this study, a global phase III trial is now underway (NCT01697072).

Selected reading

Ajani JA, Rodriguez W, Bodoky G, *et al*. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.

Al-Batran SE, Hartmann JT, Probst S, *et al*. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26:1435–42.

Cunningham D, Starling N, Rao S, *et al*. Capecitabine and oxaliplatin for advanced esophagogastric cancer. New Engl J Med. 2008;358:36–46.

Okines AF, Norman AR, McCloud P, *et al*. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol. 2009;20:1529–34.

Wagner AD, Unverzagt S, Grothe W, *et al*. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev: CD004064.

For further information on this area please also consult Chapters 109, 121, 125, 131, 134, and 135

CHAPTER 87

Early-stage colorectal cancer

Vaibhav Sahai and Al B. Benson III

Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Multiple choice and discussion questions

Stage II colon cancer

1. Which of the following tumor features would you consider for recurrence risk stratification of a patient with stage II colon cancer to determine potential benefit from adjuvant chemotherapy?

A. Lymphatic or vascular invasion
B. Deficient mismatch repair (dMMR)
C. KRAS mutation status
D. Oncotype DX

Stage II colon carcinoma is a biologically heterogeneous entity with a wide range of 5-year disease-free survival (DFS) between 45.7% and 66.7%. Treatment choices as per current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for stage II colon cancer include enrollment on a clinical trial, observation, or systemic chemotherapy (5-fluorouracil–leucovorin (5FU–LV) or capecitabine with or without the addition of oxaliplatin (CapeOx)) depending on the risk stratification. Traditional risk factors for recurrence include poorly differentiated histology, T4 disease, lymphatic or vascular invasion, bowel obstruction, less than 12 nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. While these clinicopathologic risk features offer some overall guidance, they are inadequate in terms of the biologic behavior and risk of recurrence for an individual. Microsatellite instability high (MSI-H) phenotype, defined as instability in two or more nucleotide markers within the five microsatellite loci or $\geq$30% if a larger panel is used, through either germline mutation or epigenetic silencing, has both predictive and prognostic implications for adjuvant therapy. A retrospective stratification analysis using mismatch repair (MMR) status of 1027 previously randomized patients with stage II and III colon adenocarcinoma to either 5FU with levamisole or leucovorin, or observation, was reported by Sargent *et al*. (2009, 2010). They showed that patients with defective mismatch repair (dMMR) have a 5-year DFS of 80% compared with 56% for those with proficient MMR or microsatellite stable (MSS) (HR: 0.51; 95% CI: 0.29–0.89; $P = .009$). In patients with stage II colon cancer with dMMR or MSI-H who were treated with adjuvant 5FU chemotherapy, there was a statistically decreased overall survival (OS) compared to the surgery alone arm (HR: 2.95; 95% CI: 1.02–8.54; $P = .04$). The stage III MSI-H patients did not appear to benefit from 5FU (DFS, HR: 1.01; 95% CI: 0.41–2.51; $P = .98$) and only the MSS stage III patients obtained any survival advantage from adjuvant 5FU (DFS, HR: 0.64; 95% CI: 0.48–0.84; $P = .001$).

Emerging tools include gene expression assays, such as Oncotype DX and ColoPrint. Oncotype DX includes seven recurrence risk genes and five reference genes, and it calculates a recurrence score (low, intermediate, or high) predictive of the risk of recurrence of stage II colon cancer at 3 years. Validation studies have shown significant correlation between the risk of recurrence and the recurrence score. ColoPrint probes 18 genes and results in a risk index score independent of the clinical risk factors and MSI status, similar to Oncotype Dx, but the recurrence score has been independently validated with significantly associated relapse-free and distant metastasis–free survival. These gene signatures serve as important prognostication tools, but do not yet predict response to adjuvant chemotherapy, thus limiting their use to determine the role of adjuvant therapy. Several other potential molecular markers such as oncogenic KRAS and BRAF mutations, loss of heterozygosity at chromosome 18q, overexpression and mutations of TP53, expression of thymidylate synthase, or DNA ploidy are being currently analyzed for their prognostic and predictive capability, with insufficient evidence to recommend

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

routine clinical use at this time for stage II colon cancer patients.

2. Which of the following management options would you consider for a patient with R0 resected stage II or node-negative colon adenocarcinoma with high-risk features?

A. 5FU or capecitabine alone
B. 5FU–oxaliplatin or FOLFOX
C. Capecitabine–oxaliplatin or CapeOx
D. Observation
E. All of the above

Although it is universally accepted that most stage III patients should receive adjuvant chemotherapy, there is uncertainty regarding whether stage II patients would derive sufficient benefit. The initial evidence to support the role of adjuvant chemotherapy came from the INT-0035 trial that randomized 325 patients with resected stage II colon cancer to either 5FU–levamisole for 1 year or observation. At a median follow-up of 7 years, 5FU–levamisole yielded a trend toward superior recurrence-free survival (HR: 0.69; 95% CI: 0.44–1.08; $P = .10$) over observation. However, there was no improvement noted in OS (72% in each arm; $P = .83$). The QUASAR trial also showed benefit in risk of recurrence at 2 years for 2146 patients with resected stage II colon cancer who were treated with 5FU–LV compared to patients who received no adjuvant therapy (HR: 0.71; 95% CI: 0.54–0.92; $P = .01$), with a trend toward better OS (HR: 0.86; 95% CI: 0.66–1.12). Furthermore, a large pooled analysis of seven randomized controlled trials (NCCTG, ECOG-NCCTG-INT, SWOG-INT0035, Siena, NCIC-CTG, FFCD, and GIVIO) with 1440 patients with node-negative disease revealed a 4% absolute benefit in 5-year DFS (76% versus 72%; $P = .49$), although there was no benefit in OS (81% versus 80%; $P = .11$). In contrast, the ACCENT data set, which included 6896 patients with resected stage II disease from 18 phase III adjuvant trials, showed an absolute benefit of 5% in 8-year OS (72.2% versus 66.8%; $P = .026$). Although probably real, the survival benefit from adjuvant chemotherapy for an average patient with stage II cancer is small and may not justify the involved cost, toxicity, and inconvenience to the patient.

This has prompted researchers to identify high-risk features within stage II disease (as listed in Question 1) that adversely affect the disease-specific survival and predict benefit from adjuvant chemotherapy. However, only a few adjuvant clinical trials have stratified patients according to these risk factors, and even those did not include all of them. A meta-analysis of four sequential NSABP clinical trials that compared adjuvant 5FU based chemotherapy with each other or no treatment showed that patients with Dukes' B colon cancer ($n = 1565$) who had average-risk features (absence of obstruction, localized bowel perforation, or extension of tumor into adjacent organs) had a 32% reduction in mortality (HR: 0.68; 95% CI: 0.50–0.92; $P = .01$), whereas those with high-risk features had a 20% reduction of mortality (HR: 0.80; 95% CI: 0.55–1.17; $P = .26$). This translated into 5% absolute improvement in mortality in each category, thus counteracting the argument that only patients with high-risk features would derive benefit from adjuvant chemotherapy. An NCCTG trial restricted eligibility to high-risk stage II (T4 disease, and bowel perforation or obstruction) and stage III patients, and randomly assigned 317 patients to either adjuvant 5FU–LV chemotherapy or observation. Overall, there was a clear benefit in OS (74% vs. 63%; $P = .01$) in the chemotherapy arm, with only a trend toward benefit for patients with stage II cancer ($n = 57$) on exploratory analysis (90% vs. 74%; $P = .15$). Also, a large pooled analysis of seven randomized controlled trials with 1440 patients with node-negative disease failed to show benefit of chemotherapy in T4 low-grade (69% versus 71%) or high-grade (57% versus 46%) colon cancer compared to surgery alone in an underpowered subset analysis. Despite the lack of data from randomized clinical trials, the NCCN Clinical Practice Guidelines recommend discussion of adjuvant chemotherapy with medically fit patients with stage II disease with clinicopathologic high-risk features. Furthermore, MSI-low, defined as instability in less than two nucleotide markers within the five microsatellite loci, or MSS stage II colon cancer patients with a clinicopathologic risk factor would be considered potential candidates for 5FU-based chemotherapy after detailed discussion with patients; however, the management of the subset of patients with MSI-H tumors with traditional risk factor(s) is not clear, and they should be enrolled on a clinical trial or observed without adjuvant chemotherapy.

Furthermore, there are minimal data to recommend use of oxaliplatin with 5FU-based therapy in this patient population. The MOSAIC trial randomized 2246 patients, including 899 with stage II disease, to infusion–bolus 5FU–LV versus FOLFOX4, and found no improvement in 5-year DFS or 6-year OS between the two arms (OS 86.9% vs. 86.8%; HR: 1.00; 95% CI: 0.70–1.41; $P = .986$). However, a nonsignificant trend toward improved 5-year DFS in high- versus average-risk patients was observed with the addition of oxaliplatin (HR: 0.84; 95% CI: 0.50–1.02) in an unplanned analysis. Therefore, the addition of oxaliplatin is considered an appropriate option for stage II patients with high-risk features, but not for those with average-risk features. Patients should be encouraged to enroll in clinical trials as efforts continue to link risk with benefit from adjuvant therapy.

3. Why are patients with microsatellite instability (MSI) considered to have a better prognosis than those with microsatellite stable (MSS) tumors?

Patients with MSI-H tumors have a prognostic advantage regardless of the tumor stage at diagnosis. MSI phenotype has a higher prevalence in stage II than stage III colon

cancers and has been associated with less lymph node involvement and metastasis. The precise explanation is not clear, but some of the pathologic differences include significant correlation of MSI tumors with intratumoral activated cytotoxic T-lymphocytes, increased apoptotic to proliferative index, and decreased p53 expression or KRAS mutations.

Stage III colon cancer

4. Which of the following adjuvant chemotherapy regimens would you not consider for a patient with R0 resected stage III or node-positive colon adenocarcinoma?

A. 5FU or capecitabine alone
B. 5FU–oxaliplatin or FOLFOX
C. Capecitabine–oxaliplatin or CapeOx
D. 5FU–irinotecan or FOLFIRI

There are several trials to substantiate the role of adjuvant 5FU–LV in patients with node-positive or stage III colon cancer. The Intergroup Trial INT-0035 was the first large randomized study that showed that treatment with 5FU–levamisole in patients with resected Dukes' stage C colon cancer ($N = 929$) reduced the risk of cancer recurrence by 41% ($P < .0001$) and overall death rate by 33% ($P = .006$) compared to observation (the levamisole-alone arm produced no detectable effect) after a median follow-up of 3 years. The NSABP C-03 trial randomized 1081 patients with Dukes' stage B and C either to MeCCNU, vincristine, and 5FU (MOF) or to 5FU–LV. At 3 years, the arm with 5FU–LV showed a significant increase in DFS (73% vs. 64%; $P = .0004$) as well as OS (84% vs. 77%; $P = .007$) compared to the MOF arm. The benefit was also confirmed by the NCCTG trial and the pooled analysis by IMPACT investigators solidifying the role of adjuvant 5FU–LV. The survival benefit of the addition of oxaliplatin in node-positive disease was evaluated by the MOSAIC trial that randomized 2246 patients, including 1347 patients with stage III disease ($n = 672$ and $n = 675$ in mFOLFOX4 and 5FU–LV, respectively). The probabilities of survival at 6 years were 72.9% and 68.7%, respectively (HR: 0.80; 95% CI: 0.65–0.97; $P = .023$), corresponding to a 30% reduction in risk of death in favor of adjuvant FOLFOX4 for 6 months. The addition of oxaliplatin was also evaluated in the NSABP C-07 trial with 2407 patients with stage II or III colon cancer randomized to 5FU–LV with or without oxaliplatin. After a median follow-up of 52.5 months, the OS showed improvement with the addition of oxaliplatin (FLOX regimen) (HR: 0.80; 95% CI: 0.69–0.93; $P = <.004$), but this improvement was not apparent after 8 years of follow-up (HR: 0.88; 95% CI: 0.75–1.02; $P = .08$) and did not differ by the stage of disease ($P = .38$). However, the FLOX regimen remained superior for DFS (HR: 0.82; 95% CI: 0.75–0.93; $P = .002$).

The addition of irinotecan to 5FU–LV is not considered a standard approach for adjuvant chemotherapy for resected stage II or III colon cancer based on no improvement when compared to 5FU–LV, as shown in the CALGB 89803, PETACC-3, and ACCORD-02 trials.

Use of oral fluoropyrimidines, such as capecitabine, has also been studied as both monotherapy and combination therapy for colon cancer. The phase III X-ACT trial randomized 1987 patients with stage III colon cancer to either capecitabine or bolus 5FU–LV for 6 months in a non-inferiority trial. After a median follow-up of 6.9 years, capecitabine was at least equivalent to 5FU–LV in terms of both DFS (HR: 0.88; 95% CI: 0.77–1.01) and OS (HR: 0.86; 95% CI: 0.74–1.01). There are no phase III trials comparing CapeOx to FOLFOX in adjuvant therapy for stage III colon cancer. However, a phase III trial compared CapeOx to 5FU–LV alone and reported a superior DFS (70.9% vs. 6.5%; HR: 0.80; 95% CI: 0.69–0.93; $P = .0045$) and 5-year OS (77.6% vs. 74.2%; HR: 0.87; 95% CI: 0.72–1.05; $P = .15$). To summarize, the benefit of addition of oxaliplatin to 5FU or capecitabine in resected stage III colon cancer has been shown across multiple randomized trials and is widely accepted as the first-line standard regimen. If oxaliplatin cannot be administered for some reason, monotherapy with either 5FU–LU or capecitabine is acceptable.

5. Which of the following management options would you consider for a patient with R0 resected stage III or node-positive colon adenocarcinoma with MSI-H?

A. 5FU alone
B. 5FU–oxaliplatin or FOLFOX
C. Observation

Patients with stage III disease have shown survival benefit from adjuvant 5FU-based chemotherapy across multiple trials, but optimal management of stage III patients with MSI-H may be complex. A retrospective stratification analysis using mismatch repair (MMR) status of previously randomized 1027 patients with stage II and III colon adenocarcinoma to either 5-FU with levamisole or leucovorin, or observation was reported Sargent *et al.* They showed that patients with stage III colon cancer and defective mismatch repair (dMMR) derived no benefit in overall survival from 5FU ($n = 39$) compared to surgery alone ($n = 24$) (HR, 1.01; 95% CI: 0.41 to 2.51; $P = .98$). Another retrospective study evaluated 32 patients with stage III MSI-H colon cancer treated by 5FU–LV ($n = 20$) or FOLFOX ($n = 12$) and noted improvement in DFS in patients on the FOLFOX arm (HR: 0.17; 95% CI: 0.04 to 0.68; $P = .01$) compared to the 5FU-only arm. The MMR proteins do not recognize the DNA adducts formed by the oxaliplatin, which may drive the cytotoxic effect. Sinicrope *et al.* reported a benefit of 5FU treatment for stage III patients with MSI compared with MSS tumors (time to recurrence, $P = .016$; DFS, $P = .047$; OS, $P = .041$). However, the beneficial treatment effect was restricted to MSI tumors with germline defect ($n = 99$)

(DFS: HR: 0.26; 95% CI: 0.09–0.77; $P = .009$) with no benefit noted in sporadic MSI tumors ($n = 245$) secondary to hypermethylation (DFS: HR: 0.79; 95% CI: 0.35–1.80; $P = .577$). This may suggest another subclassification in colon cancer with potential for a predictive role in determining use of adjuvant therapy for stage III disease. Currently, until there are more data evaluating the MSI-H stage III population, all medically fit patients with stage III colon cancer are recommended to receive adjuvant chemotherapy with FOLFOX.

6. What is the recommended duration of adjuvant chemotherapy in a patient with resected R0 stage III or node-positive resected colon adenocarcinoma?

A. 12 months
B. 6 months
C. 3 months

Currently, adjuvant chemotherapy is advocated for at least 6 months based on at least three trials that showed no added benefit when compared to 12 months. Based on a Cochrane review, which suggested that an even shorter duration of chemotherapy (3–6 months) compared to 9–12 months was not associated with inferior relapse-free survival or OS, there is an ongoing CALGB–SWOG 80702 trial to evaluate whether 3 months are equivalent to 6 months of chemotherapy. Other international trials are also comparing 3 versus 6 months of adjuvant therapy offering the potential for a future meta-analysis of the comparison.

7. Which of the following biological agents would you add to the adjuvant chemotherapy regimen for patients with resected stage II and III colon cancer for possible micrometastatic disease?

A. Bevacizumab
B. Cetuximab
C. Panitumumab
D. None

Several trials have investigated the use of biological agents, targeting anti-VEGF (vascular endothelial growth factor) or anti-EGFR (epidermal growth factor receptor), as potential adjuvant therapy to eradicate micrometastatic disease but have so far yielded disappointing results. In the NSABP C-08 phase III trial, 2672 patients with resected stage II and III colon cancer were randomized to either 6 months of modified FOLFOX6 or mFOLFOX6 + bevacizumab followed by 6 months of maintenance bevacizumab. The DFS at 15 months showed benefit for the bevacizumab arm (HR: 0.61; 95% CI: 0.48–0.78; $P < .001$); however, after a median follow-up of 55 months, the addition of bevacizumab to mFOLFOX6 did not result in an overall significant increase in DFS (HR: 0.93; 95% CI: 0.81–1.08; $P = .34$) or OS (HR: 0.96; 95% CI: 0.79–1.15; $P = .64$). The authors proposed several mechanisms for this incongruity, including a pure cytostatic effect of bevacizumab, masking of the recurrence due to decreased permeability that would obscure imaging findings, as well as the potential development of an aggressive phenotype after completion of anti-VEGF therapy based on preclinical murine models. The AVANT trial randomized 3451 patients with resected high-risk stage II and stage III patients with colon cancer to either mFOLFOX4 or mFOLFOX4 + bevacizumab, or CapeOx + bevacizumab followed by 6 months of maintenance bevacizumab for patients in the last two arms. There was no significant difference in DFS (HR: 1.17; 95% CI: 0.98–1.39; P = NS for the mFOLFOX6 + bevacizumab arm and HR: 1.07; 95% CI: 0.90–1.28; P = NS for the CapeOx + bevacizumab arm) or OS (HR: 1.31; 95% CI: 1.03–1.67; P = NS for the mFOLFOX6 + bevacizumab arm and HR: 1.27; 95% CI: 0.99–1.62; P = NS for the CapeOx + bevacizumab arm). Other trials investigating the role of anti-VEGF therapy include ECOG 5202 (FOLFOX vs. FOLFOX + bevacizumab in stage II high-risk MSI-L–18q LOH or MSS–18q LOH stage II patients) and QUASAR2 (capecitabine versus capecitabine + bevacizumab in high-risk stage II and stage III patients with colon cancer). Results from these trials are pending.

Anti-EGFR therapy also appeared promising with the ability to directly target the micrometastatic tumor cells even prior to angiogenesis. However, the NCCTG phase III trial N0147, which randomized 1847 patients with resected phase III wild-type KRAS colon cancer to mFOLFOX6 with or without cetuximab for 6 months, showed that the 3-year DFS favored mFOLFOX6 alone (HR: 1.2; 95% CI: 0.96–1.50; $P = .22$). In fact, the OS showed a trend toward worse survival with addition of cetuximab (HR 1.3; 95% CI: 0.96–1.80; $P = .13$). The interim analysis of the PETACC-8 phase III trial, which randomized 1602 patients with KRAS-WT to mFOLFOX4 with or without cetuximab, has also shown no difference in DFS (HR 1.05; 95% CI 0.85–1.29; $P = 0.66$) after a median follow-up of 39.6 months. In summary, to date there are no data to support the use of targeted biological agents in the adjuvant therapy of colon cancer.

8. What is the emerging role of circulating tumor cells in colon cancer?

There is an urgent demand to find new biomarkers to monitor for early metastases and monitor efficacy of systemic adjuvant therapy. Tumors shed cancer cells into the blood, and quantitative molecular analysis of these circulating tumor cells (CTCs) may provide an early insight into the clinical management far earlier than traditional imaging modalities. Current research aims to optimize detection strategies and study their clinical impact as both prognostic and predictive markers.

Multiple techniques for detection are under development, but to date, only the CellSearch™ assay has been approved by the US Food and Drug Administration (FDA).

The assay enriches CTCs by using magnetic particles coated with antibodies against the epithelial cell adhesion molecule (EpCAM) protein. Other techniques include the reverse transcriptase polymerase chain reaction, microchip array technology, and automated light microscopy with laser printing.

CTC biomarker analysis of the CAIRO-2 phase III trial and another prospective study provide strong support for use of CTCs as a prognostic marker. A more pertinent question would be to investigate whether this prognostication, prior to the first or subsequent line of therapy, can be utilized to identify whether (i) a change in therapy is warranted, and (ii) this change would be useful, if the biology of the disease is already considered unfavorable. Alternative clinical scenarios could include use in determination of risk of recurrence after metastatectomy, or duration and choice of adjuvant therapy. This window into enumeration of minimal residual disease as a risk factor, and its subsequent use for prediction of therapy may prove to be invaluable in our goal toward personalized medicine.

Rectal cancer

Case study 87.1

A 65-year-old male with a past medical history of obesity, hypertension, as well as remote history of painless bloody bowel movements presented to his primary care physician with recent worsening of symptoms along with feeling of incomplete evacuation. He denies any change in weight, fatigue, or other constitutional symptoms. Proctoscopy showed a mass at 8 cm from the anal verge, and fine-needle aspiration confirmed a moderately differentiated invasive adenocarcinoma. Rectal endoscopic ultrasound staging showed uT3N0. Chest–abdomen–pelvis CT with contrast showed no evidence of metastatic disease.

9. Which chemotherapy regimen would you consider for neoadjuvant chemoradiation therapy?

A. Infusional 5FU
B. Capecitabine
C. CapeOx
D. Infusional 5FU with oxaliplatin

Neoadjuvant infusional 5FU with concurrent radiation therapy followed by the total mesorectal surgery and adjuvant therapy is the current standard of care for patients with locally advanced rectal cancer (LARC). Historically, the 5-year OS with surgery alone was between 40% and 60%, and the addition of neoadjuvant chemoradiation with 5FU has resulted in an improvement in both local control and 5-year OS to 65–75%.

Multiple trials have explored the role of addition of oxaliplatin to 5FU in patients with resectable LARC, including the STAR-01, ACCORD 12–0405 Prodige 2, and CAO–ARO–AIO-04 trials. The phase III STAR-01, ACCORD 12/0405 Prodige 2, and NSABP R-04 trials showed that the addition of oxaliplatin significantly increased the grade 3–4 toxicity without improvement in the rate of pathological complete response (pCR) or number of patients who underwent surgery. However, the combination arm on the German CAO–ARO–AIO-04 phase III trial showed a significantly better pCR rate (13% vs. 17%; $P = .038$, respectively). Based on these trials, currently only 5FU is advocated for neoadjuvant chemoradiation, with no role for oxaliplatin due to increase in grade 3–4 toxicity without corresponding increase in the surrogate endpoint of pCR. Longer follow-up is required to determine whether this translates into a decreased recurrence rate or improved survival.

The NSABP R-04 also investigated whether oral capecitabine would be an acceptable substitution for the infusional 5FU and reported similar outcomes (pCR, surgical downstaging and sphincter-saving surgery) on both arms, suggesting that capecitabine is a reasonable and perhaps more convenient option with, possibly, increased efficacy (pCR rate 22.2% vs. 18.8%; $P = .12$) compared to the infusional 5FU arm. Therefore, the current standard for neoadjuvant therapy for LARC is either infusional 5FU or capecitabine with concurrent radiation therapy.

10. The patient received 5FU based neoadjuvant chemoradiation, underwent low anterior resection, and was found to have pathological complete response (pCR). Would you recommend adjuvant treatment for this patient?

A. Yes
B. No

Pathologic "T" and "N" stage shows a correlation with locoregional recurrence, distant metastasis, and OS. Tumor regression is an emerging concept as a prognostic marker, but randomized data are required for its use as a decision aid tool for adjuvant chemotherapy. Several studies have reported improved survival correlating with grade of tumor regression. Park *et al.* (2012) reviewed 725 patients with locally advanced rectal cancer who received neoadjuvant chemoradiation followed by resection. Twenty-two percent of patients achieved pCR, and after a median follow-up of 65 months, the OS was 90.5% in this group, compared to 78.7% and 58.5% in the intermediate and poor responders ($P = .002$).

pCR, defined as ypT0N0 disease at the time of surgery, is increasingly being used both as a surrogate endpoint for long-term outcomes (DFS and OS) and as a predictive tool to recommend adjuvant chemotherapy. A retrospective

analysis of 167 patients with T3 or higher rectal cancer who received neoadjuvant chemoradiation followed by total mesorectal excision showed that the subgroup of 16% patients who achieved pCR and did not receive adjuvant chemotherapy had 5-year DFS of 96% and OS of 100%. However, there are no prospective randomized data to support its use as a predictive marker, and currently patients with pCR should continue to undergo adjuvant chemotherapy.

Multiple choice answers

Question 1: Answer B
Question 2: Answer E
Question 4: Answer D
Question 5: Answer B
Question 6: Answer B
Question 7: Answer D
Question 9: Answer either A or B is correct
Question 10: Answer A

Selected reading

Andre T, Boni C, Navarro M, *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–16.

Benson AB, III, Bekaii-Saab T, Chan E, *et al.* NCCN clinical practice guidelines in oncology: colon cancer. Version 2014. Available from: http://www.NCCN.org

Park IJ, You YN, Agarwal A, *et al.* Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol. 2012;30:1770–06.

Sargent DJ, Marsoni S, Monges G, *et al.* Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28:3219–26.

Sargent D, Sobrero A, Grothey A, *et al.* Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2009;27:872–7.

For further information on this area please also consult Chapters 112, 121, 125, 131, 134, and 135

CHAPTER 88

Recurrent and metastatic colorectal cancer: controversies, consensus, and new targets

Davendra Sohal and Robert J. Pelley
Cleveland Clinic, Cleveland, OH, USA

Case study 88.1

A previously healthy 53-year-old man presented 4 years ago with abdominal pain and signs of large bowel obstruction. He was diagnosed with an obstructing colon cancer at the hepatic flexure. It was resected, revealing a T3N0 lesion that was microsatellite stable. You see the patient at that time and discuss and offer adjuvant chemotherapy, which he declines. He agrees to follow up with you but fails to return after his first annual blood tests and computed tomography (CT) scans, which were unremarkable. Now he returns 4 years after surgery with vague complaints of not feeling well. Carcinoembryonic antigen (CEA) is 23, and a CT scan shows new mesenteric lymphadenopathy surrounding the superior mesenteric artery (SMA) as well as new 1 cm nodules in each lung.

1. What is the most appropriate next step in management?

A. Diagnostic positron emission tomography (PET)–CT scan
B. Biopsy of the most accessible suspicious lesion
C. Surgical referral to resect all macroscopic disease
D. Initiate combination chemotherapy with FOLFOX.
E. Initiate combination chemotherapy with FOLFOX and bevacizumab.

Recurrence after curative resection should be histologically confirmed, especially if there has been an interval of more than a few months since the resection. PET scans are not diagnostic, and even if they show hypermetabolic lesions, the tissue of origin should be confirmed. Initiating chemotherapy without histologic confirmation is not recommended. While encouraging results have been reported with resection of metastatic disease in colorectal cancer, such results are best seen in low-volume visceral disease, not in the setting of abdominal adenopathy or multi-organ involvement.

The biopsy of the mesenteric lymph node identifies adenocarcinoma, which on special stains is CDX2 and CK20 positive, and CK7 negative, consistent with recurrent metastatic colon cancer. After discussion with the patient, he seeks a second opinion from his surgeon, who concurs with the diagnosis and agrees with the unresectable nature of his recurrence. He returns to discuss medical treatment. You have a discussion regarding life-prolonging combination chemotherapy.

2. Which chemotherapy backbone is most appropriate at this time?

A. FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin)
B. FOLFIRI (5-fluorouracil, leucovorin, and irinotecan)
C. CAPOX (capecitabine and oxaliplatin)
D. CAPIRI (capecitabine and irinotecan)
E. Any of the above

Combination chemotherapy using a fluoropyrimidine with either oxaliplatin or irinotecan is recommended in metastatic colorectal cancer if patient performance status and comorbidities allow. The equivalence of oxaliplatin and irinotecan has been clearly demonstrated. In addition, 5-fluorouracil is equivalent to capecitabine in this setting. Therefore, any combination is appropriate. An overall survival of around 15 months is achieved with such a first-line regimen. The decision is usually guided by toxicity profiles (neuropathy with oxaliplatin, and diarrhea and neutropenia with irinotecan) and patient preference (infusional pump vs. several pills a day).

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 88.2

A 52-year-old woman with mild hypertension presents with intermittent constipation that progresses to frank large bowel obstruction. She is seen in an emergency room and admitted when an abdominal CT shows a sigmoid mass with obstruction. Colonoscopy confirms a biopsy-proven adenocarcinoma at 30 cm, and she undergoes laparoscopic left hemicolectomy. A stage IIIB tumor (T3, N1b) with 3 out of 21 lymph nodes is resected. Neither the CT nor the surgery reveals any evidence of metastatic disease. Six weeks later, she starts adjuvant chemotherapy with modified FOLFOX6 regimen. After 10 cycles, she develops grade 2 neuropathy in her feet, and the oxaliplatin is held for the final two cycles. She completes therapy and begins surveillance. At 10 months after surgery, she complains of some pelvic fullness and back pain. She has lost 3 kg unintentionally. Her CEA is normal, but her CT scans reveal a pelvic mass, retroperitoneal lymph nodes, and two hypodense liver lesions. FNA of the pelvic mass reveals metastatic colon cancer in the right ovary. You have the archived primary tumor sample analyzed for KRAS mutations, and it has a codon 12 mutation.

1. What chemotherapy regimen would you recommend at this time?

A. FOLFOX (5-fluorouracil, leucovorin, oxaliplatin)
B. FOLFIRI (5-fluorouracil, leucovorin, irinotecan)
C. CAPOX (capecitabine and oxaliplatin)
D. CAPIRI (capecitabine and irinotecan)
E. Either A or C
F. Either B or D

A tumor recurring within 1 year of completion of adjuvant therapy is unlikely to respond to the regimen used in the adjuvant setting (fluoropyrimidine with oxaliplatin). Therefore, an irinotecan-based regimen is recommended. In addition, her prior neuropathy makes the use of oxaliplatin difficult. As mentioned above, 5-fluorouracil and capecitabine are equivalent in activity, and therefore the decision is usually based on patient preference. The continuation of a fluoropyrimidine in the metastatic setting after failure in the adjuvant setting lacks direct data support; however, from studies of the use of a fluoropyrimidine-based regimen in the second-line setting for metastatic disease after failure of a first-line fluoropyrimidine-containing regimen, it is clear that such continuation is appropriate..

2. What biologic agent would you add to the chemotherapy backbone?

A. Aflibercept
B. Bevacizumab
C. Cetuximab
D. Panitumumab
E. Regorafenib

The addition of biologic agents—anti-angiogenic agents (vascular endothelial growth factor (VEGF) antagonists) such as bevacizumab and aflibercept, or anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab—has improved outcomes in metastatic colorectal cancer. Bevacizumab and the EGFR antibodies improve progression-free (and perhaps overall) survival in this setting. The EGFR antibodies, however, do not apply in this situation as they are rendered ineffective by mutations in the KRAS gene, making KRAS testing standard-of-care prior to deciding which therapy to institute. At this time, aflibercept and regorafenib have shown improved survival in the second-line and salvage settings only.

After discussion, the patient elects to start FOLFIRI with bevacizumab (5 mg/kg). She receives four cycles with fair tolerance. Treatment is accompanied by some diarrhea, weight loss, alopecia, and nausea, but no vomiting. Her neuropathy is stable, but her blood pressure sequentially increases each cycle. CT scans are obtained to measure response, and the patient presents on the morning of cycle 5 to review results. She is anxious, and her blood pressure (BP) is 170/110. CT scan of the abdomen demonstrates a radiographic partial response of the ovarian mass and liver metastases. Repeat BP readings range around 160/105.

3. What is the most appropriate intervention at this time?

A. Reduce bevacizumab dose to 2.5 mg/kg.
B. Hold bevacizumab.
C. Hold all chemotherapy.
D. Continue all treatment as before, and start antihypertensive medication.

Bevacizumab is a monoclonal antibody that binds to VEGF, the ligand for the VEGF receptors. Ligand removal generates prominent vascular side effects, including hypertension, increased risk of cardiovascular and cerebrovascular events, and proteinuria. There are scant guidelines for management of bevacizumab-induced hypertension, but most groups recommend that in cases of grade 2 or higher hypertension (BP >160/100), bevacizumab should be stopped and antihypertensive therapy started. The bevacizumab may be restarted later when BP is controlled. A small reduction in bevacizumab dose is unlikely to have an impact on hypertension. In addition, stopping all chemotherapy is not desirable or warranted.

The bevacizumab is stopped, and amlodipine is started. After a month, BP is under good control and bevacizumab is resumed. After another two cycles, the patient appears for cycle 8 of treatment and complains to the chemotherapy nurse that she experienced left-sided chest pain, radiating

down the left arm and lasting 3 minutes occurring on day 4 of the previous cycle. On interviewing her, the physician elicits that this is accompanied by palpitations and diaphoresis.

4. What is the most appropriate step now?

A. Stop bevacizumab.
B. Stop 5-fluorouracil.
C. Consult cardiology.
D. All of the above

Cardiovascular complications of cancer therapy can lead to severe morbidity and death. While anthracyclines have been well documented as cardiotoxic agents, 5-fluorouracil (5-FU) can lead to cardiac problems as well. Coronary vasospasm appears to be the main mechanism behind 5-FU-induced cardiotoxicity, although direct myocardial injury is also described. Toxicity has been reported with the first cycle of therapy. Dihydropyrimidine dehydrogenase (DPD), the enzyme that metabolizes most of the administered 5-FU to its inactive derivatives, is deficient in a small minority of the population, but this deficiency has not been shown to be associated with cardiac complications (it is associated with other acute, severe toxicity from 5-FU, such as stomatitis, neutropenia, and severe diarrhea). In this case, there is the possibility of cumulative cardiotoxicity from 5-FU and bevacizumab. Management of significant cardiac symptoms includes stopping chemotherapy and obtaining formal cardiology evaluation. The patient may be rechallenged with chemotherapy if there is no evidence of significant cardiac events and after a careful cardiac assessment.

Case study 88.3

A 61-year-old man with type 2 diabetes and hypertension presents with left lower quadrant abdominal pain and low-grade fever. He presents to the emergency room, and a CT scan is performed. This reveals sigmoid colon thickening with a possible mass or diverticular abscess, with nearby extraluminal air. There are two hypodense lesions, 4 and 8 cm respectively, in the liver. He undergoes open left hemicolectomy. Intraoperative liver biopsy is positive for metastatic colon cancer. Both liver lesions are in the right lobe. Pathology reveals moderately differentiated adenocarcinoma penetrating serosa, with two positive LNs, T4aN1b, Stage IVA. K-ras is wild-type. You are asked to see the patient in the hospital for medical oncology consultation. The patient has poorly controlled hypertension and surprisingly significant peripheral diabetic neuropathy.

1. What is the most appropriate management plan at this time?

A. Immediate resection of liver lesions followed by chemotherapy
B. Palliative chemotherapy only
C. Chemotherapy followed by resection of liver lesions
D. Local therapy (TACE or RFA) to liver lesions followed by chemotherapy

Colorectal cancer with oligometastatic visceral disease should be approached with a curative intent. Large case series have established that median overall survival of selected patients with complete surgical resection of oligometastatic hepatic disease is 3–4 years. 5-year overall survival rates are now approaching 50%. In addition, the role of chemotherapy in this setting has been studied, and perioperative chemotherapy is associated with improved progression-free survival. Therefore, it is usually recommended that chemotherapy be started and, in the absence of disease progression, metastatectomy be performed after about 3 months of therapy. This 3-month interval is appropriate for multiple reasons, including (i) time for wound healing before a second major surgical procedure; (ii) time for tumor biology to "declare" itself with a chance for aggressive resistant metastatic disease to manifest itself; and (iii) a limited time interval for the liver to be exposed to the toxic effects of chemotherapy prior to major surgery on the liver. Local therapies such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) are useful palliative techniques that are appropriate for disease control when resection cannot be performed due to anatomy or comorbidities.

The patient is offered six cycles of FOLFIRI with cetuximab. FOLFIRI is chosen over FOLFOX because of the patient's preexisting neuropathy. Cetuximab is offered over bevacizumab to attempt to maximize response while avoiding the wound healing issues associated with anti-angiogenic antibodies and anticipated surgery. The dose of cetuximab is 250 mg/m^2 every week. After four doses (two cycles of FOLFIRI, 4 weeks), he has only a minimal fine erythematous rash on the arms.

2. What is the most appropriate strategy at this time?

A. Discontinue cetuximab and start bevacizumab.
B. Add bevacizumab to the regimen.

(*Continued*)

C. Increase dose of cetuximab sequentially to a maximum of 500 mg/m^2.
D. Reimage to assess response.

In the event of nonresponse to cetuximab, as suggested by the absence of significant rash, there is evidence that increasing the dose of cetuximab improves disease control and response rates. Although overall survival did not change, in the setting where disease control is important to allow resection, the strategy can be considered. Combined administration of the VEGF and EGFR antibodies with combination chemotherapy in the front-line setting leads to poor outcomes and is not recommended. Although reimaging could be useful, a one-month interval may be premature to assess the effect of even successful chemotherapy.

The cetuximab dose is escalated, and the patient gets a grade 2 rash. After six cycles of FOLFIRI–cetuximab, a repeat CT shows a partial response without new lesions or extrahepatic disease. The patient undergoes successful right lobe partial hepatectomy. Pathology shows adenocarcinoma with treatment effect. Margins on the two lesions are negative. Following convalescence, the patient returns to discuss best options.

3. What is the most appropriate recommendation at this time for continuing chemotherapy?

A. 5-FU–leucovorin
B. FOLFIRI
C. FOLFIRI–cetuximab
D. FOLFIRI–bevacizumab

There is a lack of good data in this setting. Since the clinical situation is analogous to adjuvant therapy for stage III disease, where treatment is recommended to control micrometastatic disease, of the given choices, 5-FU is recommended as the most logical evidence-based choice. There are no data to support the use of irinotecan, cetuximab, or bevacizumab for micrometastatic disease. Several trials have shown lack of benefit from these agents in the adjuvant setting. It is worth noting that observation alone and FOLFOX are also appropriate strategies. although most adjuvant trials to date have administered 6 months of treatment. In this patient's case, neuropathy might still preclude use of oxaliplatin. The use of FOLFIRI in this setting is interesting since it was a component of an active regimen that produced a macroscopic tumor response. However, the disconnect between the effectiveness of combination chemotherapies that are active in metastatic colorectal cancer and inactive in microscopic disease is now widely accepted.

Case study 88.4

A 49-year-old man with history of hypertension and depression presents with pathologic fracture of the left humerus, which occurred while he was doing heavy manual labor. In the emergency department, plain films show a spiral fracture and a central lucency suspicious for a tumor. He undergoes open reduction and repair. The fracture was pathologic, and the tumor was biopsied. The patient is referred to medical oncology with cancer of unknown primary. Pathology returns as adenocarcinoma, with CDX2 and CK20 positive on immunohistochemistry. Morphologically, the tumor resembles colon cancer. On questioning, the patient does relate some change in bowel habits. A colonoscopy is ordered and finds a 3 cm lesion in the sigmoid colon. It is nonobstructing and nonbleeding. Biopsies show invasive adenocarcinoma arising in an adenoma. CT scans are performed for staging and reveal retroperitoneal lymphadenopathy and a questionable liver lesion. Serum CEA is elevated to 79. The patient returns to you to discuss therapy. You request KRAS analysis on his metastatic lesion, and there is no mutation detected.

1. What do you recommend as initial management?

A. 5-FU–leucovorin
B. FOLFOX
C. FOLFOX–bevacizumab
D. Bone scan and radiation to left humerus

Bone metastases are infrequent in colorectal cancer and are usually a sign of terminal disease. If bone metastases are found, especially in the setting of a pathologic fracture, a search should be made for other bone lesions that could be at risk for fracture. This can be accomplished by bone scan, PET scan, or a skeletal survey. Therefore, this should be the initial step in management. Palliative chemotherapy should follow. Radiation to bone lesions at risk of fracture, along with bisphosphonates, are interventions to prevent such morbidity.

The bone scan demonstrates some hotspots in the right ribs that are linear in orientation. Plain films revealed old fractures, and the patient recalls having had trauma in the distant past. He begins to complain of achy midback pain, which corresponds to areas of retroperitoneal lymphaden-

opathy on the CT. You want to offer systemic therapy now because of this.

2. What are the appropriate choices for treatment in this setting?

A. FOLFOX or FOLFIRI
B. FOLFOX or FOLFIRI, with an anti-EGFR antibody
C. FOLFOX or FOLFIRI, with bevacizumab
D. Surgical sigmoidectomy because no chemotherapy combination is safe in the setting of an in situ primary tumor
E. A, B, or C

Traditionally, after assessing and staging patients with metastatic colorectal cancer, the primary tumor would be resected to avoid future complications of bleeding or obstruction. At times, upfront surgery can be a valuable adjunct to staging within the abdomen. However, recent trials have demonstrated that it is safe to leave a primary colorectal cancer in situ while administering systemic chemotherapy. Although bevacizumab is associated with a slightly higher rate of bowel perforation in patients not having had their primaries resected, the rate is still low and not a contraindication to its use. The choice of agents is somewhat arbitrary and is influenced by studies inferring a synergistic effect between irinotecan and anti-EGFR antibodies, thus leading to the associated use of FOLFIRI with one of these agents.

You choose to give FOLFOX with bevacizumab. He tolerates this very well with mild elevation of blood pressure. After two cycles, the back pain resolves. After four cycles of chemotherapy, a CT scan demonstrates resolving retroperitoneal lymph nodes (RPLNs). After six cycles, his CEA is less than 4. Repeat CT scans after eight cycles show near-complete resolution of RPLNs. The patient now complains of increasing cold sensitivity, which is continuous, and the development of subtle neuropathy in his fingers and the soles of the feet.

3. What is the most appropriate next step?

A. Continue FOLFOX; hold bevacizumab.
B. Switch to FOLFIRI with bevacizumab.
C. Switch to capecitabine with bevacizumab.
D. Allow a treatment break—stop all chemotherapy.

This is one version of a common scenario seen in the clinical setting—a patient with very good response to combination chemotherapy but now with slowly developing toxicity. The discussion in such cases is usually complex, requiring a detailed assessment of expected benefit from further chemotherapy, the severity and type of toxicities, and competing health risks. Broadly speaking, continuing chemotherapy despite progressive toxicity is seldom appropriate. The OPTIMOX-1 study showed that oxaliplatin can be discontinued after six cycles and reintroduced later without adverse effects on clinical outcomes. This stop-and-go approach led to somewhat lower rates of hematologic and neurologic toxicity; in addition, it avoids the inconvenience and potential hazards of oxaliplatin infusion, and it lowers cost. Therefore, when such toxicities become burdensome, it is reasonable to stop oxaliplatin and continue the fluoropyrimidine backbone. The OPTIMOX-2 study showed that stopping all chemotherapy after six cycles is detrimental to clinical outcomes and, therefore, cannot be recommended as usual practice. Switching to an irinotecan-containing regimen is not warranted at this time; such a strategy should be reserved for progressive disease. The issue of continuous bevacizumab is largely unresolved. However, since data now show benefit of a VEGF inhibitor in the second-line setting after disease progression on a regimen containing a VEGF inhibitor in the first-line setting, it can be inferred that these agents afford durable clinical benefit. Therefore, in the absence of toxicity from bevacizumab, it is reasonable to continue this agent.

Case study 88.5

An 84-year-old retired businessman with a history of coronary artery disease presents with symptoms of abdominal pain, bloating, and hematochezia. He is spending the winter in Florida with his wife and presents to an emergency department where a CT scan reveals a near-obstructing sigmoid mass and three hypodense lesions in the right and left lobes of the liver. He is admitted to the hospital, and colonoscopy confirms the presence of a near-obstructing adenocarcinoma of the low sigmoid colon arising in an adenoma. He elects semi-emergent surgery, and laparoscopic low anterior resection is performed with needle biopsy of the most accessible liver lesion. Pathology returns T3, N2b adenocarcinoma of the colon (nine positive lymph nodes) with metastatic colon cancer to liver. KRAS gene is tested and is positive for a codon 13 mutation. The patient convalesces well and sees an oncologist, who elicits a history of a nontransmural myocardial infarction 5 months before. He was treated with two stents and medication. The patient's family is seeking an aggressive treatment plan. The oncologist discusses combination chemotherapy followed by liver resection.

(*Continued*)

1. Which of the following systemic therapies is most inappropriate and could produce harm?

A. Capecitabine
B. FOLFOX with bevacizumab
C. FOLFIRI with cetuximab
D. FOLFOX with pelvic radiation

The use of fluoropyrimidines in the face of known coronary heart disease can be safe as long as there is continuous careful evaluation for untoward symptoms and signs. The use of cetuximab in patients with tumors harboring KRAS mutations in codon 13 has been reported in some small trials as possibly having benefit, but the data are retrospective and preliminary. Certainly, cetuximab is slightly detrimental in codon 12 KRAS mutations. Pelvic radiation is unlikely to add any benefit in a patient with a low sigmoid lesion that did not have T4 extension into the pelvis. Drainage of the lymph nodes will be along the inferior mesenteric artery and outside of the radiation port. Bevacizumab would be the most inappropriate agent here not only because of future anticipated liver surgery but also, more importantly, due to the recent myocardial infarction. The BRiTE registry documented a 20% recurrence of arterial vascular events in patients over 65 years of age with a stroke or myocardial infarction within 6 months of starting bevacizumab.

The patient is offered mFOLFOX6 alone and initiates therapy. He immediately encounters severe toxicity with cycle 1. This includes severe nausea with vomiting unrelieved by anti-emetics. He develops cold-induced dysesthesias, including muscle cramping, jaw pain, and laryngodysesthesias. His platelet count drops from 120,000 at baseline to 70,000 on day 15, and cycle 2 is delayed. He decides to get another opinion on further management from you. You find him frail-appearing with an Eastern Cooperative Oncology Group (ECOG) performance score of 1. The family is adamant about maintaining a plan for systemic therapy followed by liver surgery.

2. What is the most appropriate management plan at this time?

A. FOLFOX with pre-infusion of magnesium and calcium
B. Capecitabine
C. 5-FU and leucovorin; Mayo Clinic schedule
D. 5-FU and leucovorin; Roswell Park schedule
E. Either B or D

The infusion of magnesium and calcium prior to oxaliplatin administration has been claimed to reduce the incidence of cold-induced paresthesias and neuropathy, but data remain contradictory. In addition, calcium and magnesium will not prevent cytopenias or severe infusion reactions. The Mayo Clinic schedule for 5-FU administration is seldom used in practice now. The incidence of toxicities, such as mucositis, diarrhea, and cytopenias, is higher with this schedule than with the more protracted infusional schedules.

You choose to administer 5-FU/LV using a Roswell Park schedule after the family discovers that they had large copayments for capecitabine. After 2 months, you order a CT scan to re-evaluate the liver lesions. The patient has tolerated the 5-FU poorly with significant mucositis and diarrhea requiring careful dose adjustments, which the weekly schedule has allowed. The CT scan shows a partial response. You notice that the liver is slightly scalloped and the spleen is generous in size. There are engorged venous vessels consistent with early portal hypertension. You question the patient and elicit a history of heavy alcohol use in the past. The family is now pushing for definitive therapy to the liver.

3. Which of the following options is inappropriate for this patient?

A. Resection of liver lesions
B. Radiofrequency ablation (RFA)
C. Embolization with Y-90 beads
D. Bland embolization with glass beads
E. All of the above

Although RFA, Y-90 beads, and bland embolization have not been proven in randomized controlled trials to benefit patients with metastatic colorectal cancer, their collective risks are relatively low even in a patient with cirrhosis as long as liver function is preserved. However, formal liver resection in a patient with portal hypertension carries significant risks. Therefore, local treatment is preferable.

Case study 88.6

The patient is a 64-year-old man with a diagnosis at age 58 of a stage IIIB, T3, N1b, colon cancer at the splenic flexure. After having a left hemicolectomy, he received adjuvant FOLFOX4 for 12 cycles. Two years later, he was found to have a solitary liver metastasis. This was resected, and the patient received mFOLFOX6 chemotherapy for eight cycles resulting in significant neuropathy in the lower extremities. One year after completion of the chemotherapy, scans revealed recurrent metastatic disease within the liver and right adrenal gland. Biopsy of the adrenal mass showed recurrent colorectal cancer, and KRAS was analyzed and found to be wild-type (WT). FOLFIRI and bevacizumab were administered instead of FOLFOX, due to the preexisting neuropathy. The tumor initially responded, but after 9 months, there was evidence of progression with new lesions in the right lung. FOLFIRI and bevacizumab are stopped, and irinotecan was given at the previous dose with cetuximab added. The patient receives dose escalations of cetuximab and episodic discontinuation of the irinotecan due to toxicity. At first there is evidence of stable disease, but after 9 months, CT scans demonstrate progression within the lungs. His oncologist offers him hospice. All therapy is discontinued and 6 weeks later he has an improved performance status, which is an ECOG score of 1. He has normal liver and kidney function, and his complete blood count (CBC) shows mild anemia. He gets shortness of breath on heavy exertion and still has significant neuropathy. He comes to you for a second opinion and is seeking therapy.

1. Reviewing all of his previous treatments, you offer him any of the following except:

A. Phase I clinical trial
B. Capecitabine and mitomycin C
C. Regorafenib
D. Best supportive care

Administrating a fluoropyrimidine despite progression on two or more lines of fluoropyrimidine-based chemotherapy is not recommended in most situations. Regorafenib, a multikinase inhibitor, has been shown to achieve modest improvement in overall survival in disease refractory to all standard therapies. Mitomycin-C has no efficacy in this disease.

The patient opts for regorafenib. He starts the first 3-week cycle at full dose, which is 160 mg daily for 3 weeks. At the end of the period, he has grade 2 hand–foot syndrome. His CBC and comprehensive metabolic panel (CMP) remain unremarkable. He feels tired, and his ECOG performance status is nearing 2. After a week off, he starts cycle 2. In the second week, he complains of back pain. Labs show that the aspartate aminotransferase (AST) is now 2000, alanine aminotransferase (ALT) is 1100, alkaline phosphatase is 160, and total bilirubin is 1.5.

2. What is the next best step in management?

A. Ultrasound of the right upper quadrant to rule out biliary obstruction
B. Urine sample for myoglobin and blood test for creatinine kinase
C. CT scan with contrast to rule out progressive disease
D. Stop regorafenib.

Certainly, an obstructive process should be ruled out, but stopping the drug is the first priority. Regorafenib has been associated with serious hepatotoxicity in a few cases. It is now a black-box warning on the package insert. This manifests mostly as transaminitis; bilirubin and alkaline phosphatase are usually not very elevated. Management consists of supportive care and immediate cessation of the drug. The transaminitis usually resolves over several days to a few weeks.

Case study answers

Case study 88.1

Question 1: Answer B
Question 2: Answer E

Case study 88.2

Question 1: Answer F
Question 2: Answer B
Question 3: Answer B
Question 4: Answer D

Case study 88.3

Question 1: Answer C
Question 2: Answer C
Question 3: Answer A

Case study 88.4

Question 1: Answer D
Question 2: Answer E
Question 3: Answer C

Case study 88.5

Question 1: Answer B
Question 2: Answer E
Question 3: Answer A

Case study 88.6

Question 1: Answer B
Question 2: Answer D

Selected reading

Bennouna J, Sastre J, Arnold D, *et al*. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013; 14(1):29–37.

Hurwitz H, Fehrenbacher L, Novotny W, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.

Karapetis CS, Khambata-Ford S, Jonker DJ, *et al*. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757–65.

Lo SS, Moffatt-Bruce SD, Dawson LA, *et al*. The role of local therapy in the management of lung and liver oligometastases. Nat Rev Clin Oncol. 2011;8(7):405–16.

Nordlinger B, Sorbye H, Glimelius B, *et al*. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371(9617):1007–16.

For further information on this area please also consult Chapters 91, 112, 121, 125, 131, 134, and 135

CHAPTER 89

Pancreatic cancer

Katherine Van Loon and Margaret Tempero
University of California, San Francisco, CA, USA

Case study 89.1

1. A patient presented to the emergency room with acute-onset shortness of breath. A computed tomography (CT) angiogram of the chest revealed a segmental pulmonary embolism, for which the patient was started on anticoagulation with low-molecular-weight heparin. Limited imaging of the upper abdomen demonstrated a pancreatic head lesion with mixed cystic and solid components, interpreted as concerning for malignancy. She was referred to your office for further evaluation. What do you recommend as the next step in her diagnostic evaluation?

A. Positron emission tomography (PET)–CT
B. CT scan with multiphasic pancreatic protocol
C. Endoscopic ultrasound
D. Abdominal magnetic resonance imaging (MRI)
E. Endoscopic retrograde cholangiopancreatography (ERCP)

Cross-sectional imaging is imperative prior to any interventional procedure for a newly diagnosed pancreatic mass and is critical to careful selection of patients for whom there is a reasonable likelihood of an R0 resection. Optimal multiphase imaging must include a noncontrast phase plus arterial, pancreatic parenchymal, and portal venous phases of contrast enhancement with cuts that are $\leq$3 mm. Multiphasic protocols allow for selective visualization of critical arterial and venous structures with which to assess vascular invasion. Contrast enhancement is necessary to distinguish between a hypodense lesion in the pancreas and the parenchyma, and is greatest during the late arterial phase.

A pancreatic protocol CT scan is widely available and remains the best-validated imaging modality for diagnosis and staging of a patient with pancreatic ductal adenocarcinoma (PDAC). Pancreas protocol MRI is emerging as an alternative to CT and in 2012 was added to the National Comprehensive Cancer Network (NCCN) Guidelines as an option for the initial work-up of a pancreatic mass. While CT remains more widely available and is more cost-effective, MRI may provide the added advantage of increased sensitivity for the detection of small hepatic or peritoneal metastases in high-risk patients.

Endoscopic ultrasound (EUS) is complementary to CT as a confirmatory test for lesions that have questionable vascular or lymph node involvement. In particular, the accuracy of EUS in assessing the involvement of venous structures is high, but it is less accurate in evaluating the superior mesenteric artery (SMA) for tumor invasion. The role of PET–CT in the staging of PDAC is still evolving, although it has been demonstrated that PET–CT in combination with a standard CT protocol is associated with superior sensitivity for the detection of metastatic disease than standard CT alone or PET–CT alone (87% vs. 57% vs. 61%). ERCP is typically limited to therapeutic purposes for patients who require biliary decompression.

2. A CT scan with pancreatic protocol is performed and demonstrates a pancreatic head mass with dilation of the pancreatic duct distal to the mass. There are clear fat planes between the mass and the SMA and the hepatic artery, and there is no evidence of hepatic metastases. A CT scan of the chest is negative for metastases. A pathologic diagnosis has not yet been confirmed. What is the next step?

A. EUS with fine-needle aspiration (FNA)
B. ERCP

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

C. CT-guided percutaneous biopsy
D. Refer for resection

A histologic diagnosis can be obtained by FNA with either EUS guidance or CT guidance. EUS-directed FNA is preferred due to the higher diagnostic yield and safety, and the possible risk of peritoneal seeding with a percutaneous approach. However, for a patient with a tumor that appears resectable, a histologic diagnosis is not required prior to proceeding with surgical resection, and thus this patient should be referred for surgical resection without delay for additional diagnostic intervention. For patients who present with disease in which neoadjuvant chemotherapy is recommended, a pathologic diagnosis is imperative prior to initiation of chemotherapy.

Case study 89.2

1. A 56-year-old male presented to his primary care physician with darkening urine and pruritis. He reported a 3-month history of early satiety, 15-lb. weight loss, and greasy foul-smelling stools. A CT scan was ordered and revealed biliary constriction, with a 3 cm mass in the pancreatic head, without evidence of vascular invasion or metastatic disease. What is the next step in his management?

A. Percutaneous biliary drainage
B. Deployment of a plastic stent
C. Deployment of a metal stent
D. Refer for resection

For patients who present with resectable disease, preoperative biliary stenting does not decrease the mortality rate of a Whipple procedure. In a retrospective study of 240 consecutive patients who underwent pancreaticoduodenectomies at Memorial Sloan Kettering Cancer Center (MSKCC), those who underwent preoperative biliary decompression (53%) were subject to an increased rate of postoperative complications, including death, compared to those who were taken directly to surgery. In a randomized trial of 202 patients with cancers of the pancreatic head who presented with obstructive jaundice, a nearly twofold increase in the rate of serious complications was reported in the group who underwent preoperative stenting (74% vs. 39%). Based upon these reports, our practice for patients who present with jaundice and potentially resectable disease is to perform decompression only in patients who are symptomatic, are septic, or in whom surgery is delayed. Use of plastic stents is endorsed in these cases since patients typically do not require the longer patency of a metal stent. For patients who require neoadjuvant induction therapy prior to resection, biliary decompression with a short, expandable, metal stent is necessary prior to initiation of therapy.

2. The patient underwent an uncomplicated Whipple resection with negative surgical margins. A focus of metastatic adenocarcinoma was present in 1 out of 13 resected peripancreatic lymph nodes. He returns to your office 4 weeks after his surgery, with a well-healed surgical scar. He reports incremental improvements in his appetite and energy since his surgery. Which of the following should be performed prior to initiation of adjuvant therapy?

A. CT scan of the chest, abdomen, and pelvis
B. CA 19-9 measurement
C. PET/CT
D. A and B

CA19-9 is a tumor-associated antigen that requires the presence of sialylated Lewis (Le)[a] blood group antigen for expression. While data are conflicting regarding the predictive significance of CA19-9 in response to chemotherapy, postoperative CA19-9 measurement is valuable as a prognostic marker for those patients whose tumors express the antigen. It is known that normalization of elevated CA19-9 levels by 3 to 6 months postoperatively is associated with longer median overall survival (OS). In a prospective study of patients undergoing surgery for PDAC with curative intent, there was a significant survival advantage for the group of patients with a postoperative CA 19-9 level of <180 U/mL, compared to those with higher postoperative CA19-9 levels (hazard ratio 3.53; $P < 0.0001$). CT restaging should also be performed in the postoperative setting to exclude the interval development of local recurrence of distant metastases, as this would certainly impact prognosis and possibly therapeutic decision making.

3. What form of adjuvant therapy do you recommend for this patient?

A. Gemcitabine-based chemoradiation (CRT)
B. Fluropyrimidine-based CRT
C. Gemcitabine alone for 6 months
D. 5-fluorouracil (5-FU)–leucovorin for 6 months
E. There is no known benefit of any adjuvant therapy

The Charité Onkologie Clinical Studies in GI Cancers CONKO-001 trial randomized 354 patients without prior radiation or chemotherapy to adjuvant gemcitabine versus observation following curative surgery. Patients in the treatment arm had greater median disease-free survival (13.4 months vs. 6.9 months, $P < 0.001$); however, the median OS difference failed to reach statistical significance (22.1 vs. 20.2

months, $P = 0.06$), likely due to the fact that nearly all patients in the observation arm received gemcitabine upon relapse.

The ESPAC-1 trial tried to address the question of chemotherapy alone versus CRT. With a 2 × 2 factorial design, its four randomization schemes included observation, CRT, chemotherapy alone, and sequential CRT plus chemotherapy. In the end, the ability to answer this question was limited by the small sample size in each group, but this study did successfully demonstrate a positive impact on OS in the chemotherapy-only arm versus the observation arm. However, no survival benefit was seen in the CRT arm, which actually performed worse than the no-CRT arm.

In ESPAC-3, 1088 patients who underwent resection were randomized to receive six cycles of either 5-FU–leucovorin or gemcitabine. No differences were detected in median OS (23.0 vs. 23.6 months), progression-free survival (PFS) (14.1 vs. 14.3 months), or quality of life. Gemcitabine, however, was associated with significantly fewer serious adverse events.

The Radiation Therapy Oncology Group (RTOG) 97-04 trial randomized 451 patients with resected PDAC to receive either gemcitabine or 5-FU chemotherapy both before and after 5-FU-based CRT. For the patients with tumors of the pancreatic head, there was a nonstatistically significant increase in OS reported in the gemcitabine arm versus the 5-FU arm (20.5 vs. 16.9 months). This difference in OS was not evident in the recent 5-year analysis, but multivariate analysis showed a trend toward improved OS with gemcitabine in patients with tumors of the pancreatic head ($P = 0.08$).

As of this writing, no standard has been established in the adjuvant treatment of node-positive PDAC. The currently available clinical data are insufficient, but for patients in our practice who undergo a R0 resection and are found to have lymph node involvement on pathologic review, we recommend 6 months of adjuvant chemotherapy. In the absence of a contraindication, gemcitabine is preferred over 5-FU–leucovorin due to its favorable toxicity profile. Adjuvant chemotherapy should only be recommended in a patient who has adequately recovered from surgery, and it ideally should be initiated within 4–8 weeks. Further clarification regarding the role for adjuvant chemoradiation for patients who undergo R0 resection is anticipated from the ongoing intergroup trial, "A Phase III Trial Evaluating Both Erlotinib and Chemoradiation as Adjuvant Treatment for Patients with Resected Head of Pancreas Adenocarcinoma" (NCT01013649).

Case study 89.3

A 58-year-old man underwent a Whipple resection for recently diagnosed PDAC. He was referred to you by his surgeon for consideration of adjuvant therapy. You review his pathology report, which is notable for a positive pancreatic margin with 3 out of 15 lymph nodes involved with metastatic PDAC.

1. He is fit, and his postoperative recovery has been uncomplicated. What do you recommend?

A. CRT, followed by gemcitabine
B. Fluoropyrimidine-based CRT
C. Gemcitabine alone for 6 months
D. IMRT alone
E. There is no known benefit of any adjuvant therapy

The role for radiation therapy in the adjuvant setting remains unclear, although a subgroup analysis of data pooled from five randomized controlled trials of adjuvant therapy estimated that it is more effective than chemotherapy alone in patients with positive surgical margins. For patients who have a positive margin, upfront CRT followed by systemic chemotherapy is preferred. In subgroup analyses of CONKO-001, the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. Thus, our recommendation for this patient who underwent a R1 resection would be that he should initiate fluoropyrimidine-based CRT, followed by 6 months of gemcitabine.

Case study 89.4

A 43-year-old woman presents with a pancreatic mass and scattered hepatic lesions. A CT-guided biopsy of one of the liver lesions confirms a diagnosis of metastatic PDAC. She is otherwise healthy and has no functional limitations.

1. What do you recommend?

A. Gemcitabine monotherapy
B. Gemcitabine plus *nab*-paclitaxel
C. Gemcitabine plus erlotinib
D. FOLFIRINOX
E. Refer to hospice

Since gemcitabine was established as the standard of care for metastatic PDAC in 1997, multiple phase III studies have evaluated chemotherapy combinations with a gemcitabine backbone. Trials combining gemcitabine with irinotecan, cisplatin, oxaliplatin, capecitabine, erlotinib, or bevacizumab have all failed to demonstrate a statistically significant survival benefit compared to gemcitabine alone.

Two recent phase III trials represent the first incremental advances for patients with metastatic PDAC in decades. Results from the randomized phase III PRODIGE trial, which compared 5-FU–leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) versus gemcitabine monotherapy in good-performance-status patients with metastatic PDAC, demonstrated dramatic improvements in both PFS (6.4 months vs. 3.3 months) and OS (11.1 months vs. 6.8 months) in patients randomized to FOLFIRINOX. The randomized phase III MPACT trial compared gemcitabine plus *nab*-paclitaxel versus gemcitabine monotherapy reported in patients with metastatic PDAC and demonstrated a significant improvement in both PFS (5.5 vs. 3.7 months) and OS (8.5 vs. 6.7 months). Although FOLFIRINOX and gemcitabine plus *nab*-paclitaxel have not been compared head-to-head, these results suggest that FOLFIRINOX in the first-line setting is associated with a superior overall response rate (ORR), PFS, and OS. This comparison is limited by the fact that the FOLFIRINOX study was based at institutions throughout France, whereas the *nab*-paclitaxel study was a multinational study with a heterogeneous patient population. The use of these two active combination therapies in sequence has not been investigated, and there is no evidence for or against either therapeutic regimen in the second-line setting. We surmise that patients are more likely to be able to tolerate FOLFIRINOX in the first-line setting, and so we would favor its use as a first-line regimen for a high-performance-status patient without contraindications. For patients who are unable to tolerate FOLFIRINOX due to age, performance status, or personal preference, gemcitabine with or without *nab*-paclitaxel is recommended. Chemotherapy regimens recommended by the NCCN, albeit with varying levels of evidence, are summarized in Table 89.1.

Table 89.1 Summary of phase III data for treatment options for metastatic PDAC

Regimen	Median PFS	Median OS	ORR	1-year survival	Grade 3/4 ANC
GEM	3.3–3.8	5.9–6.8	7–12.4%	17–22%	16–22%
GEM + CAP	5.3	7.1	19.1%	24.3%	35%
GEM + erlotinib	3.75	6.24	8.6%	23%	NR
GEM + *nab*-paclitaxel	5.5	8.5	23.0%	35%	38%
FOLFIRINOX	6.4	11.1	31.6%	48.4%	45.7%

ANC, absolute neutrophil count; CAP, capecitabine; FOLFIRINOX, oxaliplatin, irinotecan, and 5-FU/leucovorin; GEM, gemcitabine; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Case study 89.5

A 47-year-old previously healthy woman presents with a 6.4 × 3.8 cm hypoattenuating, partially cystic pancreatic tail mass that abuts the superior mesenteric vein and completely encases the splenic artery. The splenic vein is attenuated and occluded. In addition, the mass abuts the left margin superior mesenteric artery, involving 120° of the circumference. Staging imaging reveals no evidence of metastatic disease. An EUS-guided biopsy is performed and confirms a diagnosis of PDAC. Her Eastern Cooperative Oncology Group (ECOG) performance status is 0.

1. What is your next step in management?

A. Refer for resection
B. Neoadjuvant CRT
C. Neoadjuvant chemotherapy with a gemcitabine-based regimen
D. Neoadjuvant chemotherapy with FOLFIRINOX

In recent years, a new subclassification of "borderline resectable" PDAC has gained traction. These are tumors that are considered technically resectable but with a high likelihood of positive margins. While the precise definition a "borderline resectable" tumor varies across the literature, the NCCN defines this as a nonmetastatic tumor that abuts the SMA, involving ≤180° of the vessel circumference; that involves the SMV–portal vein with tumor abutment, impingement, or encasement, without encasement of the nearby arteries; or that encases the gastroduodenal artery up to the hepatic artery, without extension to the celiac axis.

No randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease versus proceeding directly to surgery. The largest series of borderline resectable PDAC cases is from the MD Anderson Cancer Center (MDACC), in which 160 of 2454 (7%) of PDAC cases were classified as borderline resectable. These patients were treated initially with chemotherapy, CRT, or both. 125 (78%) completed neoadjuvant therapy and were restaged. 79 (49%) were taken to the operating room, and 66 (41%) underwent surgical resection. Among those who underwent surgical resection, 27% required vascular reconstruction; the overall R0 rate was 94%, and pathologic evidence of treatment response was seen in 56%. The median OS for patients who completed all therapy was 40 months versus 13 months for the 94 patients who did not undergo surgery ($P < 0.001$). Two retrospective reviews reported that 31–35% of borderline resectable patients who completed neoadjuvant therapy underwent R0 resections.

While there is no high-level evidence to inform our management of these patients, there is growing consensus that these tumors should be treated with neoadjuvant therapy prior to proceeding with surgery in order to increase the feasibility of an R0 resection and to avoid surgery in those patients with rapidly progressing disease. Utilization of neoadjuvant therapy addresses occult, micrometastatic disease; enhances delivery of therapy to a tumor that is undisturbed and well vascularized; and excludes poor-prognosis patients who are refractory to initial therapy from proceeding with a highly morbid surgery. From two phase II studies of neoadjuvant CRT, we conclude that the biologic waiting period serves to enrich selection of patients who are most likely to benefit from a major surgical intervention and does not result in loss of a window of opportunity for surgical resection of the primary tumor.

FOLFIRINOX in the neoadjuvant setting has been demonstrated in a small case series to be feasible and associated with manageable toxicities. A clinical trial is planned to prospectively evaluate the R0 resection rate following induction FOLFIRINOX and 5-FU-based CRT for patients with borderline resectable PDAC. In the absence of clinical trial data to guide us, our current practice for the management of borderline resectable patients with good performance status (ECOG 0 or 1) is to initiate neoadjuvant chemotherapy with FOLFIRINOX, with a repeat pancreas-protocol CT scan performed after the initial four cycles, and then to proceed with surgical resection after 4–8 cycles in patients without evidence of disease progression.

Case study 89.6

A 70-year-old male presented with epigastric pain that radiated to the back. A CT scan with pancreatic protocol demonstrated an infiltrative low-attenuation soft tissue in the region of the uncinate process measuring at least 3.7 cm, with extension posteriorly to encase the celiac axis, SMA, and common hepatic artery. There is no evidence of metastatic disease. An EUS-guided FNA confirmed a diagnosis of PDAC.

1. What do you recommend as the initial step in this patient's management?

A. Initiate chemotherapy
B. Initiate CRT
C. Refer for resection
D. Refer for Cyberknife radiosurgery

It is established that development of distant metastatic disease represents the dominant pattern of tumor progression and treatment failure among patients with locally advanced pancreatic cancer. Despite a multitude of trials that have assessed some combination of chemotherapy and radiation for the management of locally advanced disease, drawing any conclusions from this body of work is difficult due to a lack of consistency in the dose and technique of radiation, and the use of different radiosensitizing agents and chemotherapy controls across trials.

While combined CRT has established survival benefit over radiation alone or best supportive care, whether CRT improves outcomes over chemotherapy alone is less clear. Two separate meta-analyses have failed to demonstrate a survival advantage from combined CRT, despite the increased toxicity of the treatment. Most recently, the GERCOR LAP 07 phase III trial first randomized 442 patients with locally advanced pancreatic cancer to gemcitabine versus gemcitabine plus erlotinib for 4 months. Patients with controlled disease ($n = 269$) were then randomized to 2 additional months of either chemotherapy or chemoradiation. Among the patients who underwent the second randomization, there was no significant difference in survival between those who received radiation therapy and those who received chemotherapy only.

While radiation therapy following gemcitabine monotherapy clearly provides no benefit, the implications of this finding in an era of more effective chemotherapy regimens are unclear. In light of improved chemotherapy options such as FOLFIRINOX and gemcitabine plus *nab*-paclitaxel, we must consider whether improved chemotherapy-induced outcomes may heighten the impact of radiation. Thus, the concept of sequencing radiation after more effective chemotherapy will need reevaluation. We do uphold that a strategy of upfront chemotherapy is rational and spares the toxicities of radiation therapy to those patients who experience rapid, distant disease progression.

Case study 89.7

The 33-year-old daughter of one of your patients with advanced PDAC approaches you regarding recommendations for her cancer surveillance. Her mother was diagnosed with pancreatic cancer at age 58. She also provides a family history of pancreatic cancer in her maternal aunt and in a maternal cousin.

1. Which of the below testing modalities would you recommend?

A. EUS
B. CT scan
C. MRI/MRCP (magnetic resonance cholangiopancreatography)
D. ERCP
E. There is no effective way to screen for PDAC, even in high-risk individuals

Screening for PDAC is of limited utility in average-risk individuals given the low incidence at a population level and the lack of a noninvasive test with high sensitivity and specificity. Meanwhile, 5–10% of patients who are diagnosed with exocrine PDAC have a first-degree relative with the disease, suggesting a role for familial aggregation and/or genetic factors. Known syndromes in which patients are at risk for development of PDAC, in totality, account for fewer than 20% of the observed familial aggregation, suggesting that additional susceptibility genes have yet to be identified and that a diagnosis of one of these syndromes cannot be relied entirely upon for identification of patients at risk for PDAC. Individuals who are currently considered to be at high risk for PDAC and may be considered for screening are summarized in Table 89.2. For those families without a confirmed genetic syndrome, we recommend that individuals with two or more first-, second-, or third-degree relatives with pancreatic cancer, with at least one case occurring in a first-degree relative, should undergo screening. Risk also appears to be pronounced for individuals from families with a case of early onset PDAC (<50 years).

Table 89.2 Persons at an increased risk of pancreatic cancer

Genetic syndromes	Gene	RR‡
Hereditary pancreatitis	PRSS1	50–80
Familial atypical multiple mole melanoma	p16/CDKN2A	13–37
Hereditary breast ovarian cancer syndrome	BRCA2	3.5
Peutz–Jeghers syndrome	STK11/LKB1	130
Familial pancreatic cancer kindreds		
≥3 first-degree relatives with PDAC		14–32
2 first-degree relatives with PDAC		6

‡Relative lifetime risk, compared to general population.

A prospective screening study from the American Cancer of the Pancreas Screening Consortium evaluated one-time screening with CT, MRI, and EUS in 225 asymptomatic high-risk individuals. Of these, 42% were found to have at least one pancreatic mass (84 cystic and 3 solid) or a dilated pancreatic duct by any of the screening modalities. CT, MRI, and EUS detected a pancreatic abnormality in 11%, 33%, and 43% of high-risk individuals, respectively. Of the 85 individuals with proven or suspected neoplasms, 82 were intraductal papillary mucinous neoplasms (IPMNs) and 3 were malignant.

Still, no study has ever demonstrated that screening improves survival, and there is no test to identify which lesions will progress to invasive PDAC. There are currently no guidelines from the American Gastroenterological Association or the NCCN for the screening of patients at high-risk for PDAC. Even among groups that advocate for screening, there is no consensus as to when to start screening, optimal frequency, or best modality. CT scans offer low sensitivity for pancreatic neoplasms and are associated with radiation exposure. ERCP is associated with a nonnegligible risk of postprocedure pancreatitis. EUS has a higher sensitivity than CT, has a high positive predictive value for pancreatic intraepithelial neoplasia in high-risk individuals, and can detect mural nodules within IPMN. Its limitations include high interobserver variability, cost, and risk of complications associated with endoscopy. MRI/MRCP is a noninvasive method for screening that avoids the risk of radiation exposure and pancreatitis; the diagnostic accuracy for IPMN is equal to or superior to that of CT or ERCP.

Case study 89.8

A 56-year-old woman presents to your clinic for evaluation of a new diagnosis of metastatic PDAC. She reports generalized weakness and anorexia, and an ECOG performance status of 2. She states that her father died of pancreatic cancer in his 50s, and her younger sister was recently diagnosed with ovarian cancer.

1. In addition to referring her for genetic counseling, which of the following treatment options would you recommend?

A. Gemcitabine plus erlotinib
B. Gemcitabine plus capecitabine
C. Gemcitabine plus cisplatin
D. Gemcitabine plus *nab*-paclitaxel
E. Gemcitabine monotherapy

Three separate phase III randomized controlled trial data failed to demonstrate any survival benefit from the addition of cisplatin to gemcitabine in the treatment of patients with advanced PDAC. However, selected patients with BRCA or PALB2 mutations may benefit from the DNA cross-linking mechanism of a platinum agent. In a report from MSKCC, five of six patients with PDAC and known BRCA mutations had a partial radiographic response following treatment with a platinum-based regimen. In a retrospective study of 468 patients with metastatic PDAC designed to identify predictors of survival, those patients with a family history of pancreatic, breast, or ovarian cancer had a superior response to platinum chemotherapy. This benefit was most pronounced among those with a family history of PDAC (6.3 vs. 22.9 months). The sensitivity to platinum-containing regimens correlated with the number of relatives a patient reported with breast, ovarian or pancreatic cancers. By contrast, patients without a family history of cancer are not believed to benefit from the addition of a platinum agent to gemcitabine. Whether this holds true with the oxaliplatin-containing combination regimen FOLFIRINOX has not yet been studied, but this would certainly be a suitable choice for a high-performance-status patient with a family history pancreatic, breast, or ovarian cancer. For this poor-performance-status patient, gemcitabine plus cisplatin would be the most appropriate therapeutic option.

Case study 89.9

You are called by one of your internal medicine colleagues regarding a previously healthy 45-year-old marathon runner who recently presented with insidious weight loss, fatigue, and new-onset diabetes mellitus (DM) with a hemoglobin A1c of 9.5. Your colleague is perplexed by this case since this patient has no identifiable risk factors for type II diabetes. He wonders if you think he should pursue an evaluation for PDAC.

1. Which do you recommend?

A. Serum CA 19-9 measurement
B. Abdominal ultrasound
C. CT scan with pancreatic protocol
D. EUS
E. There is no indication for pancreatic cancer screening in this patient

At least half of patients with PDAC, if not more, are diagnosed with DM either concomitantly or in the 24 months prior to their cancer diagnosis. In a series of 41 diabetic patients who underwent resection for PDAC, DM resolved in 17 out of 30 patients with new-onset DM, suggesting that PDAC has a causal role in glucose intolerance.

Recognition of new-onset DM as an early manifestation of PDAC could potentially result in earlier diagnosis of asymptomatic, resectable disease. However, primary type II DM is common in the general population, while PDAC is uncommon. While strategies for early detection of PDAC are desperately needed, screening for asymptomatic PDAC in all patients with a new diagnosis of DM is not feasible or cost-effective.

Within the limitation of currently available technologies, we recommend restricting screening only to those with no clear risk factors for DM. In this otherwise healthy patient with no identifiable cause for new-onset DM, we would suggest that a CT with pancreatic protocol would be a reasonable study to exclude the possibility of asymptomatic PDAC. For the future, the development of a viable strategy to evaluate patients with new-onset DM for a concomitant diagnosis of asymptomatic PDAC will likely require the development of a sensitive and specific serological biomarker as a screening tool.

Case study answers

Case study 89.1

Question 1: Answer D
Question 2: Answer D

Case study 89.2

Question 1: Answer D
Question 2: Answer D
Question 3: Answer C

Case study 89.3

Question 1: Answer A

Case study 89.4

Question 1: Answer D

Case study 89.5

Question 1: Answer D

Case study 89.6

Question 1: Answer A

Case study 89.7

Question 1: Answer A or C

Case study 89.8

Question 1: Answer C

Case study 89.9

Question 1: Answer C

Selected reading

Callery MP, Chang KJ, Fishman EK, *et al*. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009 Jul;16(7):1727–33.

Canto, MI, Harinck F, Hruban RH, *et al*. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the

management of patients with increased risk for familial pancreatic cancer. Gut. 2012 Mar; 62(3):339–47.

Conroy T, Desseigne F, Ychou M, *et al*. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817–25.

Hammel P, Huguet F, Van Laethem JL, *et al*. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. J Clin Oncol. 2013;31, No 18_suppl (June 20 Supplement).

Tempero MA, Arnoletti JP, Behrman SW, *et al.* Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2012 Jun 1; 10(6):703–13.

van der Gaag NA, Rauws EA, van Eijck CH, *et al*. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010 Jan 14;362(2):129–37.

Von Hoff D, Ervin T, Arena F. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). N Engl J Med. 2013 October 31;369(18): 1691–703.

For further information on this area please also consult Chapters 92, 110, 121, 125, 127, 133, and 139

CHAPTER 90

Hepatobiliary cancer

Keith Stuart
Tufts University School of Medicine, Boston, MA, USA

Case study 90.1

A 57-year-old asymptomatic man presents to his gastroenterologist for routine screening. He feels healthy but overweight, and his past medical history is significant only for diabetes mellitus requiring oral hypoglycemic agents for the past 20 years. He and his girlfriend gave themselves matching tattoos in their early 20s, and he was found to be hepatitis C positive when he tried to donate blood in 1992. He admits to drinking "heavily" through his 20s and 30s, but cut down to one drink daily about 10 years ago. He has not had any known sequelae of liver disease. He is currently in a screening program of biannual alpha-fetoprotein (AFP) and ultrasound. For the first time, AFP is elevated to 203 ng/ml and ultrasound shows a 3 cm lesion in the right hepatic lobe. The magnetic resonance imaging (MRI) confirms a 3.1 cm vascular lesion with delayed filling characteristics consistent with hepatocellular carcinoma; perigastric varices, splenomegaly, and hepatic nodularity of cirrhosis with no ascites and a patent portal vein were seen as well. By the time he sees an oncologist, AFP is 450 ng/ml, with mild transaminitis and low albumin. He has stopped drinking ethyl alcohol.

1. How do various risk factors for liver disease contribute to hepatocellular carcinoma (HCC)?

The incidence of HCC has almost tripled in the United States over the past few decades. Most patients have underlying cirrhosis due to one or more etiologies.

Hepatitis C incidence has risen rapidly in the United States and around the world over the past few decades, and is becoming the most important cause of HCC in many parts of the world. Although known to be transmitted through blood–blood contact, many patients are unaware of any incident that might have caused their infection. Besides sharing dirty needles from illicit drugs or tattoos, iatrogenic causes such as blood transfusions or vaccinations are potential vectors. It is an infection that is relatively difficult to transmit sexually or with close contact compared to hepatitis B or HIV.

Unlike HBV, which leads to carcinogenesis through viral DNA integration and elaboration of the HBx protein, HCV has other methods of carcinogenesis. As an RNA virus, HCV may produce oncogenic proteins and cytokines that can cause chronic irritation, eventually leading to HCC. The timing, when known, seems to be over 20 years, and annual incidence is about 5%.

Much HCC around the world is probably still caused by alcoholic damage. It has been estimated that up to 50% of cirrhotics who die may have evidence of subclinical HCC at autopsy. The incidence rises with total lifetime alcohol consumption, but is actually more common in those who are able to stop drinking heavily, and who therefore do not die early of liver failure. Metabolism of ethanol leads to oxidative stress and accumulation of acetaldehyde, causing hepatocellular damage.

Diabetes, metabolic syndrome, obesity, and fatty liver may actually now be most responsible for the tripling of incidence of HCC over the past few decades, as the general population becomes more overweight. Although not usually a cause of cirrhosis, hepatic steatosis and nonalcoholic fatty liver disease, through accumulation of fatty acids within cells, can lead to fibrosis and HCC in some proportion of patients. Interestingly, coffee consumption may be linked to a lower incidence of HCC.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

2. What is the role for HCC screening?

The primary goal of screening programs for cancer is to reduce mortality. Pretest probability influences the positive predictive value of any screening program, so most studies have been done in populations expected to have higher incidences of HCC, such as those with chronic HBV or HCV infection. Native Alaskans, who have a high incidence of hepatitis B infection, have demonstrated that screening may increase resectability and reduce HCC-related mortality (although the most frequent cause of an elevated AFP was pregnancy). A Shanghai population (also hepatitis B) was randomized to screening with AFP and ultrasound, and this was found to lead to a 47% incidence of resectability, with a 37% reduction in HCC-related mortality. However, analyses of the literature are unable to reach a definitely positive conclusion. The HCV epidemic has led to many large-scale screening programs. This is not yet fully implemented, and there is no universal agreement as to their effectiveness.

Despite this, some cirrhotic patients undergoing screening may have tumors that are not amenable to potentially curative treatment. Mortality of any surgery in liver disease may be between 15% and 50%. Therefore, the mere finding of a tumor might not significantly change mortality. However, in the era of easy availability of local treatment options for intrahepatic tumors, there are now options that might prolong an individual's survival. Indeed, there has been a marked prolongation of OS in the HCC population since 1990, and almost all of this has been in the patients who present with localized disease amenable to intervention.

Several studies modeled the most common form of screening (AFP and ultrasound every 6 months) and found it to be cost-effective, when compared to other accepted screening programs such as mammography and colonoscopy. In terms of further screening, there is currently a CDC recommendation that everyone in the population born between 1945 and 1965 be screened for HCV infection, since it is so common. This might lead to early treatment for some patients, especially given the availability of new antiviral agents. Treatment of HCV with interferon alone or with ribavirin can decrease the incidence of HCC by 80%; this is not universally seen, however. The effect of the newer, more potent antivirals is unknown but might even be better.

3. Does the patient in Case study 90.1 require a biopsy for diagnosis of HCC?

A solitary growing lesion in a cirrhotic liver is most likely to be HCC. A rising AFP raises the likelihood, and a value greater than 500 ng/ml indicates HCC with a certainty of over 90% (although a minimal elevation is not informative). Although not all HCC produces elevated AFP, the serum level may actually be prognostic as well as diagnostic. MRI with dynamic characteristics such as a lesion of greater than 2 cm, early contrast with late washout, leads to a 90–100% chance of a lesion being HCC on biopsy. PET scans are variably helpful, as only approximately 64% of HCC lesions accumulate FDG.

The issue occasionally arises of a new solitary lesion within a cirrhotic liver in a patient known to have another cancer. In this circumstance, biopsy is probably necessary to try to insure the proper systemic therapy. However, several autopsy studies showed that even in the setting of widespread adenocarcinoma of the stomach or esophagus, liver lesions in cirrhotics were still most likely to be HCC.

Biopsies are most needed when the patient takes part in a clinical trial. Given the proliferation of known and suspected biologic markers and targets in potential HCC therapeutics, molecular characterization has become crucial in these lesions. Presumably, as treatment becomes more specific and sophisticated, biopsies will be required to guide therapy. Even now, we are learning that different metastases in many cancers have different genetic signatures, implying that multiple options may be necessary for multifocal tumors. In addition, evaluation of the surrounding liver tissue may become important, as this influences recurrence rates independently of tumor tissue characteristics. In the setting of multifocal HCC, approximately 25 to 50% of lesions in an individual may be metastases, and the rest may be secondary, unrelated primaries. Following resection, early recurrences were found to be intrahepatic metastases, while late hepatic recurrences were second primaries.

Currently, since most options revolve around local ablative techniques, biopsy of a lesion clinically certain to be HCC is not generally performed off study. There are some lesions that, no matter what they are, can only best be treated with local therapy such as radiofrequency ablation. In this setting, we frequently perform the biopsy at the same time as the ablation in order to avoid a second procedure for the patient.

4. What are the risks associated with liver biopsy for diagnosis of HCC?

Liver biopsies have become much safer over the years, especially when the interventional radiologist uses ultrasound or computed tomography (CT) guidance. Sensitivity has been reported as 65%, and specificity at 98%, when using core needles rather than fine-needle aspirate. Risk of bleeding is about 0.6%, and not necessarily related to the depth of hepatic dysfunction, or the INR; thrombocytopenia is the relevant risk factor. Tumor seeding along the needle tract has been reported to occur at the rate of approximately 3%; this is likely less now that a sheath is used to encase the actual biopsy trocar. If a patient is headed toward

potential transplantation, we try to avoid percutaneous biopsy because of the (admittedly theoretical) risk of needle tract recurrence enhanced by immunosuppression.

5. What treatment options are available for localized HCC?

The management has to take into account not only what is the best first option, but also how each treatment might affect candidacy for subsequent therapies. Surgical resection should be the first potential thought for any solitary HCC. In appropriate patients, 5-year survival may be as high as 65%. Many cases can be performed laparoscopically safely and with similar oncologic results. However, the recurrence rate is high because of unseen intrahepatic lesions, new primaries, and/or metastatic satellite tumors. Importantly, the issue of medical rather than technical resectability limits this option for most patients. In fact, generally only 15% of patients worldwide are eligible for resection; recent SEER data show that 8% of US patients over age 65 with HCC undergo surgery. In experienced hands, resection is associated with prolonged survival. Reasons for the low operability rate include the high mortality in cirrhotics (as mentioned above), multifocal tumor, and medical comorbidities (the US HCC population is older and more likely to have diabetes and heart disease).

Therefore, orthotopic liver transplantation has become the treatment of choice for solitary lesions that are potentially curable. In the setting of adherence to the Milan criteria for qualification (no more than three tumors, none greater than 3 cm if multiple, and total less than 5 cm), 5-year disease-free survival is as high as 90%, and OS may be 80%. Recurrence rates may be approximately 13%. Both the complications of long-term immunosuppression and the risk of tumor recurrence have dropped substantially since the early years of liver transplants, because of improvements in preoperative screening and imaging, better patient selection, and gentler immunosuppressive regimens.

Patients who do not fit the Milan criteria may still qualify by the more liberal University of California, San Francisco (UCSF) criteria (size limit of 6.5 cm). They can still have survival and recurrence-free results almost as high as those transplanted under the Milan criteria. Some centers are also looking at the feasibility of downstaging larger tumors to within Milan criteria before transplant. However, in practice they are unlikely to qualify to receive a cadaveric donation. Therefore, many centers are using partially matched family members as a potential source of organ donation. Patients who receive this type of donation are fundamentally different from the standard deceased-donor recipients, so it is difficult to compare the groups directly.

For instance, the timing of the surgery is variable. Where a DDLT (deceased-donor liver transplant) recipient may easily wait more than a year for an available organ, an LDLT (live-donor liver transplant) patient can schedule the exact time of surgery, usually within a couple of months. Practically, the LDLT patient may be healthier than the DDLT patient (and obviously has a very close social support system, if someone is willing to donate part of their liver). In terms of the tumor, however, waiting for over a year allows the treating team to assess the biologic aggressiveness and neoplastic behavior of the process very closely. Patients with highly aggressive tumors will demonstrate this during the wait time, and are less likely still to qualify for transplant a year or more later. This means that the patients undergoing DDLT will in general have more indolent tumors than the LDLT group, since the biologically aggressive ones drop out of consideration before surgery.

Comparative results somewhat reflect these differences in tumor biology and patient selection between the two groups. For instance, the LDLT group has a higher recurrence rate (perhaps reflecting the greater inclusion of aggressive cancers) but also a higher survival overall (because of better genetic matching of the transplant). Nonetheless, this is still a less common option for patients. Not everyone has a genetic candidate or willing donor, and there is clearly a surgical and long-term risk to the donor.

6. What is the role of localized therapies prior to transplantation for HCC?

Prior to transplantation, it is common practice to try to ablate the lesion. This is an acknowledgment of the time to transplant, and serves as a method to control the tumor growth and prevent the lesion from expanding beyond the Milan criteria. Also, because of the manipulation inherent in the surgical procedure, there is theoretically less tumor spillage during the actual transplantation if the tumor has been ablated beforehand. Chemoembolization and radioembolization are most commonly used to do this intraarterially rather than percutaneously, and have led to complete histologic necrosis of the treated tumors when the explant is evaluated pathologically. Whether or not this adds to survival or postoperative tumor control remains controversial: some studies suggest up to a 5% improvement, but others do not. The effectiveness of the procedure and amount of necrosis produced seem to be important. The benefit may only occur if the ablation is performed at least several months prior to transplantation, allowing for more complete necrosis. This implies that doing this prior to LDLT may not be as helpful, since the time to surgery is generally shorter. No randomized trial examining this question has been performed, or is contemplated.

7. What are some of the localized therapies for HCC?

Ethanol ablation is a formerly popular method of controlling small tumors. Because of the hypervascularity and

porousness of HCC lesions, there is relatively good diffusion of percutaneously injected liquids. Prior to the adoption of newer alternatives, ethanol was a straightforward method of managing small lesions. Results were good with small lesions, although many portions of the tumor remained viable because of incomplete and unpredictable diffusion. Despite the availability of more high-tech (and expensive) methods of control, this may still be relevant for some lesions.

Radiofrequency ablation (RFA) is the treatment of choice for most interventional radiologists intending to treat solitary lesions under 5 cm. Local control rates are excellent, and are dependent upon the size of the treated lesion. For instance, lesions under 3 cm have local recurrence rates of 15%, while those of 5 cm have 30%. Interesting methods to enhance local cell kill and perhaps improve the size of the ablated lesion are being developed, such as by using intravenous chemotherapy or oral biologics in combination with RFA.

Cryoablation may be used in similar circumstances as RFA. Rather than killing cells with heat, a liquid nitrogen probe is used to freeze the cells within the tumor. Using cryo rather than RFA may be advised in some situations in which the lesion to be treated is in close apposition to another thermally sensitive structure (e.g., the gallbladder, chest wall, muscle, colon, or stomach) in order to avoid unintentional collateral thermal damage. Whereas there is no simple way to monitor the outer border of the thermal necrosis as it spreads from the probe in real time, using a cryoprobe instead allows visualization of the expanding frozen tissue on CT scanning.

Percutaneous methods such as ethanol, RFA, and cryo are very good at controlling small tumors, if they are safely and technically accessible, and if there are fewer than three. However, these techniques clearly target only grossly visible disease. Moreover, smaller lesions are more difficult to target with precision, so in general these are limited to lesions between 2 and 5 cm. By nature of the targeting method, any very small or nonvisible tumor will be left untreated. Because of the known multifocality of HCC, as well as the propensity of the cirrhotic liver to generate new tumors over time, this is rarely a curative procedure. Overall survival (OS) has not been a common endpoint of any clinical reports or trials of these techniques.

Chemoembolization involves intra-arterial administration of chemotherapy (frequently doxorubicin) along with embolic material such as ethiodized oil or, more recently, polyvinyl alcohol drug-eluting beads. This method achieves very high intratumoral drug concentrations while causing local ischemia simultaneously. Side effects may range from pain, nausea, fever, and fatigue to gallbladder ischemia, abscess, and hepatic failure (although these latter are very uncommon). This modality has the advantage of potentially being able to treat multiple tumors simultaneously since the arterial supply is used as the delivery system. Frequently, smaller tumors than can be seen on CT or MRI are discovered on the pretreatment angiogram, and may then be treated. One limitation of the technique is the requirement for relatively well-preserved liver function, as well as patent portal vasculature to avoid severe hepatic ischemia. Several randomized trials and meta-analyses have demonstrated a significant survival advantage to chemoembolization over best supportive care. Current controversy persists over the advantage of this over other therapies, as well as the additive effect of the chemotherapy.

Radioembolization also employs the arterial system, to deliver microscopic glass beads coated with Yttrium-90 to the tumor. Rather than the larger 300 μm drug-eluting beads used for chemoembolization, the beads for radioembolization are approximately 32 μm . This means that they do not actually cause significant ischemia by blocking arterioles, and are only trapped as they traverse the capillaries. Beta-particle emission then will cause DNA damage in tumor cells within an approximately 2.5 mm radius. The lack of overt ischemia allows this method to be used for patients who have portal vein thrombosis.

Stereotactic radiosurgery is a recent refinement in external-beam radiotherapy that allows extremely high doses of radiation delivered specifically to intrahepatic tumor while sparing the surrounding liver. This is a critical evolution of radiation delivery systems, since the normal liver is more sensitive to radiation-induced damage than is the actual tumor. Results have been quite good for lesions that are unable to be treated by other local methods: approximately 73% response rates with doses up to 42 Gy. One-year survival is reported as high as 87%.

New local treatment options and technologies continue to appear and are being evaluated for differences in safety and efficacy. High-intensity focused ultrasound and irreversible electroporation (irreversible permeabilization of the cell membrane through the application of microsecond through millisecond electrical pulses) are two new techniques that are currently being studied and optimized for this indication.

8. What are some of the systemic therapies for HCC?

Standard chemotherapy has a long and disappointing history. Tolerable doses are limited by the cirrhotic liver, and the high hepatic expression of p-glycoprotein, a membrane-bound pump that confers resistance to multiple chemotherapeutic agents, has restricted effective regimens. In general, response rates are low, and true survival advantage has not been demonstrated. Available options include gemcitabine plus either cisplatin or oxaliplatin, 5-fluorourcial and leucovorin or oral capecitabine, or low-dose doxorubicin. Sorafenib is an oral multitargeted drug that inhibits

Raf serine–threonine kinases mediating cell proliferation and receptor tyrosine kinases involved in angiogenesis. Randomized studies in patients with HCC, both in Europe and in Asia, have demonstrated proportionately comparable improvements in survival over best supportive care. Interestingly, although the fractionate improvement was similar, the absolute difference in survival was strikingly different, depending upon the geographical area and presumably the underlying liver disease. Specifically, among primarily HCV patients in Europe, survival was prolonged from 7.9 to 10.7 months; in Hong Kong, with mostly HBV patients, survival went up from 4.2 to 6.5 months. Actual response rates of tumor shrinkage are close to zero. Novel targeted agents, such as inhibitors of the MET pathway, may hold promise for the future.

Selected reading

Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol. 2009;27:1485–91.

Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245–55.

Maggs JR, Suddle AR, Aluvihare V, *et al*. Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma. Aliment Pharm Therap. 2012;35:1113–34.

Meza-Junco J, Montano-Loza AJ, Liu DM, *et al*. Locoregional radiological treatment for hepatocellular carcinoma; Which, when and how? Cancer Treat Rev. 2012;38:54–62.

Welzel TM, Graubard BI, Zeuzem S, *et al*. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology. 2011;54:463–71.

For further information on this area please also consult Chapters 92 and 111

CHAPTER 91

Neuroendocrine tumors

Anya Litvak and Leonard Saltz
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Case study 91.1

• What imaging studies are most appropriate in the initial workup of neuroendocrine tumors (NETs)?

A 56-year-old female with small bowel, well-differentiated NET with metastasis to the liver is coming into clinic for her 6-month follow-up visit. She had previously profuse diarrhea and flushing. She was found to have a positive somatostatin scintigraphy scan (Octreoscan) and was started on octreotide with resolution of her symptoms.

1. What imaging modality is most appropriate for following the patient?

A. Contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis with liver triphasic
B. Somatostatin scintigraphy scan
C. Magnetic resonance imaging (MRI) of the abdomen and pelvis
D. Routine positron emission tomography (PET) scan
E. A or C
F. B or D

Scintigraphy with octreotide labeled with indium 111 (Octreoscan) was first used in the 1990s to localize previously undetected primary or metastatic NETs. At that time, radiopeptide functional imaging allowed for better localization and staging of neuroendocrine tumors as compared to CT or MRI scans. However, in the last decade, imaging with CT and MRIs has undergone tremendous technological advancement with improvement in resolution. A recent evaluation was performed to determine the utility of modern octreotide scans when used in conjunction with modern CT or MRI scans. The study found that multiphase contrast-enhancing CT or MRI scans detected more pathologic NET lesions than did single-photon emission computed tomography (SPECT) octreotide scanning. Particularly, octreotide scans did not identify additional primary tumors or soft tissue lesions that were not seen by CT or MRI scans, but did identify unsuspected bone metastasis that were not identified on CT or MRI. Given that cross-sectional imaging with modern CT and MRI can detect lesions down to 2–3 mm, it is no longer reasonable to expect that routine indium 111 octreotide scans would be able to detect lesions smaller than that. In general, current somatostatin scintigraphy is sensitive down to a size of approximately 7 mm. More sensitive and specific radiopharmaceuticals are under development, but have not yet been established as helpful and are not currently part of standard care.

Octreotide scans are appropriate to use as a baseline to determine the presence or absence of somatostatin receptors in vivo on the patient's tumor. This is particularly important for those patients with hormonally nonfunctional tumors. Those patients who are found to have a negative somatostatin scintigraphy scan are not appropriate for treatment with somatostatin analogs, as there is no reason to believe that somatostatin would be effective in the absence of receptors on the tumor. In our opinion, once a baseline octreotide scan is performed, there is rarely a utility for routine use of octreotide scan for staging or surveillance. Octreotide scans do appear to be very sensitive for picking up asymptomatic bone lesions, and may be performed for the detection of

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

bone lesions that are not visualized by CT or MRI if this would change management.

CT scans are potentially useful for following patients with NET. However, because neuroendocrine tumors can often be isodense with normal hepatic parenchyma, contrast enhancement is mandatory, and a triphasic view is more likely to give a complete assessment of liver involvement. MRI scans are also an excellent means of following patients with NET, as they are both sensitive and specific for neuroendocrine tumor involvement. Because well-differentiated neuroendocrine tumors tend to have a low metabolic rate, PET scans are not routinely recommended, as they have a relatively high false-negative rate.

Case study 91.2

• How does grade (low vs. intermediate vs. high grade) impact the prognosis and treatment of NETs?

A 45-year-old male has experienced increased fatigue, intermittent abdominal pain, and 30-lb. weight loss over the last 3 months. Colonoscopy and esophagogastroduodenoscopy (EGD) are negative. CT scan of the abdomen and pelvis shows a jejunal mass and innumerable liver lesions. A core biopsy of a liver lesion is performed and shows a grade 3, poorly differentiated neuroendocrine tumor with 30 mitotic figures/10 HPF and Ki67 index of 40%.

1. What treatment would be recommended?

A. Octreotide
B. Debulking surgery
C. Liver RFA
D. Platinum-based chemotherapy

NETs are epithelial neoplasms with predominant neuroendocrine differentiation and are classified histologically into two main groups, well differentiated and poorly differentiated. Well-differentiated tumors, which were traditionally referred to as carcinoid or pancreatic neuroendocrine (islet cell) tumors, are further separated into low grade (mitotic count of $<2/10$ HPF and Ki67 index of $<3\%$) and intermediate grade (mitotic count of 2-20/10 HPF and Ki67 index of 3–20%). In poorly differentiated tumors, mitotic count usually exceeds 20/10 HPF and Ki67 index is over 20%. Assignment of grade based upon the proliferative rate correlates with patient survival independent of tumor stage in both primary and metastatic gastroenteropancreatic NETs. In one series of 425 patients with a pancreatic NET, 5-year survival rates for low-, intermediate-, and high-grade tumors were 75%, 62%, and 7%, respectively. Although patients with low-grade and intermediate-grade NETs of the digestive system are treated similarly at this time, as new treatment modalities become available, it is likely that the histological grade of a low versus intermediate NET will affect the selection of appropriate treatment.

Poorly differentiated or high-grade NETs, in contrast, more closely resemble small-cell neuroendocrine carcinomas of the lung. They rarely secrete hormones or express somatostatin receptors. For this reason, octreotide scans are usually negative, and somatostatin analogs, with their limited antiproliferative effect, would be unlikely to be effective treatment. Furthermore, poorly differentiated NETs are typically associated with a rapid clinical course and median survival is poor with localized, regional, or distal disease, having an overall survival of 34, 14, and 5 months, respectively. As these tumors behave like small-cell lung cancer, a platinum-based regimen with cisplatin or carboplatin plus etoposide or irinotecan is usually recommended as first-line therapy. There is currently no standard for second-line treatment, although topotecan, paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan have all been reported to show some activity. Furthermore, even if a patient presents with local, resectable, poorly differentiated neuroendocrine tumors, local therapy with surgery and/or radiation therapy is usually not curative, and systemic chemotherapy needs to strongly be considered.

Case study 91.3

• Is there a role for adjuvant octreotide after resection of NET primary?

A 56-year-old female undergoing an elective cholecystectomy for management of gallstones is found incidentally at operation to have a small bowel tumor. A resection of 20 cm of small bowel is accomplished, and final pathology reveals a 2.5 cm well-differentiated, low-grade carcinoid tumor with three of six lymph nodes positive for tumor. A postoperative contrast-enhanced CT scan of the abdomen and pelvis with liver triphasic shows no evidence of disease, and she is currently asymptomatic.

1. What should her follow-up plan be?

A. Adjuvant octreotide
B. Adjuvant interferon alpha
C. Adjuvant streptomycin and fluorouracil
D. Observation

To date, no study has been done to investigate the use of any antineoplastic agent in the adjuvant treatment of resected carcinoid or pancreatic NET. Thus far, antitumor activity from all known agents would appear to be too modest to suggest that a meaningful survival benefit could be expected in the adjuvant setting. Given that the median survival of patients who have had resection of low-grade, local or low-grade, local-regional NETs is very long (often measured in years to decades), it would be extremely unlikely that a study could show a benefit in the absence of an agent with outstanding clinical activity.

The PROMID trial investigated the use of octreotide to treat patients with nonfunctional metastatic carcinoid tumors. The trial, which was not powered to assess a survival difference, randomized patients to octreotide versus observation at the time of diagnosis of metastatic disease. The results showed that octreotide was able to improve time to tumor progression, or progression-free survival, by approximately 7 months compared to placebo in patients with active carcinoid tumors of the midgut. However, given that the median survival exceeded 5 years in each arm, it is highly unlikely that early initiation of octreotide, as was done in this trial, is necessary in order to achieve a beneficial result. The relatively modest benefit demonstrated makes it exceedingly unlikely that the cure rate would be increased by subjecting patients to octreotide in the adjuvant setting. Furthermore, although somatostatin analogs are quite well tolerated, they do have multiple potential side effects, including abdominal pain, bloating, loose stools, fat malabsorption, mild glucose intolerance, and increased risk of gallstones.

Alpha interferon is an agent with considerable toxicity and minimal evidence of substantial antitumor activity in NETs. Early studies of interferon alpha in NETs have confused the literature by mixing "biologic" responses and "objective" responses together in their reporting, thus creating the misconception that substantial tumor regression was a common outcome from interferon therapy. In fact, regression to interferon is extremely rare. A later trial in the Mayo Clinic with interferon alpha showed a high degree of toxicity and minimal evidence of activity in carcinoid tumors. A review by Plockinger *et al*. (2007) estimated that approximately 10% of patients achieve some degree of actual tumor regression, and major objective responses are incredibly rare. Furthermore, interferon has not been studied in the adjuvant setting and has a high degree of toxicity, including flulike symptoms, fatigue, depression, myelosuppresion, alteration in thyroid function, and anorexia. Therefore, it should not be used in the adjuvant setting, and it has an extremely limited role in the treatment of NETs even in the metastatic setting.

The role of conventional chemotherapy in the metastatic setting for well-differentiated carcinoid and pancreatic neuroendocrine tumors is debated, as response rates vary considerably between different studies secondary to a wide range of assessment criteria and patient populations. In general, response to cytotoxic chemotherapy is rare in patients with advanced, well-differentiated carcinoid tumors. Cytotoxic chemotherapy for pancreatic NETs appears to be a bit more responsive than carcinoid tumors; however, older trials have been reported in a manner that may overstate the degree of actual activity. For instance, in the phase II–III Eastern Cooperative Oncology Group (ECOG) trial, 249 patients with carcinoid tumors were randomized to receive doxorubicin with fluorouracil or streptozocin with fluorouracil. The response rates were relatively low at approximately 16% for both arms, and substantial side effects were seen, with approximately one-third of patients who received streptozocin-based therapy developing mild to moderate renal toxicity. One of the earlier studies presented by Moertel *et al*. (1992) with streptozocin and doxorubicin reported a 69% response rate in patients with advanced pancreatic NETs. Modern criteria for response assessment were not applied in this trial, however, and it is likely that the objective response rates as they would be defined by today's criteria were, in fact, substantially lower than reported. A retrospective evaluation of 16 patients treated with this combination at Memorial Sloan Kettering Cancer Center found an objective response in only 1 of 16

(*Continued*)

patients, and identified many methodological flaws in response reporting in the Moertel trial. The high response rate reported is now felt to be a gross overestimate of the degree of activity with streptozocin-based chemotherapy. More recently, a retrospective review from MD Anderson Cancer Center showed an overall response rate of 39% with fluorouracil, doxorubicin, and streptozocin in patients with pancreatic NETs. Based on the only modest response rates and high rate of toxicities, systemic chemotherapy is not recommend in the adjuvant setting and rarely plays a role in early management of metastatic low grade NETs". It is usually reserved for patients with symptoms secondary to tumor bulk or uncontrolled hormonal excess once they have failed octreotide treatment. More recently, everolimus and sunitinib have been shown to have modest activity in metastatic pancreatic NETs (but not in carcinoid tumors). Use of these agents in the adjuvant setting has not been studied and is not recommended at this time.

Case study 91.4

• **Are carcinoid and pancreatic NET comparable?**
Well-differentiated neuroendocrine tumors of the aerodigestive tract and pancreas both respond similarly to molecular-targeted therapies, including small-molecule kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors.

1. Is this statement True or false?

A. False
B. True

Neuroendocrine tumors (NETs) can be divided into two groups: carcinoid tumors (neuroendocrine tumors of the aerodigestive tract) and pancreatic NETs (neuroendocrine tumors of the endocrine pancreas). Although pancreatic NETs and carcinoid tumors have similar morphologies, and were treated similarly in older investigations, it has now been clearly demonstrated that there is a substantial difference in response rates to various therapies.

For example, sunitinib, a multitargeted tyrosine kinase inhibitor (TKI) that shows activity against a range of signaling pathways and growth factors, including VEGFR and PDGFR, has been tested in advanced NETs, with studies showing efficacy thus far only in pancreatic NETs. One of the first trials that showed that sunitinib may have an oncologic benefit was the phase II study of 109 patients with advanced NETs who received 50 mg of sunitinib for 4 weeks followed by a 2-week break. 17% of patients with pancreatic NET versus 2% of patient with carcinoid tumors achieved a confirmed partial response. Furthermore, the favorable results that led to the approval of sunitinib in the United States for treatment of progressive, well-differentiated pancreatic NETs was based on a placebo-controlled multicentered randomized study. In that trial, patients with advanced progressive metastatic pancreatic neuroendocrine tumors were randomized to sunitinib versus placebo. The study was designed to enroll 340 patients but was prematurely stopped after enrollment of 171 patients showed a significantly longer median progression-free survivalwith sunitinib versus placebo (11.4 vs. 5.5, $P < 0.001$). As there is currently not a randomized study of sunitinib for carcinoid tumors, and previously documented response rates are very low, sunitinib is not approved for the treatment of carcinoid tumors.

Similarly, everolimus has greater activity in pancreatic NETs than carcinoid tumors. For instance, in the RADIANT 3 trial, everolimus was administrated orally at a dose of 10 mg once daily and was compared to best supportive care in 410 patients with advanced progressing pancreatic NETs. Everolimus was associated with a statistically significant prolongation in median progression free survival (11.0 vs. 4.6 months, $P < 0.001$). Largely based upon these data, everolimus is approved in the United States for the treatment of progressive NETs of pancreatic origin in patients with unresectable, locally advanced, or metastatic disease. The RADIANT 2 trial compared depot octreotide with or without 10 mg daily of everolimus in 429 patients with advanced carcinoid tumors, a history of carcinoid syndrome, and radiologic disease progression in the last 12 months. Combined therapy showed a modest progression-free survival difference (16.5 vs. 11.3 months, $P = 0.026$). This difference in primary endpoint of progression-free survival did not meet the predefined threshold for statistical significance. Overall survival was difficult to assess in this trial since a crossover was permitted; however, there was no indication of a survival benefit in the group initially treated with everolimus. In fact, there was a statistically insignificant trend toward inferior survival in the group initially treated with everolimus. At present, everolimus is approved for pancreatic NETs but not for treatment of carcinoid tumors.

Case study 91.5

• Is surgery for asymptomatic liver metastasis of NET useful?

An 45-year-old female is being followed for well-differentiated carcinoid tumor with diffuse, liver-only metastasis. She is asymptomatic with an ECOG 0 performance status. The patient wants to know whether or not debulking surgery without the possibility of a complete resection should be performed. Currently, the patient is asymptomatic.

1. What do you recommend?

A. Attempted, incomplete resection
B. Observation

The liver is by far the most common site of metastasis for NETs, and approximately 40% of patients with primary gastroenteropancreatic neuroendocrine tumors develop liver metastases, as hematogenous spread to the liver via the portal venous drainage system is quite common. The surgical management of liver metastasis is a particularly controversial area in the management of NETs, and not all experts agree upon management. We believe that based on the multifocal and diffuse nature of liver metastasis, the percentage of patients who can be operated on with the expectation of either cure or long-term disease-free survival is vanishingly small. Furthermore, although several, retrospective multi-institutional reviews have documented a high 5 and 10 year overall survival, up to 94% of patients develop new hepatic metastasis within 5 years of resection. Therefore, in 94% of patients, surgery has not been curative. As there is a large discordance between progression-free survival and overall survival, it is difficult to tease out whether the surgery, and not the biology of the disease, contributed to the prolonged survival. Additionally, surgical morbidity, including the risk of wound infections, intra-abdominal abscess formation, bile leak, and hepatic failure, must be considered. Given that liver resection surgery is noncurative in the overwhelming majority of patients with NET liver metastases, such liver resections are perhaps best viewed as debulking procedures rather than curative-intent procedures. Since noncurative debulking surgery is not an accepted standard approach in liver metastases of other gastrointestinal malignancies, we do not feel that, in the absence of randomized data, it can be considered routine standard management here, especially for asymptomatic patients. In selected cases, debulking surgery to alleviate symptoms of refractory excess hormonal secretion and or symptomatic tumor bulk can be considered.

Case study 91.6

• Is local-regional therapy for hormonally symptomatic liver metastasis of NET useful?

A 65-year-old male presents with diarrhea, flushing, and weight loss for 5 months. Physical exam is notable for hepatomegaly. A contrast-enhanced CT scan demonstrates a 3 cm mesenteric mass and multiple hypodense lesions in the liver. A core needle biopsy of a liver lesion reveals a well-differentiated metastatic neuroendocrine tumor. The patient is placed on octreotide, with rapid relief of diarrhea and flushing. After several years, however, his diarrhea and flushing return despite continued and increased octreotide therapy.

1. What palliative options are potentially useful for the patient?

A. Radiofrequency ablation
B. Hepatic arterial embolization (HAE)
C. Hepatic artery chemo-embolization (HACE)
D. Surgical debulking
E. All of the above

When hormonally functional carcinoid tumors metastasize to the liver, the patient can experience not only bothersome symptoms secondary to tumor bulk but also, more commonly, profuse diarrhea, bronchospasm, flushing, damage to heart valves, and a variety of other symptoms as a result of serotonin production by the tumor. In patients with a positive somatostatin scintigraphy scan, somatostatin analogs should first be used to control symptoms. Once the somatostatin analogs are no longer effective, local control with radiofrequency ablation, hepatic arterial embolization, chemo-embolization, or surgical debulking of the tumor bulk can be attempted to palliate symptoms.

Radiofrequency ablation is a procedure that uses supraphysiologic heat to cause cell death either during open or laparoscopic surgery or, more commonly, during an image-guided percutaneous procedure. Although these procedures have not been definitely proven to increase overall

(*Continued*)

survival, symptom improvement has been found to be durable. For instance, Mazzaglia *et al*. (2007) presented a prospective study of 54 patients with unresectable hepatic metastases from gastroenteropancreatic NETs. Over 90% of patients reported postablation symptomatic improvement with the median duration of symptom control of 11 months.

The basis for hepatic arterial embolization is that there is a dual blood supply of the liver—the neuroendocrine tumors that metastasize to the liver are hypervascular and derive most of their blood supply from the hepatic artery, while the healthy hepatocytes receive most of their blood supply from the portal vein. Therefore, inducing vascular ischemia to the hepatic arterial supply can result in selective necrosis of the tumor while, for the most part, sparing the normal liver. Concurrent hepatic arterial infusion of chemotherapy or drug-eluting beads (DEB-HACE) can also be performed. Currently there are no randomized data to address whether "bland" hepatic arterial embolization or chemotherapy embolization is more beneficial. These procedures are not benign as they have a 3–5% rate of treatment-related mortality in some series and >20% complication rate secondary to bleeding, pain, infection, arterial thrombosis, and hepatic failure, especially in patients who already have a compromised synthetic liver function.

Similarly to radiofrequency ablation and hepatic arterial embolization, surgical debulking is not curative (unless complete resection is possible) but can be effective as palliative treatment to control either symptoms from tumor bulk or hormonal symptoms that are refractory to medical management.

Case study answers

Case study 91.1

Question 1: Answer E

Case study 91.2

Question 1: Answer D

Case study 91.3

Question 1: Answer D

Case study 91.4

Question 1: Answer B ("False")

Case study 91.5

Question 1: Answer B

Case study 91.6

Question 1: Answer E

Selected reading

Moertel C, Rubin J, Kvols L. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. JCO 1989:865–88.

Raymond E, Dahan L, Raoul JL, *et al*. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364(6):501–13.

Reidy DL, Gollub MJ, Saltz LB. Addition of octreotide functional imaging to cross-sectional computed tomography or magnetic resonance imaging for the detection of neuroendocrine tumors: added value or an anachronism? J Clin Oncol. 2011 Jan 20;29(3):e74–5.

Rinke A, Müller HH, Schade-Brittinger C, *et al*. PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009 Oct 1;27(28):4656–63.

Strosberg JR, Cheema A, Weber J, *et al*. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol. 2011 Aug 1;29(22):3044–9.

Sun W, Lipsitz S, Catalano P, *et al*. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol. 2005;23:4897–904.

CHAPTER 92

Transarterial liver-directed therapies in oncology

Divyesh G. Mehta[1] and Jeffery Choh[2]

[1]University of Arizona College of Medicine *and* Maricopa Medical Center, Phoenix, AZ, USA
[2]Cancer Treatment Centers of America, Zion, IL, USA

Case study 92.1

A 50-year-old patient with a history of hepatitis C was recently found to have multiple liver masses. Imaging showed several 3 cm lesions with classic hypervascularity in the arterial phase and washout in the venous phase compatible with hepatocellular carcinoma (HCC). Alpha-fetal protein was also elevated. The patient did not qualify for transplant due to the multiple numbers of lesions involving both lobes. The lesions were unable to be surgically resected and unable to be ablated.

- **Outside of systemic therapy, what are the types of locoregional therapy that are available?**

If the lesions are inoperable and also unable to be ablated, a form of transarterial therapy can be considered. This procedure utilizes transarterial technique for chemoinfusion, bland embolization, chemoembolization, and radioembolization.

Transarterial chemoinfusion (aka hepatic artery infusion (HAI)) utilizes the drug's first-pass extraction rate pharmacokinetic principle. For example, floxuridine has a hepatic extraction rate of 95%, which significantly reduces the systemic toxicity. Recently, Okusaka *et al*. (2009) demonstrated that for inoperable HCC, HAI was as effective as transarterial chemoembolization. This randomized phase III prospective study with 161 patients showed there was no statistical difference of median overall survival time between chemoembolization group (646 days) versus HAI group (679 days) ($P = 0.383$). They concluded that by adding embolization, it did not increase survival over HAI in patients with HCC.

To discuss any form of transarterial embolization to the liver, one must understand the liver perfusion physiology. The liver has dual blood supply from the systemic arterial and portal inflows. Since more than two-thirds of the hepatic inflow is from the portal system, the liver can sustain itself from the portal flow alone. Embolization of the hepatic artery or of its branches will not cause liver infarction. However, tumor angioneogenesis, requiring higher oxygen content, is derived almost exclusively from the hepatic artery. This allows the introduction of antineoplastic agents directly into the tumor with significant less effect on the normal liver parenchyma.

Bland transarterial embolization employs use of various embolic materials to occlude the tumor-feeding arterioles. The primary goal is to induce ischemia and tumor necrosis without concomitant use of chemotherapy. Common embolic agents include gelfoam, polyvinyl alcohol, and calibrated acrylic copolymer microspheres. In general, the goal of embolization is to administer the agents deep into the tumor vascularity to cause cessation of flow and infarction. To obtain adequate tumor coverage, the adjacent surrounding normal liver parenchyma may be embolized as well. Embolic agents that are too small may cause severe complications. Hepatic embolization performed with gelatin powder has causes small vessel liver damage leading to biliary strictures. Even distal systemic complications, including fatal pulmonary complications, have been described.

In 2008, Maluccio *et al*. published their findings in 322 patients with inoperable HCC who underwent 766 transarterial embolizations utilizing small (50 μm) polyvinyl alcohol

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

or spherical embolic particles (40–120 μm). The median survival time was 21 months, with 1-, 2-, and 3-year overall survival rates of 66%, 46%, and 33%, respectively. Okuda stage, extrahepatic disease, diffuse disease (≥5 tumors), and tumor size were independent predictors of survival on multivariate analysis.

Chemoembolization is defined as the infusion of a mixture of chemotherapeutic agents with or without ethiodized oil followed by embolization with particles as described in this chapter. By occluding the tumor vessels after administration of chemotherapeutic agents, the goal is to obtain arterial stasis of the chemotherapeutic agent at the tumor site and also to induce concomitant ischemia. It has been reported that the tissue concentrations of the chemotherapeutic agents within tumors is as high as 40 times that of the surrounding normal liver parenchyma. Due to variations in transarterial techniques, in embolic materials, and in the combinations of chemotherapeutic agents and its doses (primarily doxorubicin, cisplatin, and mitomycin), no standardized protocol has been adopted. Marelli *et al*. (2007) reviewed 175 cohorts and randomized trials testing transarterial therapies and reached the conclusion that no chemotherapeutic agent appeared better than any other. Despite this, chemoembolization has been demonstrated to be effective with inoperable HCC. In 2002, Llovet *et al*. (2002) and Lo *et al*. (2002), both demonstrated, in their prospective randomized controlled trials, that chemoembolization improved survival of stringently selected patients with unresectable HCC over conservative treatment. Llovet *et al*. demonstrated that in 40 patients with Child–Pugh class A or B and Okuda stage I or II, survival probabilities at 1 year and 2 years were, respectively, 75% and 50% for embolization, 82% and 63% for chemoembolization, and 63% and 27% for control (chemoembolisation vs. control, $P = 0.009$). Lo *et al*. also reported findings of a select group of patients with unresectable HCC treated with chemoembolization that resulted in a marked tumor response, and the actuarial survival was significantly better in the chemoembolization group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; $P = .002$).

A more controlled and sustained method of releasing chemotherapy is thought to be obtained with chemoembolization using drug-eluting beads. These beads, made of sulfonate-modified poly (vinyl alcohol) hydrogel or copolymer microsphere and loaded with chemotherapy (e.g., doxorubicin and irinotecan), are used for chemoembolization. Significant reductions of peak plasma concentrations have been described. Malagari *et al*. (2010) reported a randomized prospective study using drug-eluting bead (DEB) chemoembolization and bland chemoembolization of intermediate-stage HCC (HCC). At 6 months, a complete response was seen in 11 patients (26.8%) in the DEB-chemoembolization group and in 6 patients (14%) in the bland embolization group; a partial response was achieved in 19 patients (46.3%) and 18 (41.9%) patients in the DEB-chemoembolization and bland embolization groups, respectively. Recurrences at 9 and 12 months were higher for bland embolization (78.3% vs. 45.7%) at 12 months. Time to progression (TTP) was longer for the DEB-chemoembolization group (42.4 ± 9.5 and 36.2 ± 9.0 weeks), at a statistically significant level ($P = 0.008$).

The final embolic material to be discussed is radioembolization. Glass or resin microspheres embedded with radioactive isotope 90Y are directly infused into the hepatic arteries feeding the tumor. The microspheres are smaller than other embolic material ranging from 20 to 60 μm, allowing them to embed within the aberrant peripheral vascular plexus of the tumor tissue. Yttrium-90 is a pure beta-emitter with a half-life of 64.2 hours. The tissue penetration range of the emissions is 2.5 to 11 mm. The treatment is also categorized as brachytherapy requiring dosimetry planning, administration and delivery of radioactive material and adjustment of dose depending on tumor and hepatic volume as well as pulmonary shunting. The radiation dose administered can be high as 150 Gy. TheraSphere (glass) is approved by the US Food and Drug Administration under humanitarian device exemption for the treatment of unresectable HCC. SIR-Sphere (resin) has full premarketing approval for the treatment of colorectal metastases in conjunction with intrahepatic FUDR. Both are being used for treatment of multiple types of liver cancers either via oversight by the local Institutional Review Board or via off-label endovascular catheter-based infusion. Carr (2004) has reported, in 65 patients with unresectable HCC treated with Y90, that a median survival for Okuda stage I patients ($n = 42$) was 649 days (historical comparison: 244 days) and for Okuda stage II patients ($n = 23$) was 302 days (historical comparison: 64 days).

- **So, which transarterial treatment options will be best for this patient?**

There are limited comparative transarterial studies evaluating advanced HCC patients. No randomized controlled trial combines all transarterial modalities. Indeed, even to propose a randomized controlled trial looking at survival between chemoembolization versus radioembolization, Salem *et al*. (2011) indicated that recruitment will require over 1000 patients to be statistically relevant.

In 2002, Llovet *et al*. and Lo *et al*. have demonstrated that chemoembolization had survival benefits in patients with unresectable HCC when compared to best supportive care. As mentioned above, Marilli *et al*. (2007) report their meta-analysis of nine randomized controlled trials confirmed that chemoembolization improves survival; but a meta-analysis of chemoembolization versus bland embolization alone demonstrated no survival difference. Kooby *et al*. (2010) reported a single-center retrospective study concluding that chemoembolization and radioembolization provided similar

effectiveness and toxicity in patients with unresectable HCC. In 2011, Salem *et al*. (2011) reported retrospective review of 122 patients who received chemoembolization and 123 patients who received radioembolization. Although time-to-progression was longer following radioembolization than chemoembolization (13.3 months vs. 8.4 months; $P = 0.046$), median survival times were not statistically different (17.4 months vs. 20.5 months; $P = 0.232$). As one can see, it is difficult to say which transarterial technique has better overall survival over another. However, it is clear that transarterial technique is better than best supported care for patients with advanced HCC.

- **What types of side effects, postembolization syndrome, postradioembolization syndrome, and complications can my patient experience?**

A set of expected symptoms for all patients undergoing embolization is the postembolization syndrome (fever, pain, nausea, vomiting, and leukocystosis), which may occur in up to 90% of patients after the procedure. Lance *et al*. (2011) reported that although the rate of postembolization syndrome was similar in the two groups, the degree of severity of the syndrome was significantly worse in the chemoembolization patients (over radioembolization patients), with significantly more patients requiring additional hospitalization and treatment ($P = .02$). After the initial treatment, patients who underwent chemoembolization were significantly more likely to have an unplanned extended hospitalization of >2 days ($P = .004$).

Postradioembolization syndrome comprises fatigue, nausea, vomiting, anorexia, fever, abdominal discomfort, and cachexia. The reported incidence of postradioembolization syndrome ranges from 20% to 50%. These are generally not severe enough to require hospitalization.

Chemoembolization also can have systemic toxicities, including alopecia, myelosuppression, leukopenia, and anemia. Brown *et al*. (2006) in the clinical practice guidelines reported the following chemoembolization complication rates requiring hospitalization:

Liver failure	2.3%
Abscess with functional sphincter of Oddi	1–2%
Abscess with biliary–enteric anastomosis, biliary stent, or sphincterotomy with premedication	0–15%
Surgical cholecystitis	<1%
Biloma requiring percutaneous drainage	<1%
Gastrointestinal hemorrhage or ulceration	<1%
Death within 30 days	2–4%

Complications associated with radioembolization have been discussed in detail. Hepatic toxicity as a complication of radioembolization can be difficult to assess due to the preexisting hepatic disease that may be progressing. Changes in the hepatic panel (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, albumin, and bilirubin) are monitored. Although rare, hepatic toxicity may be severe and can lead to significant morbidity and mortality. Abnormal hepatic function at baseline, patient's age, and the amount of activity delivered may predispose patients to the hepatotoxic effects of radioembolization. Kennedy *et al*. observed radiation-induced liver disease (a syndrome of elevated liver enzymes, anicteric hepatomegaly, and ascites) in 4% of patients after radioembolization with resin radioembolization.

Radioembolization induced biliary complications are uncommon. They include radiation-induced cholangitis and occasionally require drainage of bilomas or abscesses and cholecystectomies. Less than 2% of patients needed unplanned intervention prompted by biliary sequelae.

If the tumor contains arteriovenous shunting allowing direct passage of the microspheres into the lungs, radiation pneumonitis may occur, leading to restrictive pulmonary dysfunction. This has been described when the lung shunt fraction is greater than 13% when assessed by 99mTechnetium-labeled macroaggregated albumin (Tc-MAA) scan. An absolute contraindication to radioembolization is the predicted administration of a dose $\geq$30 Gy to the lungs in a single treatment or greater than 50 Gy as a cumulative dose on multiple treatments. The incidence of radiation pneumonitis is well below 1%.

Gastrointestinal complications mostly occur due to nontarget particle distribution. Meticulous mapping of the blood vessels to look for aberrant vasculature can prevent the occurrence of the inadvertent spread of microspheres to the gastrointestinal tract. Murthy *et al*. (2007) described a review of the reported 1140 patients in the literature where abdominal toxicities were reported; the median incidence of abdominal symptoms was six patients per reported series and 25% (range: 1% to 45.5%) for the entire cohort. The median reported ulceration rate was 8% (range: 0% to 20%) with 6% (0.4% of the entire cohort) requiring surgical intervention. Prophylactic use of proton pump inhibitors and sucralfate has been advocated.

Case study 92.2

A 45-year-old patient with liver dominant colorectal cancer has failed the standard lines of systemic chemotherapy. The liver lesions are too numerous for percutaneous or surgical ablative therapy. His ECOG status is 1, and liver functions are within normal limits.

• **Outside of systemic therapy, what are the types of locoregional therapy that are available?**

For liver-dominant metastatic colorectal carcinoma (mCRC), hepatic artery infusion (HAI) of chemotherapy, chemoembolization, and radioembolization have been described.

In the past several decades, multiple prospective randomized phase III clinical trials have been published to compare systemic treatment versus HAI therapy for mCRC. Most studies revealed some form of positive tumor response with the HAI. However, only a few studies showed benefit in overall survival. In a published, randomized, multiinstitutional trial evaluating HAI (FUDR with leucovorin or dexamethasone) versus systemic bolus fluorouracil and leucovorin in patients with mCRC, overall survival was significantly longer for HAI versus systemic treatment (median: 24.4 vs. 20 months; $P = .0034$), as were response rates (47% and 24%; $P = .012$) and time to hepatic progression (THP; 9.8 vs. 7.3 months; $P = .034$).

HAI also has been report for conversion of patients with unresectable liver CRC metastases to resectability. Kemeny *et al*. (2009) looked at conversion with HAI plus systemic oxaliplatin and irinotecan. Forty-seven percent of 49 patients were able to undergo resection in patients with extensive disease (98% with bilobar disease and 86% with greater than six segments involved). Their conclusion was that even patients with extensive hepatic metastases from CRC, whether previously treated or untreated with chemotherapy, may become resectable with combined therapy using hepatic artery infusion and systemic chemotherapy.

Recently, Arai *et al*. (2012) reported phase I/II study treatment of 25 patients who have mCRC by using a combination of HAI of fluorouracil and systemic irinotecan. Grade 3 or higher adverse events were noted which included hyperglycemia (15%), elevated γ-glutamyl transpeptidase levels (15%), and neutropenia (9%). The response rate and median survival time were 72% and 49.8 months (95% CI: 27.5–78.1 months), respectively. They concluded that delivery of fluorouracil through HAI and systemic irinotecan yielded favorable safety, response rate, and survival results.

Chemoembolization for liver mCRC can be performed with doxorubicin alone or as the combination of mitomycin C, doxorubicin, and cisplatin mixed with lipiodol followed by the injection of bland embolic particles to prevent washout of the drug and to induce ischemic necrosis. Ideal patients for chemoembolization are those with good performance status, preserved liver function, and no evidence of vascular invasion or limited extrahepatic metastasis. Albert *et al*. (2011) reported survival after chemoembolization for mCRC in 121 patients. Median survival was 33 months from diagnosis, 27 months from development of liver metastases, and 9 months from chemoembolization. Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy (11–12 months) than after third- to fifth-line therapies (6 months) ($P = .03$). Presence of extrahepatic metastases did not adversely affect survival ($P = .48$). Their conclusion was that chemoembolization provided local disease control of hepatic metastases after 43% of treatment cycles. Median survival was 27 months overall, and 11 months when initiated for salvage after failure of second-line systemic therapy.

Vogl *et al*. (2009) reported treatment of 463 patients with unresectable mCRC that did not respond to systemic chemotherapy with repeated chemoembolization in 4-week intervals. A mean of 5.3 treatment sessions per patient was noted. Sixty-seven percent had multiple (five or more) metastases, and 14.3% had three or four metastases. The chemotherapy protocol consisted of mitomycin C alone ($n = 243$), mitomycin C with gemcitabine ($n = 153$), or mitomycin C with irinotecan ($n = 67$). The 1-year survival rate after chemoembolization was 62%, and the 2-year survival rate was 28%. Median survival from date of diagnosis of liver metastases was 38 months and from the start of chemoembolization treatment was 14 months. There was no statistically significant difference between the three treatment protocols. They concluded that chemoembolization is a minimally invasive therapy option for palliative treatment of liver metastases in patients with colorectal cancer, with similar results among three chemoembolization protocols.

The use of drug-eluting beads to treat mCRC to liver also has been reported. Martin *et al*. (2011) looked at efficacy of irinotecan preloaded drug-eluting beads (DEBIRI) in metastatic colorectal cancer refractory to systemic chemotherapy. They reviewed 55 patients who had received prior systemic chemotherapy and who underwent a total of 99 DEBIRI treatments. The number of DEBIRI treatments ranged from 1 to 5. The median treatment dose was 100 mg (range: 100–200 mg), with total hepatic treatment of 200 mg (range: 200–650 mg), with 86% of treatments performed as lobar infusion and 30% of patients treated with concurrent simultaneous chemotherapy. Response rates were 66% at 6 months and 75% at 12 months. Overall survival in these patients was 19 months, with progression-free survival of 11 months. They concluded that chemoembolization with DEBIRI was safe and effective in treatment of metastatic colorectal cancer (MCC) refractory to multiple lines of systemic chemotherapy.

Safety and efficacy of yttrium-90 (Y90) radioembolization treatment in patients with liver-dominant colorectal metastases have been well documented. Gray *et al*. in 2001 reported the use of Y90 resin microspheres as adjunctive therapy to hepatic arterial infusion pump FUDR (floxuridine) administration demonstrated compelling results in a phase III randomized format utilizing 5-FU–based hepatic arterial infusional chemotherapy with and without Y90. They reported significant size-based criteria response (PR+CR) (44% vs. 17.6%; $P < .01$) and carcinoembryonic antigen response (72% vs. 47%; $P < .005$). One-, 2-, 3-, and 5-year survival for patients receiving SirSpheres was 72%, 39%, 17%, and 3.5%, compared to 68%, 29%, 6.5%, and 0% for infusional chemotherapy alone, with no significant reported toxicity and a Cox survival analysis in favor of patients receiving Y90.

Mulcahy *et al*. (2009) described 72 patients with unresectable hepatic colorectal metastases treated with a targeted absorbed dose of 120 Gy. Treatment-related toxicities included fatigue (61%), nausea (21%), and abdominal pain (25%). Grade 3 and 4 bilirubin toxicities were observed in 9 of 72 patients (12.6%). The tumor response rate was 40.3%. The median THP was 15.4 months, and the median response duration was 15 months. Overall survival from the first Y90 treatment was 14.5 months. Tumor replacement ($\leq$25% vs. >25%) was associated with significantly greater median survival (18.7 months vs. 5.2 months). The presence of extrahepatic disease was associated negatively with overall survival (7.9 months vs. 21 months). Overall survival from the date of initial hepatic metastases was 34.6 months. A subset analysis of patients who had an ECOG performance status of 0 demonstrated a median survival of 42.8 months and 23.5 months from the time of hepatic metastases and Y90 treatment, respectively. They concluded that Y90 liver therapy appears to provide sustained disease stabilization with acceptable toxicity. Asymptomatic patients with preserved liver function at the time of Y90 appeared to benefit most from treatment.

Hendlisz *et al*. (2010) analyzed a prospective, multicenter, randomized phase III trial in 44 patients with unresectable, chemotherapy-refractory liver-limited mCRC comparing intravenous fluorouracil (Arm A) and radioembolization plus intravenous FU (Arm B) until hepatic progression. The primary endpoint was time to liver progression (TTLP). Median TTLP was 2.1 and 5.5 months in arms A and B, respectively (hazard ratio (HR) = 0.38; 95% CI: 0.20 to 0.72; $P = .003$). Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median overall survival was 7.3 and 10.0 months in arms A and B, respectively (HR = 0.92; 95% CI: 0.47 to 1.78; $P = .80$). They concluded that radioembolization with (90)Y-resin microspheres plus FU is well tolerated and significantly improves TTLP and TTP compared with FU alone. This procedure is a valid therapeutic option for chemotherapy-refractory liver-limited mCRC.

Selected reading

Hendlisz A, Van den Eynde M, Peeters M, *et al*. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28(23):3687–94.

Llovet JM, Real MI, Montana X, *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–9.

Lo CM, Ngan H, Tso WK, *et al*. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002 May;35(5):1164–71.

Memon K, Lewandowski RJ, Riaz A, *et al*. Gastrointestinal cancers (AB Benson, section editor); chemoembolization and radioembolization for metastatic disease to the liver: available data and future studies. Curr Treat Opt Oncol. 2012;13:403–15.

Salem R, Thurston KG. Radioembolization with Yttrium-90 microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. J Vasc Interv Radiol. 2006;17:1251–78.

CHAPTER 93

Anal cancer

Rob Glynne Jones
Mount Vernon Cancer Centre, Northwood, UK

Introduction

Squamous cell cancer of the anus (SCCA) is a rare disease that makes up approximately 2% of all cancers in the lower alimentary tract. The incidence is increasing, with 5820 new cases registered in the United States in 2011. Squamous cell carcinoma (SCC) is commonly associated with human papilloma virus (HPV) infection (usually HPV16 or HPV18). Other risk factors include cigarette smoking, a history of receptive anal intercourse, a history of other HPV-related cancers, human immunodeficiency virus (HIV) infection, and immunosuppression after solid organ transplantation.

SCCA usually presents as and remains a loco-regional disease. The majority of patients have symptoms for long periods of time before diagnosis. Nonsurgical treatment with chemoradiation (CRT) is highly effective. Few develop distant metastases unless there is recurrence at the primary site. Hence, local control without the recourse to a colostomy and enjoyment of an optimal quality of life are the primary aims of treatment.

Three phase III trials showed that radiotherapy (RT) with concurrent 5-fluorouracil (5FU) and mitomycin (MMC) achieves better outcomes in terms of local control and recurrence- or disease-free survival (RFS and DFS, respectively) compared to RT alone, or RT combined with 5FU alone. Phase III trials by the Radiotherapy Therapy Oncology Group RTOG 98-11 and the Action Clinique Coordonees en Cancerologie Digestive ACCORD-03 phase III trial failed to show benefit for the addition of cisplatin-based neoadjuvant chemotherapy (NACT) prior to CRT in terms of colostomy-free survival (CFS). In the RTOG 9811 trial, the cisplatin arm confers a worse DFS and a higher colostomy rate. The ACCORD-03 trial also failed to show a benefit in CFS from an increase in the radiotherapy boost dose. Preliminary results of the United Kingdom National Anal Cancer Trial (ACT II) confirm the standard of 5FU and MMC CRT. Results show 3-year RFS rates overall of 73% (75% in T1/T2 tumors, and 68% for more advanced T3/T4 tumors). The dose and treatment schedule used in the ACT II trial are now the current standard of care in the United Kingdom.

However, the rarity and the different behavior and natural history (depending on whether SCCA originates predominantly at the anal margin, at the anal canal, or above the dentate line) provide limited experience for any individual oncologist.

There have been some recent developments in our understanding of the molecular biology and processes that lead to anal cancer. There have also been some notable successes in prevention, imaging, and treatment. Hence the author hopes to provide some information from the randomized and retrospective trials that can assist the medical and radiation oncologist in the practical management of this unusual cancer.

Case study 93.1

A 50-year-old woman presents with a 6-month history of pain on defecation and rectal bleeding; she was prompted to seek medical advice by a UK television advertisement. There is no significant past medical history, but the patient is a cigarette smoker. On digital rectal examination (DRE), an anterior mass is palpable extending from 11 to 3 o'clock in the anal canal, and from 1 cm within the anal verge to approximately 4.5 cm superiorly (i.e., measuring approximately 2 × 3.5 cm). No enlargement of the inguinal nodes is palpable. Colonoscopy reveals a mass in the anal canal, but no other proximal lesions. Biopsy of the mass shows a poorly differentiated SCC. The patient is therefore clinically staged as having a cT2N0 SCC of the anal canal.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

1. Should everyone with anal cancer, especially the young, be tested for HPV/p16?

Exposure to HPV infection is common, occurring in a significant proportion of the overall population who are sexually active and have not been vaccinated. HPV infection is closely correlated with SCCA. The presence of the HPV genome has been identified in 80–85% of cases, and it is similar to that seen in cervical and vulval carcinoma in women. HPV16 is the commonest high-risk HPV genotype found in anal cancer. In HPV-positive human cancers, two viral oncoproteins, E6 and E7 (which target cellular tumor suppressors), are preferentially expressed via integration of the viral genome into the host DNA. E6 binds to p53, leading to deregulation of DNA damage and apoptotic pathways. E7 targets pRb for degradation, leading to an increase in cell proliferation and genomic instability.

As in oropharyngeal cancer, HPV16-positive anal cancer patients appear to have better outcomes than other subtypes, although most of the evidence has been derived from small retrospective studies. The cell cycle regulator p16 is overexpressed in high-risk-HPV-related cervical cancers, which may represent a simple surrogate biomarker for identifying SCCs harboring HPV DNA. A recent UK study examined samples from 153 patients with anal cancer for p16 with immunohistochemistry, and found 37/137 patients (27%) with moderate or strong p16 staining subsequently relapsed. In contrast, 10 out of 16 (63%) patients with absent or weak staining relapsed.

2. Do HPV vaccines improve outcomes in invasive SCCA?

Safe and effective vaccines (HPV2 and HPV4) are commercially available for the prevention of HPV16 and HPV18 infection. Recent evidence suggests that the efficacy of these vaccines against oncogenic HPV is more than 90% for anal intraepithelial neoplasia. However, prophylactic vaccines do not prevent anal cancers in patients already infected with high-risk HPVs, or in individuals who already have anal cancer. Hence HPV vaccines will not improve outcomes at this stage. In these groups, novel therapeutic vaccines to target the HPV oncogenes or the cellular pathways they affect rather than HPV are under investigation. These vaccines potentially could improve clinical outcome for patients with anal cancer, as with other HPV-associated cancers.

3. Should cancers of the anal margin, anal canal, and rectum be treated differently or the same?

The definitions of the anal canal and anal margin used by the National Comprehensive Cancer Network (NCCN) separate the anal canal from the rectum with the landmark of the upper border of the anal sphincter and puborectalis muscles. The anal canal extends 3–5 cm in length to the anal verge. The anal margin includes the perianal skin over a 5 cm radius from the anal verge. In practice, at diagnosis most anal carcinomas have extended such that their point of origin is uncertain, and the distinction between anal canal and anal margin tumor is therefore often impossible. Local excision of anal margin cancers is possible for small lesions (usually <1 cm) allowing 1 cm surgical clearance, but it should be performed by specialist surgeons (see Question 7, this chapter).

4. Are there any biomarkers?

For more advanced stages of anal cancer, there remains considerable heterogeneity in terms of outcomes. Biomarkers that affect these outcomes would be useful to provide predictive and prognostic information and, in turn, inform individualized therapies. However, most studies have focused on the identification of factors that predict cytotoxic drug response and/or radiosensitivity. These studies have invariably analyzed only a limited number of markers in small numbers of patients, with a variety of treatment regimes, and their results can be considered preliminary. So further refinement is needed in this field.

A recent systematic review examined 29 different biomarkers belonging to nine different functional classes: tumor suppressors, epidermal growth factor receptor (EGFR), apoptosis regulation, proliferation index, angiogenesis, tumor-specific markers (e.g., SCCAg and CEA), Hedgehog signaling, and telomerase. Tumor suppressor genes *p53* and *p21* were the only biomarkers that were prognostic in more than one study. In anal cancer, p53 protein function may be modified either by mutations in its gene or by E6 viral oncoprotein of the HPV virus. In an analysis of 240 patients randomized in the UKCCR ACT I anal cancer trial, the presence of mutated p53 predicted for a poorer cause-specific survival. Recent data regarding p16 and serum SCC antigen are promising, but in summary, there are no current biomarkers that consistently predict sensitivity to chemoradiation.

5. What is the role for sentinel lymph node biopsy (SLNB) in staging anal cancers?

SNLB is validated in lymph node (LN) staging of small breast tumors with the aim of avoiding a formal axillary dissection. In anal cancer, the rationale for SLNB is to spare the patient formal inguinal irradiation and to avoid the skin morbidity associated and the potential for high-radiation doses to the femoral heads. An early systematic review of five published series (only 83 patients) evaluated the outcome of SLNB of non-enlarged inguinal nodes in patients with anal cancer. Only 21% of sentinel nodes contained tumor.

Because the initial treatment has been nonsurgical for the past 25 years, we don't know the true LN status of anal cancer. Currently, in the patient with clinically impalpable nodes, we rely on computed tomography (CT) and magnetic resonance imaging (MRI) in T1/T2, where the risks of LN involvement are low. Conventionally, routine biopsy is only performed for clinically palpable nodes or those enlarged greater than 10 mm on CT or MRI.

SLNB has not achieved its initial potential in anal cancer, partly because MRI and positron emission tomography (PET) are increasingly in the routine diagnostic work-up. Also acute morbidity is less with more conformal radiation therapy (RT) techniques (e.g., intensity-modulated RT (IMRT)) currently being used. Formal biopsy or SLNB can reveal micrometastatic spread of disease compared with the spatial resolution of CT and PET, typically in the range of 5–10 mm, but micrometastatic involvement may not be relevant if the patient is going to receive low-dose inguinal irradiation. Also, there are no validated management strategies to stratify treatment for the findings of macroscopic nodal involvement, microscopic involvement, and the presence of a few isolated cells in the light of SLNB.

There are also concerns that SLNB could prejudice the effectiveness of CRT because radiotherapy may require delay until healing is achieved. In one study of SLNB, 24% of patients had a postoperative complication in the groin. SLNB may also compromise the lymphatic drainage, and it may provoke lymphoedema if subsequent high-dose RT is required following a positive nodal finding on SLNB, compared to the low doses necessary for clinically uninvolved nodes. Current prophylactic doses are relatively low—in the region 30–36 Gy. Isolated inguinal failures in the ACT II study were very low for uninvolved nodes treated to 30.6 Gy, and late morbidity was slight for these patients. In contrast, we do not know the morbidity of irradiating to 50.4 Gy after a positive finding on SLNB, particularly as with some midline cancers some SLNB will require bilateral nodes to be removed.

In summary, SLNB may be more helpful in the setting of loco-regional recurrence after CRT to decide whether a radical inguinal dissection should be performed, when radical surgical salvage is envisaged.

6. After a local excision, what are acceptable surgical margins, whereby chemoradiation does not need to be administered?

Small, early cancers are sometimes diagnosed serendipitously following the removal of anal tags. Often piecemeal resection with numerous fragments makes this unevaluable. At other times, small lesions at the anal margin are subjected to excisional biopsy. Local excision may be considered for well-differentiated small tumors at or outside the anal margin that are less than 2 cm in size, are clinically and radiologically lymph node negative, and can be removed with a surgical clearance of greater than 5 mm. So superficial cancers (<6 mm depth) can usually be treated with surgery alone with acceptable surgical margins, and do not require chemoradiation. If attempted by surgeons less familiar with anal cancer pathology, a positive margin may result. In summary, assessment of the integrity of the biopsy specimen should be documented. The size of the tumor in terms of the largest dimension, and the resection margins (specified in millimeters), both deep and at the periphery, are required to decide if local excision is adequate or further treatment is advisable. Hence, all the relevant resection margins should ideally be inked.

7. Is there a size criterion for identifying involvement of lymph nodes?

Involved nodes are often enlarged, hard, and palpable if superficial, but historical pathology studies, using a "clearing" technique, demonstrated that almost half of all involved pelvic lymph nodes were smaller than 5 mm in diameter.

Suspicious perirectal and internal iliac nodes on imaging are rarely biopsied, so there is a significant risk of false positives.

Historically, a diameter ranging from 6 to 15 mm has been used, with 10 mm being the most commonly used criterion for the upper limit of a normal lymph node, and this is supported by recent studies. The size criterion should be modified on the basis of the site of the nodes. Historical studies on healthy volunteers suggested that the 95th percentile for the diameter of normal nodes on CT was 7 mm for internal iliac nodes, 8 mm for obturator nodes, and 10 mm for external iliac nodes. A similar study with MRI suggested normal pelvic nodes were even smaller. In contrast, the normal size of benign inguinal lymph nodes is highly variable, often measuring up to 15 mm. Some recommend a size threshold of 8 mm (short-axis diameter) for pelvic nodes and 10 mm for abdominal retroperitoneal nodes.

Both the RTOG 0529 and Mistrangelo *et al*. (2011) described nodes >3 cm in size as large-volume macroscopic involvement and treated these to a higher radiotherapy dose (i.e., nodes up to 3 cm maximum in any direction received 50.4 Gy, but for involved nodes >3 cm the dose was 54 Gy).

Other criteria such as shape, central necrosis, and the degree of contrast enhancement in pelvic nodes are often useful, but they have not been completely validated. In addition, normal-sized but potentially involved nodes can be imaged on diffusion MRI. The signal intensity on MRI within a given node can be graded as hypo-intense, isointense, or hyperintense relative to muscle. Note may also be made of the pattern of signal intensity—homogeneous or mixed on the T1- and T2-weighted sequences.

In practical terms, given the limited accuracy of relying on a single criterion alone, it seems sensible to use a combination of all of these. We therefore carefully palpate the groins and perform a pelvic CT and MRI (using Royal College of Radiologist guidelines); that is, if the short axis diameter is greater than 15 mm for inguinal, and 10 mm for external iliac, 9 mm for common iliac, 8 mm for obturator, 7 mm for internal iliac, and 5 mm for perirectal nodes. Additional criteria as above contribute to the radiological diagnosis. Clearly abnormal nodes are assumed to be involved and treated to a high-radiation dose. Equivocal nodes are either biopsied or subjected to fine-needle aspiration cytology (FNAC) if accessible, and also PET–CT to clarify. If nodes are still equivocal, our anal radiology and radiotherapy team make a decision together.

8. What are the ideal planning target volumes in anal cancer?

It is beyond the scope of this chapter to provide a comprehensive clear practical guide to target delineation for every patient with anal cancer. Historically, anal cancer has been treated in all randomized trials with doses of 1.80 Gy per day, using a shrinking-field technique over the course of treatment covering much of the pelvis.

9. Do we always have to include the groins?

For early T1N0 cancers, particularly in patients with major comorbidities, we often omit the inguinal nodes since there is a low risk of failure (possibly <5%).

10. In giving radical chemoradiotherapy for anal cancer, what is the optimal radiation dose?

The optimal dose of radiation therapy for anal canal carcinoma is unknown. Norman Nigro (1984) originally utilized 30 Gy in his study. The randomized controlled trials (RCTs) provide information on loco-regional control, relapse-free survival, and colostomy-free survival, but have not generated quality-of-life data. Also critically, in these trials there are major differences in the treatment schedules (planning volumes and doses), not only between but also within the individual RCTs, partly because of a reliance of early response—either histopathogical or clinical—to decide the appropriate total radiation dose.

The RTOG 9811 required clinically positive inguinal nodes to be biopsied by either needle aspiration biopsy or excisional biopsy of a node if needle aspiration was negative. In contrast, pelvic nodes seen on CT scan did not require biopsy. All patients were intended to be treated with a daily dose of 1.8 Gy, 5 days per week, to a dose of 45 Gy in 25 fractions over 5 to 6.5 weeks (a ≤10-day break, as indicated, was permitted for skin intolerance). T1 cancers were excluded, but patients with T3, T4, or N+ lesions or T2 lesions with residual disease after 45 Gy should receive an additional 10–14 Gy (2 Gy per fraction) to a reduced field, hence radiation doses of up to 59 Gy, depending on the burden of primary and nodal disease. The ACCORD-03 (only 307 patients randomized in four arms) also explored using initial neoadjuvant chemotherapy with 5FU–cisplatin and a higher RT dose in a second randomization where the dose administered reflected the degree of response observed. Thus, the ACCORD 03 trial did not use an MMC 5FU CRT control arm. Several possible radiation doses were therefore administered according to response. The trial failed to show a benefit in CFS from an increase in the radiotherapy boost dose from 15 to 25 Gy.

Also, varying compliance with the planned treatment as defined by protocolized dose reductions of chemotherapy for toxicity, and the potential confounding by subsequent treatment and the availability and accessibility of timely salvage surgery, may also affect some of the observed treatment effects.

In addition, no randomized study clearly reports the site of local failure (in or out of field), or within the planning target volume (PTV), clinical target volume (CTV), or gross tumor volume (GTV). The total dose of radiation therapy for anal cancer continues to be evaluated. Although the total radiation dose is known to affect local control, the benefit of a high dose over 60 Gy may be doubtful, and a high-radiation dose may be associated with complications.

A RTOG pilot study (RTOG 92-08) tested radiation dose escalation within chemoradiation with 5FU–MMC escalating to 59.4 Gy in 1.8 Gy fractions over 9 weeks with a 2-week mandatory rest. The results were compared to the RTOG 87-04 trial in which patients were treated with 45 Gy in a continuous schedule plus the same chemotherapy regimen. This schedule with 59.4 Gy and a 2-week break led to a higher colostomy rate than expected (30% vs. 9%). There are no data on late effects.

For all these reasons, it is extremely difficult to generate dose–response curves for local control against poor function for the anal canal–sphincter mechanism from RCTs. So it is not possible to assess whether loco-regional failures represent inadequate clinical target volumes, or insufficient doses or efficacy of treatment.

Macroscopic disease

Although the total radiation dose is known to affect local control, the benefit of a high dose over 60 Gy is unproven, and a high-radiation dose may be associated with complications. We consider the primary GTV (which includes the anal canal) should be treated to a maximum of 54 Gy over 30 fractions, if concurrent chemotherapy is used. However, for T1 and nonbulky T2 tumors <4 cm, a dose of 50.4 Gy in 28 fractions is appropriate according to ACT II data. Doses

to involved nodes or regions should depend on the size of nodes. Some have suggested that involved nodes should receive 50.4 Gy if <3 cm, increasing to 54 Gy if ≥3 cm in any one diameter.

Microscopic disease

In the MD Anderson Cancer Center series, no patients who were initially node negative in the inguinal area and treated prophylactically to a prescribed dose of 30.6 Gy developed subsequent inguinal disease. In the ACT II study, only 7/940 patients developed an isolated inguinal recurrence, 16/940 an isolated pelvic nodal recurrence, and a further 5/940 developed synchronous inguinal and pelvic nodal recurrence, although it is unclear how many of these patients initially had palpable or involved nodes on imaging and were treated to full dose, and how many were uninvolved and treated prophylactically with a prescribed dose of 30.6 Gy.

11. Is there a role for neoadjuvant chemotherapy prior to chemoradiation in anal cancer?

Previous authors have suggested a role for cisplatin in the neoadjuvant setting, and population studies from Sweden suggest that neoadjuvant cisplatin has been widely used. A pilot study from the Cancer and Leukaemia Group B (CALGB-9281) in 45 patients with locally advanced anal cancer (T3–T4, bulky N2, or N3) investigated NACT with two cycles of cisplatin and 5FU followed by MMC and 5FU chemoradiation. The results with 4-year follow-up showed 61% disease-free survival and 68% overall survival.

Randomized trial evidence from the large RTOG 98-11 and ACCORD-03 phase III trials failed to show a benefit for novel neoadjuvant cisplatin-based chemotherapy strategies. Induction cisplatin and 5FU, despite high observed response rates, failed to improve local control, PFS, and CFS. The colostomy rate appears higher with the use of NACT cisplatin–5FU for patients with tumors 5 cm or more, and more mature data suggest that local control and DFS are also worse. Based on data from squamous cell cancer of the head and neck (SCCHN), future studies aiming to preserve anal function should assess whether induction chemotherapy with docetaxel, cisplatin, and 5FU followed by CRT in responders improves loco-regional control and CFS compared with an unselected approach of high-dose primary CRT in all eligible patients with T3–T4 or node-positive anal SCC.

12. Even chemoradiotherapy in anal cancer for T1 cancers?

Some have argued that a pooled analysis did not show a benefit for MMC in T1 tumors, and criticize the control arm in the ACT I study as being inadequate in terms of radiation dose. Many Europeans therefore continue to treat small T1 tumors in the anal canal with radiation alone, or even very occasionally brachytherapy alone.

13. What is the ideal chemotherapy partner for concurrent 5FU-based chemoradiotherapy in anal cancer: mitomycin C or cisplatin?

Chemoradiotherapy is considered the standard of care in anal cancer, and all the phase III trials used a continuous 4- or 5-day infusion of 5FU in the first and fifth weeks of radiotherapy in combination with either MMC or cisplatin. None have used a prolonged venous infusion or an oral fluoropyrimidine during the radiotherapy phase as in rectal cancer. Current guidelines (European Society for Medical Oncology and NCCN) recommend 5FU and mitomycin C in patients with anal cancer.

14. Are there new developments to integrate different chemotherapy agents?

Other combinations with platinum drugs have been investigated. A phase II trial at the MD Anderson Cancer Center has explored the combination of capecitabine and oxaliplatin with concomitant radiotherapy. Preliminary results suggest response rates of 91–100% and CFS of 100%

The EORTC 22011-40014 randomized phase I/II study (78 eligible patients) compared 5FU and MMC in combination with radiation versus MMC and cisplatin with radiation. The MMC–cisplatin arm used a schedule more associated with cervical cancer—25 mg/m^2 per week—giving a total of (25 mg/m^2 × 7) 175/mg/m^2. With a median follow-up of 2 years, the 1-year progression free survival was 76.3% in the control versus 94.2% in the MMC–cisplatin arm, and 1-year event-free survival was 74.4% versus 89.2%, respectively. This combination of MMC and cisplatin could be further evaluated, but it might be difficult to take into a phase III setting because of its limited compliance.

15. What assessments should be performed following radical CRT to confirm that the treatment has been successful, and when are they ideally performed?

Following radical CRT, clinical regression is often slow. Follow-up to assess response should start 6 to 12 weeks after the completion of CRT. Recommended methods of assessment include DRE, inguinal lymph node palpation, anoscopy, endoscopic ultrasound, MRI, and thoracoabdominal CT scan, especially for more advanced disease. Even though DRE alone might miss early local recurrences, controversy persists concerning the use of multiple random biopsies of normal-appearing tissue versus biopsy limited to suspicious lesions only. In practice, ulceration can cause concerns. The recent national UK trial (ACT II) collected

data on clinical response at all three time points (11, 18, and 26 weeks), and these data may define the optimal time point for assessment. PET at 1 month might enhance assessment of clinical response.

Patients should be evaluated for recurrence every 3 months in the first year, every 6 months in the second year for a period of 2 years, and subsequently every 6–12 months until 5 years, with clinical examination including DRE and palpation of the inguinal lymph nodes. Patients tend to relapse loco-regionally rather than at distant sites and within the first 2–3 years—with less than 1% of patients and less than 7% of all relapses after 3 years. Hence, some have argued for regular pelvic MRI surveillance in the first 3 years. Because of the rarity of metastatic disease, regular CT scans for metastatic surveillance outside trials remain controversial.

16. Are there newer targets and ongoing or anticipated trials?

Recent authors have advocated integration of biologically targeted agents. Squamous cell carcinoma of the anus commonly overexpresses EGFR, and Kras and BRAF mutations appear rare. As yet, there are no data regarding the efficacy of biologicals combined with chemoradiation, although several trials have been performed but not reported (ECOG E3205, AMC045, and a FNLCC trial). Preclinical data show that cetuximab increases radiation-induced apoptosis, and the effect of EGFR inhibition appears greater if administration is extended beyond the end of radiotherapy. So there may be a therapeutic role for EGFR inhibition using cetuximab as a single agent or in combination with irinotecan. Data on the efficacy of biological agents combined with chemoradiation are awaited.

Partial remissions have been observed in patients with wild-type K-ras with relapsed anal cancer using cetuximab as a single agent or cetuximab in combination with irinotecan, some of whom had been heavily pretreated. However, side effects of cetuximab include G3 diarrhea, which could prove a problem of overlapping toxicity with pelvic radiation. Cells that survive radical CRT may express factors that promote cell survival and aggressiveness by virtue of AKT activation, increased VEGF secretion, and enhanced transcription of EGFR and transforming growth factor alpha. Hence, a future clinical strategy could employ consolidation or maintenance treatment inhibiting EGFR after chemoradiation.

17. Is there a standard for palliative chemotherapy in the case of metastatic disease?

Approximately 10–20% of patients relapse with distant metastases. Prognosis for these patients is poor with only 10% of patients with distant disease surviving 2 years or more. Fit patients with metastatic or recurrent disease not amenable to surgery or radiofrequency ablation (RFA) should receive chemotherapy, but there is no international standard. The choice of chemotherapy is usually influenced by the patient's previous chemotherapy received for early disease, the disease-free interval, and performance status. Current NCCN guidelines recommend the use of cisplatin and infusional 5FU chemotherapy as first-line treatment, which offers approximately a 50% response rate. Responses are rarely complete and usually of short duration. In these circumstances, therapy is aimed at palliation.

Other potential agents include paclitaxel (a microtubule-stabilizing agent), which is active in other SCCs, such as cervical and head and neck cancers. As monotherapy paclitaxel is associated with moderate response rates, the combination of carboplatin and paclitaxel has been used in metastatic anal cancer. A recent retrospective analysis of 77 evaluable patients showed that the combination was associated with a PFS of 5 months and has a favorable toxicity profile.

There is a strong biological rationale and some preliminary evidence for targeting the EGFR pathway in anal cancer. In one study, 96% of invasive HPV-driven anal SCCs displayed strong membrane immunoreactivity to EGFR expression. EGFR is overexpressed in anal SCC and mutations in the downstream effectors KRAS and BRAF appear to be a rare event. Cytotoxic combinations with Cetuximab in anal cancer have been reported to be effective in small case series.

Conclusion

In anal cancer, a multidisciplinary approach is essential with close cooperation and communication required between the surgeon, radiologist, medical oncologist, radiation oncologist, pathologist, and nursing specialists. The results of six randomized phase III trials in anal cancer confirm that the paradigm of external beam radiation therapy with concurrent 5FU and mitomycin remains the standard of care. However, we need much more data regarding severe complication rates and the proportion of patients who maintain a functioning anus.

Selected reading

Ajani JA, Winter KA, Gunderson LL, *et al*. Fluorouracil, mitomycin and radiotherapy vs fluorouracil, cisplatin and radiotherapy for carcinoma of the anal canal: a randomised controlled trial. JAMA 2008;199:1914–21.

Benson AB 3rd, Arnoletti JP, Bekaii-Saab T, *et al*. Anal carcinoma, version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2012 Apr;10(4):449–54.

Glynne-Jones R, Sebag-Montefiore D, Adams R, *et al*. Prognostic factors for recurrence and survival in anal cancer: generating hypotheses from the mature outcomes of the first United

Kingdom Coordinating Committee on Cancer Research Anal Cancer Trial (ACT I). Cancer 2012 Sep 25. doi:10.1002/cncr.27825. [Epub ahead of print]

Gunderson LL, Gunderson LL, Winter KA, *et al*. Long-term update of US GI Intergroup RTOG 98-11 phase iii trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012 Dec 10;30(35):4344–51.

Kochhar R, Plumb AA, Carrington BM, *et al*. Imaging of anal carcinoma. Am J Roentgenol. 2012 Sep;199(3):W335–44.

For further information on this area please also consult Chapters 112, 121, 134, 135, and 139

PART 5

Genitourinary Oncology

CHAPTER 94

Renal cancer: tumor diversity, molecular taxonomy, and prognostic algorithms

Henry J. Conter[1] and Eric Jonasch[2]

[1]University of Western Ontario, London, ON, Canada
[2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 94.1

A 49-year-old Caucasian woman is diagnosed with stage IV clear cell renal cell carcinoma (RCC). The patient has personally sought out genetic sequencing of her tumor and presents to you with the report created by the sequencing provider.

1. Aside from von Hippel–Lindau (VHL), which of the following genetic mutations are commonly found in clear cell renal cancer?

A. c-met
B. TP53
C. PBRM1
D. No other mutations

VHL loss of heterozygosity, inactivating mutations, or methylation may be present in 50–80% of conventional RCC. These mutations result in hypoxia-inducible factor (HIF) overexpression with downstream upregulation of vascular endothelial growth factor (VEGF). Although a multitude of other mutations have been identified, *PBRM1,* involved in chromatin modification, is the second most common mutation found in conventional renal cancer (21%). *PBRM1* mutation may portend a worse prognosis. *TP53* mutations are present in 6% of clear cell RCC.

Case study 94.2

A 24-year-old black man is referred for a newly diagnosed solitary renal mass discovered after presentation to the local emergency room with flank discomfort and hematuria. He states that he has had night sweats and unexplained weight loss of 20 lbs. over the last 3 months. On further questioning, you learn that his fraternal grandparents died of colon cancer and prostate cancer, and his maternal grandparents both died of heart disease. His sister has been diagnosed with sickle cell disease, but is otherwise healthy.

1. Which of the following is true?

A. Biopsy will most likely reveal medullary RCC.
B. Genotyping will most likely reveal the presence of a mutation in chromosome 3.
C. Biopsy will likely demonstrate a benign tumor.
D. Genotyping will likely demonstrate a mutation in chromosome 17.

Medullary RCC typically affects young individuals, under the age of 30, with the sickle cell trait. Medullary renal cancer tends to be highly aggressive and presents with distant metastases. The genetic signature of renal medullary cancer relates more closely with urothelial carcinoma of the renal pelvis than conventional RCC. Chromosomal abnormalities in 3 and 17 are associated with VHL disease and Birt Hogg Dube (BHD) syndrome, respectively. A mutation in folliculin, found on chromosome 17p, is the driver mutation in patients with BHD. BHD is associated with spontaneous pneumothoraces, fibrofolliculomas, trichodiscomas, achrocordons, and an array of renal tumors, including chromophobe renal cancer, clear cell renal cancer, and oncocytomas.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 94.3

A 57-year-old Hispanic woman presents to your office with type I papillary RCC with documented metastatic disease in the lungs, liver, and thoracic lymph nodes. She was previously treated with pazopanib, axitinib, and everolimus, but had progression on all three agents. She is being considered for a phase I clinical trial.

1. Which of the following trials has the best biologic rationale?

A. Vandetinib
B. Bevacizumab + erlotinib
C. Cabozantinib
D. Ridaforolimus

Dysregulation of the MET pathway is typical of papillary RCC type I. Activating MET oncogene mutations are found in most hereditary papillary type 1 kidney cancers and in 13% of sporadic cases. Cabozantinib is a multitargeted kinase inhibitor of MET and VEGF receptor 2 (VEGFR2), which may both play a role in this disease. Both erlotinib and gefitinib have been studied in the phase II setting, but were not considered successful drug candidates, indicating empirically that epidermal growth factor receptor (EGFR) may play less of a role in the management of these patients; consequently, vandetinib, an EGFR and RET ("rearranged during transfection") inhibitor, would not be considered an ideal phase I choice. Ridaforolimus is a mammalian target of rapamycin (mTOR) inhibitor.

Case study 94.4

A 62-year-old Caucasian man was recently diagnosed with a 3 cm renal mass found incidentally while undergoing a computed tomography (CT) scan for surveillance of his previously treated follicular lymphoma (currently in remission). Given the mass' concerning appearance, he underwent partial nephrectomy. Preliminary pathology was reported as spindle cell sarcoma, with high cellularity and atypical cells. A final report supported possible malignant fibrous histiocytoma.

1. Which of the following would confirm the diagnosis?

A. Whole-exome sequencing
B. Conventional karyotyping
C. Absence of renal cell component
D. Absence of epithelial markers

Despite the spindle cell appearance, sarcomatoid RCC does not usually express mesenchymal markers. Although frequently mixed with an identifiable subtype of kidney cancer, renal tumors can be present with 100% sarcomatoid cells on histopathological evaluation. Clinical history, tumor location, and the presence of epithelial markers are sufficient to make the diagnosis of sarcomatoid renal cancer. Whole-genome sequencing or conventional karyotyping may be useful in identifying the underlying cell of origin; each histological RCC subtype has a distinct copy number profile that can be elucidated from the nonsarcomatoid elements present in the tumor.

Case study 94.5

A 43-year-old Caucasian woman underwent partial nephrectomy for a 4 cm mass. This limited-stage renal mass was found on CT scan after she presented to her primary care physician with a 1-month history of flank discomfort. Pathology showed clear cell RCC with mixed papillary RCC.

1. Which of the following tests would confirm the diagnosis?

A. Xp11 translocation by florescence in situ hybridization
B. Hypodyploidy of multiple chromosomes
C. Genetic analysis for 1q alteration
D. t(2;10)(p23;q22) translocation

Mixed clear cell and papillary RCC should prompt an investigation for translocation RCC. Although many abnormalities in the TFE3 gene expression have been identified, they all involve a break at Xp11. FISH has been shown to have high sensitivity and specificity for the Xp11 translocation, but it may underdiagnose translocation renal carcinoma.

Case study 94.6

A 57-year-old, previously healthy woman presented to her primary care physician with hematuria and sudden-onset flank pain. A renal ultrasound demonstrated nephrolithiasis and a 6 cm left kidney mass. She underwent a radical nephrectomy and was found to have a follicular malignancy, resembling follicular thyroid cancer. Further workup with CT chest and abdomen showed retroperitoneal lymphadenopathy. She is referred to medical oncology for systemic therapy.

1. Which of the following characterizes the prognosis of this patient?

A. With VEGF inhibition, median progression-free survival approaches 11 months.

B. With radioactive iodine therapy, the patient may achieve long-term remission.

C. With mTOR inhibition, median progression-free survival approaches 11 months.

D. With surgical resection, the patient may achieve long-term remission.

Follicular RCC resembles follicular carcinoma of the thyroid. It should be considered an indolent disease given its low potential for metastatic spread. However, even after metastases have developed, it may be curable by surgical resection. A case of follicular RCC presenting with metastatic disease was treated with sunitinib for 1 year followed by surgical resection, and has been disease free for over 4 years.

Case study 94.7

A 25-year-old Hispanic woman was recently diagnosed with a 6 cm clear cell RCC. She underwent laproscopic nephrectomy. Final pathology confirmed clear cell RCC with areas of papillary RCC. Her family asks about performing a genetic analysis of the tumor, and whether information from this analysis can provide prognostic information.

1. Which of the following is accurate with regard to the work-up and prognosis of this patient?

A. If she is found to have an Xp11 translocation in her tumor, her prognosis would be worse than if she is not found to have any genetic aberration.

B. If she is found to have an Xp11 translocation in her tumor, her prognosis may be better than average.

C. If she is found to have a somatic *VHL* mutation, then the diagnosis of clear cell carcinoma will be confirmed and her prognosis is better than average.

D. Clinically, her prognosis is unrelated to the genetic abnormality and she does not require testing.

Given the mixed papillary and clear cell components of this renal cancer, confirmation of translocation RCC should be made. In general, translocation renal cancers have a more indolent clinical course compared to conventional and papillary RCC. Younger age at diagnosis and female sex appear to be good clinical prognostic features of newly diagnosed translocation renal carcinoma. Clear cell RCC is considered a midpoint in overall prognosis when considering the totality of potential histological subtypes. In a 25-year-old person with clear cell carcinoma, especially if there is evidence for multifocality, a germline *VHL* mutation needs to be considered, and genetic testing to rule out VHL disease should be performed.

Case study 94.8

A 63-year-old woman presented to her primary care physician with night sweats and significant weight loss over the past 4 months. A chest radiograph showed multiple large pulmonary lesions. The subsequent CT evaluation of the chest abdomen and pelvis confirms an 8 cm renal mass with innumerable pulmonary lesions, the largest measuring 3 cm. She undergoes a renal biopsy that demonstrates tumor papillae with large, irregular eosinophilic cells.

1. Which of the following is true?

A. HIF proteins are overexpressed in this tumor type, providing rational for VEGF therapy.
B. HIF proteins are suppressed in this tumor type, indicating that VEGF-directed therapy is unlikely to provide benefit.
C. MET amplification is common in this tumor type, and MET inhibition should be strongly considered as first-line therapy,
D. This tumor genetically appears similar to urothelial cancer and should be treated as such.

This patient has metastatic papillary RCC type 2. Although the MET oncogene is frequently mutated in type 1 papillary renal cancer, type 2 is more commonly associated with fumarate hydratase (FH) tumor suppressor gene loss. Loss of FH leads to overexpression of HIF proteins, similar to conventional RCC. Despite the different histology, this common pathway suggests that anti-VEGF may remain useful in this subtype. MET amplification is more common in papillary RCC type 1. Renal medullary and collecting duct RCCs are genetically similar to urothelial cancer.

Case study 94.9

A 60-year-old black man presents to your office for a second opinion. He was recently diagnosed with a localized renal cancer. He underwent partial nephrectomy for the 7 cm mass. He was found to have one lymph node with microscopic metastatic disease. The pathology is read as chromophobe RCC because of the presence of large, polygonal cells with prominent cell membrane.

1. Which of the following accurately describes the genetic work-up for this tumor?

A. If this tumor is chromophobe, renal cancer should stain positive for KIT.
B. Genetic sequencing should be performed to identify typical oncogene mutations.
C. A BHD germline mutation predisposes patients specifically to this tumor.
D. VHL mutations are frequently discovered in chromophobe RCC.

KIT protein expression is frequently increased in chromophobe RCC and is apparent on immunohistochemical staining. The clinical importance of the presence of this overexpression is still under investigation, and c-KIT inhibitors are not considered standard of care. Although BHD syndrome does predispose patients to chromophobe RCC, it also predisposes affected individuals for clear cell and papillary renal cancers, and so is not specific to the chromophobe subtype. VHL mutations are not prominent in chromophobe RCC.

Case study 94.10

A 23-year-old woman presents to her primary care provider with sudden onset of loss of vision in her right eye. Fundoscopic examination reveals multiple hypervascular retinal lesions bilaterally. MRI of the brain shows four enhancing lesions, and CT of the abdomen shows multiple bilateral renal lesions. The patient has no family history of any malignancies.

1. Which of the following is essential to the long-term management of this patient?

A. Genotyping for mutation in chromosome 1
B. Genotyping for mutation in chromosome 3
C. Genotyping for mutation in chromosome 7
D. Genotyping for mutation in chromosome 17

This patient presents with classic features of hereditary VHL mutation, which exists on chromosome 3p25. Up to 20% of cases occur de novo and have no relevant family history. Patients with diagnosed hereditary VHL should be regularly screened for the development of clear cell RCC, as well as retinal, cerebellar, and spinal hemangioblastomas; pheochromocytomas; pancreatic neuroendocrine tumors; and endolymphatic sac tumors. Mutations in chromosomes 1, 7, and 12 are associated with hereditary leiomyomatosis RCC syndrome, hereditary papillary renal cell, and BHD syndrome respectively.

Case study 94.11

A 68-year-old man with recently diagnosed clear cell RCC, treated with nephrectomy 14 months ago, returns to your clinic for surveillance. Over the past 2 months, he has noticed increasing fatigue (Karnofsky performance status of 80%), and worsening shortness of breath. Bloodwork shows normal hemoglobin and calcium, but an elevated neutrophil and platelet count. A CT scan of the chest and abdomen is negative for local recurrence, but demonstrates new multiple bilateral lung metastases.

1. Which of the following represents this man's risk classification in the targeted-therapy era?

A. Favorable risk
B. Intermediate risk
C. Poor risk
D. No risk stratification that has been validated in the targeted-therapy era exists.

The renal cell database consortium prognostic model is a newly developed and externally validated prognostic scoring system that has been developed and tested in the targeted-therapy era. In it, patients are divided into favorable-risk (0 factors), intermediate-risk (1–2 factors), and poor-risk (3 or more factors) categories based on the presence or absence of anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status <80%, and <1 year from diagnosis to treatment. This patient has neutrophilia and thrombocytosis, but no other risk factors.

Case study 94.12

1. Which one of the following renal cancers has a natural history and management most similar to those of nonrenal urinary tract cancers?

A. Papillary renal cell carcinoma type 1
B. Papillary renal cell carcinoma type 2
C. Chromophobe renal cell carcinoma
D. Collecting duct renal cell carcinoma

The genetic signature of renal medullary and collecting duct carcinoma by gene expression profiling clusters more closely with urothelial carcinoma of the renal pelvis than clear cell renal cancer, and these tumors do not generally respond to treatment with targeted agents. Conversely, the other listed subtypes behave more similarly to clear cell renal cancer, but chromophobe tumors are generally more indolent.

Case study answers

Case study 94.1
Question 1: Answer C

Case study 94.2
Question 1: Answer A

Case study 94.3
Question 1: Answer C

Case study 94.4
Question 1: Answer D

Case study 94.5
Question 1: Answer A

Case study 94.6
Question 1: Answer D

Case study 94.7
Question 1: Answer B

Case study 94.8
Question 1: Answer A

Case study 94.9
Question 1: Answer A

Case study 94.10
Question 1: Answer B

Case study 94.11
Question 1: Answer B

Case study 94.12
Question 1: Answer D

Selected reading

Dalgliesh GL, Furge K, Greenman C, *et al*. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes Nature 2010 Jan 21;463(7279):360–3.

Dhillon J, Tannir NM, Matin SF, *et al*. Thyroid-like follicular carcinoma of the kidney with metastases to the lungs and retroperitoneal lymph nodes Hum Pathol. 2011 Jan;42(1): 146–50.

Heng DY, Xie W, Regan MM, *et al*. External validation and comparison with other models of the international metastatic renal-cell carcinoma database consortium prognostic model: a population-based study. Lancet Oncol. 2013 Feb;14(2): 141–8.

Malouf GG, Camparo P, Molinie V, *et al*. Transcription factor E3 and transcription factor EB renal cell carcinomas: Clinical features, biological behavior and prognostic factors. J Urol. 2011 Jan;185(1):24–9.

Pawlowski R, Muhl SM, Sulser T, *et al*. Loss of PBRM1 expression is associated with renal cell carcinoma progression. Int J Cancer 2013 Jan 15;132(2):E11–7.

CHAPTER 95

Medical management of renal cancer

Gary R. MacVicar and Timothy M. Kuzel
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Case study 95.1

A 53-year-old man with metastatic clear cell renal cell carcinoma presents for a second opinion. He is asymptomatic and has an excellent performance status. On imaging, a large, right renal mass and pulmonary nodules are identified. His bloodwork is only notable for hemoglobin of 11 mg/dl. He asks whether or not there is a role for nephrectomy in his treatment plan.

1. How do you respond?

A. No data support the role of nephrectomy
B. Nephrectomy should be considered only for patients with symptoms
C. He should be referred to a urologic oncologist for consideration of nephrectomy
D. Surgery should only be considered if he responds to systemic therapy first

Resection of a primary renal lesion in the setting of metastatic disease is referred to as a cytoreductive or debulking nephrectomy, and its practice is initiated in conjunction with immunotherapy.

Whether or not a benefit of cytoreductive nephrectomy exists with the advent of targeted therapies for renal cell carcinoma remains in question. However, in the initial trials of many of the targeted agents, the majority of patients had undergone nephrectomy prior to enrollment. In a retrospective analysis of patients who received vascular endothelial growth factor (VEGF)-targeted therapies, those who underwent cytoreductive nephrectomy appeared to experience an improvement in overall survival. On univariate analysis, the overall survival of the surgery arm was 19.8 months versus 9.4 months for those treated with systemic therapy alone (hazard ratio (HR): 0.44; 95% confidence interval (CI): 0.32–0.59; $P < 0.01$). An improvement in survival persisted on multivariate analysis. In subgroup analyses, those patients with poor-risk disease or a Karnofsky performance status of <80% did not appear to benefit. Thus, we consider cytoreductive nephrectomy for patients with good- or intermediate-risk disease with an adequate performance status who we plan to treat with targeted therapy. An industry-sponsored phase III trial is ongoing, randomizing patients with metastatic renal cell carcinoma to nephrectomy followed by sunitinib or to sunitinib alone (NCT00930033). Another phase III trial sponsored by the EORTC is also ongoing and is randomizing patients to immediate or delayed nephrectomy, both in combination with sunitinib (NCT01099423).

Patient selection for cytoreductive nephrectomy is critical. Proposed selection criteria have included greater than 75% debulking of tumor burden possible; no central nervous system, bone, or liver metastases; adequate pulmonary and cardiac function; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and predominantly clear cell histology. A retrospective analysis identified the following characteristics to be predictors of an inferior overall survival with nephrectomy prior to systemic therapy: elevated lactate dehydrogenase (LDH), hypoalbuminemia, symptoms at presentation due to a metastatic site, liver metastases, retroperitoneal lymphadenopathy, supradiaphragmatic adenopathy, and clinical tumor classification as T3 or greater. Inferior overall survival and increased risk of death correlated with the number of risk factors, and patients with four or more risk factors did not appear to benefit from cytoreductive nephrectomy.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 95.2

A 45-year-old woman with a recent diagnosis of a renal mass that is concerning for renal cell carcinoma presents to your office, stating that she has been experiencing double vision as well as right shoulder pain. On laboratory testing, her calcium is normal, but her alkaline phosphatase is elevated.

1. Routine staging evaluation should include all of the following EXCEPT which?

A. Chest, abdomen, and pelvis computed tomography (CT)
B. Bone scan
C. Brain magnetic resonance imaging (MRI)
D. Positron emission tomography (PET) scan

Current National Comprehensive Cancer Network (NCCN) guidelines recommend a staging evaluation of patients with a renal mass to include complete blood count (CBC), comprehensive metabolic profile, CT or MRI of the abdomen and pelvis with contrast, and chest imaging. A bone scan and MRI brain are recommended if clinically indicated based on symptoms, hypercalcemia, or elevated alkaline phosphatase. CT imaging is most typically utilized for staging with a sensitivity of up to 100% and specificity of over 90% for retroperitoneal disease, venous tumor thrombus, and metastases. Although data exist to suggest MRI is superior to CT in determining the extent of vascular invasion, the presence of which impacts prognosis and surgical approach, recent reports demonstrate CT and MRI to be similar in terms of their ability to detect vascular invasion. However, the combination of the two increases the ability to identify the extent of tumor thrombus to 95%.

When detecting specific sites of metastatic disease, particular imaging modalities may have advantages. While commonly used to detect bone metastases, bone scans have been reported to have a sensitivity of 10–60% and to underestimate the extent of metastases with a false-negative rate of 30%. MRI may be more sensitive and specific for bone metastases. The sensitivity of PET scans to detect metastases has been reported to range from 63% to 100%, and they are thought to be less sensitive for the detection of retroperitoneal lymphadenopathy, lung metastases, and bone metastases. However, at least one report suggests that fluoro-deoxyglucose PET (FDG-PET) may be superior to bone scans, in terms of both sensitivity and accuracy, in the ability to detect bone metastases. Nonetheless, while positive studies are suspicious for disease, negative studies cannot reliably exclude the spread of disease. Thus, we do not routinely include PET scans in a staging evaluation of our renal cell carcinoma patients. Brain metastases may be detected by both CT and MRI with contrast, but MRI is more sensitive than CT for the detection of small brain metastases.

Case study 95.3

A 62-year-old man with a history of a T2, grade 3 clear cell renal cell carcinoma underwent a left nephrectomy 5 years ago. Last week, he presented to his PCP with a cough and right-sided chest pain, and on a chest X-ray, he was noted to have a 2 cm pulmonary nodule. You ask him to undergo a CT scan of his chest, abdomen, and pelvis, and only a 2 cm right upper lobe nodule is noted. An interventional radiology (IR) guided biopsy of the lesion confirms recurrent, clear cell renal cell carcinoma.

1. What is the most appropriate treatment option at this time?

A. Observation
B. Sunitinib
C. High-dose interleukin-2 (IL2)
D. Refer to surgical oncology for resection

At least a portion of patients with recurrent disease may benefit from metastectomy, defined as the surgical resection of metastases. While no randomized data exist, retrospective analyses have reported that metastectomy yields 5-year survival rates on the order of 35% to 60% for patients with solitary metastases. Further, patients with multiple sites of involvement may also experience prolonged survival following metastectomy provided the disease is completely resected. Patients with recurrences to the liver, lung, brain, and bone have benefited from surgical resection. Patient selection is of paramount importance, and predictors of long-term survival after surgical metastectomy include having a solitary metastasis as opposed to multiple lesions and a disease-free interval from treatment of the primary tumor to the time of developing recurrent disease of at least 12 months. Site of involvement may also be predictive. Patients with metastases to glandular sites (thyroid, salivary gland, pancreas, adrenal, and ovary) may have a more favorable prognosis, while a metastasis to the brain is likely associated with a poorer outcome. Finally, the risk category (per Memorial Sloan Kettering criteria) may also be predictive of outcome, with favorable-risk patients potentially experiencing a survival benefit with metastectomy.

We typically consider surgical resection of metastatic disease on an individual basis, weighing factors such as time to recurrence, number and location of metastases, feasibility, Memorial Sloan Kettering risk category, performance status, and comorbidities. Such an approach potentially affords patients a prolonged disease-free status, potentially sparing or delaying exposure to and toxicity from systemic therapies until a time at which they are clearly necessary.

Case study 95.4

A 55-year-old man undergoes a right nephrectomy for a 10cm renal mass. Pathology is consistent with a T3b, grade 3 clear cell renal cell carcinoma. He presents for follow-up post-nephrectomy, and he is feeling well other than slight fatigue and incisional pain, consistent with postoperative recovery. Based on examination, laboratory studies, and postoperative imaging, he is without evidence of recurrent disease.

1. What would appropriate therapy include?

A. Adjuvant sunitinib
B. Adjuvant radiation
C. Adjuvant high-dose IL2
D. Observation

While nephrectomy is curative for a number of patients with clinically localized renal cell carcinoma, on the order of 20% to 40% of patients will subsequently develop metastatic disease. The risk of recurrence appears to increase with advancing stage and increasing grade, and other factors potentially associated with risk of recurrence include histologic subtype, presence of sarcomatoid features, collecting system invasion, and performance status. A number of studies have evaluated the utility of adjuvant therapy to reduce the risk of recurrence following nephrectomy, and these have included chemotherapy, vaccines, immunotherapy, and biochemotherapy. A meta-analysis of 10 such studies, including over 2500 patients, concluded that adjuvant therapy provided no benefit in terms of overall survival or disease-free survival when compared to no treatment. Rather, adjuvant therapy was associated with an increased frequency of serious adverse events. Similarly, a meta-analysis of seven trials assessing postnephrectomy radiation concluded that while adjuvant therapy may decrease rates of locoregional failure, postnephrectomy radiation does not improve survival outcomes.

Based on favorable outcomes with targeted agents in metastatic populations, studies are underway to evaluate their utility in the adjuvant setting. The ASSURE trial (NCT00326898), sponsored by ECOG, randomized patients post-nephrectomy to single-agent sorafenib, sunitinib, or placebo. While the trial has completed accrual, results are pending. Other large adjuvant trials are ongoing and are comparing sunitinib (NCT00375674), sorafenib (NCT00492258), or pazopanib (NCT01235962) to placebo. The primary endpoint of these trials is disease-free survival.

With no adjuvant therapy proven effective to date, our preference is to consider a clinical trial for our postnephrectomy patients, particularly those patients at high risk for recurrence. If a trial is not available, or if patients are ineligible or decline participation, then we recommend observation only.

Case study 95.5

A 70-year-old woman with metastatic renal cell carcinoma presents to discuss treatment options. While reviewing a clinical trial, she asks what her prognosis is.

1. Which of the following is NOT prognostic for the overall survival of metastatic renal cell carcinoma patients receiving systemic therapy?

A. Presence of symptoms
B. Hypercalcemia
C. Anemia
D. The length of time between initial diagnosis and start of treatment

Historically, the median survival for patients with metastatic renal cell carcinoma has been 13 months. However, taken as a whole, patients with metastatic renal cell carcinoma are a fairly heterogeneous group, and while many have rapidly progressive disease, a portion will have more indolent disease with a longer natural history. Analysis of patients treated at the Memorial Sloan Kettering Cancer Center (MSKCC) identified the clinical characteristics of patients that are predictive of shortened survival. These included Karnofsky performance status less than 80%, LDH greater than 1.5 times the upper limit of normal, hemoglobin less than the lower limit of normal, corrected serum calcium greater than the upper limit of normal, and an interval from time of initial diagnosis to start of treatment of less than one year. An increasing number of adverse features correlated with poorer prognosis. A prior analysis of prognostic factors determined the absence of nephrectomy to be a poor prognostic feature (Table 95.1).

While the MSKCC criteria were developed by utilizing data collected from patients treated during the cytokine era, the risk groupings also appear to predict outcomes of patients included in phase III trials of targeted therapies. In an analysis of patients treated with the VEGF-directed therapies sunitinib, sorafenib, or bevacizumab, four of the of five MSKCC adverse prognostic factors were predictors of short survival. These included hemoglobin less than the lower limit of normal, corrected calcium greater than the upper

(*Continued*)

Table 95.1 Characteristics of patients predictive of shortened survival.

Prognostic factors	Risk group	Number of factors	Median survival (months)
• Karnofsky PS < 80% • LDH > 1.5 × ULN • Hemoglobin < LLN • Corrected calcium >10 mg/dL • Time from original diagnosis to treatment < 1 year	Favorable risk Intermediate risk Poor risk	0 1 or 2 ≥3	30 14 5

LDH, lactate dehydrogenase; LLN, lower limit of normal; PS, performance status; ULN, upper limit of normal.

Table 95.2 Additional characteristics of patients predictive of shortened survival.

Prognostic factor	Risk group	Number of factors	Median survival (months)	2-year overall survival
• Karnofsky PF <80% • Time from original diagnosis to treatment < 1 year • Hemoglobin < LLN • Serum calcium > ULN • Neutrophil count > ULN • Platelet count > ULN	Favorable risk Intermediate risk Poor risk	0 1 or 2 ≥3	Not reached 27 months 8.8 months	75% 53% 7%

LLN, lower limit of normal; PS, performance status; ULN, upper limit of normal.

limit of normal, Karnofsky performance status less than 80%, and time from diagnosis to treatment of less than 1 year. Neutrophilia and thrombocytosis were also independent adverse prognostic factors. As with the MSKCC criteria, an increasing number of prognostic features correlated with a shortened survival (Table 95.2).

We believe the ability to stratify patients by prognostic category is important for several reasons. Determining prognosis has value academically in terms of trial design. More practically, identifying prognostic variables assists us in our discussions with individual patients in our clinics regarding expected disease course. We also utilize risk category in part to determine choice of therapy. As an example, we typically consider only good-risk patients and select intermediate-risk patients for high-dose IL2. Based on the population included in the temsirolimus study, we only recommend temsirolimus for clear cell carcinoma patients who are considered to be poor risk.

Case study 95.6

A 55-year-old man presents with clear cell metastatic renal cell carcinoma after having undergone a nephrectomy for T3 disease 18 months ago. He is asymptomatic, and his hemoglobin, corrected calcium, and LDH are all within normal limits.

1. All of the following are possible first-line treatment options EXCEPT which?

A. High-dose IL2
B. Gemcitabine
C. Interferon–bevacizumab
D. Pazopanib

Patients with metastatic renal cell carcinoma are generally treated with systemic therapy. A portion of patients may present with no symptoms and a low burden of disease. Arguably, these patients may be observed, particularly if their disease is indolent in terms of progression. No data exist to suggest that early treatment in this population improves survival, and delaying therapy allows patients to avoid toxicities associated with systemic therapies.

Cytotoxic chemotherapy is generally ineffective despite numerous trials studying a variety of agents. A review of 72 trials of patients with metastatic disease reported a response rate to chemotherapy of only 5.6%.

Immunotherapy—namely, interferon alpha (IFNα) and IL2—has been incorporated into the treatment of metastatic clear cell renal cell carcinoma for a number of years. The use of IFNα has decreased in part due to low response rates and an unfavorable toxicity profile. As a single agent, IFNα has been shown to be inferior to either targeted agents or a combination of targeted agents and IFNα in phase III trials. IFNα remains a front-line option for patients when given with bevacizumab. High-dose IL2 yields objective responses in approximately 20% of patients, but only a minority of patients (between 6% and 9%) will experience a complete response to therapy. However, these complete responses are often durable and last on the order of years. Thus, IL2 is the only therapy to date that is potentially "curable." The toxicity profile of IL2 limits its use to patients with an excellent performance status and few comorbidities.

For patients with good-risk disease, a good performance status, and limited comorbidities, high-dose IL2 is a reasonable choice (if available) in that it is the only agent to date shown to be able to induce durable responses. Targeted agents are appropriate for good-risk patients who are not candidates for or who decline IL2, as well as patients with intermediate- or poor-risk disease. Sunitinib, pazopanib, or bevacizumab with interferon are all acceptable options regardless of risk category, but temsirolimus is typically considered for poor-risk patients exclusively. Axitinib and tivozanib do not currently have a US Food and Drug Administration indication as front-line therapy.

Case study 95.7

A 49-year-old woman with metastatic clear cell carcinoma who has been treated with sunitinib as front-line therapy presents for follow-up. While she initially had responded to treatment and had tolerated the drug well, more recent imaging is consistent with radiographic progression of disease. Currently she only notes fatigue, and her ECOG performance status is 1.

1. Options at this time include which of the following?

A. Everolimus
B. Sunitinib
C. Sorafenib
D. Any of the above

Exactly how to best sequence therapies for individual patients remains a somewhat unanswered question. Investigators have demonstrated the activity of both everolimus and axitinib among patients who progress on an initial line of therapy. Everolimus is an oral mammalian target of rapamycin inhibitor, and in a phase III study of patients with metastatic renal cell carcinoma who had progressed on a VEGF-targeted therapy, patients were randomized to either everolimus or placebo with a primary endpoint of progression-free survival. An improvement in progression-free survival from 1.9 months with placebo to 4.9 months with everolimus was observed ($P < 0.001$), but overall survival was similar in the two arms at 14 to 15 months. The lack of a survival advantage is likely explained by the high rate of crossover of placebo patients at the time of progression. Further, many patients were treated with more than one agent prior to enrollment; for example, 26% of patients in both arms had previously received both sunitinib and sorafenib. In another phase III trial, patients progressing despite front-line therapy with sunitinib, bevacizumab and interferon, temsirolimus, or cytokines were randomized to either axitinib or sorafenib. The study met its primary endpoint, progression-free survival, as patients in the axitinib arm had a progression-free survival of 6.7 months compared to 4.7 months with sorafenib ($P < 0.0001$). Thus, the data are most robust for the use of either everolimus or axitinib after an initial line of targeted therapy.

Data also exist for the use of other agents in previously treated populations. While axitinib was superior to sorafenib in the second-line setting, a prior phase III trial randomized patients with metastatic clear cell renal cell carcinoma previously treated with cytokines to either sorafenib or to placebo. Sorafenib resulted in an improvement in progression-free survival (5.5 months vs. 2.8 months ($P < 0.01$), but no difference in overall survival was appreciated, likely due to crossover. Sunitinib too has shown activity post-cytokines with a progression-free survival on the order of 8 to 9 months in early studies, and in the phase III trial of pazopanib versus placebo, a cohort of patients had been previously treated with cytokines and experienced a progression-free survival of 7.4 months versus 4.2 months with placebo. A number of smaller, largely retrospective studies suggest a portion of patients will respond to sorafenib after sunitinib or vice versa, perhaps due to incomplete resistance between the similar agents.

Case study 95.8

A 52-year-old man presents with a renal mass and pulmonary nodules on imaging. You send him for a needle biopsy of a pulmonary nodule, and pathology is consistent with metastatic papillary renal cell carcinoma.

1. Which of the following is the preferred treatment option?

A. Enrollment in a clinical trial
B. Temsirolimus
C. Sunitinib
D. Gemcitabine

On the order of 85% or more of renal cell carcinomas are clear cell carcinomas, and the remaining portion are composed of several histologic variants, including papillary or chromophobe histology. All of these subtypes, regardless of histology, can display sarcomatoid features, which are generally associated with a poor prognosis. Medullary carcinoma that is typically associated with sickle cell anemia or trait, collecting duct carcinoma that is thought to be biologically similar to urothelial carcinoma, and Xp translocation tumors identified in younger populations are three rare subtypes of non–clear cell renal cell carcinoma that typically behave aggressively.

Due to their relative rarity, no phase III data exist to direct therapy for non–clear cell histology patients, but smaller analyses exist that assist in management decisions. Immunotherapy is thought to have less activity in this patient population and is not considered an option, but rare responses have been reported in patients with papillary and chromophobe histology. In terms of targeted agents, temsirolimus is likely thought by most to be the preferred agent for patients with non–clear cell histologies. In the phase III trial with temsirolimus versus interferon, 10% of patients had non–clear cell histology. Subset analyses suggest that these patients did as well or better with temsirolimus as compared with interferon. In terms of tyrosine kinase inhibitors, small reports as well as data from expanded access studies suggest that sunitinib and sorafenib may exhibit activity in a subset of patients with non–clear cell histology, but activity is likely less than that seen in the clear cell population. Similarly, at least one study suggests that VEGF-targeted agents may have some efficacy in patients with an Xp11.2 translocation. Erlotinib, an EGFR tyroskine kinase inhibitor, has demonstrated activity in patients with papillary renal cell carcinoma with an overall response rate of 11% and median overall survival of 27 months.

Although chemotherapy is thought to have little activity in typical renal cell carcinoma, it appears to have efficacy is selected non–clear cell subtypes. In patients with sarcomatoid disease, a doublet of gemcitabine and doxorubicin given every 2 weeks with growth factor support yielded a response rate of 16% and a median overall survival of 8.8 months in a phase II study sponsored by ECOG. In patients with collecting duct carcinoma and medullary carcinoma, regimens historically utilized in urothelial carcinoma are considered. A study of gemcitabine with either cisplatin or carboplatin in patients with collecting duct carcinoma demonstrated a response rate of 26% and an overall survival of 10.5 months. Minimal data exist to direct the management of patients with medullary carcinoma. The Southwest Oncology Group is currently sponsoring a phase II trial for patients with papillary renal cell carcinoma, randomizing them to the MET inhibitor tivantinib alone or in combination with erlotinib (NCT01688973). ECOG is conducting a study that is randomizing patients with sarcomatoid histology to sunitinib alone or in combination with gemcitabine (NCT01164228).

Case study 95.9

A 62-year-old woman with metastatic renal cell carcinoma has completed two cycles of sunitinib at 50 mg daily, 4 weeks on and 2 weeks off. She presents with imaging that is consistent with an excellent response to treatment. Although she has tolerated the agent well, you note that her blood pressure today is 160/90, and looking over prior clinic notes, she has been hypertensive at more than one clinic visit since starting sunitinib.

1. The most appropriate management consists of which of the following?

A. Continue current treatment with no changes in medications
B. Reduce the dose of sunitinib
C. Discontinue sunitinib and start pazopanib
D. Continue sunitinib without dose reduction, and start an antihypertensive

Hypertension has been associated with the use of sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab. In a retrospective analysis of patients treated with sunitinib, the development of either systolic or diastolic hypertension, defined as a systolic blood pressure of 140 or higher or a diastolic blood pressure of 90 or higher, was associated with improvements in objective response rate, progression-free survival, and overall survival. The development of sunitinib-associated hypertension did not appear to increase risk for hypertension-associated adverse events. For the patient in this question, we would suggest continuing sunitinib at 50 mg in that her cancer is responding to treatment, but an antihypertensive should be added.

Case study answers

Case study 95.1

Question 1: Answer C

Case study 95.2

Question 1: Answer D

Case study 95.3

Question 1: Answer D

Case study 95.4

Question 1: Answer D

Case study 95.5

Question 1: Answer A

Case study 95.6

Question 1: Answer B

Case study 95.7

Question 1: Answer D

Case study 95.8

Question 1: Answer A

Case study 95.9

Question 1: Answer D

Selected reading

Culp SH, Tannir NM, Abel EJ, *et al.* Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 2010;116:3378–88.

Eisen T, Sternberg CN, Robert C, *et al.* Targeted therapies for renal cell carcinoma: review of adverse event management strategies. J Natl Cancer Inst. 2012;104:93–113.

Mendez-Vidal MJ, Martinez Ortega E, Montesa Pino A, *et al.* Management of adverse events of targeted therapies in normal and special patients with metastatic renal cell carcinoma. Cancer Metastasis Rev. 2012;31(Suppl. 1):S19–27.

National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology kidney cancer, version 1.2013. 2013. http://www.nccn.org (accessed February 6, 2014).

Shablak A, Sikand K, Shanks JH, *et al.* High-dose interleukin-2 can produce a high rate of response and durable remissions in appropriately selected patients with metastatic renal cancer. J Immunother. 2011;34:107–12.

For further information on this area please also consult Chapters 113, 122, 123, 126, 129, and 131

CHAPTER 96

Medical management of bladder cancer

Gary R. MacVicar and Timothy M. Kuzel
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Case study 96.1

A 68-year-old man with muscle invasive bladder cancer undergoes a radical cystectomy for muscle invasive bladder cancer.

1. Which of the following is true regarding a lymph node dissection?

A. The extent of pelvic lymph node dissection affects survival outcomes post cystectomy
B. Pelvic lymph node dissection is only necessary for patients with nodal involvement
C. Pelvic lymph node dissection is unnecessary in patients who have received neoadjuvant chemotherapy
D. Lymph node dissection only benefits patients with negative surgical margins

A radical cystectomy is an extensive operation. In men, the urinary bladder is removed along with the prostate and seminal vesicles. In women, en bloc resection of the uterus, cervix, ovaries, and anterior vagina is performed. A lymph node dissection is also undertaken in all patients, and a urinary diversion, typically an ileal conduit or orthotopic neobladder, is created. Multiple groups have published outcomes on series of patients who have undergone cystectomy, and primary T stage and lymph node involvement appear to be predictive of outcomes. The 5-year recurrence-free survival rates range from as high as 70% to 80% for patients with organ-confined disease and absence of nodal involvement to as low as 30% to 35% for those with positive nodes. Patients with a clear extension through the bladder wall (pT3b) and negative nodes have a 5-year recurrence-free rate on the order of 50% to 60%. The median time to recurrence in one series was 12 months.

The quality of the radical cystectomy performed affects patients' outcomes, particularly in regard to lymph node dissection and margin status. Much debate has centered over the extent of surgery required to optimize outcomes for bladder cancer patients. However, several reports suggest that an extended lymph node dissection improves survival relative to a limited lymph node dissection, regardless of nodal status. Positive surgical margins confer a significant independent risk of reduced recurrence-free and overall survival, but even these patients benefit from a quality pelvic lymph node dissection. Analyses vary in regard to the ideal number of nodes that should be removed, ranging from as few as 3 nodes to at least 10 nodes. One group has concluded that rather than a minimum number of nodes, the probability of survival continues to rise as the number of lymph nodes removed increases. In the Southwest Oncology Group's SWOG 8710, a randomized trial of neoadjuvant chemotherapy followed by cystectomy versus surgery alone, obtaining negative margins and removing 10 or more lymph nodes were associated with a longer postcystectomy survival regardless of the assigned treatment arm.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 96.2

A 77-year-old woman with multiple medical problems presents to you for a second opinion regarding management of her high-grade, muscle-invasive urothelial carcinoma of the bladder. On a CT scan, asymmetric thickening of the bladder wall is noted, but no lympadenopathy, hydronephrosis, or evidence of visceral metastases is identified. Her urologist is recommending surgery, but she is refusing. While she states that she is appalled at the idea of not having a bladder, she desires active treatment for her cancer. You worry about her ability to tolerate surgery given her multiple comorbidities, including coronary artery disease and diabetes mellitus. She asks if she has options other than surgery.

1. How do you respond?

A. Reassuring her and sending her back to her urologist for cystectomy
B. Offering her MVAC in place of surgery
C. Considering a bladder-sparing or trimodality treatment strategy
D. Referring for radiation alone

A number of patients are not appropriate for radical cystectomy. Often, this is because of comorbidities or performance status, but occasionally patients refuse surgery. Definitive radiation has been utilized instead of surgery, but as a single modality it may be inferior to surgery as up to 70% of patients may experience a local recurrence and 5-year survival rates are generally suboptimal. The addition of chemotherapy has been shown to improve local control but not overall survival.

Bladder-sparing or trimodality approaches involve a maximum TURBT followed by bladder irradiation concurrent with radiosensitizing chemotherapy. Ideal patients have undergone a complete TURBT as this is a prognostic factor for long-term survival with this approach. Other clinical patient factors to consider include the ability to tolerate platinum-based chemotherapy, urothelial carcinoma histology, and early-stage as opposed to bulky disease. Periodic imaging studies and cystoscopies are performed to monitor for recurrence, and if disease is noted, patients undergo salvage radical cystectomy. To date, there has not been a randomized trial to compare bladder preservation versus neoadjuvant chemotherapy followed by cystectomy.

A phase III trial was recently reported in which patients who had undergone a complete TURBT were randomized to radiation alone or to radiation in combination with mitomycin-C and fluorouracil. Two-year loco-regional disease-free survival was improved from 54% with radiation alone to 67% with combination therapy. However, the difference in overall survival at 5 years, 35% with radiation alone versus 67% with combination therapy, did not reach statistical significance. While the 11% rate of cystectomy at 2 years in the combination arm was less than a rate of 17% with radiation alone, this difference also did not reach statistical significance. With the exception of gastrointestinal toxicity, which increased from 3% with radiation alone to 10% with the addition of chemotherapy, toxicity was similar in the two arms of the study.

For the patient in this question, a trimodality approach is likely the best option. Radiation alone likely has inferior results, and the addition of the mitomycin and 5-fluorouracil regimen does not appear to increase toxicity for most patients. Systemic chemotherapy alone is not a substitute for local therapy, and in this elderly woman with multiple comorbidities, her ability to tolerate platinum-based regimens is questionable, although in smaller phase II studies the results are best when cisplatin is included with radiation. In our practice, we do utilize a trimodalty approach, but only for select patients who are poor cystectomy candidates due to either advanced age or comorbidities or for rare patients who refuse cystectomy. Otherwise, neoadjuvant chemotherapy followed by cystectomy is our preferred treatment strategy.

Case study 96.3

1. A 72-year-old man with muscle-invasive bladder cancer presents to you for a second opinion. Aside from hypertension, he has no significant past medical history or comorbidities. He states that although he is reluctant to undergo cystectomy as recommended to him by his urologist, he wishes to be aggressive with his treatment plan, taking advantage of any possibility to improve his outcome. You realize that his urologist has not discussed neoadjuvant chemotherapy, and you discuss it with the patient, stating that it has which of the following advantages?

A. An improvement in overall survival
B. An increase in pathologic complete response rate
C. No increase in surgical complication rates compared with surgery alone
D. All of the above

(*Continued*)

Long-term survival following surgery has been evaluated in multiple surgical series, and the 5-year survival for patients with pathologically organ-confined bladder cancer (pT2) is 68%, while those with extravesicular extension or lymph node involvement have a 25 to 30% 5-year survival rate. As a means to improve outcomes, perioperative chemotherapy has been evaluated in a number of studies. The goal of neoadjuvant chemotherapy is to eradicate micrometastatic disease and improve survival. This approach has several advantages. These include potential downstaging of disease, being able to monitor an intact bladder lesion for response, and avoiding potential postoperative issues or complications that may complicate the delivery of chemotherapy. However, opponents argue that patients may progress such that they become inoperable, losing an opportunity for cure. Further, given the inaccuracies of clinical staging, some patients may be exposed to chemotherapy unnecessarily.

The benefit of neodjuvant chemotherapy is supported by clinical trial data. An Intergroup-sponsored study, INT-0080, randomized patients with clinical T2 to T4a disease to either neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) followed by radical cystectomy or to surgery alone. Neoadjuvant chemotherapy increased the pathologic complete response rate significantly from 15% with surgery alone to 38% with neoadjuvant MVAC. Further, 85% of patients with a pathologic complete response were alive at 5 years. Median overall survival also was greater with neoadjuvant chemotherapy at 77 months versus 46 months with cystectomy alone, but this difference was not statistically significant. While increased toxicity was observed with the addition of MVAC, no chemotherapy-related deaths occurred, and surgical complication rates did not differ between the two arms. A phase II study with a dose-dense version of MVAC given in 2-week cycles with growth factor support yielded a similar pathologic complete response rate, and the regimen was well tolerated. Another randomized trial evaluated neoadjuvant CMV (cisplatin, methotrexate, and vinblastine) prior to local therapy versus local therapy. Overall survival at 10 years was improved significantly by 6% with neoadjuvant CMV. Gemcitabine and cisplatin have only been studied retrospectively as neoadjuvant chemotherapy, but reports suggest similar pathologic complete response rates and survival data. A meta-analysis including 3005 patients with T2 to T4a urothelial carcinoma from 11 trials reported a significant survival benefit for patients treated with neoadjvuant platinum-based combination chemotherapy equivalent to a 5% absolute improvement in survival at 5 years.

Despite data demonstrating both its feasibility and its efficacy, few patients are considered for neoadjuvant chemotherapy. Studies suggest rates of its use as low as 17% among patients with T2 or greater disease, even at academic centers. We typically recommend neoadjuvant chemotherapy for all patients with muscle-invasive urothelial carcinoma who are undergoing cystectomy and are appropriate for platinum-based chemotherapy, consistent with National Comprehensive Cancer Network (NCCN) bladder cancer guidelines.

2. Despite your recommendations, this patient opts to undergo surgery without neoadjuvant chemotherapy. His radical cystectomy pathology is notable for extension through the bladder wall, and two lymph nodes are positive for malignancy. His urologist now refers him back to you for consideration of adjuvant chemotherapy. His postoperative course was complicated by pneumonia, and as a result he became deconditioned and required a stay in an extended care facility. He presents today several weeks postoperatively, and he states that he is nearly back to his preoperative baseline. In regard to adjuvant chemotherapy, which of the following is true?

A. Randomized trials provide conclusive data that adjuvant therapy improves outcomes

B. Postoperative complications do not interfere with its administration

C. Only patients at high risk for recurrence should be considered for adjuvant therapy

D. Only patients with p53-expressing tumors benefit from adjuvant chemotherapy

This man is at particularly high risk for developing recurrent bladder cancer. Patients with extravesicular extension or positive nodes have a 5-year survival on the order of 25% to 30%. The rationale for adjuvant therapy, as opposed to neoadjuvant therapy, is that pathologic findings allow patients to be stratified based on risk of recurrence, thus avoiding overtreatment and only exposing those at particular risk for recurrence to the toxicities of chemotherapy. However, in the adjuvant setting, no target lesion is present to assess sensitivity to chemotherapy.

Limited data exist that support that adjuvant therapy improves outcomes. Trials to date that have evaluated adjuvant therapy are limited by inadequate power, flawed statistical analyses, inconsistent salvage therapy at recurrence, and ineffective chemotherapy regimens. While a recent systematic analysis of adjuvant trials concluded that no definitive data to support the use of adjuvant therapy exist, a retrospective review of nearly 4000 patients from 11 centers suggested an improvement in survival with adjuvant therapy, particularly those at high risk for recurrence.

Larger trials of adjuvant contemporary cisplatin-based chemotherapy have been attempted, based on data suggesting that p53-positive patients are at higher risk of recurrence. A SWOG-sponsored study stratified patients based on p53 expression, and randomized those who were p53 positive to either observation or adjuvant chemotherapy. The study was halted early as a result of an interim analysis determining

futility. No difference in recurrence or survival was noted regardless of p53 status or whether or not adjuvant chemotherapy was given. Two European studies of adjuvant chemotherapy have been presented. One randomized patients to observation or to adjuvant gemcitabine and cisplatin following cystectomy. No differences in relapse rates or survival were observed between the two arms. A second study randomized patients post cystectomy with pT3 or pT4 disease or node positivity to either observation or to the triplet paclitaxel, gemcitabine, and cisplatin. The 5-year overall survival improved significantly from 31% in the observation arm to 60% with adjuvant chemotherapy. Further, disease free survival, time to progression and disease-specific survival were all significantly improved with adjuvant chemotherapy. Both of these European studies were terminated due to poor accrual, and as a result well-conducted, large randomized controlled trials are still needed to better define the role of adjuvant therapy.

While we favor neoadjuvant chemotherapy for patients with muscle-invasive disease undergoing cystectomy, we will consider adjuvant therapy for patients at high risk for recurrence, namely, those with pathologic T3 or T4 disease or node-positive disease, and typically we give four cycles of cisplatin-based chemotherapy. This is consistent with NCCN guidelines. Patients are carefully counseled that little data exist that demonstrate a conclusive positive effect on outcomes, and we proceed only if they are willing to accept toxicities of treatment despite this caveat.

Case study 96.4

A 78-year-old woman presents to you with a recent diagnosis of metastatic bladder cancer. She presents with her family today, who states that she rests most of the day and requires assistance with activities of daily living. She was found to have a bladder mass after experiencing hematuria, and biopsy pathology was consistent with muscle-invasive high-grade urothelial carcinoma. Body imaging is notable for a bladder mass, pelvic lymphadenopathy, and pulmonary nodules concerning for metastases. Today, she states that she has been experiencing urinary frequency and pelvic pain, which you suspect is due to her bladder mass. They ask you about prognosis.

1. Which of the following characteristics of her presentation is prognostic of outcomes in metastatic bladder cancer patients?

A. Performance status
B. Visceral metastases
C. Both A and B
D. Neither A and B

A number of characteristics, both clinical and molecular, have been associated with prognosis or with response to chemotherapy. In terms of prognostic clinical characteristics, a poor performance status and the presence of visceral metastases have reproducibly been shown in analyses of clinical trial data to be predictive of outcomes. In an Intergroup study comparing cisplatin alone to MVAC in patients with metastatic disease, the presence of bone or liver metastases, as evidenced by either radiographic studies or elevated alkaline phosphatase, and poor performance status were most predictive of poor response and survival. The median survival of the group with favorable features was 18.2 months versus 4.4 months for the group with unfavorable features. In a subsequent follow-up report, no patients with liver or bone metastases and only one patient with a poor performance status, defined as a Karnofsky performance status (KPS) of less than 80%, survived 6 years. Investigators at Memorial Sloan Kettering Cancer Center analyzed the follow-up data of 229 patients treated with MVAC, and they demonstrated that a KPS <80%, and the presence of visceral metastases, defined as lung, liver, or bone metastases, were associated with decreased survival. The median survival of patients who had none, one, or two of these factors was 33, 13.4, and 9.3 months respectively. A long-term follow-up of patients from a trial randomizing patients to MVAC or gemcitabine and cisplatin confirmed a poor performance status or the presence of visceral metastases as independent prognostic variables for survival. Stadler *et al*. determined prognostic factors by reviewing the long-term follow-up survival data of three phase II trials of gemcitabine and cisplatin in patients with advanced disease. In a univariate analysis, the presence of visceral metastases and a hemoglobin level less than 12.5 mg/dL were adverse prognostic factors, but in a multivariate analysis, only the presence of visceral metastases retained its prognostic value. They observed a 12% 4-year survival rate in all patients and a 20% rate in those without visceral metastases. Performance status was not prognostic, perhaps due to the small numbers of patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or more. In a recent analysis of metastatic patients who had progressed despite initial platinum-based chemotherapy, ECOG performance status more than 0, hemoglobin level less than 10 g/dL, and the presence of liver metastases were adverse prognostic factors for overall survival. Patients with none of these features had a median overall survival of 14.2 months versus 1.7 months among those with all

(*Continued*)

three. These findings are important when considering phase II and phase III trials, as an imbalance of patients in terms of performance status or visceral metastases may influence the survival outcomes.

Molecular prognostic factors are also being developed based on translational study of bladder cancer specimens and preclinical models. Mutations in the p53 gene have been observed in approximately 45% of patients with bladder cancer and are associated with higher grade and stage. Furthermore, patients with metastatic disease and altered p53 expression are thought to have a worse outcome. Whether or not altered p53 expression results in resistance to MVAC is unclear, but reports of the multidrug-resistant p-glycoprotein, multidrug-resistance-associated protein, glutathione, and metallothioneins as markers of resistance and toxicity exist. An analysis of levels of messenger RNA expression of DNA repair genes determined by reverse transcription polymerase chain reaction (RT-PCR) of tumor DNA from patients with advanced bladder cancer treated with cisplatin-based chemotherapy determined that the level of the protein excision repair cross complementing 1 (ERCC1) was predictive of survival. With a median follow-up of 19 months, the median survival was 25.4 months in patients with low ERCC 1 levels versus 15.4 months in those with high levels of expression ($p = 0.03$). These results demonstrate that molecular determinants may allow physicians in the future to tailor therapy to individual tumor characteristics as a means to improve outcomes. However, none of these markers have been validated prospectively for clinical decision making.

Case study 96.5

A 60-year-old woman who underwent a radical cystectomy 12 months ago presents with new back pain and fatigue. Laboratory studies reveal a hemoglobin level of 10.5 g/dL and an elevated alkaline phosphatase. Her renal function, hepatic function, and serum calcium are all normal. She is noted on CT scan to have retroperitoneal lymphadenopathy, pulmonary nodules, and vertebral lesions, and the bone lesions have uptake on a bone scan. She recognizes that treatment involves chemotherapy, but she is very concerned about toxicity because of multiple side effects her sister experienced when treated for breast cancer.

1. You recommend which of the following regimens?

A. MVAC (methotrexate, vinblastine, adriamycin, and cisplatin)
B. Gemcitabine and cisplatin
C. Gemcitabine and carboplatin
D. Gemcitabine, cisplatin, and bevacizumab

MVAC has long been the standard first-line regimen for patients with metastatic urothelial carcinoma. Two randomized phase III studies established MVAC as the standard first-line regimen. The first was a US Intergroup study randomizing 269 patients with advanced urothelial carcinoma to either single-agent cisplatin or to MVAC. Response rates (39% vs. 12%), progression-free survival (10.0 vs. 4.3 months), and overall survival (12.5 vs. 8.2 months; $P = 0.0002$) favored combination chemotherapy significantly. The second study randomized 110 patients with metastatic transitional cell carcinoma either to a regimen consisting of cisplatin, cyclophosphamide, and doxorubicin (CISCA) or to MVAC. A significantly higher response rate (65% vs. 46%; $P < 0.05$) and median survival (48.3 weeks vs. 36.1 weeks) were observed with MVAC versus CISCA.

In hopes of improving outcomes, a high-dose intensity MVAC regimen given in 2-week cycles with growth factor support was compared to standard MVAC given in 4-week cycles. In the initial report by the European Organization for Research and Treatment of Cancer (EORTC), the overall response rate (63% vs. 50%), complete response rate (21% vs. 9%), and progression-free survival (9.1 months vs. 8.2 months) favored the high-dose arm significantly. The primary endpoint of the study, median overall survival, was not significantly different, with a median survival of 15.5 months in the high-dose arm and 14.1 months in the standard-dose arm. A subsequent report with a median follow-up of over 7 years revealed similar median survival outcomes, but HD-MVAC produced a borderline statistically significant relative reduction in the risk of progression and death compared to MVAC. While this regimen is reasonable to use to increase the likelihood of a response, perhaps in a symptomatic patient, its nonhematologic toxicity and lack of a clinically significant improvement in survival cause many to hesitate to use it routinely.

Toxicity is a serious consideration with MVAC as the typical bladder cancer patient is elderly or has multiple comorbidities, making them less resilient to aggressive treatment. Myelosuppression, neutropenic fever, sepsis, mucositis, and nausea and vomiting are all common, and patients in some MVAC trials were routinely hospitalized due to toxicity. Furthermore, toxicity-related deaths of advanced patients are reproducibly reported; typically, less than 5% but up to 9% have been observed.

A phase III study randomized 405 patients with advanced urothelial carcinoma to either gemcitabine and cisplatin (GC) or MVAC, both administered over 28-day cycles. The overall response rate (49% for GC vs. 46% for MVAC), time to progression (7.4 months for both GC and MVAC), and

median survival (13.8 months for GC vs. 14.8 months for MVAC) were identical between the two arms. However, the toxicity profile favored GC in terms of rates of grade 3 or 4 neutropenia, neutropenic sepsis, and grade 3 or 4 mucositis. This study was not powered to determine equivalency between the two regimens, but an updated analysis of long-term follow-up continued to show similar outcomes between the two arms. The overall survival at 5 years was 13.0% with GC and 15.3% with MVAC, a difference that was not statistically significant. Based on these results demonstrating similar efficacy between the two regimens, but a superior toxicity profile with GC, many consider GC to be the standard first-line regimen for patients with advanced urothelial carcinoma of the bladder.

Limited studies have compared cisplatin and carboplatin. A phase II study randomizing patients to gemcitabine with either cisplatin or carboplatin demonstrated similar overall response rate, time to progression, and survival. However, another small phase II study randomized patients to MVAC or to the triplet methotrexate, carboplatin, and vinblastine (M-CAVI). The two were similar in terms of response rates, but MVAC yielded a superior overall survival of 16 months compared with 9 months in the M-CAVI arm ($P = 0.03$). The lack of adriamycin with M-CAVI and possible underdosing of carboplatin were possible explanations for the difference in survival suggested by the investigators. A phase II comparison of MVEC (methotrexate, vinblastine, epirubicin, and cisplatin) to MVECa (methotrexate, vinblastine, epirubicin, and carboplatin) favored the cisplatin arm significantly in terms of response rates. While an exact comparison of carboplatin and cisplatin cannot be obtained from these data, most prefer cisplatin given the hint of increased activity.

Many patients with advanced bladder cancer are not appropriate for cisplatin-based regimens, often due to advanced age, impaired performance status, or renal insufficiency. A phase III study in Europe (EORTC 30986) randomized patients with impaired renal function, poor performance status, or both to either gemcitabine and carboplatin or to MCAVI. No differences in overall response rate, progression-free survival, or overall survival were noted between the two regimens. However, overall toxicity and rates of neutropenia and febrile neutropenia were lower with gemcitabine and carboplatin. For patients who are not considered appropriate for cisplatin-based chemotherapy, we typically utilize gemcitabine and carboplatin or single-agent therapy.

New agents for urothelial carcinoma are sorely needed, and phase II studies enrolling chemotherapy-naïve patients have begun to incorporate targeted agents such as trastuzumab, cetuximab, and bevacizumab with standard chemotherapy. A phase III cooperative group trial is randomizing advanced urothelial carcinoma patients to gemcitabine and cisplatin alone or in combination with bevacizumab as first-line therapy (NCT00942331). Currently, however, no targeted therapy is indicated in metastatic bladder cancer.

Case study answers

Case study 96.1

Question 1: Answer A

Case study 96.2

Question 1: Answer C

Case study 96.3

Question 1: Answer D
Question 2: Answer C

Case study 96.4

Question 1: Answer C

Case study 96.5

Question 1: Answer B

Selected reading

Dhar NB, Klein EA, Reuther AM, *et al*. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. J Urol. 2008;179:873–8; discussion 8.

Fritsche HM, Burger M, Svatek RS, *et al*. Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol. 2010;57:300–9.

James ND, Hussain SA, Hall E, *et al*. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med. 2012;366:1477–88.

NCCN. NCCN clinical practice guidelines in oncology: bladder cancer. Version 1, 2013. 2013. http://www.NCCN.org (accessed February 6, 2014).

Yeshchina O, Badalato GM, Wosnitzer MS, *et al*. Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. Urology. 2012;79:384–90.

For further information on this area please also consult Chapters 114, 122, 123, 126, and 134

CHAPTER 97

Prostate cancer: Screening, surveillance, prognostic algorithms and independent pathologic predictive parameters

Megan G. Lockyer and Thomas M. Wheeler
Baylor College of Medicine, Houston, TX, USA

Case study 97.1

A 56-year-old white male with no past medical history presents to his primary care physician for his yearly physical. His exam and laboratory results are all negative with the exception of an elevated prostate serum antigen (PSA) level at 8 ng/mL (normal <4 ng/mL). Prostate biopsy is scheduled.

1. In an asymptomatic patient with a normal digital rectal exam, should PSA screening be standard?

A. Yes
B. No
C. It depends

Since the introduction of the PSA test for early detection of prostate cancer in 1987, its use has steadily increased with an estimated 47–58% of all new prostate cancers being screen-detected in 2000. This, in turn, has led to an increased incidence with a corresponding decreased proportion of metastatic or locally advanced stage disease at diagnosis. The primary goal of PSA-based screening is to find men in whom treatment would reduce morbidity and mortality. Although the risk of prostate cancer varies with the PSA level in the serum, the PSA level is not specific to prostate cancer, and the majority of men with an increased PSA do not have cancer.

However, PSA screening has become controversial recently. The latent prevalence of disease detected by screening, as reported by Draisma *et al.*, is much higher than the incidence in the absence of screening. The possibility of causing harm from overdiagnosis and treatment in patients whose cancer would otherwise have remained latent has many physicians asking if screening is appropriate or even beneficial in some patient populations.

The US Preventive Services Task Force released a recommendation against the use of PSA screening in May 2012, citing several studies that could not demonstrate a benefit in overall or all-cause mortality with routine screening. It argues that the harms associated with screen-detected diagnosis and treatment in men who would have remained asymptomatic are too prevalent, and thus outweigh the benefits of screening.

The American Society of Clinical Oncology (ASCO), however, recommends testing for asymptomatic men with a life expectancy of 10 years or greater. It emphasizes the further findings of the European Randomized Study of Screening for Prostate Cancer (ERSPC), and other studies including the Goteberg trial, which demonstrate a decrease in prostate cancer–related death of 20–44% with the use of screening in men 55–69 years, indicating that in some studies the benefits of screening validate its continued use.

Most recently (March 2014), the National Comprehensive Cancer Network (NCCN) has released a new recommendation to begin PSA screening as early as age 45. The purpose of this revision is to allow for possible future cancer risk stratification. This new recommendation is based on observational studies, including a large study group in Sweden where a PSA test prior to age 50 predicted prostate cancer risk up to 30 years later. The frequency of future testing would be based on risk stratification according to age-specific PSA levels released by the NCCN (0.7 ng/mL for age 40–49 years and 0.9 ng/mL for age 50–59 years), and annual or biannual follow-up for all men with a PSA greater than 1 ng/mL. Additionally, the NCCN released new recommendations for when to stop screening. The panel suggests discontinuing screening at 69, continue screening up to age 74 (allowing for

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

an increase in PSA threshold in men age 70–74), or discontinue screening at age 75 years for patients with a PSA less than 3 ng/mL. The updated guidelines also suggest any patient with a PSA greater than 3 ng/mL should be considered for biopsy.

Although there is no across-the-board right or wrong answer to the debate, many patients will continue to request PSA screening, and physicians will continue to offer it. The use of PSA screening, therefore, should be used at the physician's discretion, taking into consideration the patient's clinical information, including age, comorbidities, ethnicity, and family history of prostate cancer.

The patient underwent a 12-core prostate biopsy, and pathology results are adenocarcinoma, Gleason Score $3 + 3 = 6$, involving two cores (40% of one and 20% of the second core). After discussing his options with his primary care physician, a decision is made to undertake active surveillance.

2. Does the patient qualify for active surveillance?

A. Yes

B. No

This is according to the following widely accepted criteria (Epstein):

- Two or fewer cases with cancer and no more than 50% involvement in any one core
- PSA density <0.15%
- Gleason score ≤6 (no Gleason pattern 4 or 5)
- PSA <10 ng/mL
- Clinical stage T1

The aim of active surveillance is to identify low-risk or clinically insignificant prostate cancer that, if untreated, would not pose an immediate threat to the patient. Active surveillance is strict surveillance with the intent to cure when necessary. Unlike watchful waiting, which does not have treatment with intent to cure as an endpoint, the premise of this treatment is based on the ability to determine low-risk disease that may be followed without causing harm. Low-risk disease has been characterized by the D'Amico risk classification and Epstein criteria, which can be summarized as follows: less than one-third of the biopsy cores are positive, with <50% involvement of any one core; PSA density <0.15%; a Gleason score less than or equal to 6; PSA <10 ng/mL; and stage T1 disease. The Epstein criteria are more stringent with no more than two positive cores. Our patient meets these criteria for risk stratification as a low-risk prostate cancer.

The above criteria are predominantly based on biopsy results. Although there has been a trend toward increasing the number of biopsies performed from 6 to 10–12, there is still inherent undersampling of the gland. This could cause an underestimation of disease burden, and, therefore, an improper diagnosis of insignificant prostate cancer. It is for this reason that several published protocols have modified the triggers of the criteria discussed here. Instead of relying entirely on a PSA level, it has been proposed to follow the course of the PSA, and treat if it rises dramatically. The rate of change in the PSA level is the PSA velocity. The current recommendation is that a biopsy should be considered with a PSA velocity greater than 0.35–0.4 ng/mL per year. PSA doubling time as a method to assess the status of prostate carcinoma is also being studied. It is well understood that the median PSA doubling time of nonmetastatic prostate carcinoma is approximately 36 months. A short PSA doubling time has been observed in 7–47% of patients, and it has been postulated that these patients may have carcinoma in an exponential-growth phase resulting in rapidly increasing PSA levels. In contrast, 30% of patients with relatively stable or declining PSA levels likely have carcinoma in a linear phase of growth that could be followed safely without treatment. Additionally, staging re-biopsy prior to the enactment of active surveillance has also been recommended.

There are currently no reported data from randomized trials showing whether patients who undergo active surveillance have better or worse outcomes in comparison to patients who were treated immediately following diagnosis. However, noncomparative cohort studies have shown comparable disease-free and overall survival rates to patients given curative therapy initially. There are side effects and morbidities as a result of any treatment for prostate cancer, even active surveillance. Therefore, treatment options should be discussed with the patient in association with the patient's risk profile.

The patient's PSA level continues to increase over the next several years, and a second prostate biopsy is performed. His pathology report now describes a Gleason pattern 4 in one of two involved cores. The patient undergoes radical prostatectomy (RP).

3. Can the patient's disease-free survival rate be estimated preoperatively?

A. Yes

B. No

The Kattan, preoperative nomogram may be used to determine the patient's disease-free outcome post-surgery. Although, in the beginning, RP resulted in nearly 100% occurrence of impotence (and, rarely, incontinence), the advent of "anatomical" RP with sparing of the posterior nerve bundle has been far more successful with less morbidity to the patient. The risk of mortality from surgery is also relatively low (it is currently at <0.5%), making RP a viable treatment option. RP is associated with excellent long-term

(*Continued*)

cancer control, with a 40% decrease in the risk of death from prostate cancer in comparison to watchful waiting in some series in a selected subset of patients. Relapse of disease, however, has been reported to be as high as 15–53%. However, the recently completed PIVOT trial in the United States failed to show a difference in cancer specific all-cause mortality in those treated with RP versus observation. Although, there was a trend for better outcome in those patients treated surgically with high-risk disease. This high level of variability has led to the advent of nomograms to delineate patient-specific outcomes.

The preoperative Kattan nomogram using preoperative PSA levels, clinical staging, and Gleason scoring from the biopsy specimen are currently used by some clinicians. However, final pathologic staging determined from an RP specimen is far more accurate in recurrence prediction. The Kattan postoperative nomogram, first described by Kattan *et al*. in 1998, is a postoperative nomogram that relies heavily on the pathologic information from analysis of the RP specimen. It uses several parameters that are well understood to be important prognostic factors to calculate disease-free survival. The independent predictive parameters (preoperative PSA, Gleason score, extraprostatic extension, seminal vesicle invasion, surgical margin, and lymph node status) are each assigned a numerical value according to the nomogram. The sum is then used to predict the likelihood of an 84-month disease-free survival.

The Gleason score of an RP specimen is far more accurate than that of the biopsy due to the significant probability of a higher Gleason grade cancer being present adjacent to the biopsied tumor. The presence of any Gleason 4/5 is an indicator of worse prognosis.

Extraprostatic extension (EPE) is the extension of tumor into adjacent tissues beyond the prostate capsule, commonly peri-prostatic adipose tissue. This is not equivalent to positive surgical margins (+SM), which is tumor present at the inked margin. Although some institutions report the quantity of capsular invasion, most only report the presence or absence of EPE, which is qualified as "focal" for marginal EPE and "nonfocal" or established for greater amounts of EPE. Interestingly, metastasis almost never occurs in prostate cancer without invasion through the capsule (i.e., EPE).

Seminal vesicle involvement (SVI) by tumor can occur by three pathways. It can occur by tumor expansion along the ejaculatory duct complex and, less commonly, across the base of the prostate. The least common mechanism is by isolated deposits (metastasis) without contiguous tumor. Eggner *et al.* (2011) argue that SVI is one of the most important predictors of poor prognosis.

A positive surgical margin (+SM) is defined as tumor cells at the inked margin. The specimen is inked entirely, with different colors to designate right from left, before processing. The apical and bladder base margins are shaved off first, and may be submitted in two ways. If submitted *en face*, any tumor cells present in the stained section indicate +SM. Many institutions, however, prefer to cut the margins into pie-shaped pieces perpendicular to the prostatic urethra. This allows for better differentiation between near-surgical margins and +SM. Positive bladder neck margins historically were regarded as T4. However, recent studies have shown microscopic bladder neck invasion tumors to behave more like T3 prostate cancer, and these are now classified as T3a. The remainder of the prostate is sliced from apex to base parallel to the prostatic urethra to assess surgical margins and EPE.

Perineural invasion (PNI) is present in 75–84% of cases. Since it occurs relatively commonly, it is not a reliable indicator of prognosis, and is not included in the Kattan nomogram. The assessment of PNI with relevance to prognosis is not approved by the Cancer Committee of the College of American Pathologists. Recent studies, however, have showed an association with volume of PNI as a predictor of tumor recurrence and progression. Maru *et al*. (2001) showed an association between the maximum diameter of PNI and adverse pathologic features. A large focus of PNI ($\geq$0.25 mm) is also associated with higher rates of progression. More studies will be necessary to validate these findings.

Several years after his surgery, the patient's nonexistent level of PSA begins to rise from undetectable to 0.1 ng/mL to 0.2 ng/mL to 0.4 ng/mL over an 8-month period. The digital rectal exam is normal postoperatively.

4. Should you proceed to biopsy the prostate bed or give local radiotherapy?

A. Biopsy
B. Radiotherapy
C. Both

What the patient has is biochemical relapse, which is defined as an increase in serum PSA in three consecutive measurements. In the presence of biochemical relapse, there may be local disease recurrence, distant recurrence, both local and distant recurrence, or no detectable recurrence but an increased serum PSA. In the evaluation of suspected recurrence, it is important to differentiate between local and metastatic. After determining it is local recurrence only, it should be decided if the patient is a candidate for local therapy so as to limit morbidity and maximize quality of life.

Kundel *et al.* (2004) determined salvage radiation therapy following RP with biochemical failure to be a safe and effective treatment option. In their study, 66% of patients were disease free and biochemical failure-free at 34.3 months. The therapeutic benefit of salvage radiation therapy, however, is most evident in the presence of a low serum PSA level ($<$0.5 ng/mL).

Other systemic therapies, including chemotherapy, hormonal therapy, and androgen deprivation, may be considered in cases with metastatic disease.

The patient is treated with radiotherapy to the prostatic bed, and the PSA level drops to undetectable.

Case study answers

Case study 97.1

Question 1: Answer C
Question 2: Answer A
Question 3: Answer A
Question 4: Answer B

Selected reading

Eggener SE, Scott E, Scardino PT, *et al.* Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J. Urol. 2011;185:869–75.

Epstein JI, Feng Z, Trock BJ, *et al.* Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified gleason grading system and factoring in tertiary grades. Euro Urol. 2012;61:1019–24.

Lawrentschuk N, Laurence K. Active surveillance for low-risk prostate cancer: an update. Nature 2011;8:310–20.

Lilja H, Ulmert D, Vickers AJ. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. Nature 2008;8:268–79.

Ohori M, Kattan M, Scardino PT, *et al*. Radical prostatectomy for carcinoma of the prostate. Mod Pathol. 2004;17:349–59.

CHAPTER 98

Medical management of prostate cancer

Elizabeth K. O'Donnell and Philip Kantoff
Dana-Farber Cancer Institute Boston, MA, USA

Multiple choice and discussion questions

1. A patient has a rising prostate-specific antigen (PSA) level several years after definitive therapy with prostatectomy (or radiation therapy). When is the correct time to start androgen deprivation therapy (ADT)?

There is very little published literature comparing early- versus delayed-initiation of ADT in men with recurrent or advanced prostate cancer. The best evidence in support of early initiation of ADT can be extrapolated from papers by Studer and Moul. Studer (2006) studied 985 patients with newly diagnosed prostate cancer who either refused local definitive treatment or were judged not suitable for it because of decreased life expectancy, advanced local tumor stage, and/or severe comorbidities. Patients were randomized to either immediate ADT or deferred treatment only at the time of symptomatic progression, defined as: new symptomatic metastases or metastases whose location threatened to produce serious complications, such as pathologic fracture or paralysis; increase in pain score; deterioration in World Health Organization (WHO) performance status by two levels due to prostate cancer; and evidence of ureteric obstruction caused by either the primary tumor or metastases. The overall survival hazard ratio was 1.25 (95% confidence interval (CI): 1.05–1.48; non-inferiority $P > .1$), favoring immediate treatment, although this appeared to be due to fewer deaths by causes other than prostate cancer ($P = .06$). There was no significant difference in prostate cancer mortality or symptom-free survival.

Moul *et al*. (2008) conducted a retrospective review of clinical outcomes of men with PSA recurrence after prostatectomy, comparing early- versus delayed-use of ADT. Early ADT was associated with delayed clinical metastasis in patients with a pathological Gleason sum greater than 7 or PSA doubling time of 12 months or less (HR = 2.12; $P = 0.01$). The conclusion of this analysis was that early ADT administered for PSA recurrence after radical prostatectomy was an independent predictor of delayed clinical metastases for high-risk cases only.

In conclusion, there is no level I evidence to guide the timing of ADT in our typical patients with a rising PSA after local therapy. Data from other scenarios as well as retrospective data modestly favor the use of ADT earlier rather than later. However, decision making must be made on an individual basis factoring in the adverse effects associated with long-term ADT as well as patient anxiety from postponing therapy. Use of early ADT is probably overtreatment with associated toxicity for patients with indolent features such as a slowly rising PSA or significant comorbidities.

2. A patient presents with newly diagnosed metastatic prostate cancer. What does appropriate therapy for this patient include?

A. Androgen deprivation therapy (ADT) alone
B. ADT plus zoledronic acid
C. ADT plus denosumab
D. ADT with a baseline dual-energy x-ray absorptiometry (DEXA) scan

There is currently no evidence to support the use of an antiresorptive agent at the time of diagnosis of de novo metastatic disease. The single best treatment for androgen-sensitive prostate cancer is ADT. Patients being started on ADT should have a DEXA scan to calculate a WHO Fracture Risk Assessment (FRAX) score to assess the risk of skeletal-related events (SRE). Patients should be started on calcium and vitamin D supplementation. Antiresorptive agents

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

should be considered for men ≥50 with a history of prior hip or vertebral fracture *OR* osteoporosis (T score: < −2.5) *OR* osteopenia (T score: −1 to −2.5) *AND* one of the following: (i) concurrent ADT use (≥6 months), (ii) fracture at site other than hip or spine, (iii) FRAX score showing a 10-year risk of hip fracture ≥3%, or (iv) a 10-year risk of osteoporosis ≥20%.

3. Abiraterone acetate (AA) was recently approved by the US Food and Drug Administration (FDA) as first-line therapy for castration-resistant prostate cancer (CRPC). What is the mechanism of action for this drug?

A. Luteinizing hormone receptor agonism
B. Luteinizing receptor antagonism
C. CYP17A1 inhibition
D. Inhibition of androgen receptor signaling

AA is a novel, potent inhibitor of CYP17A1. It decreases production of testosterone by inhibiting CYP17A1, an enzyme that is expressed in testicular, adrenal, and prostatic tumor tissues and needed for androgen biosynthesis. AA was shown to improve overall (OS) and progression-free survival (PFS) after treatment with docetaxel in the COU-AA-301 trial. Patients were randomized 2:1 to receive AA versus placebo with 5 mg prednisone twice daily. OS was improved in the AA group (14.8 vs. 10.9 months; HR: 0.65; 95% CI: 0.54–0.77; $P < .001$). PFS and PSA response rates were also superior in the AA arm. The significant side effects of this medication are due to mineralocorticoid excess (hypertension, edema–fluid retention, and hypokalemia). This study led to the approval of the drug as second-line therapy after docetaxel. The more recent COU-AA-302 study compared AA plus prednisone with prednisone alone in patients with progressive metastatic CRPC who had not received chemotherapy and in whom clinically significant cancer-related symptoms had not developed. The study was unblinded at the interim analysis. Patients on the AA arm demonstrated improved radiographic PFS, and they showed a trend toward improved OS and delayed time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, and decline in performance status. This study led to the recent FDA approval of AA as first-line therapy for metastatic CRPC.

4. Are there any new chemotherapeutics beyond docetaxel?

Cabazitaxel is a novel taxane with activity in the preclinical models of cancer resistant to paclitaxel and docetaxel that has demonstrated improved OS when compared with mitoxantrone in the post-docetaxel setting in the TROPIC trial. In this trial, patients received 10 mg of prednisone daily and were randomized to 12 mg/m^2 mitoxantrone or 25 mg/m^2 cabazitaxel every 3 weeks. Overall survival was 15.1 months in the cabazitaxel group versus 12.7 months in the mitoxantrone group (HR: 0.70; 95% CI: 0.59–0.83; $P < .0001$), response rate was 11.4% versus 4.4% ($P = .0005$), and progression-free survival was 2.8 versus 1.4 months ($P < .0001$), respectively.

At the dose administered, cabazitaxel was associated with increased toxicity compared with mitoxantrone. The most significant toxicities seen were grade 3 or greater neutropenia (82%), neutropenic fever (8%), and diarrhea (6%). 12% required dose reductions and 18% required discontinuation of therapy because of these adverse events. Careful monitoring is recommended when administering this agent with a low threshold for dose reduction and for use of growth factor support with granulocyte colony-stimulating factor.

The FIRSTANA trial is currently comparing the efficacy of cabazitaxel to docetaxel as first-line therapy. Patients receive 10 mg prednisone daily with docetaxel at 75 mg/m^2, cabazitaxel at 25 mg/m^2, or cabazitaxel at a lower dose of 20 mg/m^2 every 3 weeks with the primary endpoint of OS.

5. Enzalutamide is not recommended for the treatment CRPC in patients with which of the following conditions?

A. Renal insufficiency
B. Seizures
C. Cardiovascular disease
D. Diabetes
E. All of the above

Enzalutamide is a potent inhibitor of the androgen receptor that prevents androgen binding to the androgen receptor and androgen receptor translocation into the nucleus. It was approved by the FDA in 2012 for the treatment of patients with metastatic CRPC who have previously been treated with docetaxel.

In the phase III AFFIRM study, patients with metastatic CRPC previously treated with docetaxel were randomized 2:1 to receive enzalutamide 160 mg/day versus placebo. OS in the enzalutamide arm was 18.4 months versus 13.6 in the placebo arm. However, it was notable that 7 of 800 patients treated with enzalutamide experienced a seizure versus none in the control group. Consequently, this medication is not recommended for patients with predisposing factors for seizure such as a history of seizure or cerebral vascular accident, a recent transient ischemic attack, brain metastases, or concomitant use of other medication that lowers the seizure threshold.

6. What is the role of sipuleucel-T in the treatment of CRPC?

Sipuleucel-T was the first immunotherapy to demonstrate an OS benefit in the treatment of metastatic CRPC. This agent is produced by isolating autologous peripheral

blood mononuclear cells, including antigen-presenting cell, through leukopheresis and then culturing them with medium that contains the recombinant fusion protein PA2024, consisting of prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor.

This therapy was evaluated in the IMPACT study wherein asymptomatic or minimally symptomatic patients with metastatic CRPC were randomized 2:1 to receive three infusions of sipuleucel-T versus placebo. Overall survival was 25.8 months in the sipuleucel-T arm versus 21.7 months in the placebo arm, and the relative risk of death was 22% lower in the sipuleucel-T group versus placebo (HR: 0.78; 95% CI: 0.61–0.98; $P = .03$). Of note, there was no difference in PSA response rate or PFS associated with this therapy. Interestingly and not surprisingly, Kaplan–Meier survival curves for sipuleucel-T versus placebo diverge after 6 months of treatment. Understanding the mechanisms of OS benefit without improving PFS and identifying who is likely to benefit from therapy remain unclear. The treatment is generally well-tolerated, and it was approved by the FDA for asymptomatic or minimally symptomatic patients with metastatic CRPC who are chemotherapy-naïve or who have received prior chemotherapy. The adoption of this drug into practice was initially slow because of a lack of immediate benefit and cost. Use of this agent has increased over the past year. It is reasonable to consider using sipuleucel-T, particularly in asymptomatic or minimally symptomatic patients or in patients with low PSAs. It should not be used in patients with poor performance status or with rapidly progressive or symptomatic disease.

7. When starting a patient on ADT for rising PSA after definitive therapy, should one start a single agent or use combined androgen blockade for more potent therapy?

Medical or surgical castration is the treatment of prostate cancer that has recurred following definitive therapy with radiation or surgery or de novo metastatic disease. There are several types of agents that can be used to achieve medical castration, including luteinizing hormone–releasing hormone (LHRH) agonists and LHRH antagonists. LHRH agonists stimulate the LHRH receptors, causing an initial testosterone flare. Antiandrogens are typically co-administered with LHRH agonists to mitigate these symptoms. In 2008, Degarelix was the first LHRH antagonist approved by the FDA for the treatment of advanced prostate cancer. LHRH agonists and antagonists are equally effective in achieving medical castration. The advantage of degarelix is that it achieves castration levels of testosterone within 3 days without necessitating the use of a concomitant antiandrogen.

Combined androgen blockade (CAB) is continuous therapy with an LHRH agonist and an antiandrogen. Although randomized trials have not consistently demonstrated a survival benefit to CAB, systematic review and meta-analysis of monotherapy compared with CAB showed a modest increase in overall survival at 5 years for CAB (10 trials; HR: 0.871; 95% CI: 0.805–0.942). For the subgroup of patients with good prognosis, there was no statistically significant difference in survival. Adverse events were more common in the CAB population.

The decision to treat with CAB must balance the risks of adverse effects and the potential for affecting quality of life with a modest survival benefit. Although CAB may be more potent than single-agent therapy, the benefits are probably modest. This area will likely be redefined with the newer androgen-blocking agents such as abiraterone and enzalutamide; however, they are not yet approved for this indication.

8. Is intermittent ADT safe in locally advanced or metastatic prostate cancer?

ADT is associated with side effects of hot flashes, loss of libido, decreased sexual performance, weight gain, accelerated osteoporosis, increased risk of diabetes mellitus, altered lipid profile, and increased cardiovascular risk. For many men with rising PSA after primary therapy, there is the potential to be on ADT for many years. A reasonable question for these men is whether or not they need to remain on ADT continuously or whether there is a role for intermittent therapy.

Several studies have looked at this question of continuous versus intermittent ADT. In a randomized, phase III study, Calais *et al*. (2009) enrolled 766 patients with locally advanced or metastatic prostate cancer. All patients received 3 months of induction therapy with a luteinizing hormone–releasing hormone (LHRH) agonist. Of those, 626 achieved a PSA <4 ng/ml or a decrease in PSA to 80% below the initial value and were randomized to intermittent versus continuous ADT. There was no difference in the overall deaths, and the greater number of cancer-related deaths in the intermittent arm was balanced by the greater number of cardiovascular deaths in the continuous arm. Men in the intermittent arm reported better sexual function. Side effects of therapy were more pronounced in the continuous arm.

In a large study sponsored by the National Cancer Institute of Canada (NCIC), patients with PSA recurrence after radical radiotherapy were randomized to intermittent versus continuous ADT. There was no statistically significant difference in OS in the two arms; however, time to CRPC was significantly improved in the intermittent arm (HR: 0.80; 95% CI: 0.67–0.98; $P = 0.024$). There were no differences in adverse events, including myocardial events or osteoporotic fractures. Hussain *et al*. published preliminary data on their cohort of 1535 patients randomized to con-

tinuous versus intermittent ADT that demonstrated non-inferiority of intermittent versus continuous ADT, but suggested statistically inferior OS in the intermittent cohort of patients with minimal disease.

In conclusion, intermittent ADT is reasonable to consider for patients with locally advanced cancer, a rising PSA post local therapy, or metastatic prostate cancer. While there may be some patients with early metastatic disease who do modestly inferior, overall this approach may offer significant quality-of-life benefits.

9. What is the appropriate duration of ADT with radiotherapy in patients with locally advanced, high-risk prostate cancer?

For the past 25 years, studies have been conducted that compare the survival in patients treated with radiation therapy for locally advanced prostate cancer with and without the addition of ADT. The data overwhelmingly support the use of ADT in this setting; however, the optimal duration of therapy has been the subject of ongoing investigation.

The largest trial to date, RTOG Protocol 92-02, randomized 1554 patients with T2c–T4 prostate cancer with no extrapelvic lymph nodes involvement and PSA less than 150 ng/mL to receive 4 months of goserelin and flutamide, with 65 to 70 Gy given to the prostate and a dose of 44 to 50 Gy to the pelvic lymph nodes with either no additional ADT or 24 months of additional goserelin. The long-term ADT arm showed significant improvement in disease-free survival, cause-specific survival, time to biochemical failure, time to distant metastases, and time to local progression but failed to show a difference in OS. However, in a subset of patients with Gleason 8–10 prostate cancer, long-term ADT had significantly better OS (31.9% vs. 45.1%; $P = .0061$). Bolla *et al*. (2009) randomized patients who had received external-beam radiotherapy and 6 months of ADT to no further treatment or 2.5 years of further treatment. Unlike the RTOG 92-02 trial, Bolla showed an OS benefit with a 5-year overall mortality of 15.2% in the long-term group versus 19.0% in the short-term group.

For a patient with locally advanced prostate cancer (Gleason grade 8 to 10) who are opting for external-beam radiation therapy, long-term (up to 3 years) concomitant, continuous ADT is recommended.

10. How do you determine the best treatment plan for a patient with clinically localized prostate cancer when choosing between active surveillance (AS), prostatectomy (RP), and radiation therapy (RT)?

It is difficult to define a simple standardized treatment plan for patients with localized prostate cancer. The decision must take into consideration a number of factors, including age, life expectancy, comorbidities, logistics, and patient preferences.

AS should be considered in patients with Gleason 6 prostate cancer that involves no more than three cores and no more than 50% of one core, clinical stage T1c, and PSA density <0.15 mg/mL/g. Typically, in such patients if AS is used, periodic reassessments of the prostate are made through biopsy. The main rationale for this is that sampling error may occur on a biopsy. In addition, the degree to which Gleason 6 cancer evolves into higher-grade cancer is not yet known. The rationale for AS in this population is that it is enriched for many who will never require treatment and thus avoids unnecessary treatment and consequent side effects. The risk of delaying such definitive therapy is that the window of opportunity to cure the disease could be lost or that by allowing the prostate cancer to continue to grow, surgery could become more complicated and the side effects of the procedure more pronounced. The emotional welfare of the patient must also be considered when recommended active surveillance. Some patients may find the emotional distress of deferring therapy more significant than the side effects associated with the therapy itself. For patients with a limited life expectancy in whom prostate cancer is not likely to be the ultimate cause of death because of age or other comorbidities, a less invasive strategy such as watchful waiting may be indicated. In this scenario, treatment is only used if symptoms occur attributable to the cancer.

Radical prostatectomy can be a good treatment option for younger, healthier patients, particularly those with a life expectancy >10 years. Prostatectomy can be performed either by an open procedure or with robotic assistance. When studied, disease-specific survival was comparable with these modalities, but length of stay for the robot-assisted procedure was reduced by one day as compared with the open procedure (however, rates of incontinence and impotence were higher). Recovery of erectile function is related to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Urinary continence is also related to nerve-sparing techniques; thus, the skill of the surgeon is important in the quality of life outcomes of the surgery. High-volume surgeons at high-volume medical centers typically demonstrate better outcomes. For patients with inflammatory bowel disease or bladder outlet obstruction requiring an indwelling Foley catheter, prostatectomy would be the preferred method of treatment over radiation therapy.

Radiation therapy is another reasonable option and comes in a variety of forms, including external beam or brachytherapy. External beam might be considered for patients in whom surgery is too risky (e.g., they have comorbidities that might make surgery more challenging) or for those who have locally advanced cancer in which ADT is used in combination. Brachytherapy may be

considered in patients with good-risk disease who prefer treatment over AS. Higher-risk patients should avoid brachytherapy monotherapy. RT avoids many of the complications of surgery such as blood loss, myocardial ischemia, or pulmonary embolism. The risk of urinary incontinence is comparatively very low. The treatment course of external beam extends over 8+ weeks, so the patient must be able to accommodate the logistics of travel to a radiation facility daily during this period of time. Brachytherapy can be administered in a single day. Both surgery and radiation can cause decline in erectile function.

Again, the decision about the management of localized prostate cancer must be individualized and should take into consideration the relative pro's and con's of each modality for each patient.

11. What sequence of therapy would you recommend for CRPC?

With the approval of abiraterone as first-line therapy and enzalutamide likely to follow, the landscape of how metastatic CRPC is treated is rapidly changing. The major branch point in clinical decision making is whether or not the patient is symptomatic from his disease.

For nonmetastatic CRPC, there is no standard therapy. One could consider clinical trials or use of second-line hormonal therapy such as antiandrogens, antiandrogen withdrawal, and glucocorticoids. There is no therapy that has been shown to improve survival in this setting. Observation is also reasonable for those patients with a slow PSA velocity.

For asymptomatic, metastatic CRPC, initial therapy recommendations include immunotherapy (sipuleucel-T), androgen-signaling inhibitors (abiraterone (approved) and enzalutamide (not yet approved)), and clinical trials. A bone-modifying agent such as zoledronic acid or denosumab should be considered for prevention of skeletal-related events.

For symptomatic, metastatic CRPC first-line therapy remains docetaxel. Chemotherapy should be used for patient with high-volume disease, symptomatic bone metastases, short duration or response to ADT, or a rapid PSA doubling time. Pending approval, radium-223 (Alpharadin) would also be an option. In the phase III ALSYMPCA study, patients with CRPC post docetaxel with two or more bone metastases and no visceral metastases were randomized 2:1 to receive radium-223 or placebo. Overall survival was 14.0 in the radium-223 group versus 11.2 months in the placebo group (HR: 0.695; 95% CI: 0.552–0.875; $P = .00185$). Time to SREs was 13.6 for radium-223 versus 8.4 for placebo ($P = .00046$). It is currently available through an expanded-access protocol for patients with symptomatic bone metastases who are ineligible for chemotherapy.

Post-docetaxel options depend, in part, on response to docetaxel. If a patient is sensitive to docetaxel with good response, it is reasonable to retreat and consider a chemo holiday. If resistance and hormonal-signaling agents were not used first-line, enzalutamide or abiraterone rather than further chemo would be advisable as they are easier for the patient to tolerate than cytotoxic chemotherapy. If the patient is asymptomatic at this point, sipuleucel-T would also be a consideration. For progressive, symptomatic disease next-line therapies include cabazitaxel, mitoxantrone, radium-223, and clinical trials.

12. Should routine PSA screening be offered to men?

Introduced in the late 1980s, the PSA was initially used as a marker of relapse or progression, similar to the Ca-125. In 1991, Catalona *et al*. published a paper stating that the combination of PSA measurement and digital rectal exam (DRE) with ultrasound for abnormal findings was a superior screening method as compared with DRE alone. Over time, the PSA was adopted for cancer screening, but there was no Level 1 evidence that screening changed outcome.

In 2009, two large, randomized trials for prostate cancer screening were published. The European Randomized Study of Screening for Prostate Cancer (ERSPC) involved over 182,000 men from seven countries. Participants were randomized to invitation to screen an average of every 4 years versus not invited to screen. There were almost twice as many cancers diagnosed in the screening arm compared to the nonscreened arm (8.2% vs. 4.8%) and a 20% reduction in prostate cancer mortality in the prespecified core group of men ages 55–69. The number needed to screen to prevent one cancer death was 1410, and the number needed to treat to prevent one cancer death was 48.

The second large study was the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial, which randomized 76,693 men at 10 US study centers to either annual PSA testing for 6 years and DRE for 4 years or control. One of the major criticisms of this trial is that 52% of the control group had PSA testing over the course of the study. 22% more cancers were found in the screening arm (as compared with almost 50% in the ERSPC trial), which likely is a reflection of the degree of contamination in the control group of this study. At 7 years, the reduction in mortality from screening was not statistically significant. This low number suggests that longer follow-up and more events are needed to draw conclusions from this paper.

In response to these studies and growing concern that men were being overtreated for their prostate cancers, in 2012, the US Preventive Services Task Force (USPSTF)

updated its guidelines to recommend that men not be screened for prostate cancer, concluding that there was moderate certainty that the benefits do not outweigh the harms of overtreatment. The American Urological Association continues to recommend PSA-based screening beginning at age 40. The American Cancer Society (ACS) has taken a more cautious approach, recommending a discussion of the risks and benefits but favoring screening starting at the age of 50.

It is probably safe to say that the benefits of screening in the first decade will likely be very modest such that men with less than a 10-year life expectancy should probably not be screened. We would recommend a discussion of risks and benefits with patients, recognizing that most patients will rely on us to make the judgment. We would recommend PSA testing and DRE with a full understanding that while there is likely a benefit with regard to mortality, overtreatment may occur. Thus, not all with prostate cancer that is diagnosed should be treated.

13. True or false? Is ADT is a reasonable alternative to consider for localized prostate cancer in elderly patients?

A. True
B. False

The use of primary androgen therapy for localized prostate cancer should be discouraged. Standard therapies include prostatectomy, radiation therapy, or active surveillance. In 2008, Lu-Yao *et al*. published analysis of pooled data from the SEER database and included 19,271 men older than 66 years old, 41% of who received primary androgen deprivation therapy (luteinizing hormone receptor agonists) as first-line treatment for localized prostate cancer versus conservative management. Primary ADT was associated with a lower 10-year prostate cancer-specific survival (HR: 1.17; 95% CI: 1.03–1.33) and no increase in 10-year overall survival (HR: 1.00; 95% CI: 0.96–1.05) compared with conservative management (deferral of treatment until necessitated by disease signs or symptoms).

Anti-androgen therapy is also not recommended. Iversen *et al*. randomized 8113 patients to receive either oral bicalutamide 150 mg daily or placebo. For patients with clinically localized prostate cancer, there was no progression-free survival benefit and no overall survival benefit. In fact, there was a survival trend in the placebo arm favoring surveillance over bicalutamide (HR: 1.15; 95% CI: 1.00–1.32; $P = 0.054$).

In addition to the data that fail to demonstrate a survival benefit for hormonal therapy in clinically localized prostate cancer, one must also consider the quality of life and treatment-related side effects associated with ADT such as hot flashes, loss of libido, decreased sexual performance, weight gain, accelerated osteoporosis, increased risk of diabetes mellitus, altered lipid profile, and increased cardiovascular risk. Taken together, ADT should not be recommended for primary treatment of localized prostate cancer.

14. What is the role of antiresorptive agents in the prevention of SREs in men with metastatic CRPC?

Over the last decade, bone-modifying agents have become recognized as an important therapy in patients with metastatic CRPC. In 2004, Saad *et al*. demonstrated that zoledronic acid, a bisphosphonate, reduced the risk of skeletal-related events in patient with metastatic CRPC. In the 24 months on study, 20% fewer patients had at least one SRE when receiving zoledronic acid as compared with placebo. In 2011, Fizazi *et al*. randomized 1909 patients to receive denosumab, a human monoclonal antibody against RANKL, or zoledronic acid. Overall survival and time to progression were the same. However, denosumab delayed the time to first on-study SRE (pathological fracture, spinal cord compression, and need for radiation therapy or surgery to bone) by 18% compared with zoledronic acid. Overall adverse events were similar between the two groups. Hypocalcemia was more common with denosumab (13%) than zoledronic acid (6%) ($P < 0.0001$). Osteonecrosis was rare and not significantly different between the two groups. Acute-phase reactions during the first 3 days of treatment were more common with zoledronic acid (18%) versus with denosumab (8%).

In conclusion, zoledronic acid and denosumab are both reasonable options for the delay or prevention of SREs in CRPC. Optimal scheduling of these agents has not been determined. When deciding which agent to choose for a patient, consider factors such as dentition, convenience for the patient (denosumab: subcutaneous; and zoledronic acid: IV), renal function, cost, and co-pay when making the decision.

15. What is the significance of PSA surveillance in ADT?

Androgen deprivation therapy is the backbone of systemic therapy for metastatic prostate cancer. Once a patient is started in ADT, PSA is typically monitored every 3 months for evidence of relapse. The expectation is that the PSA will rapidly decline after the initiation of therapy and remained suppressed until such a point in time as the prostate cancer begins to grow independent of its hormone-deprived state. Hussain *et al*. (2006) concluded that the absolute level of PSA at nadir was significant in predicting survival in metastatic prostate cancer.

1345 men with a PSA of 4 ng/mL or less after 7 months of ADT induction were randomized to either continuous or intermittent ADT thereafter. The authors concluded that a PSA of 4 ng/mL or less after 7 months of ADT is a strong

predictor of survival. Patients with a PSA of 0.2 mg/mL or less have the greatest survival advantage.

In conclusion, PSA is used to follow prostate cancer and the PSA nadir after induction with ADT is predictive of overall survival, with lower PSAs favoring improved survival.

Multiple choice answers

Question 2: Answer D
Question 3: Answer C
Question 5: Answer B
Question 13: Answer B

Selected reading

Berger MF, Lawrence MS, Demichelis F, *et al*. The genomic complexity of primary human prostate cancer. Nature. 2011; 470:214–20.

Chen Y, Clegg NJ, Scher HI, *et al*. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. Lancet Oncol. 2009;10:981–91.

Gaster B, Edwards K, Trinidad SB, *et al*. Patient-centered discussions about prostate cancer screening: a real-world approach. Ann Intern Med. 2010;153:661–5.

Hayes JH, Ollendorf DA, Pearson SD, *et al*. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. JAMA. 2010;304:2373–80.

Hoffman R. Screening for prostate cancer. N Engl J Med. 2011; 365:2013–9.

For further information on this area please also consult Chapters 115, 122, 126, 128, 136, and 140

CHAPTER 99

Germ cell tumors

Timothy Gilligan

Taussig Cancer Institute and Center for Excellence in Healthcare Communication, Cleveland Clinic, Cleveland, OH, USA

Multiple choice and discussion questions

1. When staging a man with a disseminated germ cell tumor (GCT), at what time point should serum tumor markers (STMs) be drawn in order to determine his prognosis and stage?

A. Prior to orchiectomy
B. Following orchiectomy
C. On day 1 of cycle 1 of chemotherapy
D. Whichever of the above numbers is highest

For men with disseminated GCTs, prognosis should be based on the burden of disease at the time that systemic therapy is started. Therefore, the optimal time to measure serum beta-hCG (human chorionic gonadotropin), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH) is immediately prior to initiating chemotherapy. The analysis used to develop our current prognostic classification and staging of GCTs was based on tumor marker levels at the time that systemic therapy was started.

The STMs beta-hCG and AFP should be drawn prior to orchiectomy but not for prognostic purposes. The STM levels prior to orchiectomy reflect the primary tumor as well as any metastatic disease, and thus are an unreliable indicator of the extent of any disseminated disease. The value of pre-orchiectomy beta-hCG and AFP is twofold: an elevated AFP excludes a diagnosis of pure seminoma regardless of the histopathological findings (unless an alternative, non-GCT explanation for the AFP elevation is established), and having pre-orchiectomy markers facilitates interpretation of post-orchiectomy markers. In other words, if STMs are elevated after orchiectomy, it is helpful to know whether the levels are higher or lower than they were prior to orchiectomy. If beta-hCG or AFP is persistently elevated or rising following orchiectomy, this is indicative of disseminated disease even in the absence of any radiographic evidence of metastases, and the standard treatment is chemotherapy. In contrast to AFP and beta-hCG, the only role for measurement of serum LDH is to establish prognosis at the start of chemotherapy. An elevated LDH may result from myriad different conditions and is often unrelated to the patient's cancer. There is no clear reason to measure LDH levels before or after orchiectomy unless the patient is going to start treatment with chemotherapy for metastatic disease.

2. Is surveillance the best option for all men with stage I nonseminomatous germ cell tumors (NSGCTs) of the testis?

A. Yes
B. No

Surveillance is an excellent option for most men with stage I NSGCTs but is not the best option for everyone. It does not make logical sense to choose surveillance if the patient will not be able to comply with the surveillance schedule. There may be psychological, economical, geographical, or other obstacles to compliance. Assessing the feasibility of frequent visits for blood tests and physical examination and less frequent visits for imaging studies is essential prior to deciding upon surveillance as a management strategy. Primary chemotherapy lowers the risk of relapse from about 30% to about 2%, and thus the benefit of surveillance and the risk associated with noncompliance with surveillance are much smaller in a patient who has been treated with primary chemotherapy. RPLND also lowers the risk of relapse but by a lesser degree than primary chemotherapy.

A second reason that surveillance may not be the best option for some men with clinical stage I (CSI) NSGCT has to do with patient preference. Being diagnosed with cancer is often psychologically traumatic and disruptive, resulting

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

in time away from work or school, lost income, as well as anxiety and distress. Relapse of the cancer repeats this trauma and disruption, often with greater severity. Moreover, relapse comes at an unpredictable time and cannot be planned or incorporated into the patient's schedule with regard to education, career, or family. For some patients, the ability to choose to have chemotherapy now (rather than to possibly receive it at an unpredictable future time) and to have greater peace of mind as a result of a near-zero risk of relapse outweighs the downsides of receiving chemotherapy that they probably don't need. Shared decision making is thus appropriate with regard to management of stage I NSGCT so that the patient's values and priorities can be incorporated into the decision-making process.

In choosing a management strategy, assessing risk of relapse is important. The most commonly used risk factor for relapse is the presence of lymphovascular invasion (LVI) in the primary tumor. The other often-used risk factor is a predominance of embryonal carcinoma (EC). Roughly half of men with LVI will relapse, and in some studies a predominance of EC further increases that risk. While it is well documented that men with a high risk of relapse can be safely managed with surveillance, surveillance is often less attractive to these men and their physicians. Some experts prefer a risk-adapted approach, while others prefer surveillance for all patients able to comply with a surveillance schedule. A risk-adapted approach typically means treating men with LVI while surveilling men without LVI. Studies of this approach have generally given two cycles of BEP chemotherapy to men with an increased risk of relapse, although a single cycle of BEP produces a relapse rate of less than 5%.

In summary, surveillance is a good option for all men with CSI NSGCT who are willing to comply with the surveillance schedule, but some men may prefer treatment with chemotherapy. Men without LVI can be treated with a single cycle of BEP, but men with LVI who decline surveillance should be treated with two cycles of BEP. Retroperitoneal lymph node dissection (RPLND) is also an option but should only be performed if a surgeon who performs the operation frequently is available. RPLNDs performed by surgeons who perform the operation infrequently yield inferior results.

3. Is surveillance the best option for all men with stage I testicular seminomas?

No. Surveillance is the best option for most but not all men with stage I testicular seminoma. Following orchiectomy, the risk of relapse for CSI seminoma of the testis is about 15% to 18%: surveillance spares more than four out of five men unnecessary additional therapy. Moreover, surveillance results in long-term disease specific survival of over 99%. So treating with carboplatin chemotherapy or radiation therapy after orchiectomy does not increase either disease-specific or overall survival. The rationale for treating CSI seminoma is not based on preventing deaths from testis cancer but rather on wanting to lower the risk of relapse because relapse and the subsequent need for treatment can be highly disruptive.

Treatment options for clinical stage I seminoma include surveillance, one or two cycles of single-agent carboplatin chemotherapy, and radiation therapy to either a para-aortic strip field or a dogleg (aka hockey-stick) field that includes the para-aortic strip plus the proximal ipselateral hemipelvis. Relapse rates are 15–18% with surveillance, 5% with a single cycle of carboplatin, 4% with radiation therapy, and 2% with two cycles of carboplatin. Radiation therapy has been less popular over the past decade because of extensive data showing an increased risk of being diagnosed with a variety of cancers after radiation therapy for seminoma. Whether carboplatin at the doses used in this setting is associated with significant late toxicity is not yet clear, but both cisplatin and carboplatin have been associated with a higher risk of second cancers when used at higher doses. The bottom line is that surveillance is the preferred option for most men, but two doses of carboplatin produce the lowest relapse rate for men who prefer active treatment.

4. What are the preferred surveillance schedules for testicular seminomas and nonseminomas?

For patients with clinical stage I testis cancer, surveillance schedules must balance the benefit of detecting a relapse as early as possible against the potential harm of radiation exposure and the need not to waste medical resources on unnecessarily intensive testing. Clinical stage I testicular seminoma typically relapses in the retroperitoneum with normal STM levels. As a result, cross-sectional imaging is the only reliable way to detect relapse. Fortunately, seminomas tend to grow more slowly than nonseminomas. There are a variety of different scanning schedules that have been published. The Princess Margaret Hospital schedule has been used in one of the largest experiences with surveillance, and they have obtained a computed tomography (CT) scan of the abdomen and physical examination at the following intervals: every 4 months for the first 3 years, every 6 months for the next 3 years, and then once a year until the patient is 10 years out. Chest X-ray is obtained at alternating visits for the first 6 years and then annually until year 10. While magnetic resonance imaging may one day replace CT scans and thus eliminate ionizing radiation, it is not clear that they are as reliable for detecting relapse due to the increased difficulty of interpreting them accurately.

Table 99.1 Surveillance schedule of clinical stage I (CSI) nonseminomatous germ cell tumors (NSGCTs).

	Serum tumor markers AFP and beta-hCG and physical exam	Chest X-ray	CT abdomen and pelvis
Year 1	Monthly	Every 2 months	At 3 and 9 months
Year 2	Every 2 months	Every 2 months	At 18 months
Year 3	Every 3 months	Every 3 months	At 30 months
Year 4	Every 4 months	Every 4 months	At 42 months
Year 5	Every 6 months	Every 6 months	At 60 months
Years 6–10	Every 12 months	Every 12 months	

AFP, alpha-fetoprotein; CT, computed tomography; hCG, human chorionic gonadotropin.

For stage I nonseminomas, a more intensive surveillance schedule is used, but a number of guidelines recommend obtaining CT scans at frequent intervals that are not supported by solid evidence. An international study compared a surveillance schedule that obtained CT scans at months 3 and 12 to a schedule that included scans at months 3, 6, 9, 12, and 24 months. No difference in outcome was reported. Nonetheless, many experts are uncomfortable with stopping CT scans at 12 months due to the fact that a significant number of relapses occur in the second and third years. The surveillance schedule shown in Table 99.1 is thus recommended.

Case study 99.1

• If I treat a stage I testis cancer patient with chemotherapy, should I give one or two cycles?

A 32-year-old man with a newly diagnosed mixed GCT of the right testis that shows lymphovascular invasion and consists of 80% embryonal carcinoma and 20% seminoma elects to undergo chemotherapy. A chest X-ray and CT of the abdomen and pelvis show no evidence of metastases, and his STMs are normal following orchiectomy.

1. Which of the following would be the most appropriate regimen for this man?

A. One cycle of bleomycin, etoposide, and cisplatin chemotherapy
B. One cycle of carboplatin chemotherapy
C. Two cycles of bleomycin, etoposide, and cisplatin chemotherapy
D. Two cycles of carboplatin chemotherapy

It must be emphasized that there is no specific level I evidence to address this question with regard to whether to give one or two cycles of BEP. Both have produced excellent results. What is clear is that no data support the use of carboplatin in this setting, and the substitution of carboplatin for cisplatin in multi-agent regimens has been shown to result in inferior outcomes in patients with metastatic disease.

Regarding one versus two cycles of BEP, data support each approach. Studies of two cycles of BEP (and similar cisplatin-based multiagent regimens) have been published reporting outcomes on over 750 men, and the overall relapse rate averaged over studies is 2.0%. Results have also been published on over 500 men with CSI NSGCT who were treated with a single cycle of BEP (or a similar regimen), and the average reported relapse rate is a similar 2.2%. However, the studies of two cycles of BEP have tended to focus on high-risk patients, typically defined as men whose tumors had lymphovascular invasion. In contrast, much of the data on a single cycle of BEP are from men whose tumors did not have lymphovascular invasion. In surveillance studies, men with LVI+ tumors have a relapse rate of roughly 50%, while men with LVI− tumors have a relapse rate of less than 15%. Therefore, studies of BEP ×2 have generally studied a different group of patients than the studies of BEP ×1. In addition, the SWENTOTECA group has reported better outcomes for two cycles of chemotherapy for high-risk patients. Their earlier studies of PVB (cisplatin, vinblastine, and bleomycin) in CSI NSGCT patients reported a relapse rate of 1.7% in 60 LVI+ patients who received two cycles of chemotherapy compared to a rate of 10% in 40 LVI− patients treated with a single cycle of chemotherapy. Similarly, a subsequent SWENTECA study of BEP in LVI+ patients reported that two cycles resulted in a relapse rate of 0% in 70 men compared to a relapse rate of 3.2% in 157 men treated with a single cycle of BEP.

(*Continued*)

These data indicate that while a single cycle of BEP appears to be adequate for men without lymphovascular invasion in their tumors, two cycles may be more effective for men at high risk of relapse based on LVI.

For men with clinical stage I pure seminomas, a similar dilemma exists. The randomized controlled trial of a single cycle of carboplatin dosed at an area under the curve (AUC) of 7 reported a relapse rate of 5.3%, while studies of two cycles of carboplatin dosed at an AUC of 7 or 400 mg/m^2 have reported an average relapse rate of 2.0%. No trial has compared one versus two doses of carboplatin, but given the minimal toxicity of this regimen, giving a second dose to cut the relapse risk by more than 50% seems justifiable.

2. If the decision is made to perform a retroperitoneal lymph node dissection, should I refer the patient to the local urologist I work with or to a surgeon who performs a high volume of these operations?

A. To the local urologist who I normally work with
B. To a urologist who performs a high volume of RPLNDs

The favorable outcomes that have been reported for RPLNDs come almost exclusively from centers and surgeons who have extensive experience with performing the operation. In contrast, data from urologists without extensive experience are disappointing. For instance, a randomized control trial comparing a single cycle of BEP chemotherapy to RPLND in clinical stage I NSGCT testis cancer patients that was conducted at community hospitals rather than specialized centers reported that more than half the relapses after RPLND (over 4% of patients) occurred in the retroperitoneum. In contrast, the expected rate of retroperitoneal relapse at centers of excellence is fewer than 2% in their CSI and CSII patients treated with RPLND. In addition, a skilled surgeon can preserve antegrade ejaculation in almost all men with CSI NSGCTs without compromising the oncologic effectiveness of the operation by applying nerve-sparing techniques. It is thus strongly advisable to refer patients to a high-volume surgeon at a center of excellence when RPLND is indicated.

5. Should all stage II testis cancer patients be treated with chemotherapy?

A. Yes
B. No

Chemotherapy is not the preferred treatment for most men with stage IIA seminoma or nonseminoma who have normal STM levels. For clinical stage IIA nonseminomas, the false-positive rate on CT scans is 10–40%, so three cycles of BEP chemotherapy represent substantial overtreatment for many men. Close surveillance to watch for progression or RPLND to confirm stage of disease is preferred to chemotherapy for these patients. Exceptions to this recommendation include men with numerous enlarged nodes, particularly when the nodes are in the primary landing zone for the cancer (which is different for left- and right-sided testis cancers). Of note, men with persistently elevated STMs following orchiectomy should undergo chemotherapy for disseminated disease regardless of the presence or absence of retroperitoneal adenopathy.

The false-positive rate for clinical stage IIA seminomas is not known. Men with borderline normal scans can be closely observed for progression, but the standard treatment for Stage IIA patients is radiation therapy rather than chemotherapy. However, there are no randomized controlled trials comparing outcome after these two approaches, so the practice is based on habit and past experience rather than level I data. Most men with stage IIB seminomas are also managed with radiation therapy, although chemotherapy with BEP ×3 (or EP ×4) represents an acceptable alternative. Exceptions to this practice include men with IIA or IIB disease with enlarged nodes in multiple regions of the retroperitoneum; such men should be treated with BEP ×3 (or EP ×4) In general, the acute side effects of radiation are milder than those of three cycles of BEP chemotherapy, but there are insufficient data to compare chronic and late toxicity. Although the risk of death from stage IIA seminomas treated with radiation or chemotherapy is less than 5%, both modalities have been associated with an increased risk of secondary malignancies.

6. For men with good risk disseminated GCTs, which should I give?

A. Three cycles of BEP
B. Four cycles of EP

Although both regimens are entirely acceptable, the data supporting three cycles of BEP are stronger. Numerous trials have been conducted comparing regimens that include bleomycin to regimens that do not include bleomycin, and in each trial, the trend has favored the bleomycin arm. The one randomized controlled trial comparing three cycles of standard-dose BEP to four cycles of standard-dose EP reported that the risk of death for men in the EP ×4 arm was more than twice as high as in the BEP ×3 arm (HR: 0.42; 95% CI: 0.15–1.20) but the difference was not statistically significant. Most centers thus prefer BEP ×3 to EP ×4, but both are highly effective. EP ×4 is the preferred regimen for men with a contraindication to bleomycin and for men started on BEP who develop signs or symptoms of bleomycin pulmonary toxicity. In addition, because bleomycin is cleared by the kidneys, patients with compromised renal

function due to comorbidity or advanced age may be better off receiving EP ×4.

7. If a man has reduced renal function, should I substitute carboplatin for cisplatin?

A. Yes
B. No

With rare exceptions, carboplatin should not be substituted for cisplatin because randomized controlled trials have demonstrated that cisplatin results in superior outcomes. When carboplatin was substituted for cisplatin in BEP chemotherapy, the number of deaths doubled in one trial and quadrupled in another. When etoposide plus carboplatin was compared to etoposide plus cisplatin, there were four times as many relapses in the carboplatin arm. In general, the thinking is that it is better to be alive with renal failure (after cisplatin) than dead with normal kidneys (after carboplatin). However, even though carboplatin is not as effective as cisplatin, it is still highly effective. For instance, among good-risk patients with normal renal function who are treated with four cycles of etoposide and carboplatin for metastatic disease, fewer than 20% relapse.

Men with disseminated GCTs and renal insufficiency should be referred to centers with extensive experience with treating testis cancer, and they should be treated with cisplatin and etoposide. There are case reports of administration of full-dose cisplatin and etoposide to patients on hemodialysis. For patients with a GFR less than 50 cc/min, bleomycin either should not be used or else the dose should be reduced as recommended in the package insert. Bleomycin is renally cleared, and patients with renal insufficiency are at high risk of bleomycin pulmonary toxicity, which is often fatal. For patients with intermediate- or poor-risk disease, etoposide, ifosfamide, and cisplatin (VIP) appears to be the preferred regimen in the setting of renal failure but there is little data to guide the management of these patients

8. When should VIP ×4 be used instead of BEP ×4 to treat dissminated germ cell tumors?

A. When the patient has brain metastases
B. When the patient has liver or bone metastases
C. When the patient has a mediastinal primary nonseminomatous germ cell tumor
D. When the patient has lung metastases

For most men, BEP ×4 is preferred because it is less toxic, with a lower rate of high-grade hematologic toxicity and a lower incidence of renal failure. However, in two randomized controlled trials, there was no significant difference with regard to treatment-related deaths, overall survival, or other cancer outcomes. For men with a contraindication to bleomycin and for men who develop evidence of bleomycin pulmonary toxicity during treatment, VIP is an alternative therapy that appears to be equally effective. In addition, four cycles of VIP is the preferred regimen for men with a primary mediastinal nonseminoma because they will require major chest surgery following chemotherapy and exposure to bleomycin would place them at high risk for perioperative pulmonary complications. For the same reason, VIP may be preferred for men with intermediate- or poor-risk nonseminoma and bulky lung metastases who are likely to require postchemotherapy resection of residual masses.

9. What is the preferred second-line chemotherapy regimen?

A. Vinblastine, ifosfamide, and cisplatin (VeIP)
B. Paclitaxel, ifosfamide, and cisplatin (TIP)
C. Two cycles of high-dose carboplatin and etoposide (HDCE)
D. Any of the above

Data support all three of these regimens, and there is no persuasive evidence that one is better than the others. However, for most centers, four cycles of either VeIP or TIP represent the best option. Although promising results have been reported for tandem cycles of HDCE, these data come from a center where hematopoietic stem cell collection and subsequent high-dose chemotherapy could begin almost immediately without the need to give cycles of standard-dose chemotherapy while waiting for insurance approval for stem cell transplantation. At most centers, there is a substantial delay involved in waiting for insurance approval and scheduling pheresis, and patients typically receive several cycles of TIP or VeIP while waiting, which can make them less fit for high-dose chemotherapy. It is not clear that the exciting single-center results of HDCE can be replicated elsewhere at this time.

10. Should men with brain metastases be treated with whole-brain radiation therapy?

A. Yes
B. No
C. Only if there are multiple residual lesions following chemotherapy

Brain metastases from gonadal and extragonadal GCTs in men are rare, and there are no trials that inform us about optimal management. In practice, systemic chemotherapy is the primary treatment of brain metastases in GCTs in men. Most brain tumors occur in the setting of widespread metastatic disease, and in the absence of a neurological emergency necessitating local therapy first, the initial treatment is typically four cycles of BEP chemotherapy. If there is a residual mass, then resection is preferred when feasible to resect chemoresistant and potentially radiation-resistant tumor. When surgery is not feasible,

stereotactic radiosurgery should be considered. Whole-brain radiation should be reserved for patients with multiple residual tumors or an extensive solitary residual mass not amenable to stereotactic radiosurgery.

11. If a patient is receiving chemotherapy for a GCT, under which circumstances should I delay chemotherapy and/or reduce the dose?

A. When the neutrophil count is less than $1000/mm^3$
B. When the platelet count is less than $50{,}000/mm^3$
C. When the creatinine is above 1.7 mg/dL
D. When the patient has febrile neutropenia

Febrile neutropenia represents a clear reason to delay chemotherapy and to consider a dose reduction for subsequent cycles (etoposide, ifosfamide, and paclitaxel doses should be reduced by 25% if dose reducing, but the cisplatin dose should not be reduced). An alternative to dose reduction in this setting is to add a granulocyte colony-stimulating factor to subsequent cycles if it wasn't used in the cycle complicated by febrile neutropenia. Throbocytopenic bleeding is also an indication to reduce doses (as discussed here) for subsequent cycles. Chemotherapy doses should not be delayed due to myelosuppression alone. No dose adjustments are indicated for a serum creatine less than 2.0 mg/dL. See Question 8 of this chapter for additional information on chemotherapy in the setting of renal failure.

Case study answers

Case study 99.1

Question 1: Answer C
Question 2: Answer B

Multiple choice answers

Question 1: Answer C
Question 2: Answer B ("No")
Question 5: Answer B ("No")
Question 6: Answer A
Question 7: Answer B ("No")
Question 8: Answer C
Question 9: Answer D
Question 10: Answer C
Question 11: Answer D

Selected reading

Chung PW, Bedard P. Stage II seminomas and nonseminomas. Hematol Oncol Clin North Am. 2011;25(3):529–441,viii.

de Wit R, Stoter G, Sleijfer DT, *et al*. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. Br J Cancer. 1998;78(6):828–32.

Einhorn LH, Williams SD, Chamness A, *et al*. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007;357(4):340–8.

International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol. 1997;15(2):594–603.

Oliver RT, Mead GM, Rustin GJ, *et al*. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol. 2011;29(8):957–062.

For further information on this area please also consult Chapters 71, 122, 127, and 141

PART 6

Skin Malignancies

CHAPTER 100

Medical management of melanoma

Ana M. Ciurea[1] and Kim Margolin[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]University of Washington, Seattle, WA, USA

Introduction

Rising incidence rates of cutaneous melanoma have been observed during the last 4 decades in Caucasians in the United States and around the world. Melanoma accounts for less than 5% of skin cancer cases but causes a large majority of skin cancer deaths.

The outcome is highly dependent on the stage of the disease; primary cutaneous melanoma, when excised appropriately, is highly curable, while metastatic melanoma comes with a very poor prognosis despite treatment. Because early disease is significantly more favorable in prognosis, there has been much focus on the need to identify those at greatest risk for melanoma for screening and prevention measures.

Case study 100.1

A 54-year-old man with history of hypertension and a family history of melanoma in his uncle, presents for a complete skin examination. Patient has fair skin complexion and reported numerous blistering sunburns as a child. He used tanning beds briefly in the past. He denies new, changing, or symptomatic skin lesions. On physical examination, patient has multiple solar lentigines and five uniformly pigmented 1–2 mm brown macules with regular borders located on his trunk and legs.

1. The patient is concerned about developing melanoma. The most important risks factors include all EXCEPT which of the following?

A. Fair skin complexion
B. History of blistering sunburns as a child
C. Prior tanning bed use
D. Family history of melanoma in uncle
E. Presence of five nevi on the skin

The major risk factors for development of melanoma are essential to optimize primary and secondary prevention strategies. The main environmental risk factor is excessive exposure of fair-skinned individuals to ultraviolet (UV) radiation. It has been suggested that intermittent sun exposure resulting in sunburns in unacclimatized fair skin is a greater risk factor for melanoma than chronic lifetime sun exposure.

The patients with an increased number of benign melanocytic lesions have increased risk for the development of melanoma. A suggested number over which patients are at increased risk is 50. More than five atypical (dysplastic) nevi that are larger than 5 mm in diameter, asymmetric in shape and color, and with irregular edges are also a risk factor for melanoma, especially if they occur in families as manifestation of the dysplastic nevus syndrome (DNS). There is a correlation between CDKN2A mutations in family members with the DNS in about 20% of the patients, and CDK4 mutations have been described.

Large congenital nevi (>20 cm in diameter) have an estimated lifetime risk of between 5% and 20% for malignant transformation.

Further risk factors include phenotypic factors (pale skin, light eyes and hair, the presence of freckles, inability to tan, and burns easily), personal history of melanoma (3–5% risk of developing a second melanoma in the absence of atypical

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

nevi), immunosuppression, DNA repair defects (e.g., xeroderma pigmentosum), and equatorial latitudes.

About half of all melanoma skin cancers occur in men over age 50. In a new survey, 51% of US men reported using sunscreen in the past 12 months and 70% did not know the warning signs of skin cancer.

Indoor UV tanning bed users are 74% more likely to develop melanoma than those who have never tanned indoors. Additionally, the more time a person has spent tanning indoors, the higher the risk. One tanning bed session raises melanoma risk by 20%, according to Boniol *et al*. (2012).

Early detection is crucial in reducing melanoma morbidity and mortality. Potential interventions include educating patients about the importance of self-skin examinations, increasing total-body skin screenings by physicians, creating specialized skin cancer clinics, and developing diagnostic tools through advances in technology.

Case study 100.2

A 49-year-old man diagnosed with melanoma in situ on the left anterior thigh presents for a complete skin examination. He is concerned about risks of developing a secondary malignancy.

1. In discussing with the patient, what do you inform him that he is at high risk for?

A. Lung cancer
B. Brain cancer
C. Non-Hodgkin lymphoma (NHL)
D. Colon cancer

There are approximately 900,000 melanoma survivors in the United States in 2012. In addition to melanoma, survivors of melanoma are at increased risk of several other types of cancer, the most frequent of which are female breast cancer, prostate cancer, and NHL.

Melanoma survivors have an approximately ninefold increased risk of developing subsequent melanoma compared to the general population. The highest risk is noted within the first year of diagnosis; however, it remains elevated more than 20 years after the diagnosis. The subsequent melanomas are more likely to be thin at diagnosis, likely due to either being followed up closely or the patient seeking subsequent medical care quickly. Although the individuals with melanoma of the head and neck and patients younger than 30 years have higher relative risks of subsequent melanomas, large numbers of subsequent melanoma occur among men older than 50.

Among melanoma in situ survivors, there is a 32% increased risk of subsequent primary cancers of all sites compared to 35% in women. Elevated risk for subsequent invasive melanoma was detected in age groups 15 years and older, confirming that in situ melanoma is a strong risk factor for later development of invasive melanoma. This could be attributed to higher risk or continued UV exposure among survivors.

Elevated risk for subsequent chronic lymphocytic leukemia (CLL) is noted among both men and women with in situ melanoma, particularly after the first year of diagnosis. This is likely due to increased surveillance, and the role of impaired immunological status should be considered. Elevated risks for prostate cancer among men and thyroid cancer among women after 1 year of diagnosis suggest a genetic or environmental exposure.

Male and female invasive melanoma survivors have a 57% and 64% respectively, increased risk of subsequent primary cancers of all sites. Elevated risk for subsequent NHL is noted particularly in women after the first year of melanoma diagnosis. Elevated rates of diagnosis of CLL and kidney cancers among men and women and thyroid cancer among men during the first 12 months after diagnosis could be the result of medical surveillance. Persistent elevated risk for prostate cancer in men and breast cancer among women remains significantly high after 12 months of diagnosis.

Colorectal and lung–bronchus cancers are significantly less common in both men and women after invasive and in situ melanoma diagnosis.

Although there is no general consensus for follow-up after the initial melanoma diagnosis, intensified skin surveillance and follow-up after a first melanoma have been advocated. Patient education on self-skin examination based on the ABCDE mnemonic (where A is for asymmetry, B for irregular border, C for color variation, D for diameter $\geq$6 mm, and E for recent elevation or evolution), proper sun protection, posttreatment surveillance, and vigilant screening for subsequent primary cancers are necessary.

Case study 100.3

A 74-year-old woman with significant photodamage presented with a 3 mm nonspecific scarlike lesion located on the right cheek that was present for several months. Patient denies antecedent trauma. Histopathologic evaluation showed invasive melanoma with abundant collagenous matrix and prominent component of desmoplasia throughout the majority of the tumor (>90%).

• Which immunohistochemical study will most likely distinguish desmoplastic melanoma from nonmelanocytic mimickers?

S-100. Desmoplastic melanoma is an uncommon variant of spindle cell melanoma that accounts for less than 4% of primary cutaneous melanomas, with an incidence rate of 2.0 per 1 million US persons. The risks factors include older age, male gender, and excessive sun exposure. Men have twice the risk of developing DM compared to women.

It is often amelanotic, is highly infiltrative, and has a greater potential to recur than conventional melanoma. Early diagnosis of DM is quite challenging as it often presents as a benign-appearing scar, cyst, or melanocytic nevus on sun-damaged skin, especially the head and neck area. Other body sites, including mucosal surfaces, can be affected. Since DMs have a prominent stromal component, palpation remains an important part of the diagnosis. Perineural invasion is common and is responsible for recurrence and spread along the nerves.

DMs have been classified into pure DM (pDM) and mixed DM (mDM) based on the degree of growth of the connective tissue and stroma present in the tumor (desmoplasia). Usually pDMs have more and mDMs less than 90% desmoplasia throughout the tumor. It is associated with lentigo maligna in most cases, followed by superficial spreading melanoma. In approximately one-third of DMs, there is no identifiable melanoma in situ; therefore, the histopathologic diagnosis can be challenging.

S-100 is one of the most valuable diagnostic tools for the disease. Other melanocytic markers such as Melan-A/Mart-1 and gp 100 are usually negative in DMs. Sox-10 can be useful in selected cases.

Molecular profile demonstrated a decrease in the expression of genes involved in melanin synthesis and increased expression of clusterin, a glycoprotein involved in tissue remodeling and cell adhesion.

The classification of DMs into two histologic subtypes has significant prognostic differences; patients with mDM have 3.5-fold increased risk for metastasis and death and a shorter time to recurrence. pDMs are less likely to metastasize to the lymph nodes (1%) compared to mDM (10%) and other melanoma subtypes (6%). Systemic metastases occur in 7–44% patients, with lung, liver, and bone the most commonly involved.

Wide-local excision remains the first line of treatment. DMs excised with margins >2 cm offer the highest cure rate. Adjuvant radiotherapy should be considered for tumors at high risk of local recurrence. Selective sentinel lymph node biopsy (SLNB) should be considered in patients with mDM and pDM with additional high-risk factors such as younger age, high mitotic rate, the presence of neurotropism, and tumor ulceration.

Case study 100.4

A 41-year-old woman with a history of dysplastic nevi and no family history of melanoma presents for a routine physical examination. She noted a lesion on her abdomen that recently "changed." Patient had more than 30 dysplastic nevi removed in the past, none requiring re-excision.

1. What are the most important steps she needs to do in order to avoid melanoma?

A. Perform monthly-self skin examinations using the ABCDE criteria
B. Strict sun protection and tanning bed avoidance
C. Full-body mole mapping
D. Full skin screening by a dermatologist every 3–6 months
E. All of the above

Dysplastic nevi are distinct clinico-pathological entities that span the banal nevus on one end of the spectrum and melanoma at the other end. In most instances, DN is a benign lesion that infrequently eventuates to a melanoma, and it should be viewed as a phenotypic discriminator that identifies persons at increased risk for melanoma.

The condition is readily diagnosed on clinical grounds, and removal of dysplastic nevi is only necessary when one cannot exclude melanoma. A striking feature of dysplastic moles is their heterogeneity, and separating them from primary melanoma clinically can be impossible. Histopathology evaluation is often required to make this distinction.

Ultraviolet radiation exposure remains the only known preventable cause of melanoma. Primary methods of prevention include broad-spectrum sunscreens with SPF >30, wearing barrier protective clothing, seeking shade, and limiting sun exposure during peak hours.

(*Continued*)

An effective self-skin examination for detection of melanoma is a prerequisite for a successful secondary prevention. The rule of clinical ABCDE continues to be valid among dermatologists. However, this may not apply for self-skin examination of those at high risk of developing melanoma. Instead, recent data suggest that the following clinical signs may be useful for primary care physicians and people in high-risk groups for acquiring melanoma: the clinical "impression" of an irregular lesion; the "ugly duck" sign, which is the dissimilar appearance of melanoma to the rest of melanocytic lesions; the significant change of the inspected lesion; and the history of recent change.

Affected individuals should be screened regularly, the frequency of which depends on the risk for developing melanoma. The ideal frequency has yet to be established; individuals with few nevi and 1–2 DN can be reviewed 6–12 months or sooner if any changes are noted, while individuals from melanoma-prone families should be screened every 3–6 months.

Individuals diagnosed with DN should be questioned regarding family history of DN or melanoma. The more family members affected with either entity, the greater the risk of melanoma and therefore heightened need for more frequent follow-ups.

Surveillance with total body photography has been shown to reduce the number of nevi that needed to be removed for histopathologic assessment, and to result in the early detection of thin, potentially curable melanoma.

Genetic testing for cancer-risk genes in individuals with DN are currently not recommended by the American Society of Clinical Oncology since the role of melanoma susceptibility has not been adequately investigated and no changes in the current management strategy are available for patients with positive testing. It is advisable to either prevent melanoma development or at least allow for early detection.

Systemic therapy of melanoma in the adjuvant setting and for metastatic disease

Adjuvant therapy

Surgical resection is the mainstay of curative therapy for melanoma, because systemic agents and radiotherapy have limited ability to control the disease. Patients who have undergone curative-intent surgery for primary, nodal, or distant metastatic disease remain at risk of relapse due to the high propensity of melanoma to invade and spread and through hematogenous and lymphatic circulation.

Staging systems for melanoma are useful to estimate the risk of relapse associated with selected prognostic factors, but the indication for adjuvant therapy must be based not only on the probability of relapse but also on the availability of therapy with proven activity in this setting. In order to demonstrate benefit, an agent or strategy given as adjuvant therapy must be compared with an inactive or established control, and it remains to be determined whether the activity and safety of a treatment for advanced melanoma is the best model for its application in the adjuvant setting.

There is to date little evidence for substantial benefit for any adjuvant therapy tested so far. Most agents have been studied in patients with stage III disease, the group that is considered most in need of effective adjuvant therapy. Patients with a lower risk of relapse, such as those with deep or ulcerated primary tumor or with one or more mitosis per square millimeter, have a substantial risk of relapse, particularly in the presence of one or more positive sentinel nodes, and patients with surgically resected oligometastatic disease are at extremely high risk of relapse, so an effective and safe adjuvant approach would also be valuable for those groups. So far, interferon alpha (IFNα) is the only agent that has shown benefit for the adjuvant therapy of high-risk melanoma, and the majority of the data supporting its use come from cohorts of patients with stage III melanoma based on the presence of micro- or macroscopic nodal metastases. The most popular regimen consists of IFNα, given 5 days/week intravenously for 4 weeks and then at a lower dose subcutaneously three times per week to total a year of therapy. Based on three trials with slightly different designs and therapeutic procedures, IFNα demonstrated significant early relapse-free and overall survival benefit when compared with observation. With longer periods of follow-up and subsequent meta-analysis, the favorable impact of IFNα has waned, so that its absolute survival benefit is less than 5% after 10 years, and the slightly greater improvement of relapse-free survival comes at the cost of major toxicities and a negative impact on quality of life.

A variety of other interventions have been tested for adjuvant therapy, generally in patients with stage III disease, but some studies have included or have been limited to patients with lower-risk disease (IIB or C) or very high-risk disease (M1a–c, fully resected). These therapies have included chemotherapy, a variety of vaccine strategies, cytokines such as granulocyte-macrophage colony-stimulating factor, and aggressive combinations of cytokines and cytotoxic chemotherapy. While in some studies there appears to be an enhancement of relapse-free survival for the intervention group, survival benefit has been elusive, and, for the chemotherapy-containing regi-

mens, toxicities are excessive. While the development of autoimmunity secondary to IFNα adjuvant therapy has shown a strong association with a significant survival benefit, additional work in this area is needed to confirm and better understand the mechanisms of this association and how it can lead to the identification of predictive factors to assign patients to this therapy or to avoid its toxicities. Further evidence of controversies regarding the benefits of IFNα are the recent or ongoing trials in which experts could not agree on whether the control treatment should be placebo or one of the IFNα regimens. It is increasingly clear that important improvements in this field will await a better understanding of not only the biology and immunology of the malignancy (e.g., the ongoing investigation of a potential association between the immune gene signature of melanoma with the adjuvant benefit of whole protein-based vaccine) but also that of the host.

Case study 100.5

A 29-year-old previously healthy woman with stage IIIB melanoma is seen at 3 weeks following her wide local excision and SNLB. The tumor was 5 mm deep with 3 mitoses/mm^2 and ulceration. Two sentinel nodes each contained a tiny focus of melanoma 1 mm in diameter, and the patient will undergo completion lymph node dissection (CLND) in 1 week. After recovery from the CLND, she wishes to receive adjuvant therapy that may reduce her risk of relapse and, if possible, provide an increased lifespan.

1. Which would be the best adjuvant therapy for this patient?

A. High-dose IFNα, starting with 1 month at 20 mU/m^2/day, 5 days per week, IV, followed by 11 months of 10 mU/m^2 three times per week, subcutaneously (s.c.)

B. Polyethylene glycol IFNα, using 6 million units/m^2 three times per week s.c. ×8 weeks, followed by 3 million units/m^2 weekly until 5 years following institution of therapy

C. Same as (A), limiting therapy to the first month of IV high-dose IFNα

D. Granulocyte–monocyte colony-stimulating factor, 250,000 units s.c. daily, 14 days on and 14 days off, up to 3 years

A subset analysis of a large phase III trial of pegylated IFNα (PEG-IFNα) showed a strong survival benefit only in the subset of patients with ulcerated primary melanoma and microscopic involvement of the sentinel node(s). While this observation remains to be confirmed with a properly designed randomized trial (ongoing), consideration can be given to offering this approved adjuvant therapy to appropriate patients (the best approach is a clinical trial).

Imaging considerations

One of the most stressful and important topics for patients diagnosed with melanoma is the question of how to diagnose relapse and whether early diagnosis of recurrence can lead to interventions that improve prognosis. While early detection and prompt surgical resection are paramount in the primary management of nearly all solid tumors, the benefits from early detection of relapse depend on several factors that are difficult to study with the necessary trial designs. Therefore, strong evidence for any choice of follow-up in patients with melanoma is lacking and likely to be eclipsed by efforts to find better therapies for advanced disease that is not amenable to resection with curative intent. Nevertheless, it is important to recognize certain features of melanoma that can guide the clinician in following these patients and may be part of the multidisciplinary management that is recommended for all patients with melanoma.

1. *Dermatology:* While the risk of new cutaneous primaries is increased in patients with a history of melanoma, the contribution of heightened screening and a change in the dermatologic management of these patients need to be studied under more controlled conditions. Nevertheless, skin-screening procedures are low risk and may lead to collateral benefits such as enhanced awareness of risk among family members that leads to skin screening, avoidance of sunbeds, and early reporting of changes in a mole. Recent data suggest a survival benefit of primary screening of unselected populations but need to be validated in different demographic settings.

2. *Surgery:* While early detection and surgery for asymptomatic, oligometastatic disease remain of uncertain benefit, the surgeon should be involved in management decisions for such patients. In the absence of contraindications to surgery, such patients should always be considered for resection to no evidence of disease status and, whenever possible, enrollment in clinic trials to study the benefit of new systemic therapies in patients with surgically resected metastatic melanoma.

3. *Medical oncology:* Overall management of melanoma patients is often provided by the medical oncologist (particularly in the United States), except in patients with very

low-risk melanoma. Decisions about the frequency and type of follow-up include discussions of physical exams, laboratory testing (these are generally very insensitive for any organ involvement, and no blood biomarker is validated for melanoma), and scanning (which should address the absence of clear evidence for a benefit of routine scanning). Further controversy surrounds the use of fluorodeoxyglucose positron emission tomography (FDG-PET) scans in conjunction with computed tomography (CT) scanning; while melanoma is one of the most FDG-avid malignancies and this form of imaging can add important information (the detection of occult disease not seen on CT as well as the characterization of small undefined masses are of particular interest in melanoma with its propensity to widespread and unpredictable metastasis), the routine use of CT or PET-CT for melanoma follow-up screening remains uncertain and thus often unreimbursed. Furthermore, the radiation exposure associated with imaging can increase the risk of second malignancies and thus alter the risk–benefit consideration of serial imaging for this form of screening.

Case study 100.6

A 42-year-old man underwent primary surgical management of melanoma 2 years ago, when he had a stage IIA melanoma and several other resections for dysplastic nevi on the trunk that are being followed with mole mapping by his dermatologist. His son, age 14, has started to see the dermatologist and has become an advocate for risk-reducing sun behaviors among the members of his soccer team. At the time of diagnosis, the patient had a negative staging work-up, including FDG-PET and CT fusion scan and laboratory determinations. Now the patient complains of a painful mass in the right chest and mild left hip pain. He undergoes another complete work-up that shows normal laboratory determinations, a negative brain magnetic resonance imaging (MRI) scan, and the findings on an FDG-PET and CT fusion scan of an FDG-avid, expansile mass in a right anterior rib and a lytic lesion in the left iliac wing. He is seeking the optimal treatment that may have curative potential and is less concerned about the bone pain.

1. After confirming the diagnosis with a fine-needle aspirate of the iliac bone lesion that showed sparse single cells with features consistent with melanoma, what should the optimal recommendation now be?

A. High-dose interleukin-2 (IL2) or ipilimumab
B. Biochemotherapy using IL2, IFNα, cisplatin, vinblastine, and dacarbazine
C. Temozolomide or dacarbazine
D. Molecular analysis of the primary tumor for the presence of an activating BRAF mutation followed, if appropriate, by vemurafenib
E. Radiotherapy to the painful iliac bone lesion and institution of IV bisphosphonate therapy

None of these choices would be altogether wrong. However, in view of the difficulty of controlling bone pain with any of the systemic therapies for melanoma, it is recommended that a patient with disease limited to or predominant in the bone initially receive local radiotherapy to reduce the risk of pathologic fracture and relieve pain.

After all of the symptomatic bone lesions have been irradiated, this patient will be grossly free of metastatic tumor, although certainly at risk of progression very soon. In the absence of evidence for adjuvant benefits in patients rendered disease-free by focal therapies, it is most appropriate to avoid toxic therapies without followable disease. However, it would be important to know the patient's BRAF mutational status, as it is possible he will relapse with more symptomatic disease that requires an intervention with high activity and rapid symptom relief, such as oral inhibitors of the mitogen-activated protein kinase (MAPK) pathway (vemurafenib or dabrafenib inhibit BRAF v600 trametinib, inhibits MEK, and the latter two are approved as a combination MAPK inhibitor combination). Conversely, if the patient relapses with a relatively nonaggressive pace of tumor growth, immunotherapy in the form of IL2 or ipilimumab (or, preferably, participation in a clinical trial) should be offered. Both of these therapies require management by a highly experienced medical team, and each of these immunotherapies offers the chance of long-term disease control for an important minority of patients. They have not been compared head to head, so the choice of therapy remains somewhat arbitrary and based in part on the setting and the patient's preference (the best approach is a clinical trial). As a general consensus, MAPK inhibitors are offered to patients with an activating BRAF mutation who have aggressive, symptomatic disease unlikely to be controlled by immunotherapy, which tends to require a longer time to exert its antitumor effects and has a low overall benefit rate. It may also be difficult to administer immunotherapy following targeted agents due to changes in the biology of disease that has become resistant to targeted therapy, while the latter appears to work just as well following immunotherapy as it does in patients naïve to therapy. Cytotoxic chemotherapy such as temozolomide or dacarbazine (oral versus intravenous alkylating agents with the same active moiety) has a very modest benefit, with response rates in the 8–15% range and only rare durable complete remissions, but it is well

tolerated and may be indicated in motivated patients who lack other therapeutic options (a clinical trial should always be sought—the most promising current trials involve the use of adoptive T-lymphocyte therapies following chemotherapy-induced lymphodepletion, which can provide durable complete remissions in 5–20% of patients even after the failure of prior standard therapies). Also of promise but remaining to be studied in adequately powered phase II and definitive phase III trials is the use of a new immunotherapy strategy, the use of an antibody (against PD1 or PDL1) that blocks another checkpoint receptor–ligand interaction that occurs preferentially in the tumor microenvironment and results in the programmed death of T-cells. This form of immunotherapy, while not specific for antigens or any characteristic of the patient such as HLA type, nevertheless appears more specific to the tumor–T-cell interaction and appears to cause less of the nonspecific immune-related adverse events than does ipilimumab.

Management of brain metastases

Melanoma is the solid tumor with the highest propensity to metastasize to the brain, a complication that affects at least one-third of patients with metastatic disease during life and twice that many patients reported in autopsy series. In recent years, a high frequency of brain MRI in neurologically asymptomatic patients undergoing routine staging of melanoma has confirmed the high incidence of brain involvement. Fortunately, this observation has changed many aspects of clinical investigation in the field, including the assessment of new agents in patients with active brain metastases. Further, the use of stereotactic brain radiosurgery, which appears far more active against melanoma than whole-brain radiotherapy, has allowed for relaxation of previous restrictions on protocol entry for patients with previously treated and controlled brain metastases. The remaining clinical controversies in the management of melanoma patients with brain metastases include the selection of patients who would benefit from surgical excision, the potential benefit of adding whole-brain radiotherapy after focal lesion control, and the optimal sequencing of therapy for the brain and systemic therapy.

Case study 100.7

A 70-year-old man with melanoma arising in a chronically sun-damaged area of the scalp has had multiple local recurrences treated successfully with electron beam (superficial) radiotherapy. The patient develops gradual-onset visual disturbances, and the brain MRI demonstrates a small occipital lobe lesion with little surrounding edema. Staging scans demonstrate no systemic disease, and a short-interval follow-up brain MRI demonstrates progression of the original lesion and the development of four others, with a maximum volume of 2.5 cm and modest surrounding edema without midline shift. The tumor biopsy had previously been tested for c-kit mutation and was found to be positive. The patient has no symptoms and wishes to optimize therapeutic outcome while avoiding the side effects of therapy if possible.

1. What should the next step be?

A. Dasatinib, 70 mg orally, twice daily
B. Ipilimumab 10 mg/kg IV every 3 weeks ×4, followed by maintenance every 12 weeks
C. Temozolomide plus whole-brain radiotherapy
D. Stereotactic radiotherapy to five lesions and withhold systemic therapy
E. Enrollment in a clinical trial comparing PD1 antibody with chemotherapy

This patient also illustrates the concept of judging carefully whether locoregional therapy or systemic therapy (or both) is more appropriate. In this case, there is no detectable disease outside of the brain, and the patient's brain disease is both symptomatic and aggressive. There is no mutation for molecularly targeted therapy, and the need for steroid to treat the peritumor edema in the central nervous system (CNS) will likely reduce the chance of benefit from immunotherapy as well as preclude his participation in a clinical trial. For all of these reasons, the most appropriate therapy is treatment of each lesion with stereotactic radiotherapy, with close observation thereafter and the selection of subsequent treatment based on where and when progression occurs. While whole-brain radiotherapy could be considered to sterilize micrometastases in the brain that the patient is likely to harbor, its activity in melanoma patients who have had definitive stereotactic radiotherapy to all visible lesions has not been adequately studied. However, based on the poor results from whole-brain radiotherapy in patients with macroscopic metastases and the availability in many centers of high-quality equipment and experienced radiation oncologists, repeat stereotactic radiotherapy procedures can often control subsequent CNS relapses at least for a few months' interval. Other options for progression in the CNS after the first stereotactic treatment of multifocal disease would be consideration of immunotherapy (if not steroid-dependent) or targeted therapy (if the tumor has an actionable mutation).

Case study answers

Case study 100.1

Question 1: Answer E

Case study 100.2

Question 1: Answer C

Case study 100.4

Question 1: Answer E

Case study 100.5

Question 1: Answer B

Case study 100.6

Question 1: Answer E

Case study 100.7

Question 1: Answer D

Selected reading

Bradford PT, Freedman DM, Goldstein AM, *et al*. Increased risk of second primary cancers after a diagnosis of melanoma Arch Dermatol. 2010 Mar;146(3):265–72.

Jaimes N, Chen L, Dusza SW, *et al*. clinical and dermoscopic characteristics of desmoplastic melanomas. JAMA Dermatol. 2013 Jan 16:1–9.

Jang S, Atkins MB. Which drug, and when, for patients with BRAF-mutant melanoma? Lancet Oncol. 2013;14(2):e-60–9.

Kudchadkar RR, Smalley KS, Glass LF, *et al*. Targeted therapy in melanoma. Clin Dermatol. 2013;31(2):200–8.

Margolin K, Ernstoff MS, Hamid O, *et al*. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13(5):459–65.

Topalian SL, Hodi FS, Brahmer JR, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.

For further information on this area please also consult Chapters 71, 116, 123, 127, and 129

CHAPTER 101

Nonmelanoma skin cancers

Daniel Christiansen[1] and Anna Sancho Clayton[2]

[1]Vanderbilt University, Nashville, TN, USA
[2]Vanderbilt University Medical Center, Nashville, TN, USA

Case study 101.1

1. A 45-year-old woman with a history of multiple basal cell carcinomas is seen in clinic. She is noted to have an eroded 5 cm basal cell carcinoma on her nasal bridge extending onto her left medial canthus. Physical exam also demonstrates palmar pits. Further history reveals that her mother and brother have been treated for multiple basal cell carcinomas and odontogenic cysts in the past. The patient is diagnosed with Gorlin's syndrome. In addition to surgery and radiation, what medication might be useful for treating this patient?

A. Ipilimumab
B. Acitretin
C. Ustekinumab
D. Vismodegib

Basal cell carcinomas (BCCs) are the most common malignancy in the world, with an estimated incidence of more than 800,000 cases per year in the United States alone. They account for roughly 75–80% of all nonmelanoma skin cancers and may result in significant patient morbidity. The economic impact of these malignancies is staggering, with an estimated cost of $650 million per year in the United States.

The majority of BCCs are treated with either surgical or destructive methods. Surgical options vary based on tumor location and include the use of Mohs surgery or routine excision. Destructive modalities include the use of electrodessication and curettage, photodynamic therapy, or radiation therapy. Topical medications, such as imiquimod and 5-fluorouracil, are also sometimes employed to treat superficial malignancies.

In 2012 a new oral medication, vismodegib, was approved by the US Food and Drug Administration (FDA) for the treatment of metastatic BCC and locally advanced BCCs in patients who are not candidates for surgery or have experienced recurrent tumors after surgery, nonamenable to radiation. It is a small-molecule inhibitor of Smoothened that acts on the Sonic Hedgehog pathway, which is mutated in a large percentage of sporadic BCCs. Increased Hedgehog activity has also been demonstrated in colon, ovarian, prostate, and pancreatic adenocarcinomas, representing possible future therapeutic targets for this novel medication.

This patient has a rare autosomal dominant syndrome classified as nevoid basal cell carcinoma syndrome, aka Gorlin's syndrome. This syndrome results from a mutation in the PTCH1 ("Patched") gene on chromosome 9q22–31 that also causes constitutive activation of the Sonic Hedgehog pathway. Affected individuals tend to develop palmar pits and odontogenic cysts at a young age. BCCs tend to occur frequently after puberty, with a median age of 20 years old in Caucasians. Patients may become severely disfigured due to the sheer size, number, and overall frequency of these skin cancers. Frequent skin exams and treatment of rapidly growing lesions are needed to minimize the overall morbidity and mortality associated with this disease.

Vismodegib has shown promise in this patient population to decrease the size of some BCCs and result in complete clearance of others. The main limiting factors for this medication are side effects and overall cost. Patients tend to develop ageusia, hair loss, and debilitating cramps. Management of these side effects is often difficult, and patients may require drug holidays or reduced dosages to tolerate the medication. The cost, currently estimated at $7500 monthly, is also a major drawback of this medication.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

2. If this patient were to develop metastatic squamous cell carcinomas nonamenable to surgery, what chemotherapeutic agent should not be considered for treatment?

A. Carboplatin
B. Cisplatin
C. Cyclophosphamide
D. Capecitabine
E. Cetuximab

Aggressive and/or metastatic cutaneous squamous cell carcinomas are most frequently treated with platinum-based chemotherapy, including carboplatin and cisplatin. Additional chemotherapeutic options include the use of capecitabine, a purine analog derivative of 5-fluorouracil, and cetuximab, an epidermal growth factor inhibitor. Cyclophosphamide, an alkylating agent, has been shown to promote development of cSCC when used for the treatment of Wegener's granulomatosis and would make a poor choice to treat this malignancy.

Case study 101.2

A 60-year-old male cardiac transplant recipient is diagnosed with a 1.9 cm cutaneous squamous cell carcinoma (cSCCs) of his right ear. Histopathology demonstrates perineural invasion and a depth of 1 mm. The patient has no palpable lymphadenopathy.

1. What is the most accurate stage for this patient according to the American Joint Committee on Cancer (AJCC) 7th edition tumor staging system?

A. Stage I
B. Stage II
C. Stage III
D. Stage IV

cSCCs are the second most common type of skin cancer, occurring in a 1:4 ratio with BCCs within the general population. This ratio is reversed in solid organ transplant recipients, where cSCCs are the most frequently identified cutaneous malignancies. In the United States alone, an estimated 2500 people die yearly from cSCC. The overall incidence is increasing worldwide, and excessive ultraviolet light exposure is believed to play a causative role.

The risk of metastases for all cSCCs is approximately 5%, with the most commonly involved sites being the regional lymph nodes. High-risk tumors have a 10–20% risk of metastases, and perineural invasion of nerves measuring 0.1 mm or larger has been associated with an increased risk of disease-specific death. Outcomes in immunosuppressed patients, who are at a 65-fold increased risk of developing cSCCs, can be disastrous if managed inappropriately.

The AJCC 7th edition tumor staging system for cSCC (shown in Tables 101.1 and 101.2) was developed to provide practitioners with improved staging and prognostic data for patients with cSCC. The patient described here has a tumor less than 2 cm in size with two high-risk factors—perineural invasion and location on the ear. His tumor is considered T2. The patient has no palpable lymphadenopathy or evidence suggestive of metastases, so he is classified as stage II.

Surgery is widely regarded as the treatment of choice for localized cSCC in this patient population. Depending on the anatomic location of tumor, either routine excision or Mohs surgery may be considered. In high-risk tumors that demonstrate perineural invasion, with nerve calibers >0.1 mm, radiation therapy may play a limited adjuvant role, but a definitive survival benefit has not been conclusively demonstrated. Due to the paucity of data available, patient characteristics should be carefully weighed against the risks of radiation therapy in this setting.

Table 101.1 AJCC 7th ed. primary tumor (T) classification (Source: Edge SB, *et al.*, eds. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010. Reproduced with permission of Springer).

Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension with less than 2 high-risk features*
T2	Tumor >2 cm in greatest dimension with or without one additional high-risk feature,* or any size with greater than or equal to 2 high-risk features*
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

*High-risk factors include tumors greater than 2 mm in thickness, perineural invasion, location on ear or nonglabrous lip, poorly or undifferentiated histology, and Clark level ≥IV.

Table 101.2 AJCC 7th ed. stage classification (Source: Edge SB, *et al.*, eds. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010. Reproduced with permission of Springer).

Stage	T	N	M
0	In situ	0	0
I	1	0	0
II	2	0	0
	3	0	0
III	4	0	0
	any	1	0
IV	any	any	1

Case study 101.3

1. A 79-year-old female is diagnosed with extramammary Paget's disease (EMPD) of her vulva. What percentage of patients with genital EMPD have an underlying visceral malignancy?

A. 1–10%
B. 11–26%
C. 27–38%
D. 39–45%

EMPD is a rare cutaneous adenocarcinoma of apocrine gland origin that predominately affects 50–80-year old Caucasian women. It is histologically identical to Paget's disease of the breast, and the most commonly involved sites are the vulva (76%) followed by the perianal area (20%). EMPD often presents as a nondescript pruritic rash, which may lead to a delay in diagnosis. All patients with EMPD should have a thorough age-appropriate cancer screening as 11–45% of EMPD cases are associated with a secondary malignancy. Associated malignancies that have been reported include breast, colorectal, genitourinary, and hepatocellular carcinomas.

2. What FDA-approved topical medication should be used to treat this patient?

A. Imiquimod
B. 5-Fluorouracil
C. Topical nitrogen mustard
D. Clobetasol
E. None of the above

Mohs surgery and wide local excision are widely regarded as the treatments of choice for EMPD. Despite advances in tissue-staining techniques, both Mohs and wide local excisions are associated with high recurrence rates, ranging from 16% to 33–60%, respectively. Imiquimod, topical 5-fluorouracil, and photodynamic therapy have all been used off-label to treat patients with EMPD. None of these modalities have been FDA approved for this indication. Clobetasol, a class 4 topical steroid, is not an effective therapy for this malignancy. Topical nitrogen mustard has not been reported as a treatment for this malignancy.

Case study 101.4

1. A 46-year-old female presents to your clinic with a history of breast cancer and a sebaceous adenoma of her lip. She was recently diagnosed with two keratoacanthomas arising on her right arm and trunk. What additional diagnostic testing should be considered in this patient?

A. Colonoscopy
B. Chest X-ray
C. Urinalysis
D. Bone marrow biopsy

This patient likely has Muir–Torre, a genodermatosis first described in 1967 by Muir *et al*. It is an autosomal dominant syndrome resulting from a mismatch repair gene defect in hMSH1 or hMLH1. Muir–Torre is classified as a variant of Lynch syndrome, aka hereditary nonpolyposis colorectal cancer syndrome. These patients present with a combination of sebaceous neoplasms, visceral malignancies, and multiple keratoacanthomas. The visceral malignancies may include endometrial carcinoma, ovarian cancer, and gastrointestinal malignancies. Undiagnosed patients tend to present at a mean age of 45 years old with colorectal carcinoma. In patients with a history of sebaceous adenomas, considered pathognomonic for this genodermatosis, it is prudent to screen for Muir–Torre with genetic testing for mismatch repair genes and to consider a screening colonoscopy.

Case study 101.5

An 84-year-old man is diagnosed with a Merkel cell carcinoma (MCC) of his scalp.

1. How would you suggest he be managed following primary surgery?

A. No further treatment is needed
B. Adjuvant radiation should be considered
C. Adjuvant chemotherapy should be considered
D. Fractional ablative laser therapy should be considered

MCCs are rare cutaneous neoplasms of neuroendocrine cells most frequently seen on elderly Caucasian men in sun-exposed areas. The mean age of patients is 71–76 years old with a male-to-female ratio of 2:1. The most common sites affected are the head and neck. Patients with HIV, chronic lymphocytic leukemia, and/or solid organ transplantation with immunosuppression are at the highest risk for developing this aggressive malignancy. MCCs have a propensity to recur locally following treatment and to metastasize, leading to a 5-year survival estimate of only 45–49%.

(*Continued*)

MCCs are typically managed with surgical excision followed by adjuvant radiation. It is widely regarded as a radiosensitive tumor, and a meta-analysis demonstrated a survival advantage for patients with stage I and II disease treated with combination surgery and adjuvant radiation. In patients with large tumors or evidence of lymphatic involvement, adjuvant radiation therapy should be considered to try to minimize the risk of recurrence.

2. What virus family has been implicated as an etiologic factor of MCC?

A. Herpesviridae
B. Papillomavirus
C. Polyomavirus
D. Enterovirus

Merkel cell polyomavirus (MCPyV) was first discovered in 2008 after analysis of four MCC tumors, utilizing digital transcriptome subtraction, revealed previously unknown viral transcripts. The MCPyV is a double-stranded DNA virus that is now known to be ubiquitous in the human population. Serum antibodies to MCPyV appear during the first decade of life, after an asymptomatic infection, and are subsequently found in 80% of all adults. Causality is still unproven, but 75–80% of tumors contain the viral genome. It has been shown to integrate within the cellular genome of MCC, and even metastatic MCCs demonstrate the viral DNA.

Case study 101.6

A 41-year-old man with newly diagnosed human immunodeficiency virus (HIV) is found to have multiple nonblanchable violaceous patches on his feet, hands, and oral mucosa.

1. After a biopsy confirms the suspected diagnosis, what is the most appropriate next step in management?

A. Institute combination antiviral therapy (cART)
B. Order a radiation oncology consult
C. Send patient for surgery
D. No treatment needed

Kaposi's sarcoma (KS) is a rare tumor of endothelial origin that predominately occurs in immunosuppressed patients. It is over 20,000 times more common in patients with acquired immunodeficiency syndrome (AIDS) than in the general population and is classified as an AIDS-defining illness. Human herpesvirus 8 is believed to play a causative role in the pathogenesis of this tumor, possibly through the upregulation of vascular endothelial growth factor (VEGF).

Initial management for all patients with HIV infections diagnosed with KS is institution of cART therapy to reduce viral loads and bolster the immune system. Studies have demonstrated improved survival and prolonged time to treatment failure with this regimen.

Case study 101.7

A 36-year-old female renal transplant recipient presents with lesions similar to the patient in Case study 101.6.

1. What alternative medication has been shown to be useful for reducing tumor burden in this population?

A. Cyclosporine
B. Sirolimus
C. Doxorubicin
D. Isotretinoin

Sirolimus is an immunosuppressive medication used in solid organ transplant recipients (SOTR) to prevent transplant rejection. It works by inhibiting the mammalian target of sirolimus, resulting in decreased cell-cycle progression. It also inhibits angiogenesis, via impaired VEGF release, and has antineoplastic activity. Sirolimus is an alternative to the traditional approach of managing KS in SOTR, which predominately involved decreasing immunosuppression. Patients risked transplant rejection with the prior strategy, and tumors tended to recur after restarting therapy. Studies have shown complete regression of KS in renal transplant patients switched from cyclosporine-based immunosuppression to sirolimus, making it a viable treatment option in this population.

Case study 101.8

A 22-year-old female is diagnosed with a dermatofibrosarcoma on her back. She presents to clinic to discuss treatment options, including chemotherapy.

1. What do you advise as standard of care for this malignancy?

A. No treatment is needed. Advise close observation
B. Refer patient for Mohs surgery to site
C. Recommend patient have wide local excision with sentinel lymph node biopsy
D. Enroll patient in a clinical trial for a new chemotherapeutic agent

Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma most commonly found on the trunk and upper extremities of individuals between 20 and 50 years old. It tends to be ill defined and is associated with high recurrence rates after routine excision. Tumors tend to invade deeply, and cases of metastatic disease have exceedingly poor prognoses.

Mohs surgery is generally regarded as the treatment of choice for DFSP due to a lower risk of recurrence compared to wide local excision alone. Multidisciplinary approaches have also been used for select tumors that combine Mohs surgery with WLE and/or radiation to reduce local recurrence. Chemotherapy, including the use of imatinib, is generally reserved for cases of metastatic disease. Sentinel lymph node biopsies are not generally indicated for patients with DFSP.

Case study 101.9

A 73-year-old Caucasian man presents to clinic with a 4-year history of mycosis fungoides. He reports it started out as a pruritic rash involving his axillae and buttocks but has recently spread to his trunk. In the past, he used topical nitrogen mustard, clobetasol, and narrow-band ultraviolet B with adequate control, but the rash is no longer responding. In addition to the patches, he now reports having multiple new bleeding nodules on his back.

A review of his prior biopsy report confirms the previous diagnosis of MF with the findings of haloed epidermotropic cells scattered in the superficial dermis with cribriform nuclei. Immunohistochemical staining showed CD4 > CD8 in a 3.5:1 ratio.

A biopsy is performed of a bleeding nodule and shows dense infiltrates of large anaplastic T-cells with cerebriform nuclei. The cells extend throughout the entire dermis and are composed of greater than 75% CD30-negative blasts. The patient is diagnosed with large-cell transformation in mycosis fungoides.

1. Which of the following treatment options is least appropriate?

A. Denileukin diftitox
B. Total skin electron beam therapy
C. Photopheresis
D. Interferon alpha
E. None of the above

Mycosis fungoides is a rare primary cutaneous T-cell lymphoma of CD4+–CD45RO+ helper T-cells within the skin that comprises roughly 75% of all cutaneous lymphomas. Early stages are generally associated with an indolent course. The patient described here has developed large-cell transformation (LCT), a poorly understood and prognostically significant event. It is defined as the presence of greater than 25% large T-cells (four times larger than small lymphocytes) within a biopsied infiltrate. The reported incidence of progression varies widely, from 8% to 55%. Patients tend to have a decreased median survival after transformation compared to those with nontransformed MF. In tumor and advanced-stage MF, such as LCT, treatment options include the oral retinoid bexarotene, extracorporeal photopheresis, denileukin diftitox, interferon alpha, and total skin electron beam therapy.

Case study answers

Case study 101.1

Question 1: Answer D
Question 2: Answer C

Case study 101.2

Question 1: Answer B

Case study 101.3

Question 1: Answer B
Question 2: Answer E

Case study 101.4

Question 1: Answer A

Case study 101.5

Question 1: Answer B
Question 2: Answer C

Case study 101.6

Question 1: Answer A

Case study 101.7

Question 1: Answer B

Case study 101.8

Question 1: Answer B

Case study 101.9

Question 1: Answer E

Selected reading

Christenson LJ, Borrowman TA, Vachon CM, *et al*. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA. 2005;294(6):681–90.

Farasat S, Yu SS, Neel VA, *et al*. A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: creation and rationale for inclusion of tumor (T) characteristics. J Am Acad Dermatol. 2011;64(6):1051–59.

Medina-Franco H, Urist MM, Fiveash J, *et al*. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol. 2001;8(3):204–8.

Sekulic A, Migden MR, Oro AE, *et al*. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012;366(23):2171–79.

Tang JY, Mackay-Wiggan JM, Aszterbaum M, *et al*. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012;366(23):2180–88.

Tessari G, Girolomoni G. Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors, and management. Dermatol Surg. 2012;38(10):1622–30.

*For further information on this area please also consult Chapters **128** and **141***

PART 7

Gynecological Malignancies

CHAPTER 102

Ovarian cancer: neoadjuvant, adjuvant, and surgical issues

Alpa M. Nick and Robert L. Coleman

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 102.1

A 60-year-old female with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, who completed carboplatin and paclitaxel 18 months ago for completely resected, stage IIIC, high-grade serous ovarian cancer, presents with right lower quadrant pain and a doubling of her CA125 (from 25 to 50). Computed tomography (CT) scan of the abdomen and pelvis demonstrates a 2.5 cm mass at the right vaginal apex, a 1.5 cm right external iliac lymph node, and no evidence of ascites.

1. What is the role of secondary cytoreduction in a patient with platinum-sensitive recurrent ovarian cancer?

A. The patient should initiate systemic platinum doublet chemotherapy

B. The patient should proceed with an attempt at surgical cytoreduction only

C. The patient should proceed with an attempt at surgical cytoreduction followed by systemic platinum doublet chemotherapy

The question of secondary cytoreduction for recurrent ovarian cancer is a matter of ongoing debate and one in which a paucity of level I–II evidence in favor of secondary cytoreduction remains. Criticisms of existing literature on this topic focus on the fact that studies are largely retrospective, span a long period of time encompassing differing surgical practices, and are not randomized. As a result, there is significant heterogeneity in the treatments rendered as well as a high risk for selection bias. Given that ovarian cancer, when it recurs, seldom results in cure, patients with long disease-free intervals represent a relatively "chemotherapy-sensitive" population, and consequently it is reasonable to consider surgery as a therapeutic option in this select subset of patients. Existing data to support secondary cytoreductive surgery are highly biased, scattered, and nearly all retrospective single- or multi-institution studies. However, collectively these studies have raised the hypothesis that patients with selected presenting characteristics might benefit from secondary surgery. The two most consistent variables in favor of secondary cytoreduction identified by multivariate analyses are prolonged treatment-free survival (first recurrence varies from 6 months to 24 months) and postoperative tumor residuum (described as "<0.5 mm," "microscopic," or "none"). Median overall survival of an individual study's "optimal" cohort is generally 2–3 times the median survivorship of their "suboptimal" cohort.

Many would argue that it is too early to adopt secondary cytoreduction as the standard of care for patients with recurrent ovarian cancer. Three randomized trials are still underway. Currently, recurrent ovarian cancer is considered an incurable disease, so salvage chemotherapy is generally accepted as the standard of care.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 102.2

A 30-year-old nulliparous female with a complex pelvic mass measuring 11.5 cm and an elevated CA125 CT scan of the abdomen and pelvis demonstrates no evidence of extra-ovarian spread of disease. Intraoperative evaluation demonstrates complete replacement of the right ovary with a cystic mass that cannot be separated to safely perform a cystectomy.

1. After unilateral salpingo-oophorectomy, frozen section reveals grade 1 endometrioid adenocarcinoma. What is the role of fertility conservation in early-stage invasive epithelial ovarian cancer?

A. The patient needs no additional surgical intervention and no additional therapy postoperatively
B. The patient should undergo comprehensive surgical staging followed by systemic therapy for stage 1A disease
C. The patient should undergo comprehensive surgical staging followed by observation for stage 1A disease

A small proportion of women with invasive epithelial ovarian cancer are diagnosed in the reproductive-age group. Approximately 25% are stage I, and bilaterality is dependent on cell type. The majority of mucinous and clear cell tumors are unilateral, but approximately 50% of serous tumors are bilateral. Thus, fertility-sparing surgery may be performed in selected young patients with apparent disease confined to one ovary (stage 1A). There is generally a greater risk of relapse in this patient cohort. When relapse occurs in the residual ovary alone, salvage treatment may result in cure. However, if disseminated recurrence with peritoneal carcinomatosis occurs, cure is uncommon. In a study that examined the natural history of stage I ovarian cancer managed without chemotherapy, the 5-year survival rate was 94% for stage 1A lesions, 92% for stage 1B tumors, and 84% for stage 1C neoplasm.

Comprehensive surgical staging is the overarching surgical principal for those women with clinically apparent stage 1 ovarian cancer. Comprehensive surgical staging generally consists of peritoneal cytologic washings, systematic inspection and palpation of all peritoneal contents, multiple biopsies of upper abdominal and pelvic peritoneal surfaces, omentectomy, and pelvic and para-aortic lymphadenectomy. In general, if extraovarian disease is apparent at the time of surgical intervention, maximal surgical resection to achieve no gross residual disease is the goal. Postoperatively, if the tumor were a low-grade serous carcinoma, mucinous carcinoma, or well-differentiated endometrioid subtype, most would recommend surveillance without postoperative therapy. Cure rates for women with low-risk stage 1 tumors are in the 80–90% range. However, for those women with high-grade serous carcinoma, undifferentiated carcinoma, transitional carcinoma, and high-grade endometrioid carcinoma, or women with stage 1C disease, standard chemotherapy with carboplatin and paclitaxel is recommended. Cure rates for these high-risk women range from 50% to 60%.

A major concern after conservative therapy for early-stage ovarian cancer centers around the ability to achieve pregnancy after treatment, particularly because many patients with stage 1 disease will receive adjuvant chemotherapy. Studies of young women with germ cell tumors of the ovary, breast cancer, and Hodgkin's lymphoma have indicated that many women will resume menstrual function after cytotoxic chemotherapy. Among women with early-stage ovarian cancer who underwent fertility conserving surgery, menstrual function was preserved in 94% of patients in one series. Reports of pregnancy outcomes after fertility-sparing surgery for invasive epithelial ovarian cancer are limited to retrospective case series as no prospective randomized study on this specific issue has been published. Park *et al.* (2008) reviewed records of 62 patients with invasive epithelial ovarian cancer who underwent fertility-sparing surgery, defined as the preservation of ovarian tissue in one or both adnexa and the uterus, between May 1990 and October 2006. The majority of patients had stage IA disease and mucinous histology with a median follow-up of 56 months. Eleven patients had a tumor recurrence, six died of disease, two were alive with disease, and 54 were alive without disease. Patients with greater than stage 1C or grade 3 tumors had significantly worse survival. Nineteen women attempted to conceive; there were 22 term pregnancies and no congenital anomalies in any of the offspring. Interestingly, none of the patients with serous histology recurred.

Finally, the question of whether completion oophorectomy and/or hysterectomy should be undertaken in women after the conclusion of childbearing frequently arises. Completion surgery is appealing, because many of the recurrences in patients who initially underwent conservative surgery occur in the contralateral adnexa. Whether completion surgery alters long-term outcome is unknown; thus, the decision to undergo completion surgery should be individualized.

Case study 102.3

A 50-year-old underwent laparoscopic bilateral salpingo-oophorectomy for a 6 cm ovarian cyst and a normal CA125 under the direction of her general gynecologist.

1. Postoperative pathology is significant for a grade 1 endometrioid adenocarcinoma of the ovary. What is the role of staging in low-risk epithelial ovarian cancer?

A. The patient should be initiated on chemotherapy
B. The patient should be referred to a gynecologic oncologist for complete surgical staging
C. The patient needs no additional treatment

Approximately 20–30% of women with early-stage ovarian cancer eventually succumb to their disease. Adequate treatment for this subset has been the topic of much controversy with the greatest dispute being the role of adjuvant therapy after surgical staging. Stage 1 epithelial ovarian cancers portend an excellent prognosis when comprehensively staged. It has been well recognized that a complete surgical staging procedure can detect microscopic extraovarian spread in about 30% of patients with cancer only grossly confined to the ovary, thereby indicating the need for further adjuvant therapies to reduce recurrence risk. Unfortunately, a significant number of patients with apparent early-stage ovarian cancer are still not staged according to the recommended surgical protocol. The management of unstaged patients with apparent early disease is problematic. One option for treatment would be to offer reoperation to complete the surgical staging procedures in an effort to rule out metastatic foci prior to making decisions about the need for adjuvant therapy. This can potentially be associated with a significant chance for postsurgical morbidity and delays in treatment for patients who truly need adjuvant chemotherapy. Limited retrospective data exist in support of both the safety and therapeutic utility associated with reoperation. The second option would be to offer adjuvant chemotherapy based on the presence of high-risk factors for recurrence.

Two relatively large European phase III randomized studies have conclusively demonstrated that an adjuvant platinum-based regimen can improve 5-year overall survival compared with observation only (until relapse) among patients with early-stage epithelial ovarian cancer. The Adjuvant Clinical Trial in Ovarian Neoplasms (ACTION) was a European Organization for Research and Treatment of Cancer (EORTC)-sponsored randomized trial comparing observation with platinum-based chemotherapy in patients with surgically early-stage epithelial ovarian cancer. The other large trial, the International Collaborative Neoplasm Studies (ICON1) trial, had more liberal inclusion criteria, not requiring adequate surgical staging and randomizing patients to six cycles of platinum-based chemotherapy versus observation. In the ACTION study, the disease-free survival and overall survival differences were 11% and 8%, respectively. In the ICON1 study, the disease-free survival and overall survival differences were 10% and 7%, respectively. Unfortunately, both studies failed to recruit their respective target number of patients.

A combined analysis of the two parallel randomized clinical trials in early ovarian cancer, ICON1 and ACTION, comparing platinum-containing adjuvant chemotherapy to observation following surgery has been performed, with survival as the primary endpoint and time to recurrence as a secondary endpoint. A total of 924 patients were randomized. With over 4 years of median follow-up among survivors, the hazard ratio for recurrence-free survival is 0.64 (95% CI: 0.50–0.82; $P = 0.001$) in favor of adjuvant chemotherapy, with an absolute difference of 11%. For overall survival, the hazard ratio is 0.67 (95% CI: 0.50–0.90; $P = 0.008$) in favor of adjuvant chemotherapy. These results translate into an absolute difference of 8% in the adjuvant chemotherapy group and indicate that adjuvant platinum-containing chemotherapy improves survival and disease-free survival. Subgroup analysis demonstrated in the ACTION trial that completeness of surgical staging was an independent factor for prognosis, both for progression-free and for overall survival (along with histological type and tumor grade), while in suboptimally staged patients, adjuvant chemotherapy did improve the outcome. A report of a 10-year follow-up of the ICON1 trial has revealed that the improvement in 5-year overall survival persists even one decade following the completion of adjuvant chemotherapy.

In a systematic review of the evidence for adjuvant chemotherapy in early-stage epithelial ovarian cancer, Winter-Roach and colleagues set out to determine whether there is a survival advantage for those patients treated with chemotherapy over observation following surgery and if there are different prognostic clinical subgroups that may gain more from chemotherapy based on histological subtype, or completeness of surgical staging. Five randomized controlled trials, enrolling 1277 women, with a median follow up of 46–121 months, met inclusion criteria. Four trials were included in the meta-analysis. Results indicated that women who received adjuvant chemotherapy had better progression-free survival than those who did not (HR: 0.67; 95% CI: 0.53–0.84). The trials included in these meta-analyses gave consistent estimates of the effects of chemotherapy. Subgroup analysis suggested that women who had optimal surgical staging of their disease were unlikely to benefit

(*Continued*)

from adjuvant chemotherapy (HR for OS: 1.22; 95% CI: 0.63–2.37), whereas those who had suboptimal staging did benefit from adjuvant chemotherapy (HR for OS: 0.48; 95% CI: 0.32–0.72). Consequently, adjuvant platinum-based chemotherapy is effective in prolonging survival for the majority of patients who are assessed as having early-stage epithelial ovarian cancer; however, it may be withheld from women with stage 1A (grade 1) or those with comprehensively staged 1B with grade 1 or 2 tumors. Others with unstaged early disease or those with poorly differentiated tumors should be offered chemotherapy.

Given the added clarity to the question of surgical staging provided by the ACTION and ICON1 trials and subsequent analyses, the question remains if individuals with high-risk early-stage epithelial ovarian cancer are overtreated systemically. The Gynecologic Oncology Group conducted a phase III trial regarding the management of early-stage disease. This study compared three versus six cycles of carboplatin and paclitaxel combination chemotherapy as the treatment regimen for women with high-risk surgically staged disease. The results showed that there was an approximately 25% increased risk of relapse associated with the truncated course of chemotherapy, although this difference did not reach statistical significance, mainly due to the inadequate sample size. The risk of recurrence in this patient population seems to have remained relatively unchanged over the years, leaving opportunities for innovative research.

In the future, it may be possible for the risk of relapse of ovarian cancer to be more definitively defined based on the tumor's molecular markers or genetic profile, such that patients with a very low risk of recurrence can avoid cytotoxic therapy. However, until such data are available and confirmed through appropriately conducted clinical investigations, the standard of care in the setting of high-risk early-stage ovarian cancer should include a strategy identical to that employed in advanced-stage disease.

Case study 102.4

A 56-year-old with stage IIIC high-grade serous ovarian cancer is now 3 weeks postop from an optimal cytoreduction with microscopic residual disease.

1. What is the optimal postoperative management of treatment-naïve epithelial ovarian cancer after completion of optimal tumor-reductive surgery?

A. Standard dosing of carboplatin and paclitaxel every 3 weeks intravenously (IV)
B. Dose-dense paclitaxel with carboplatin IV
C. IV or intraperitoneal cisplatin–taxol
D. Standard dosing carboplatin and paclitaxel every 3 weeks IV plus bevacizumab 15 mg/kg followed by bevacizumab maintenance
E. A, B, or C

Advanced-stage epithelial ovarian tumors are generally managed with cytoreductive surgery and chemotherapy consisting of carboplatin and paclitaxel, achieving clinical complete remission in the majority of patients. With the incorporation of paclitaxel, the utilization of intraperitoneal therapy or dose-dense weekly scheduling of paclitaxel in selected patients has resulted in incremental improvements in median progression-free or overall survival. However, none of these strategies have appreciable changed the overall mortality from ovarian cancer. Undoubtedly, platinum compounds remain the most active primary cytotoxic agent for ovarian cancer.

Given that the majority of ovarian cancer recurrences are generally confined to the peritoneal cavity, there is a strong rationale for administering cytotoxic drugs directly into the abdominal cavity, thereby increasing the dose intensity delivered to residual tumor implants while simultaneously avoiding additional systemic toxicity associated with increased systemic dose intensity. There have been three large phase III randomized trials comparing IP chemotherapy with IV chemotherapy. Despite improvements in disease-free and overall survival documented in these trials, there is significant impact on host toxicity, including abdominal pain, nausea, vomiting, and neuropathy that leave many yet-to-be-answered questions regarding the optimal dosing of IP platinum, the type of platinum agent that should be administered IP, and the optimal clinical scenario in which IP chemotherapy should be administered. Many of the noted side effects can be attributed to the dose of cisplatin. As a result, it has become common practice to utilize a better-tolerated lesser dose in clinical practice. Furthermore, there has also been interest in the substitution of cisplatin for IP carboplatin. Both cisplatin and carboplatin are rapidly absorbed from the peritoneal cavity; however, carboplatin requires a much longer time for activation. Consequently, it remains unknown if IP carboplatin will be equivalent to cisplatin. The potential role of carboplatin in IP therapy of ovarian cancer is currently being investigated in a phase 3 randomized trial.

In view of the importance of paclitaxel, a number of studies have its evaluated the dose, schedule, sequence, and route of administration. There is a developing school of thought that the efficacy of IP chemotherapy is related to the density of chemotherapy administered and perhaps some of the most intriguing data in the management of ovarian

cancer are those that support dose modification of paclitaxel. Prolonged infusions of paclitaxel (96 h) have demonstrated increased mucosal and bone marrow toxicity, but without improved efficacy. Shorter infusions of paclitaxel (<3 h) are generally better tolerated from a hematologic perspective, although higher individual doses can increase the risk of arthralgia-myalgia and neuropathy. Reducing intervals between chemotherapy cycles is a strategy that has been considered to improve the activity of drugs used to treat ovarian cancer. Dose-dense scheduling, reducing the time for tumor regrowth between cycles, has good scientific rationale and in gynecological cancers was the focus of a randomized study conducted by the Japanese Gynecologic Oncology Group, which demonstrated superiority of weekly dose-dense paclitaxel plus standard-dosing carboplatin compared with bolus-dosing paclitaxel plus carboplatin.

As we establish a greater understanding of the molecular pathways involved in carcinogenesis and tumor growth, a large number of potential therapeutic targets have been identified. Perhaps the most mature concept is abrogation of blood vessels that tumors require to grow and metastasize. Among the antiangiogenic agents, bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is the furthest in development and has seeded itself as an appropriate line of therapy for recurrent disease. The role of bevacizumab in the treatment of primary ovarian cancer remains in question. Two first-line trials have been completed and published, which demonstrated an improvement in progression-free survival but no improvement in overall survival associated with the addition of bevacizumab to the carboplatin plus paclitaxel regimen. These landmark trials leave many unanswered questions regarding the dose, scheduling, and patient selection appropriate for bevacizumab in the primary setting, but have provided evidence to support the incorporation of bevacizumab into future studies.

Case study 102.5

A 56-year-old with stage IIIC high grade serous ovarian cancer underwent suboptimal tumor reduction under the direction of a gynecologic oncologist followed by three cycles of postoperative carboplatin and paclitaxel IV every 3 weeks.

1. Posttreatment imaging reveals small-volume pelvic carcinomatosis. What is the role of interval surgery after suboptimal primary surgery?

A. The patient should continue systemic chemotherapy
B. The patient should undergo re-attempt at cytoreduction followed by no additional therapy if cytoreduction is complete
C. The patient should undergo re-attempt at cytoreduction followed by additional systemic therapy

The value of cytoreductive surgery in the management of ovarian cancer has been debated for years. Large tumors have slower growth rates and tend to have central necrosis, making them less well perfused and, consequently, insensitive to cytotoxic chemotherapy. Small tumors are better perfused, allowing for better diffusion of chemotherapeutic agents. Further, the removal of large tumors also reduces the likelihood that drug-resistant clones will appear as a result of spontaneous mutations. Small tumors require fewer cycles of chemotherapy, thus decreasing the probability of drug-induced resistance. Several nonrandomized single-institution studies, randomized controlled trials, and cooperative group trials have clearly demonstrated differential survival by status of residual disease among patients with ovarian cancer, with those with no gross residual disease having the best outcome compared to those with <1 cm residual versus those with ≥1 cm residual disease in the primary setting; however, the value of debulking surgery after induction chemotherapy has been more difficult to assess with limited evidence in the literature.

Studies evaluating the potential benefit of surgery are flawed secondary comparisons of patients who undergo primary cytoreductive surgery versus those who undergo interval cytoreductive surgery, making it challenging to draw any clinically useful conclusions regarding the impact of cytoreduction alone. A small prospective randomized study has addressed the value of cytoreduction. With a limited number of total patients ($n = 79$), the median survival for the group of patients who underwent cytoreduction was 15 months compared to 12 months among those randomized to chemotherapy alone, suggesting that debulking may not improve survival in patients with ovarian cancer. The strongest evidence for the role of surgery in ovarian cancer comes from a study carried out by Van der Berg and colleagues, in which patients with suboptimal primary surgery were randomly assigned to interval secondary debulking surgery after three cycles of cyclophosphamide and cisplatin or no further surgery followed by additional chemotherapy. Both progression-free and overall survival were significantly longer in the group that underwent surgery. The difference in median survival was 6

(*Continued*)

months among those who underwent surgery, and there was a 10% difference in survival at 2 years again in favor of tumor reductive surgery (56% vs. 46%), supporting pursuance of additional surgical intervention in those patients with ovarian cancer who have undergone induction chemotherapy. The question that remains is what influence does surgeon expertise on decision to pursue additional surgical intervention. Clinically, if a patient has undergone maximum surgical effort by a gynecologic oncologist that has been deemed suboptimal, disease remaining after induction chemotherapy is deemed biologically aggressive and managed with additional systemic treatment.

Case study answers

Case study 102.1

Question 1: Answer A

Case study 102.2

Question 1: Answer B

Case study 102.3

Question 1: Answer A

Case study 102.4

Question 1: Answer A

Case study 102.5

Question 1: Answer A

Selected reading

Armstrong DK, Bundy B, Wenzel L, *et al*. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354:34–43.

Bristow RE, Tomacruz RS, Armstrong DK, *et al*. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002;20:1248–59.

Burger RA, Brady MF, Bookman MA, *et al*. Incorporation of bevacizumab in the primary treatment of ovarian cancer. New Engl J Med. 2011;365:2473–2783.

Katsumata N, Yasuda M, Takahashi F, *et al*. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3 open-label, randomized controlled trial. Lancet 2009;374:1331–38.

Vergote I, Tropé CG, Amant F, *et al*. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943–53.

For further information on this area please also consult Chapter 123

CHAPTER 103

Ovarian cancer: second-line treatment strategies

Maurie Markman

Cancer Treatment Centers of America *and* Drexel University College of Medicine, Philadelphia, PA, USA

Case study 103.1

A 66-year-old ovarian cancer patient develops abdominal pain and bloating 9 months after the completion of carboplatin–paclitaxel chemotherapy. The serum CA-25 level is now 395 U/ml (repeat value 436 U/ml), having declined to 27 U/ml at the end of the first-line treatment program. A computed tomography (CT) scan of the abdomen–pelvis reveals a small amount of ascites and possible peritoneal wall nodules.

1. All of the following would be reasonable subsequent management strategies EXCEPT which?

A. Initiate chemotherapy with a non-platinum-containing regimen
B. Initiate chemotherapy with a platinum-containing regimen
C. Obtain a biopsy of the peritoneal wall nodule to confirm the presence of ovarian cancer
D. All of the listed options are appropriate

With a treatment-free interval of 9 months, the cancer in this patient would reasonably be considered to have a modest opportunity to again respond to a platinum agent, and either employing or not employing platinum (cisplatin or carboplatin) in the second-line setting would be an appropriate option. There is no need to re-biopsy a patient with known ovarian cancer whose has recurrent symptoms and a definite increase in the serum CA-125 level if this procedure is being performed solely for the purpose of confirming the presence of recurrent disease.

Multiple choice questions

1. Which of the following statements regarding the second-line treatment of epithelial ovarian cancer is correct?

A. There is no rationale for delivering more than three different chemotherapy regimens in ovarian cancer as the chances of producing serious side effects beyond this number of regimens far outweighs the opportunity for clinical benefit
B. The overall "duration of survival" following initial disease progression in ovarian cancer now frequently exceeds the time from diagnosis to the date of initial progression
C. There are no oral agents with known activity in ovarian cancer currently available for routine clinical use
D. None of the above

Increasingly, patients with ovarian cancer are able to experience extended survival (including prolonged survival after initial progression following front-line platinum–taxane chemotherapy) due to the activity of multiple active anti-neoplastic agents in this malignancy. There are no reasonable arbitrary limits on the number of chemotherapy regimens that may be employed, assuming care is taken to minimize the risk of excessive and sustained toxicity. Several oral anti-neoplastic agents (e.g., tamoxifen, etoposide, and altretamine) are utilized in routine clinical practice in the management of ovarian cancer.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

2. Which of the following molecular markers have been shown to be clinically relevant in the selection of second-line therapy of ovarian cancer?

A. Activating mutations in epidermal growth factor receptor
B. Her2 overexpression
C. BRAF mutations
D. None of the above

There are currently no molecular or genomic markers of known clinical relevance in the treatment of ovarian cancer. Provocative data have suggested the utility of PARP inhibitors in ovarian cancer patients with BRCA1 and BRCA2 mutations, but there are unfortunately currently no such anti-neoplastic agents available for routine clinical use.

Case study 103.2

A 52-year-old female with epithelial ovarian cancer develops recurrent disease with a treatment-free interval of 19 months following the completion of her primary chemotherapy regimen (carboplatin–paclitaxel).

1. Which of the following statements regarding the opportunity for this individual to respond to another platinum-based chemotherapy regimen is *incorrect*?

A. There is at least a 50% chance for an objective response to be observed
B. Compared to single-agent platinum, platinum-based combination chemotherapy has been shown to improve both progression-free and overall survival in this setting
C. Cure is a realistic goal in this clinical setting
D. None of the above

There is a high probability (greater than 50%) that a patient with this rather prolonged treatment-free interval will achieve a second response following reintroduction of a platinum strategy. Several phase III trials have documented the superiority of combination platinum-based compared to single-agent platinum in recurrent ovarian cancer. While second-line therapy in ovarian cancer has been shown to improve both progression-free and overall survival, there is currently no evidence that such therapy can cure the malignancy.

Case study 103.3

A 65-year-old asymptomatic female with epithelial ovarian cancer is found to have a rising serum CA-125 antigen level approximately 16 months following the completion of her primary chemotherapy regimen. A CT scan of the abdomen reveals a small amount of ascites as well as a number of small (less than 3 cm in maximum diameter) pelvic and peritoneal nodules.

1. Which of the following statements is correct regarding the clinical utility of secondary surgical cytoreduction in this clinical setting?

A. A phase III trial has revealed the superiority of an attempt at secondary cytoreduction in epithelial ovarian cancer compared to initiating treatment with chemotherapy (and no surgery)
B. A phase III trial has documented the clear lack of benefit associated with secondary cytoreduction in epithelial ovarian cancer
C. Existing phase III trial data strongly suggest that secondary cytoreduction surgery is only of value if it is followed by a high-dose chemotherapy regimen with stem cell support
D. None of the above

Currently, there are no prospective phase III trial data that demonstrate the benefits, or harm, associated with secondary cytoreductive surgery in epithelial ovarian cancer, although several phase III trials are in progress that will hopefully answer this question

3. For several reasons, randomized phase III trials have been required to answer the question of the utility of secondary cytoreduction in ovarian cancer, versus simply accepting the results of retrospective analyses comparing patients undergoing or not undergoing such procedures. These include all of the following, EXCEPT which?

A. Any benefit of surgery may result from selection bias associated with the patient population chosen to undergo such surgery (e.g., superior performance status and fewer comorbidities)
B. Any benefit of surgery may result from similar biological factors that influence the ability to successfully surgically cytoreduce the cancer and that determine the growth, spread, and development of drug resistance
C. Both A and B
D. Neither A nor B

Both of the issues of "selection bias" and "similar biological factors" are critical factors in any discussion of the relevance of retrospective analyses in defining the utility of secondary cytoreduction in ovarian cancer. As a result of the compounding influence of these factors, only the conduct of a well-designed randomized phase III trial can resolve the issue.

Case study 103.4

A 47-year-old woman with a 2-year history of ovarian cancer undergoes secondary cytoreduction and is left with only microscopic residual disease. She inquires about the potential role of intraperitoneal chemotherapy in her management.

1. Which of the following statements regarding this strategy in the second-line management of ovarian cancer is correct?

A. Phase III trial data have revealed a survival advantage for this approach compared to systemic administration in this clinical setting
B. This strategy should not be employed in the second-line setting due to the potential for severe intraperitoneal side effects in multiple clinical trials
C. Phase II trial data have revealed the opportunity to achieve surgically documented complete responses following second-line intraperitoneal cisplatin-based chemotherapy
D. None of the above

Multiple phase II trials have revealed the biological and clinical activity (including surgically confirmed complete responses) associated with the second-line delivery of platinum-based chemotherapy in epithelial ovarian cancer. However, there remain no phase III trial data to demonstrate the therapeutic superiority of this approach compared to systemic drug administration in this clinical setting.

Case study 103.5

A 53-year-old female will be initiating second-line carboplatin-based chemotherapy for ovarian cancer.

1. Which of the following platinum-associated toxicities are somewhat unique to this clinical setting?

A. Hypersensitivity reactions
B. Peripheral neuropathy
C. Severe emesis
D. Cardiac dysfunction

Considerable retrospective data have revealed that the incidence of platinum-associated (most frequently, carboplatin) hypersensitivity increases rather dramatically after a total of at least 5–6 cumulative doses of the agent, which in most circumstances will occur in the second-line setting. This is presumably due to a requirement for multiple exposures of the susceptible immune system to very low concentrations of free platinum that may be present within the anti-neoplastic drug preparation.

Case study 103.6

A 62-year-old ovarian cancer patient experiences recurrent abdominal pain following completion of her second-line carboplatin treatment regimen.

1. Which of the following statements are correct regarding the ability to retreat this patient with another platinum program?

A. Platinum-based regimens should only be used a maximum of two times due to the development of excessive side effects with additional treatment
B. The probably of another response (third-line) to a platinum program will be dependent on the duration of time the patient has been off treatment from the second-line regimen
C. Phase III trial data have revealed that non-platinum therapy is superior to a platinum-regimen for third-line treatment of ovarian cancer
D. Because of the low probably of a response to any cytotoxic therapy in ovarian cancer, there is essentially no role to re-administer a platinum regimen in this setting

As with second-line therapy of ovarian cancer, the probability of a third response to a platinum agent appears to be related to the duration of time a patient has been off treatment from a second-line platinum program. Of course, this assumes that the patient had exhibited a response to that regimen. If not, alternative non-platinum-based options will need to be considered.

Case study 103.7

A 49-year-old female with ovarian cancer experiences abdominal pain and is found to have a new pelvic mass on imaging studies 4 months after the completion of her primary chemotherapy program.

1. All of the following statements concerning her future management are correct, EXCEPT which?

A. The cancer is considered to be platinum resistant
B. High-dose chemotherapy with stem cell rescue has not been shown to be of value in this clinical setting
C. The administration of a two-drug cytotoxic chemotherapy program has been shown to result in improved survival compared to single-agent cytotoxic delivery
D. A and B

This cancer is considered to be platinum resistant (recurrence within 6 months of the completion of primary chemotherapy). High-dose chemotherapy plays no role in patients with platinum-resistant disease, and there is no evidence that combination cytotoxic therapy is superior to single-cytotoxic-agent treatment in this setting.

Case study 103.8

A 52-year-old ovarian cancer patient experiences recurrence of her disease 22 months following the completion of primary chemotherapy.

1. Which of the following statements regarding management of recurrent potentially platinum-sensitive ovarian cancer is correct?

A. Compared to single-agent platinum, combination platinum-based chemotherapy has been shown in randomized trials to improve both the time to subsequent disease progression and overall survival in this clinical setting
B. Cisplatin has been documented to be more active than carboplatin in recurrent ovarian cancer
C. On the basis of existing phase III trial data, there is currently no evidence for the superiority of any one platinum-based combination chemotherapy regimen compared to another in the setting of recurrent ovarian cancer
D. None of the above

Two phase III randomized trials have revealed the superiority of a platinum-based combination regimen, compared to single-agent platinum in improving progression-free survival, while one such study has demonstrated an improvement in overall survival. There is no evidence for the superiority of cisplatin compared to carboplatin in recurrent disease. In a phase III trial, the combination of carboplatin plus pegylated liposomal doxorubicin improved progression-free survival compared to carboplatin plus paclitaxel in recurrent ovarian cancer.

4. In the phase III randomized trial of carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin (PLD) in recurrent ovarian cancer, patients treated with the PLD-containing regimen experienced an unexpectedly low incidence of which carboplatin-associated toxicity (compared to that observed in the paclitaxel-containing program)?

A. Emesis
B. Bone marrow suppression
C. Peripheral neuropathy
D. Hypersensitivity reactions

In this trial, 5.6% of patients treated on the PLD arm experienced a carboplatin-associated hypersensitivity reaction ($\geq$ grade 2) compared to an incidence of 18.8% with paclitaxel. A biological explanation for this highly provocative finding remains elusive, although a second smaller randomized trial has reached a similar conclusion. The lower risk of carboplatin hypersensitivity may explain (at least in part) the statistically significant improvement in time to disease progression noted in this trial in favor of the PLD-containing regimen as a lower percentage of patients on this study arm had treatment with carboplatin discontinued as a result of this potentially highly relevant side effect.

5. An overall survival advantage was revealed in favor of single-agent PLD in a phase III trial that compared this agent to topotecan as a second-line therapy of epithelial ovarian cancer. This survival advantage was confined to what subset of patients?

A. Platinum-resistant disease
B. Platinum-sensitive disease
C. An overall survival advantage was observed in both subgroups
D. There was no overall survival advantage observed in this trial, only an improvement in progression-free survival

In this important phase III trial, patients with potentially platinum-sensitive (treatment-free interval of >6 months) recurrent ovarian cancer treated with PLD experienced superior overall survival compared to second-line therapy with topotecan. There was no difference in survival for patients with platinum-resistant disease.

6. Which statement is correct regarding the activity of weekly paclitaxel in patients previously treated with every-3-week paclitaxel delivery in the front-line setting?

A. Weekly paclitaxel administration is inactive in this clinical setting
B. An objective response rate of 20% can be anticipated with weekly paclitaxel delivery
C. Weekly paclitaxel is associated with an unacceptably high risk of peripheral neuropathy in patients previously treated with every-3-week paclitaxel
D. None of the above

Several phase II studies have revealed an objective response rate of approximately 20% when weekly paclitaxel is administered to patients who have previously received and progressed on a regimen where the agent was delivered on an every-3-week schedule. In addition, in most patients this approach is associated with a favorable side effect profile.

7. Single-agent PLD is commonly administered in the management of platinum-resistant ovarian cancer at a dose of 40 mg/m^2 (delivered on an every-28-day schedule). This has been done to reduce the risk of patients experi-

encing highly clinically relevant toxicity (e.g., hand-foot-syndrome, mucositis, and stomatitis) commonly observed at the dose level, which received US Food and Drug Administration approval for delivery as second-line therapy of ovarian cancer. What is this dose level?

A. 50 mg/m^2 every 28 days
B. 60 mg/m^2 every 28 days
C. 70 mg/m^2 every 28 days
D. None of the above

While there have been no direct comparison studies of PLD administered at a dose of 40 versus 50 mg/m^2 in ovarian cancer, retrospective data from several centers have suggested equivalent activity of the two dose levels. Further, randomized trials have compared the same control arm (gemcitabine) to PLD at either the 40 or 50 mg/m^2 levels with equivalent survival outcomes. Of greatest relevance, however, is the observation that the lower dose level is associated with a substantially more favorable toxicity profile for the agent in this palliative clinical setting.

Case study 103.9

A 67-year-old female with epithelial ovarian cancer has received several prior chemotherapy regimens and is considering possible options for her again-progressing malignancy.

1. Which of the following clinical factors in this individual's medical history would suggest the possible inadvisability of employing bevacizumab?

A. Several recent episodes of medically managed partial small-bowel obstruction
B. Medication controlled hypertension
C. Platinum-resistant ovarian cancer
D. History of carboplatin-associated hypersensitivity reaction

Existing clinical trial data have suggested a relatively high risk of bowel perforation (10%) associated with bevacizumab administration in heavily pretreated patients with ovarian cancer with the greatest risk noted in individuals with evidence of bowel involvement with tumor. The presence of small-bowel obstruction likely suggests such involvement and would be a relative contraindication for the use of this anti-neoplastic medication.

8. Despite the documented benefits of bevacizumab when combined with cytotoxic chemotherapy in a number of tumor types, the single-agent activity of this anti-angiogenic agent in these cancers has been quite modest. What is the reported single-agent response rate in the second-line (or later) setting for bevacizumab in epithelial ovarian cancer?

A. <2%
B. 5%
C. 15%
D. 35%

In one well-designed and -conducted single-agent phase II trial involving heavily pretreated patients with epithelial ovarian cancer, an objective response rate of 15% was observed. Of note, this level of activity is comparable to a number of cytotoxic agents routinely employed in this clinical setting (e.g., PLD, topotecan, paclitaxel, and docetaxel).

9. In a phase III trial comparing chemotherapy with or without bevacizumab in recurrent platinum-sensitive ovarian cancer, what was the cytotoxic regimen examined?

A. Cisplatin plus paclitaxel
B. Carboplatin plus paclitaxel
C. Carboplatin plus PLD
D. Carboplatin plus gemcitabine

Carboplatin plus gemcitabine was the control arm in this trial, with the experimental regimen adding bevacizumab.

10. In the above noted study, the bevacizumab-containing regimen was found to result in a statistically significant improvement in which clinical parameter(s)?

A. Progression-free survival only
B. Overall survival only
C. Progression-free and overall survival
D. Progression-free and overall survival and objective response rate

The so-called OCEANS trial revealed a statistically significant improvement in progression-free survival (median: 12.4 vs. 8.4 months; $P < 0.0001$), but no difference in overall survival associated with the addition of bevacizumab to the carboplatin–gemcitabine program.

11. In a phase III trial that compared the administration of cytotoxic chemotherapy with or without bevacizumab in platinum-resistant ovarian cancer, there was a choice of three different cytotoxic regimens. These included all of the following, EXCEPT which?

A. Topotecan
B. PLD
C. Weekly paclitaxel
D. Pemetrexed

The times to disease progression on each of the three chemotherapy regimens (topotecan, weekly paclitaxel, and PLD) included in this study were shown to be prolonged with the addition of bevacizumab.

Case study answers

Case study 103.1

Question 1: Answer C

Case study 103.2

Question 1: Answer C

Case study 103.3

Question 1: Answer D

Case study 103.4

Question 1: Answer C

Case study 103.5

Question 1: Answer A

Case study 103.6

Question 1: Answer B

Case study 103.7

Question 1: Answer C

Case study 103.8

Question 1: Answer A

Case study 103.9

Question 1: Answer A

Multiple choice answers

Question 1: Answer B
Question 2: Answer D
Question 3: Answer C
Question 4: Answer D
Question 5: Answer B
Question 6: Answer B
Question 7: Answer A
Question 8: Answer C
Question 9: Answer D
Question 10: Answer A
Question 11: Answer D

Selected reading

Aghajanian C, Blank SV, Goff BA, *et al*. OCEANS: A randomized double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal or fallopian tube cancer. J Clin Oncol. 2012;30:2039–45.

Dhillon S. Bevacizumab combination therapy for the first line-treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. Drugs 2012;72(7):917–30.

Fong PC, Yap TA, Boss DS, *et al*. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin. 2010; 28(15):2512–19.

Hennessy B, Coleman RL, Markman M. Ovarian cancer. Lancet 2009;374:1371–82.

Markman M. Pharmaceutical management of ovarian cancer. Drugs 2008; 68(6):771–89.

For further information on this area please also consult Chapter 123

CHAPTER 104

Endometrial and cervical cancers

Maurie Markman

Cancer Treatment Centers of America *and* Drexel University College of Medicine, Philadelphia, PA, USA

Cervical cancer

Case study 104.1

A 39-year-old female is diagnosed with locally advanced squamous cell cervical cancer.

1. Which of the following statements is NOT correct regarding the demonstrated clinical utility of concurrent chemoradiation in this clinical setting?

A. In standard clinical practice, cisplatin is administered at a dose of 40 mg/m^2/week along with external-beam radiation

B. Carboplatin has been demonstrated to be equally effective when combined with external-beam radiation therapy this clinical setting

C. Extended follow-up of patients treated on the landmark clinical trials demonstrating the utility of chemoradiation has revealed a survival advantage extending >5 years after the completion of treatment

D. A and B

To date, there are no phase III trials that have documented the therapeutic equivalence of carboplatin compared to cisplatin when administered as a component of a chemoradiation strategy in locally advanced cervical cancer. Cisplatin is routinely administered at a dose of 40 mg/m^2/week based on the results of one of the landmark studies that demonstrated the clinical utility of this approach, and long-term follow-up data have documented the continued survival benefits (>5 years) associated with the use of this strategy.

Multiple choice questions

1. Which of the following combination chemotherapy regimens has been shown in a phase III randomized trial to result in a superior survival outcome compared to single-agent cisplatin when employed as a component of a chemoradiation strategy in locally advanced cervical cancer?

A. Cisplatin–gemcitabine
B. Cisplatin–paclitaxel
C. Cisplatin–topotecan
D. None of the above

A phase III randomized trial conducted in South America has revealed the superiority of the combination of cisplatin plus gemcitabine compared to cisplatin alone when employed as a component of a concurrent chemoradiation strategy. Despite this outcome, this strategy has not been adopted for routine use as several groups have found excessive toxicity associated with this chemotherapy combination when added to external-beam radiation.

Case study 104.2

A 45-year-old female is found to have cervical cancer. Further work-up reveals several 1–3 cm nodules in the lung and a 4 cm mass in the liver.

1. Which chemotherapy regimen has been shown to improve overall survival, compared to single-agent cisplatin, in metastatic cervical cancer?

A. Cisplatin–gemcitabine
B. Cisplatin–paclitaxel
C. Cisplatin–vinorelbine
D. Cisplatin–topotecan

A phase III trial has revealed the survival advantage of the combination of cisplatin plus topotecan compared to cisplatin alone in this clinical setting.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

2. Despite the favorable survival outcome in this phase III trial, the study results have been criticized for which of the following reasons?

A. A higher-than-expected percentage of patients in the cisplatin-only arm being more than 65 years of age
B. A higher-than-expected percentage of patients in the combination chemotherapy arm who had not previously received external-beam radiation
C. A higher than expected percentage of patients in both study arms who were HIV-positive
D. A large percentage of patients had previously received cisplatin as a component of a chemoradiation program

While this is not the fault of the study investigators, the relevance of this study has been questioned because a substantial proportion of individuals entered into the trial had previously received (and failed) a cisplatin-containing chemoradiation program. Thus, one rational interpretation of this study is that it actually compared "single agent topotecan" to "no chemotherapy" rather than defining the activity of this combination cisplatin-based regimen.

3. In a multi-arm phase III trial in metastatic and recurrent cervical cancer, which of the following regimens was shown to result in a statistically significant improvement in time to disease progression compared to the other study arms?

A. Cisplatin–paclitaxel
B. Cisplatin–gemcitabine
C. Cisplatin–topotecan
D. None of the above

In this landmark Gynecologic Oncology Group study, there was no statistically significant difference in either time to disease progression or overall survival in any of the study arms (cisplatin–paclitaxel, cisplatin–gemcitabine, cisplatin–topotecan, or cisplatin–gemcitabine).

4. In the above-noted study, which of the following clinical factors were NOT found to negatively impact a patient's opportunity to achieve a clinical response to cisplatin-based combination chemotherapy?

A. Prior documented human papilloma virus (HPV) infection
B. Prior chemoradiation
C. Disease in a previously radiated region
D. None of the above

Both prior chemoradiation and disease in a previously radiated area will negatively impact the opportunity for a response to platinum-based systemic therapy for metastatic or recurrent cervical cancer.

5. What noncytotoxic agent, when combined with chemotherapy, has been shown in a phase III randomized trial to improve survival in metastatic or recurrent cervical cancer?

A. Erlotinib
B. Venurafinib
C. Bevacizumab
D. Gefitinib

In a report of a phase III randomized trial, the addition of bevacizumab to combination chemotherapy was shown to result in a statistically significant improvement in overall survival in metastatic and recurrent cervical cancer. This was the first randomized trial to document the utility of a noncytotoxic agent in this clinical setting.

Case study 104.3

Parents of an 11-year-old girl inquire regarding the benefits of HPV vaccination for their daughter.

1. It would be appropriate to state that, to date, HPV vaccination has been documented to result in a statistically significant reduction in the risk of all of the following, EXCEPT which?

A. Persistent HPV infection
B. CIN 3
C. Invasive cervical cancer
D. None of the above

Due to the time required for the development of cervical cancer, it will take long-term follow-up of large vaccinated populations to definitively document the ability of HPV vaccination to reduce the risk of invasive cervical cancer. However, based on definitive evidence that such vaccination is remarkably effective in preventing the development of well-established precursor lesions for the malignancy (e.g., CIN 3), it is virtually certain that such evidence will become available at some point in the future.

6. Cisplatin has been recognized for more than 30 years to be an important agent in the management of cervical cancer. Which of the following strategies has NOT been established as being an effective cisplatin-based approach to improve survival in cervical cancer?

A. Cisplatin-based chemoradiation
B. Cisplatin-based adjuvant chemotherapy
C. Cisplatin-base neoadjuvant chemotherapy
D. B and C

There is currently no evidence from well-designed phase III trials that either adjuvant or neoadjuvant chemotherapy employing a cisplatin-based strategy favorably impacts overall survival in cervical cancer.

7. Which of the following statements is correct regarding the role of platin-based chemotherapy in metastatic or recurrent cervical cancer?

A. A phase III randomized trial has revealed the equivalence of cisplatin and carboplatin in this clinical setting
B. A phase III randomized trial has revealed the therapeutic equivalence (survival outcome) of cisplatin delivered at a dose of either 50 or 100 mg/m^2
C. A phase III randomized trial has revealed the superiority of cisplatin delivered until documented disease progression compared to discontinuing treatment following the documentation of either an objective response or stable disease (for a minimum of two cycles)
D. None of the above

A phase III trial has revealed no difference in survival for patients treated with single-agent cisplatin at a dose of either 50 or 100 mg/m^2, with the lower dose regimen being associated with a substantially superior toxicity profile.

Endometrial cancer

Case study 104.4

A 73-year-old female is diagnosed as having adenocarcinoma of the endometrium. Computed tomography scan of the chest reveals multiple 0.5–1 cm lung nodules.

1. Considering her age, hormonal therapy is being considered as a possible therapeutic option. Hormonal therapy has been shown to be a useful strategy in metastatic endometrial adenocarcinoma in each of the following situations, EXCEPT which?

A. Low.grade cancers
B. High-grade cancers
C. Cancers expressing the progesterone receptor
D. None of the above

Patients with high-grade cancers rarely (if ever) respond to hormonal therapy (e.g., systemic progesterone delivery). As a result, in this setting systemic chemotherapy is the preferred initial treatment option even in patients who present with low-volume metastatic disease.

8. Which of the following statements is correct regarding the combination of chemotherapy and hormonal therapy in endometrial adenocarcinoma?

A. Randomized phase III trial data reveal the favorable impact of this strategy on progression-free survival in metastatic low-grade endometrial adenocarcinoma
B. Randomized phase III trial data reveal the favorable impact on overall survival when employed as an adjuvant strategy in low- and intermediate-grade endometrial adenocarcinoma
C. Randomized phase III trial data reveal an increase in treatment-related mortality when hormonal therapy is combined with chemotherapy in metastatic endometrial adenocarcinoma
D. None of the above

There is no solid evidence-based data supporting the combination of chemotherapy and hormonal therapy in endometrial adenocarcinoma. Similarly, while there is no strong biological reason to believe toxicity will worsen if the strategies are combined, any benefits associated with a superior side effect profile with the use of hormones will be lost if the two approaches are given together.

Case study 104.5

1. A 52-year-old female is diagnosed with stage IV endometrial cancer with evidence of metastatic spread to the peritoneal cavity, lung, and liver. Which combination chemotherapy regimen has been found in a phase III randomized trial to improve overall survival compared to cisplatin plus doxorubicin in metastatic endometrial adenocarcinoma?

A. Carboplatin–paclitaxel
B. Cisplatin–doxorubicin–paclitaxel
C. Cisplatin–docetaxel
D. Carboplatin–paclitaxel–doxorubicin

In a phase III trial conducted by the Gynecologic Oncology Group, the combination of cisplatin–doxorubicin–paclitaxel improved overall survival (median: 15.3 months vs. 12.3 months; $P = 0.037$) compared to cisplatin–doxorubicin.

2. Despite the favorable survival outcome associated with this regimen, there was a statistically significant increase in all of the following toxicities for this program compared to cisplatin–doxorubicin, EXCEPT which?

A. Secondary acute leukemia
B. Peripheral neuropathy
C. Metabolic abnormalities
D. None of the above

The phase III trial revealed an increased risk of clinically relevant peripheral neuropathy and metabolic dysfunction associated with the three-drug regimen, but no increase in secondary acute leukemia was noted.

Case study 104.6

A 62-year-old female is diagnosed with metastatic endometrial cancer. Because of clinically relevant comorbidities, it is decided to treat her with sequential single-agent therapy.

1. Based on phase III trial results, which is the most active individual cytotoxic agent in endometrial adenocarcinoma?

A. Cisplatin
B. Doxorubicin
C. Paclitaxel
D. None of the above

Phase III trial data are not available to document the single most biologically and clinically active cytotoxic agent in endometrial adenocarcinoma. Unfortunately, only single-arm phase II trial data exist to draw any indirect comparisons. As a result, it is only appropriate to state that the platinum agents (cisplatin and carboplatin), doxorubicin, and paclitaxel are active drugs in this clinical setting.

Case study 104.7

A 51-year-old female is diagnosed with stage III endometrial cancer with only microscopic residual disease remaining in the peritoneal cavity at the completion of exploratory surgery.

1. Compared to the delivery of whole abdominal radiation in stage III endometrial adenocarcinoma, which cytotoxic chemotherapy program has been shown in a phase III randomized trial to improve overall survival?

A. Single-agent doxorubicin
B. Cisplatin–doxorubicin
C. Carboplatin–paclitaxel
D. Cisplatin–doxorubicin–paclitaxel

In a landmark phase III trial, the combination of cisplatin and doxorubicin as primary therapy was shown to improve overall survival compared to whole abdominal radiation (without chemotherapy).

Case study 104.8

A 47-year-old female is diagnosed as having a stage I papillary serous carcinoma of the endometrium.

1. Which of the following statements is correct regarding adjuvant chemotherapy for high-risk early-stage endometrial adenocarcinoma?

A. A phase III trial has revealed the favorable impact of this strategy (employing carboplatin–paclitaxel) on overall survival
B. A phase III trial has documented inferior overall survival and quality of life associated with the administration of adjuvant chemotherapy (cisplatin–doxorubicin–paclitaxel) compared to an "observation" control arm
C. A phase III trial has documented the favorable impact on survival for this strategy in patients with specific subtypes of endometrial cancer, while no benefit was observed in other subtypes
D. None of the above

There is currently no evidence based on the results of phase III trials that the adjuvant delivery of cytotoxic therapy will improve overall survival in high-risk, early-stage endometrial adenocarcinoma. However, retrospective data from a number of centers have suggested a possible benefit when comparing historical experiences for patients who received, or did not receive, some form of adjuvant therapy.

Case study 104.9

A 67-year-old female in otherwise excellent health is diagnosed as having metastatic endometrial adenocarcinoma. You are now in the process of considering therapeutic options.

1. Compared to cisplatin–paclitaxel–doxorubicin, the combination of carboplatin–paclitaxel results in all of the following in patients with metastatic endometrial adenocarcinoma, EXCEPT which?

A. Equivalent progression-free survival
B. Equivalent overall survival
C. Increased toxicity
D. None of the above

A phase III randomized trial conducted by the Gynecologic Oncology Group revealed equivalent survival (progression-free and overall) for the combination of carboplatin–paclitaxel compared to cisplatin–paclitaxel–doxorubicin with a more favorable toxicity profile. As a result, the two-drug combination of carboplatin–paclitaxel should in most circumstances be considered the "standard of care" in the management of metastatic or recurrent endometrial adenocarcinoma.

Case study 104.10

A 65-year-old female is diagnosed with a stage I carcinosarcoma and is treated with adjuvant external-beam radiation. Unfortunately, 9 months lager she experiences metastatic spread to the lung.

1. Compared to single-agent ifosfamide, which combination chemotherapy regimen has been shown in a phase III randomized study to improve overall survival in this clinical setting?

A. Ifosfamide–paclitaxel
B. Cisplatin–paclitaxel
C. Carboplatin–paclitaxel
D. Docetaxel–gemcitabine

In a phase III trial conducted by the Gynecologic Oncology Group, the combination of ifosfamide and paclitaxel was shown to improve overall survival (median: 13.5 months vs. 8.4 months) compared to single-agent ifosfamide.

Case study 104.11

A 50-year-old female is diagnosed with a stage IV endometrial sarcoma.

1. Which of the following statements regarding chemotherapy in this clinical setting is incorrect?

A. The combination of gemcitabine–docetaxel is an active strategy in metastatic endometrial leiomyosarcoma, but its superiority to other approaches has yet to be proven in a phase III randomized trial
B. In patients with endometrial carcinosarcoma, the metastatic sites are most commonly revealed to be principally composed of adenocarcinoma rather than sarcoma
C. The combination of a platinum agent and paclitaxel produces objective responses in endometrial carcinosarcomas
D. High-dose chemotherapy with stem cell rescue has been shown to have curative potential in a carefully defined subset of patients with metastatic endometrial sarcomas

There is currently no evidence for the curative potential of high-dose chemotherapy in metastatic endometrial carcinomas. Metastatic components from carcinosarcoma have been shown to be principally composed of adenocarcinoma. Carcinosarcomas can be responsive to the combination of a platinum agent and paclitaxel, and the combination of docetaxel and gemcitabine is active in endometrial leiomyosarcomas.

Case study answers

Case study 104.1
Question 1: Answer B

Case study 104.2
Question 1: Answer D

Case study 104.3
Question 1: Answer C

Case study 104.4
Question 1: Answer B

Case study 104.5
Question 1: Answer B
Question 2: Answer A

Case study 104.6
Question 1: Answer D

Case study 104.7
Question 1: Answer B

Case study 104.8
Question 1: Answer D

Case study 104.9
Question 1: Answer C

Case study 104.10
Question 1: Answer A

Case study 104.11
Question 1: Answer C

Multiple choice answers

Question 1: Answer A
Question 2: Answer D
Question 3: Answer D
Question 4: Answer A
Question 5: Answer C
Question 6: Answer D
Question 7: Answer B
Question 8: Answer D

Selected reading

Amant F, Coosemans A, Debiec-Rychter M, *et al*. Clinical management of uterine sarcomas. Lancet Oncol. 2009;10: 1188–98.

Hill EK, Dizon DS. Medical therapy of endometrial cancer. Drugs 2012;72(5):705–13.

Markman M. Chemoradiation in the management of cervix cancer: current status and future direction. Oncology. 2013; 84:246–50.

Medeiros LR, Rosa DD, daRosa MI, *et al*. Efficacy of human papillomavirus vaccines: A systematic quantitative review. Int J Gynecol Cancer 2009;19:1166–76.

Moore DH, Tian C, Monk BJ, *et al*. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2010;116:44–9.

For further information on this area please also consult Chapter 123

PART 8

Sarcomas

CHAPTER 105

Bone sarcomas

Nicole Larrier, William C. Eward, and Richard F. Riedel
Duke University Medical Center, Durham, NC, USA

Case study 105.1

A 17-year-old Caucasian male is diagnosed with Ewing sarcoma of the left humerus. Staging studies reveal no evidence of metastatic disease.

- **Chemotherapy with surgery and/or radiation therapy is recommended. Is there a role for interval compressed chemotherapy for the treatment of localized Ewing sarcoma?**

Yes. The concept of interval-compressed chemotherapy was explored in a prospective, multicenter, randomized controlled trial by the Children's Oncology Group (COG). In this study, 587 patients were randomly assigned to receive chemotherapy as part of a 21- or 14-day cycle. Both treatment arms received VDC (vincristine, doxorubicin, and cyclophosphamide) alternating with IE (ifosfamide and etoposide) for a total of 14 cycles, and daily filgrastim was used for growth factor support. Across all patients, the mean cycle duration in the standard chemotherapy arm was 22.45 $\pm$ 4.87 days compared to 17.29 $\pm$ 5.40 days in the interval compressed arm ($P < 0.001$). The 5-year event-free survival was improved in the interval compressed versus standard treatment arm, 73% versus 65% respectively ($P = 0.048$). Five-year overall survival, however, was not statistically significant between the two arms (83% vs. 77%) for interval compressed versus standard arms, respectively ($P = 0.056$). Importantly, there was no significant difference in toxicity between treatment arms. In summary, interval compressed chemotherapy resulted in a 22% decrease in the risk of disease recurrence with no significant increase in toxicity. As a result, we feel that it is reasonable to consider interval compressed chemotherapy for this patient with localized Ewing sarcoma despite the lack of an overall survival benefit.

While the COG study enrolled patients up to 50 years of age, it is important to note that patients $\geq$18 years of age represented a minority of patients enrolled (12% total) in this study. An analysis of the patients $\geq$18 years of age, reported at American Society of Clinical Oncology (ASCO) 2008, showed no benefit for the use of interval compressed therapy, but the total number of patients in the analysis was small ($n = 67$), limiting the power to detect a difference. As a result, the ability to draw firm conclusions on the use of interval compressed chemotherapy in patients $\geq$18 years of age is limited, in our opinion.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 105.2

A 52-year-old Caucasian male presents with 1-year history of worsening back pain despite conservative treatment. Imaging is performed and reveals a 20 cm mass arising from the sacrum (Figure 105.1). Biopsy reveals a diagnosis of giant cell tumor of bone (GCT). Based on tumor size, location in the high sacrum, and anticipated surgical morbidity, the mass is deemed unresectable. The patient received a total of four embolizations over an 8-month time period with minimal improvement in symptoms.

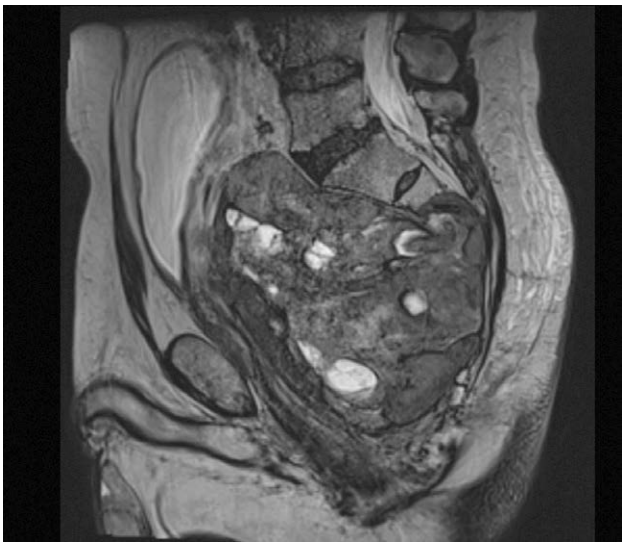


Figure 105.1 Sagittal MRI of the pelvis revealing a large sacral mass.

1. He is subsequently referred to medical oncology. Which of the following therapies has shown activity in GCT of bone?

A. Rituximab
B. Bevacizumab
C. Denosumab
D. Cetuximab

GCT of bone is a primary tumor of bone with a relatively low metastatic potential, indolent growth pattern, and high rate of local recurrence. Surgery has traditionally been the preferred treatment when anticipated surgical morbidity is limited. Additional therapies such as radiation therapy and embolization have been considered as well. Studies supporting the use of systemic therapy, including chemotherapy and interferon, are of limited quality.

Denosumab is a fully human, monoclonal antibody targeting the RANK ligand, a protein with a crucial role in osteoclast differentiation. Its use has been shown to inhibit osteoclast-mediated bone destruction, and it is currently approved by the US Food and Drug Administration for the prevention of skeletal-related events in patients with osseous metastatic disease from solid tumors and for men and postmenopausal women at risk for developing osteoporosis.

An open-label phase II study explored the use of denosumab in GCT of bone. Thirty-seven adult patients with recurrent or unresectable GCT of bone were enrolled and received monthly denosumab as a 120 mg subcutaneous injection (with additional loading doses on days 8 and 15). Patients continued denosumab until resection, disease progression, or patient desire to discontinue. Tumor response, defined as no radiographic progression up to week 25 or $\geq$90% elimination of giant cells from a pathologic specimen, was seen in 86% of patients. Treatment-related adverse events were limited. Of note, all patients in whom an on-study biopsy was performed ($n = 20$) exhibited a decrease of $\geq$90% giant cells with a reduction in tumor stromal cells. Studies exploring the effect of denosumab on tumor reduction, as assessed by radiographic measures, are anticipated.

Case study 105.3

A 54-year-old Asian male is diagnosed with a large chordoma of the sacrum. Staging studies reveal no evidence of metastatic disease. Surgical resection alone is recommended as the primary treatment.

• For patients presenting with localized chordoma, are there any factors that affect morbidity and survival?

Yes. Chordomas are malignant neoplasms of purported notochordal origin that most commonly arise in the sacrum. They are typically very large by the time of diagnosis, rendering surgical resection difficult. Because conventional cytotoxic chemotherapy and radiation therapy have not been proven as effective treatment modalities, surgical resection remains the mainstay of treatment. Factors that contribute to improved local control and survival were evaluated in a large series of patients undergoing resection for sacral chordomas between 1990 and 2005. Having undergone a prior resection ($P = 0.046$) and having a high-grade ($P = 0.05$) tumor were associated with lower disease-free survival. Local recurrence ($P = 0.0001$) and metastasis ($P = 0.0001$) were associated with lower disease-free survival. Local recurrence, in turn, was more likely to occur for

patients who had undergone a prior resection ($P = 0.0001$) or who underwent an intralesional resection ($P = 0.0001$). This underscores the need for a wide, margin-negative excision during the index procedure. The issue of surgical margins was also identified as being critically important by investigators at the Rizzoli Institute. An investigation of 53 patients treated surgically for sacral chordomas found that patients with marginal or intralesional resections experienced local recurrence 63–67% of the time. Patients with wide margins or wide-contaminated margins (meaning that the tumor or its pseudocapsule was exposed intraoperatively, but further tissue was removed to achieve wide margins) were significantly less likely to experience local recurrence (22–33% of the time). Although radiation therapy may not have a pivotal role in treatment of this condition, it has been shown that patients with a positive margin do not have increased risk of local recurrence or death if they are treated with adjuvant radiation therapy. As a result, we recommend careful operative planning that permits wide excision of sacral chordomas at the index operation. This planning should consider the need for bowel and/or urinary diversion if the level of resection required to achieve a negative margin will interfere with sphincteric function. Patients in whom a negative margin is not achieved should undergo additional resection or receive adjuvant radiation therapy.

Case study 105.4

A 58-year-old Caucasian male presented with a 5-month history of worsening groin and pelvic pain with weight bearing. Radiographs and an MRI revealed a 14 cm mass arising from the right acetabulum. Biopsy revealed a diagnosis of conventional chondrosarcoma. Internal hemipelvectomy with preservation of the ipsilateral lower extremity was recommended.

1. Which of the following reconstructive options is reasonable to consider in association with hemipelvectomy?

A. Reconstruction using a saddle prosthesis
B. Reconstruction using a custom periacetabular endoprosthesis
C. Resection alone without reconstruction ("flail hip")
D. All of the above
E. None of the above

Of all tumors in or near the pelvis, those involving the acetabulum present the greatest challenge to the reconstructive surgeon. Resections involving the acetabulum, known as type II resections, disrupt the axis of weight transfer from the lower extremity to the axial skeleton. In this situation, resection of the bone does not preclude limb preservation, but it does elicit the question of how best to maximize the patient's postoperative function. The saddle prosthesis, as its name suggests, is shaped like a saddle, and the semilunar geometry articulates in a mobile way with the remnant ilium following resection. It is coupled to the femur by means of a conventional endoprosthetic replacement of the femoral neck and head. It does not require a precise anatomical fit and is therefore available on short notice. Requirements for adequate function are sufficient bone stock in the ilium to support the device and appropriate restoration of length such that the periacetabular muscles are adequately tensioned. Although the overall complication rate is high with this implant (65%), this remains a popular reconstructive option.

More recently, a semicustom periacetabular reconstruction endoprosthesis (PAR) was developed in an attempt to address the high complication rate associated with the saddle prosthesis (i.e., the common occurrences of cephalad migration and instability). The PAR consists of a wide iliac component that is transfixed to the remnant ilium by three cross-bolts and cement. Like the saddle, the PAR employs a standard femoral component and a constrained ball-and-socket joint. The functional outcomes, complication rates, and implant survivorship compare favorably relative to the saddle prosthesis. However, the iliac component of the PAR requires custom fabrication based on cross-sectional imaging and takes a minimum of 6 weeks to acquire. Additionally, its use in the United States currently depends on obtaining a compassionate use waiver from the US Food and Drug Administration.

It is important to consider whether any given patient requires an endoprosthetic reconstruction at all. Many patients do well with a "flail hip"—meaning resection of the acetabulum and preservation of the lower extremity without reconstruction of the joint itself. Although the extremity shortens significantly over time, the resultant leg length discrepancy can be corrected with shoe modification. When considering functional outcomes based on Musculoskeletal Tumour Society Scores (expressed as a percentage), the following has been shown: resection alone ("flail hip") 48–74%, saddle endoprosthesis 51–63%, and PAR 67%.

For these reasons, each of the three fundamental options—reconstruction with a saddle, reconstruction with a PAR, and

(*Continued*)

resection alone—should be under consideration for any patient undergoing a type II pelvic resection. For patients at high risk for prosthetic failure (those undergoing adjuvant radiation therapy, those with a history of infection, etc.), we favor resection alone. For those patients requiring prompt resection and who are good candidates for endoprosthetic reconstruction, we favor a saddle prosthesis. For those patients in whom surgery might be delayed (e.g., a patient receiving neoadjuvant chemotherapy), we have had good success with acquisition of a semicustom PAR.

Case study 105.5

A 20-year-old Caucasian male is evaluated for unremitting left knee pain. Radiographs and magnetic resonance imaging (MRI) demonstrate a permeative bone-forming lesion in the distal left femoral metaphysis with an impending fracture. An open biopsy confirms high-grade intramedullary osteosarcoma. Staging studies reveal no evidence of metastatic disease. Although the patient has been told that this condition is typically treated with preoperative chemotherapy, resection, and postoperative chemotherapy, attention is given to his high risk of fracture and the unlikely possibility that limb salvage could succeed following fracture through this lesion (Figure 105.5).

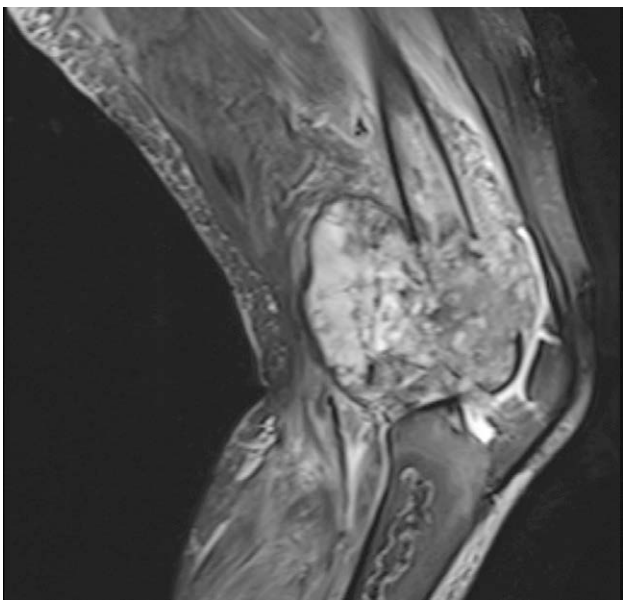


Figure 105.5 Sagittal MRI of left lower extremity revealing a distal femoral lesion with extensive soft tissue component.

- **Does neoadjuvant chemotherapy improve resectability of osteosarcoma in the extremities? If not, are there other purported benefits that would prevent immediate resection or reconstruction, with all chemotherapy deferred to the postoperative period?**

While neoadjuvant chemotherapy has long been assumed to improve resectability of osteosarcomas, this effect has not been proven and may be an incorrect assumption. Large osteosarcomas at high risk of fracture may need to be treated with resection first.

Treatment of high-grade osteosarcoma has been repeatedly evaluated in randomized clinical trials, and the standard of care has changed little in recent decades. Purported benefits of this treatment paradigm have included delay to permit fabrication of custom implants, measurement of treatment effect on the primary tumor, and increased resectability of the tumor. Custom implants are now rarely utilized. Although measurement of the treatment effect is prognostically valuable, changing chemotherapy protocols in response to a low rate of tumoral necrosis have shown little effect on survival. The final benefit—improved resectability of tumors due to the effect of chemotherapy—has been assumed but not demonstrated.

Recently, the *perception* that neoadjuvant chemotherapy renders resection of osteosarcoma easier and safer has been investigated. Twenty-four consecutive patients with distal femoral osteosarcoma with MRIs obtained before and after neoadjuvant chemotherapy were scrutinized with regard to operative planning. Four musculoskeletal oncologic surgeons and two musculoskeletal radiologists reviewed blinded and randomly ordered MRIs with regard to surgically critical anatomic details. Surgeons' expectations that chemotherapy would result in increased resectability were exposed by the fact that they believed scans in which more ablative operations were planned to be pre-chemotherapy scans. This expectation was correct only 53% of the time. In addition to this, more amputations (rather than fewer) were planned on the basis of MRIs acquired following neoadjuvant chemotherapy. We continue to keep the traditional treatment order (neoadjuvant chemotherapy, resection, and additional adjuvant chemotherapy) as our default plan. However, we acknowledge that there is no reason to delay surgery in the hopes that neoadjuvant chemotherapy will improve resectability of a large tumor. In fact, if limb salvage is threatened due to either critical tumor size or impending fracture, we recommend proceeding with prompt resection and completing all adjuvant chemotherapy postoperatively.

Case study 105.6

A 15-year-old female is diagnosed with localized Ewing sarcoma of the right ilium.

1. True or false? Studies have consistently shown that pelvic Ewing sarcoma should be treated preferentially with surgery over radiation therapy for definitive local control.

A. True
B. False

All patients with Ewing sarcoma require a multidisciplinary treatment approach. Multi-agent chemotherapy has played a critical role in improving patient outcomes. Data have been conflicting, however, in identifying the most appropriate modality for definitive local control of pelvic Ewing sarcoma. A large institutional series from the Rizzoli Institute evaluated the role of surgery and radiation for local control of pelvic Ewing sarcoma in 129 patients. Improved local control (83 vs. 67%) was observed in those patients who received surgery, with or without radiation therapy, as part of definitive local treatment as compared to radiation therapy alone. In addition, 5-year event-free survival was also improved in those who received surgery (74% vs. 30%; $P = 0.036$) compared to radiation therapy alone. The retrospective nature of the study, however, is a significant limitation. Furthermore, patients who received radiation therapy alone were more likely to have had larger tumor volumes at diagnosis and/or subsequent progression on chemotherapy, factors portending a poor prognosis.

An analysis of 75 patients with pelvic Ewing sarcoma treated on the Children's Oncology Group INT-0091 trial showed no difference in local control or event-free survival when comparing patients who received surgery, radiotherapy, or the combination for local control. The study, which randomized patients to two different chemotherapy regimens, did show an 11% improvement in local control for the use of a five-drug regimen (VAC–IE) compared to a standard three-drug regimen (VAC).

Overall, the data emphasize the importance of aggressive multi-agent chemotherapy to provide the best local control of pelvic primaries regardless of local treatment choice. With five-drug therapy, it is possible that the specific local treatment modality employed is less important. If a tumor is readily resectable with a functional reconstruction, then surgery would be the preferred modality for definitive local control. This avoids the risk of malignancy induction and possible infertility associated with radiotherapy. For those tumors where there is still a significant soft tissue mass after induction chemotherapy, and where it is felt that resolution of the residual mass would result in a margin-negative and functional resection, then radiotherapy may be employed followed by surgery. If the effect of surgery would be such that there would be gross physical dysfunction or that negative surgical margins are unattainable, then definitive radiotherapy is recommended.

Case study 105.7

A healthy 60-year-old man is diagnosed with an unresectable base-of-skull conventional chondrosarcoma.

1. Which of the following are acceptable local treatment modalities?

A. Proton therapy
B. Radiosurgery
C. Carbon ion therapy
D. All the above
E. None of the above

Standard therapy for conventional chondrosarcoma consists of gross total resection. Tumors in the hip and pelvis can be treated with surgery with acceptable survival and reasonable morbidity. In locations such as the base of skull, however, tumors are often only partially resectable or deemed unresectable. In this scenario, radiotherapy is recommended. Even in the situation of a gross total resection, the risk of local recurrence is high, and adjuvant radiotherapy should be considered.

Historically, chondrosarcomas were considered to be radioresistant. However, it is now known that doses in excess of 60 Gy are needed to demonstrate local control of these malignancies. Conventionally delivered radiotherapy in the brain is limited to approximately 60 Gy due to the risk of damage to surrounding normal tissues.

The radiotherapy modality with the longest and largest experience for treating base-of-skull lesions is proton therapy. Protons have a defined path length with rapid dose drop-off. This relatively spares the normal tissues downstream of the tumor. The largest single institution experience is from the Massachusetts General Hospital. With over 200 patients in their cohort, the local control rate at 10 years was 94%. Approximately 20% of these patients underwent only

(*Continued*)

biopsy, and the majority of the remainder had a subtotal resection. The complication rate is reported as acceptable but includes a risk of blindness and other severe neurologic morbidity. Other institutions in the United States and Europe have replicated these results. Even though the number of proton therapy machines is rapidly expanding in the United States, the experience of a given center in surgery (if applicable) and in designing and executing these complex radiotherapy plans must be considered.

Heavy (carbon) ion therapy is currently only available at three centers in Europe and Japan. The advantage of heavy ions is similar to that of protons in the lack of exit radiation dose, and in their increased biological effectiveness in treating malignancy. The number of chondrosarcoma patients treated with this promising modality is low. The local control rate, however, appears similar to that of proton therapy. Currently, enrollment in protocols to evaluate maintaining efficacy, while decreasing the risk of severe morbidity, is encouraged. A randomized phase III study of carbon ion therapy versus proton therapy is ongoing in patients with low- to intermediate-grade chondrosarcoma.

Photon therapy is used to deliver the majority of radiotherapy worldwide. New methods of treatment planning and delivery such as intensity-modulated radiotherapy (IMRT) and stereotactic radiosurgery and radiotherapy have allowed dose escalation in many sites. Recently, investigators have revisited the use of photons to treat chondrosarcoma. Doses in excess of 60 Gy have been delivered. In the handful of patients treated, the local control seems to be acceptable.

In conclusion, proton therapy at an experienced center remains the gold standard for treatment of base-of-skull chondrosarcoma. Heavy ion therapy and highly conformal photon therapy show promising results, but they are not considered the standard of care. Enrollment in clinical trials to evaluate the latter modalities is encouraged.

Case study 105.8

A 58-year-old African-American female presents with pain in her left leg with weight bearing. Plain films reveal a 3 cm intramedullary calcific lesion in the distal left femur. A biopsy is performed, with pathology revealing a high-grade, dedifferentiated chondrosarcoma (CHS). Staging studies do not show any evidence of metastatic disease. She is referred to a medical oncologist.

1. Which of the following statements is true regarding National Comprehensive Cancer Network (NCCN) recommendations for chemotherapy use in dedifferentiated CHS?

A. NCCN guidelines do not recommend the use of chemotherapy in dedifferentiated CHS
B. NCCN guidelines recommend treating dedifferentiated CHS with Ewing sarcoma regimens
C. NCCN guidelines recommend treating dedifferentiated CHS with osteosarcoma regimens
D. None of the above

Dedifferentiated chondrosarcoma is a CHS variant characterized histologically by the juxtaposition of a well-differentiated cartilaginous component with a higher-grade noncartilaginous component. Five-year survival rates remain poor. NCCN guidelines recommend treating dedifferentiated chondrosarcoma in a similar fashion to osteosarcoma, although it is important to recognize that the recommendation is based on lower-level evidence. Two small retrospective studies of 22 and 25 patients, respectively, showed conflicting results regarding overall survival benefit for those who received chemotherapy in the neoadjuvant or adjuvant setting compared to those who did not. In a large, multicenter, retrospective study of 266 patients with localized dedifferentiated CHS, the use of chemotherapy ($n = 81$) in the neoadjuvant or adjuvant chemotherapy was found to have no significant benefit on patient outcomes. A good response (necrosis $\geq$90%), however, was seen in 2 of 13 evaluable patients, suggesting that there may be some chemotherapy sensitivity in a small cohort of patients. Participation in clinical trials should be encouraged.

Case study answers

Case study 105.2

Question 1: Answer C

Case study 105.4

Question 1: Answer D

Case study 105.6

Question 1: Answer B

Case study 105.7

Question 1: Answer D

Case study 105.8

Question 1: Answer C

Selected reading

Grier HE, Krailo MD, Tarbell NJ, *et al*. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003 Feb 20;348(8):694–701.

National Comprehensive Cancer Network (NCCN). NCCN guidelines: bone cancer (version 1.2013). http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf (accessed February 3, 2014).

Ruggieri P, Angelini A, Ussia G, *et al*. Surgical margins and local control in resection of sacral chordomas. Clin Orthop Relat Res 2010;468(11):2939–47.

Thomas D, Henshaw R, Skubitz K, *et al*. Denosumab in patients with giant-cell tumor of bone: an open-label, phase 2 study. Lancet Oncol. 2010;11(3):275–80.

Womer RB, West DC, Krailo MD, *et al*. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2012;30(33):4148–54.

CHAPTER 106

Soft tissue sarcomas

Neeta Somaiah and Shreyaskumar Patel
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 106.1

A 38-year-old social worker noted a slowly growing lump on her right posterior upper arm. Physical exam reveals a 4 cm fatty mass suggestive of a lipoma.

1. What should the next step in her diagnostic work-up include?

A. To send her for a diagnostic biopsy
B. To set up an excisional biopsy
C. To set up an incision and drainage
D. Obtain an ultrasound or magnetic resonance imaging (MRI) of the right upper arm
E. Clinical follow-up in 6 months

Lipoma is a benign tumor composed of mature adipocytes that represent the most common adipocytic tumor. Imaging studies show a homogeneous soft tissue mass that is isodense to the subcutaneous tissue and demonstrates fat saturation. If these radiographic characteristics are confirmed, it can be followed and biopsy would be considered unnecessary. It could be excised for cosmetic reasons. Atypical lipomatous tumors or well-differentiated liposarcomas on the other hand, are low-grade, locally aggressive malignant adipocytic tumors that demonstrate prominent fibrous stranding in a fatty tumor on imaging. De-differentiated liposarcomas are tumors that show evidence of a transition, either in the primary or in a recurrence, from atypical lipomatous tumor or well-differentiated liposarcoma to a nonlipogenic pleomorphic spindle cell sarcoma, usually of high histological grade. Radiological imaging shows the coexistence of both fatty and non-fatty solid components in the tumor. If features of malignancy are noted on imaging, a biopsy or planned resection should be done to confirm the histology.

Case study 106.2

A 60-year-old male executive is diagnosed as having a 7.3 cm high-grade pleomorphic undifferentiated sarcoma of the left distal thigh after an ultrasound-guided biopsy.

1. Which of the following should be obtained as part of his sarcoma work-up?

A. MRI of the left thigh and computed tomography (CT) of the chest
B. Positron emission tomography (PET)–CT scan
C. MRI of the left thigh and bone scan
D. MRI of the thigh and MRI of the total spine

Adequate imaging is part of the essential work-up for a sarcoma and should provide details about the size of the tumor and proximity to nearby visceral structures and neurovascular landmarks. Chest imaging is vital especially in high-grade extremity sarcomas as the lung is one of the most common sites of metastasis. For patients with alveolar soft parts sarcoma, brain imaging should be considered in patients with metastatic disease. Lymph node metastases are rare in soft tissue sarcoma but can be seen in certain histologies such as small cell sarcomas, synovial sarcomas, clear cell sarcoma, angiosarcoma, and epithelioid sarcoma. Myxoid round cell liposarcomas have a propensity to metastasize to fat-containing areas and bone in addition to the lungs, and occasionally an MRI of the spine and CT of the chest, abdomen and pelvis is included in staging evaluation. PET–CT are not yet approved for routine management of soft tissue sarcomas.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 106.3

A 56-year-old male construction worker had a 4.5 cm tumor removed from his right lateral leg, midway between the knee and ankle with the medial margin of the tumor adjoining the bone. The final pathology revealed a high-grade pleomorphic sarcoma, and all other margins were negative per the report. Postop MRI shows surgical changes, and CT chest shows no metastasis.

1. Which of the following statements is true?

A. He requires a below-knee amputation
B. Considering the tumor size is less than 5 cm, no further therapy is recommended
C. He should have a limb-sparing re-resection by a sarcoma surgeon
D. Adjuvant radiation therapy

Adjuvant radiation therapy (RT) should be considered in certain extremity tumors, especially following a resection with close margins (<1 cm) or a microscopically positive margin on bone, a major blood vessel, or nerve, where limb-sparing re-resection is not feasible. Randomized trials and retrospective analyses support the use of preoperative or postoperative external-beam RT in appropriately selected patients with soft tissue sarcoma of extremity. The efficacy of postoperative RT was demonstrated in a prospective randomized trial comparing limb-sparing surgery with postoperative RT and limb-sparing surgery alone. Postoperative RT reduced the 10-year local recurrence rate in patients with high-grade sarcoma (no local recurrences vs. 22%) as well as low-grade sarcoma (5% vs. 32%). The Canadian Sarcoma group conducted a phase III randomized trial looking at preoperative RT (50 Gy in 25 fractions) versus postoperative RT (66 Gy in 33 fractions) in patients with localized primary or recurrent extremity sarcoma and showed that local control and progression-free survival (PFS) rates were similar for both groups. However, preoperative RT was associated with a greater incidence of acute wound complications (35% vs. 17% for postoperative RT), and late treatment-related side effects such as fibrosis, edema, and joint stiffness were more common in patients receiving postoperative RT, most likely due to the higher RT dose and larger treatment volume. Preoperative RT is preferred due to these reasons, especially if margins are expected to be close.

Case study 106.4

A young engineer in his mid-30s presents with an 11.6 cm soft tissue mass above his right elbow, which he first noted several months ago and which has since noticeably increased in size. Biopsy is consistent with a monophasic synovial sarcoma with 30 mitoses per 10 high-power field (HPF). Immunohistochemical studies show nuclear reactivity for TLE1, weak reactivity for SMA, and patchy weak to equivocal reactivity for desmin. Fluorescence in situ hybridization (FISH) on interphase nuclei in paraffin-embedded sections reveals a clonal population of cells with rearrangement of the *SYT/SS18* locus (18q11).

1. Out of the following, what is the best recommendation for his treatment?

A. Neoadjuvant chemotherapy, followed by radiation and then surgery in a multidisciplinary care setting
B. An above-elbow amputation
C. Limb-sparing surgery followed by adjuvant chemotherapy
D. Limb-sparing surgery followed by radiation therapy

Limb-sparing surgery ± radiation is recommended for most patients with soft tissue sarcoma of extremities to achieve local tumor control with minimal morbidity. Preoperative RT and/or neoadjuvant chemotherapy are used in certain situations to augment surgery to achieve a margin-negative resection. The benefit of adjuvant chemotherapy continues to be debated due to the challenge of performing an adequately powered randomized controlled study in a rare tumor that has tremendous heterogeneity in chemo-responsiveness of the various sarcoma subtypes. To address the problem of inadequately powered adjuvant sarcoma studies showing nonsignificant benefit in survival outcomes, the Sarcoma Meta-analysis Collaboration (SMAC) performed a meta-analysis of 14 studies, initially published in 1997. Eight of these studies used varying combinations of doxorubicin, and six studies used single-agent doxorubicin. The 10-year disease-free survival was improved (45 to 55%; $P = 0.0001$), but 10-year overall survival (OS) did not reach significance (50 to 54%; $P = 0.12$). Patients with extremity tumors appeared to have the clearest survival benefit with chemotherapy based on a subgroup analysis. An update of the SMAC analysis was published in 2008 and included four additional randomized trials. The pooled data from a total of 1953 patients demonstrated a statistically significant improvement in local and distant recurrence with adjuvant chemotherapy. There was a statistically significant survival benefit for doxorubicin combined with ifosfamide (OR 0.56; 95% confidence interval (CI): 0.36–0.85; $P = 0.01$)) but not for doxorubicin alone (OR of 0.84; 95% CI: 0.68–1.03;

(*Continued*)

$P = 0.09$)). This study did not include the largest adjuvant study by the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC) study evaluating five cycles of adjuvant doxorubicin (75 mg/m^2) and ifosfamide (5 gm/m^2) versus observation in resected grade 2 and 3 extremity tumors. Survival in the observation arm was better than expected, leading to an interim analysis of futility. The dose of ifosfamide used in the trial was lower than what is routinely used in combination therapy for advanced disease. A separate update of the SMAC meta-analysis including this EORTC study, with a total of 2170 patients, showed a benefit of adjuvant chemotherapy for disease-free survival and OS after 5 years, but only a nonsignificant trend toward improved survival after 10 years (OR 0.87; $P = 0.12$).

Based on retrospective analyses however, the benefit of adjuvant chemotherapy appears to be much higher in patients with high-grade ≥5 cm tumors with certain chemosensitive histologies (i.e., myxoid or round cell liposarcomas and synovial sarcomas). Neo-adjuvant chemotherapy in this setting has the advantage of response assessment to allow for a more personalized risk–benefit approach while downsizing the tumor to improve chances of margin-negative surgery. Multidisciplinary care in a center with expertise in sarcoma is preferred as it leads to improved outcomes.

Case study 106.5

A 42-year-old businessman in otherwise good health noted an enlarging mass on the medial aspect of his left thigh. Ultrasound revealed a 5.3 cm superficial mass. He underwent a resection by his local surgeon, and pathology revealed a myxoid liposarcoma with tumor extending to the resection margin. Chest X-ray shows no abnormality. MRI of the arm shows some soft tissue enhancement next to the surgical bed.

1. Which of the following would be the best option?

A. Watchful waiting with a 3-month follow-up in clinic
B. Adjuvant radiation therapy alone
C. Re-resection to obtain negative margins, and then consider postop RT
D. Adjuvant chemotherapy with a doxorubicin-based combination

Microscopically positive surgical margins are associated with a higher rate of local recurrence and lower rate of disease-free survival, especially in patients with extremity sarcomas. Both the surgeon and the pathologist should document surgical margins in evaluating a resected specimen. Surgical re-resection to obtain negative margins should strongly be considered if resection margins are positive on final pathology (unless on bone, nerve, or major blood vessels). Referral for postoperative radiation therapy should be made for high-risk patients or if the margin status is close or unclear.

Case study 106.6

A 48-year-old female, lifetime nonsmoker with a history of well-controlled hypertension is found to have two suspicious lung nodules on a chest X-ray. CT chest confirms two peripheral nodules measuring 8 mm and 7 mm. She has a history of a 12 cm uterine leiomyosarcoma diagnosed 18 months ago, following which she received six cycles of adjuvant gemcitabine and docetaxel. Follow-up CT of the chest, abdomen, and pelvis in 3 months shows an increase in size of these two lung nodules (now measuring 1.3 cm and 9 mm), but no new nodules are noted.

1. Out of the following options, what is the most appropriate?

A. Restart chemotherapy with gemcitabine and docetaxel, and assess response
B. Refer to a thoracic surgical oncologist to evaluate for diagnostic and therapeutic resection of the two nodules
C. Continue to observe, and repeat a CT for chest, abdomen, and pelvis in 3 months. If further increase is noted, obtain a diagnostic biopsy of the larger nodule
D. Start doxorubicin-based chemotherapy and assess response

In patients with limited metastasis, confined to a single organ, metastasectomy can be considered with or without chemotherapy or radiation. Data support the use of pulmonary metastasectomy in selective cases using thoracotomy or video-assisted thoracic surgery. In this case, considering the long disease-free interval after diagnosis, with limited lung nodules one could consider resection. Prior to starting chemotherapy, histologic confirmation of metastasis would be required.

Case study 106.7

A 45-year-old interior decorator with a history of stage I right breast carcinoma (T1cN0Mo) 6 years ago now has a superficial mass in the right breast that has become more prominent over the past month, measuring around 2.5 cm, with two similar-appearing erythematous-violaceous satellite nodules on exam. She was treated with a lumpectomy, four cycles of TAC chemotherapy (docetaxel, doxorubicin, and cyclophosphamide), and adjuvant radiation therapy for her breast cancer. Biopsy of the main mass is consistent with an angiosarcoma. CT of the chest, abdomen, and pelvis shows no evidence of metastasis.

1. Her treatment recommendations are likely to include which of the following?

A. A total mastectomy alone
B. A total mastectomy followed by chemotherapy and radiation
C. Systemic chemotherapy until maximal response or tolerance, followed by surgery
D. A repeat lumpectomy followed by radiation therapy

This patient has a radiation-induced sarcoma (RIS), which is a clinical definition based on an antecedent history of radiation exposure before the development of the sarcoma, occurrence of the sarcoma in or near the field of radiation, and pathologic confirmation of sarcoma that is histologically unique from the primary cancer. It usually presents at least 3 years after RT exposure, but there have been reports of these tumors presenting earlier. The most common histologic subtypes for RIS are malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma) and osteosarcoma, although other histologies (e.g., angiosarcoma, rhabdomyosarcoma, and malignant peripheral nerve sheath tumor) can occur. The prognosis for RIS is significantly worse compared to sporadic soft tissue sarcoma of the same histology. The therapy is dictated by the risk of distant metastases. High-grade tumors that are larger than 5 cm or have other high-risk features (e.g., satellite nodules or aggressive histology, i.e. angiosarcoma) should be treated with primary chemotherapy followed by a margin-negative surgical excision of the residual disease. Low-grade tumors and high-grade tumors 5 cm or smaller should be treated with a margin-negative surgical excision, and systemic chemotherapy should be considered when a negative margin is difficult.

Case study 106.8

A otherwise healthy 40-year-old male has a history of a 7 cm myxoid round cell liposarcoma of the left calf status post complete resection 3 years ago, after which he was lost to follow-up. He now presents with increasing right hip pain, and an initial hip joint X-ray was normal. Bone scan and CT of the chest, abdomen, and pelvis show multiple bone metastases in the axial skeleton. Bone biopsy is consistent with his initial tumor harboring the *FUS-DD1T3* translocation. His pain is now well controlled, and he denies any other symptoms.

1. Which of the following therapies would be the most appropriate in the front line?

A. Doxorubicin-based therapy
B. Dacarbazine
C. Pazopanib
D. Gemcitabine and docetaxel
E. Refer the patient for a phase I clinical trial

Myxoid round cell liposarcoma (MRCL) tends to occur in the pediatric and young adult population, and even though majority patients present with localized disease and undergo successful local therapy for their primary tumor, 30–50% of these patients will develop metastasis and ultimately succumb to their disease. The use of adjuvant or neoadjuvant chemotherapy and/or RT has improved outcomes for these patients. MRCL is characterized by a chromosomal translocation, most frequently t(12;16) (*FUS-DDIT3*) or less commonly t(12;22) (*EWSR1-DDIT3*), that is thought to play a role in tumor initiation. MRCL is known for its relative sensitivity to radiotherapy and certain chemotherapeutic agents, with an approximately 50% response rate with doxorubicin and ifosfamide. The new antitumor compound trabectedin is also very effective in inducing durable responses in myxoid round cell liposarcoma patients and is currently in phase III testing in the United States. Dacrabazine and gemcitabine–docetaxel combination therapy are reasonable salvage options. Fixed-dose-rate gemcitabine plus docetaxel yielded higher response rates, PFS, and OS compared to fixed-dose-rate single-agent gemcitabine in a randomized trial for patients with soft tissue sarcoma who had received up to three prior regimens. The best response for the small number of MRCL patients on this trial was stable disease. Considering this patient has not seen standard chemotherapy, a phase I trial would not be appropriate.

Case study 106.9

A 48-year-old African American female presents to her gynecologist with dysfunctional uterine bleeding. Pelvic exam reveals an enlarged uterus. She undergoes a vaginal hysterectomy. Path report shows a 10 cm high-grade leiomyosarcoma with vascular and lymphatic invasion. Tumor stains weakly positive for estrogen receptor (ER) and is negative for progesterone receptor (PR). She is referred to you 6 weeks postoperatively, and you order staging CT chest, abdomen, and pelvis, which show bilateral lung metastases.

1. What would you recommend?

A. Thoracic surgical consult for resection of lung metastases
B. Hormonal therapy with letrozole
C. Chemotherapy with gemcitabine and docetaxel
D. Supportive care

The most common histologic types of uterine sarcomas include carcinosarcomas (mixed mesodermal sarcomas (40–50%)), leiomyosarcomas (30%), and endometrial stromal sarcomas (15%). Uterine leiomyosarcomas tend to be high-grade tumors, and the standard of care for advanced disease is chemotherapy. Even though hormone receptor expression has been reported, there is no evidence to support the use of hormonal therapy unlike for the lower-grade endometrial stromal sarcomas. The combination of gemcitabine and docetaxel has high reported response rates in uterine leiomyosarcoma and hence is frequently used in the front line.

Case study 106.10

A 26-year-old mother of 2-year-old twins was diagnosed with a 6.5 cm alveolar soft part sarcoma on her chest wall and underwent an R0 resection 15 months ago. She now has new onset headache and was found to have a solitary brain metastasis. CT of the chest reveals bilateral new lung nodules. Biopsy of the lung nodule was consistent with her known sarcoma.

1. Which of the following statements is accurate?

A. Neurosurgical consultation for resection of brain metastasis
B. Referral to hospice should be discussed as this is an ominous sign.
C. She has a greater than 40% chance of responding to doxorubicin and ifosfamide combination therapy.
D. Her 1-year survival rate is less than 10%.

Alveolar soft part sarcoma (ASPS) is a histologically distinct, rare soft tissue sarcoma characterized by the t(X;17)(p11;25) translocation and usually presents in young patients with an unusual clinical behavior. It has a relatively indolent course with a propensity for late metastases. Brain metastasis is a known complication but tends to occur in association with metastasis to other sites. The 5-year survival in the reported case series at diagnosis is greater than 60% and in patients with metastatic disease is around 20%. At the current time, surgery is the standard treatment, and there are no convincing data in support of conventional chemotherapy or radiation therapy. New molecularly targeted therapies (MET inhibitors) and antiangiogenic agents are being investigated with some promising results thus far. Suntinib and Cediranib have shown promising activity and are currently being tested in a randomized trial with crossover.

Case study 106.11

A retired businessman in his early 60s recently underwent resection of a 6.3 cm de-differentiated liposarcoma arising in the left retroperitoneum. He has a history of a 19 cm retroperitoneal well-differentiated liposarcoma resected approximately 2 years ago with left nephrectomy. Postop CT scan of the abdomen and pelvis shows fat-containing areas around the surgical bed but no evidence of any residual de-differentiated tumor.

1. What is the next best step in his management?

A. Follow-up imaging with chest X-ray and CT abdomen and pelvis at 3-month intervals
B. Adjuvant chemotherapy for six cycles
C. Adjuvant radiation therapy
D. No further follow-up required

Surgery is the mainstay of treatment for localized retroperitoneal soft tissue sarcoma. Well-differentiated and dedifferentiated liposarcomas (WD and DD LSs) represent the most common soft tissue sarcomas in the retroperitoneum. On a molecular level, both WD and DD LSs are characterized by amplification of chromosome 12q13–15, which includes the MDM2 and CDK4 genes and can be used for confirming the histology. Although the clonal relationship between WD and DD LSs remains unclear, it is thought that tumor cells progressively accumulate genetic lesions as they transition to a less differentiated, nonlipogenic state. With regard to clinical outcome, the presence of DD histology is clearly associated with worse overall and recurrence-free survival and has a potential for distant metastasis (e.g., to the lung); however, the frequency of metastasis is only 10–15%. For the majority of patients with retroperitoneal WD or DD LSs, the burden of disease is loco-regional. Responses to chemotherapy and radiation are poor in this liposarcoma subtype, and hence adjuvant therapy is not routinely recommended.

Case study 106.12

A 40-year-old male psychiatrist underwent a laparoscopic resection of a 5.7 cm tumor that was arising from the small bowel after the biopsy showed it to be a c-KIT-positive spindle cell sarcoma. Final pathology confirms a gastrointestinal stromal tumor with 22 mitosis per 50 HPF, and evidence of tumor necrosis. CT imaging postop shows no evidence of metastases.

1. The current guidelines support which of the following?

A. Adjuvant therapy with 400 mg of imatinib once daily for 1 year
B. Adjuvant therapy with 400 mg of imatinib once daily for at least 3 years
C. Adjuvant therapy with 800 mg of imatinib once daily for 1 year
D. Close follow-up with CT of abdomen and pelvis in 3 months

Gastrointestinal stromal tumors (GISTs) are the most common type of gastrointestinal mesenchymal tumors, resulting from activating mutations in one of the receptor protein tyrosine kinases. KIT (CD117) staining is present in approximately 95% of tumors. Around 80% to 88% of these tumors have mutations in the *KIT* proto-oncogene, leading to constitutive activation of the receptor. Approximately 5% of GISTs, have activating mutations in platelet-derived growth factor alpha (*PDGFRA*), a related receptor tyrosine kinase.

Risk of recurrence for patients with large (>5 cm) higher-risk GISTs is as high as 85% to 90%. Tumor size, mitotic index, tumor rupture, and location of the primary tumor (gastric more favorable than others) are factors impacting recurrence rates and disease-specific survival based on retrospective studies. The first American College of Surgical Oncology Group phase II adjuvant study in high-risk patients demonstrated that the tyrosine kinase inhibitor imatinib at a daily oral dose of 400 mg for 1 year was well tolerated and the 3-year OS rate was 97%. A subsequent phase III double-blind trial randomized patients with primary resected KIT-positive GIST tumors larger than 3 cm in size, to receive either imatinib 400 mg daily or placebo for 1 year. Accrual was stopped early after 713 patients were randomized, based on a preplanned interim analysis showing significant benefit in recurrence-free survival (RFS) in the imatinib arm. The 1-year RFS for the imatinib group compared with placebo was 98% versus 83% (hazard ratio (HR): 0.35; 95% confidence interval (CI): 0.22–0.53; 1-sided $P < .0001$). The Scandinavian Sarcoma Group study, SSGXVIII, evaluated 1 year versus 3 years of adjuvant treatment in patients with a high risk of recurrence (tumor greater than 5 cm in size with a high mitotic rate (>5 mitoses/50 HPF) or a risk of recurrence of greater than 50%) after surgery. After 54 months of follow-up, the RFS and OS rates were significantly higher in the 3-year group compared with those receiving 1 year of imatinib (5-year RFS: 65.6% vs. 47.9%; HR: 0.46; 95% CI: 0.32–0.65; $P < .0001$; and 5-year OS: 92.0% vs. 81.7%; HR: 0.45; 95% CI: 0.22–0.89; $P = 0.019$). Based on the results of the SSGXVIII trial, the US Food and Drug Administration approved the use of 3 years of imatinib as adjuvant therapy for patients following the complete gross resection of KIT-positive GIST for intermediate- to high-risk patients.

Case study 106.13

A 59-year-old female schoolteacher has a gastrointestinal stromal tumor arising in the stomach with biopsy-proven bilobar liver metastasis that had a KIT mutation in exon 11. She has been on 400 mg of imatinib once daily for 18 months with complete resolution of all visible tumors after the first 10 months on therapy. She has some fleeting joint pains but is otherwise tolerating her imatinib quite well. She comes with restaging CT of the abdomen pelvis with and without contrast showing no evidence of disease.

1. What would you recommend?

A. Continue imatinib for a total of 3 years, and then stop if no recurrence is noted
B. Continue imatinib indefinitely
C. Stop imatinib, and follow her with surveillance scans
D. Refer her to a gastrointestinal surgeon for an exploratory laparotomy

Randomized trials have established the efficacy and tolerability of imatinib at a starting dose of 400 mg once daily for patients with unresectable GIST. Analysis of the kinase genotype in patients with advanced or metastatic GIST has allowed for correlation between the sites of mutation in the *KIT* and *PDGFR* genes and response and survival outcomes with tyrosine kinase therapy. Patients with tumors that have mutations in *KIT* at exon 11 have the best overall outcome with imatinib treatment. Those with *KIT* exon 9 mutations are relatively resistant to lower doses of imatinib; therefore, in these patients it is now recommended to start with the higher dose of 400 mg twice daily when treating advanced and metastatic disease. Escalating the dose from the low to high over a 4- to 8-week period leads to better tolerability than starting at the higher dose. Certain PDGFRA mutations like the D842V kinase domain mutation confer primary resistance to imatinib, and novel PDGFRA inhibitors are being tested in these patients.

Prospective data support the continuation of imatinib therapy until disease progression or drug intolerance. The French Sarcoma Group tested the interruption of imatinib therapy at 1 and 3 years in patients with advanced GIST and demonstrated that treatment discontinuation is associated with a significant relapse rate and a median progression-free survival of 6 months. Of note, even patients with no residual tumor had a high rate of disease recurrence when treatment was interrupted. Although the tumors remained sensitive to the reintroduction of imatinib, the quality of response upon reintroduction did not reach the tumor status observed at randomization.

Case study 106.14

A young female in her early 30s has been experiencing increasing abdominal discomfort, early satiety, and nausea and presents to you for a second opinion. CT of the abdomen from 2 months ago shows an infiltrating irregularly shaped mass approximately 6 cm involving the root of the mesentery. The biopsy is consistent with desmoid fibromatosis. She has a history of a stage III colon cancer with multiple adenomatous polyps throughout her colon for which she underwent a near-total colectomy with re-anastamosis over a year ago. She completed adjuvant chemotherapy with FOLFOX 6 months ago. You obtain a follow-up CT that shows an increase in this mesenteric mass by 2 cm.

1. What would you recommend?

A. Recommend systemic therapy
B. Refer to radiation oncology for definitive radiation therapy
C. Refer to surgery immediately
D. Continue close observation

Desmoid tumors, also known as aggressive fibromatoses, are a fibroblastic proliferation of well-circumscribed fibrous tissue that are locally invasive but do not have metastatic potential. They vary in presentation and location, from the abdominal wall of young pregnant females, to intra-abdominal mesenteric masses, and to large extremity masses in older individuals. Intra-abdominal desmoids are common in patients with familial adenomatous polyposis (Gardner's syndrome) and may also arise after a surgical intervention such as a colectomy and lead to significant morbidity. The Wnt/beta-catenin signaling pathway is thought to be key in the molecular pathogenesis of desmoid tumors. Somatic APC mutations as well as activating mutations of the beta-catenin gene have been discovered in the majority of sporadic desmoids.

Surgery is the primary treatment for patients with resectable desmoid tumors. Observation may be appropriate for selected patients with resectable tumors if they have a small-sized, asymptomatic tumor located at a site where increase in size will not alter the outcome of surgery or lead to functional limitation, as suggested by some retrospective analyses. For patients with large tumors causing morbidity, pain, or functional limitation, treatment choices should be based on the location of the tumor and potential morbidity of the treatment. Surgery and/or radiotherapy and/or systemic therapy are all reasonable options. Radiation is not generally

recommended for retroperitoneal or intra-abdominal desmoid tumors. Since this patient's tumor involves the root of the mesentery and is likely to cause significant morbidity if untreated, systemic therapy options need to be discussed.

A variety of systemic therapy options, including nonsteroidal anti-inflammatory drugs (sulindac or celecoxib), hormonal or biological agents (tamoxifen, toremifene, or low-dose interferon), cytotoxic agents (methotrexate, vinblastine, and doxorubicin-based regimens), and tyrosine kinase inhibitors (imatinib and sorafenib), have shown promising results for patients with advanced or unresectable desmoid tumors. Doxorubicin-based chemotherapy and the combination of methotrexate and vinblastine have shown good efficacy in patients with unresectable or recurrent tumors, and are preferred if aggressive therapy is required. Tyrosine kinase inhibitors such as imatinib or sorafenib are less toxic options that have also demonstrated good clinical benefit (response or disease stabilization).

Case study answers

Case study 106.1

Question 1: Answer D

Case study 106.2

Question 1: Answer A

Case study 106.3

Question 1: Answer D

Case study 106.4

Question 1: Answer A

Case study 106.5

Question 1: Answer C

Case study 106.6

Question 1: Answer B

Case study 106.7

Question 1: Answer C

Case study 106.8

Question 1: Answer A

Case study 106.9

Question 1: Answer C

Case study 106.10

Question 1: Answer A

Case study 106.11

Question 1: Answer A

Case study 106.12

Question 1: Answer B

Case study 106.13

Question 1: Answer B

Case study 106.14

Question 1: Answer A

Selected reading

Gladdy RA, Qin LX, Moraco N, *et al.* Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? J Clin Oncol. 2010 Apr 20;28(12):2064–69.

Hoffman A, Lazar AJ, Pollock RE, *et al.* New frontiers in the treatment of liposarcoma, a therapeutically resistant malignant cohort. Drug Resist Updat. 2011 Feb;14(1):52–66.

Joensuu H, Eriksson M, Sundby Hall K, *et al.* One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307(12):1265–72.

Ogura K, Beppu Y, Chuman H, *et al.* Alveolar soft part sarcoma: a single-center 26-patient case series and review of the literature. Sarcoma 2012;2012:907179.

Quintini C, Ward G, Shatnawei A, *et al.* Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012 Mar;255(3):511–6.

PART 9

Multidisciplinary Approach: Consultation with Surgical Oncology Team

CHAPTER 107

Surgical aspects of head and neck cancers

Constance E.H. Teo[1] and Randal S. Weber[2]

[1]Singapore General Hospital, Singapore
[2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Surgical treatment of head and neck cancers traditionally has been treated with a radical open approach that is associated with significant morbidity. Thus, for situations where radiation and chemotherapy can achieve equivalent oncological results, the patient is often treated nonsurgically. However, with improved understanding of the disease and improvements in technology, early and selected advanced cases may now be treated with less extensive and less invasive surgical approaches. It is, however, important to know which cases are suitable for such approaches. We present four cases in this chapter to highlight the rationale in selecting the appropriate treatment.

Case study 107.1

A 35-year-old white female discovered a 1 cm pigmented nodule over her left parietal scalp. Her dermatologist has done a punch biopsy, which reported nodular-type melanoma with a thickness of 0.8 mm. She has seen another surgeon who recommended a wide local excision and sentinel lymph node biopsy (SLNB). She is concerned about having surgical scars on her neck and would like to avoid SLNB if possible. There is no evidence of satellite lesions or in-transit metastasis. She has no previous history of any skin cancers and has no family history of melanoma.

1. In which of the following situations would you do an SLNB?

A. No ulceration, no mitosis, and Clark's level II
B. Ulceration present, no mitosis, and a Clark's level II
C. No ulceration, mitosis of 2 per mm^2, and Clark's level II
D. No ulceration, no mitosis, and Clark's level IV

The aim of an SLNB is to identify patients with micrometastasis in the lymph nodes who would then benefit from a therapeutic neck dissection. It is now well established that for patients who have clinically N0 melanomas that are thicker than 1 mm, SLNB is indicated and for those less than 0.76 mm it is not necessary as the risk of occult metastasis is <5%. The risk of occult metastasis for melanomas between 0.76 and 1 mm ranges from 3.9% to 18%, with an overall rate of 6.2%. For this group of patients, the National Comprehensive Cancer Network (NCCN) guidelines (v1.2013) recommend considering SLNB if high-risk features are present. There is, however, little consensus currently with regard to which high-risk features should be used to determine the need for SLNB. In a multivariate analysis of the AJCC database, it was found that after tumor thickness, mitotic rate was the second most important predictor of survival. The 10-year survival rate for a patient with a T1 non-ulcerated melanoma with mitotic rate $<1/mm^2$ is 95% but decreases to 88% in those with mitotic rate $\geq 1/mm^2$. In T1 melanomas that are ulcerated, the 10-year survival is 85% to 87%. In a study by Gershenwald *et al.*, based on an 2002 AJCC definition, the SLN positivity rate for T1a versus T1b (ulceration or Clark's level of IV–V) is 3.6% and 8.4%. Thus, we would recommend SLNB for patients with a Breslow thickness of 0.76 to 1 mm with mitosis $\geq 1\,mm^2$, the presence of ulceration, or a Clark's level of IV or higher.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 107.2

A 50-year-old male smoker presents to you with a right lateral tongue ulcer that has been gradually increasing in size for the last 3 months. On examination and imaging, the ulcer measures 2 cm in diameter, it is located at the lateral aspect of the oral tongue, and there are no enlarged cervical lymph nodes. Biopsy of the nodule showed moderately differentiated squamous cell carcinoma (SCC) with a depth of invasion of 4 mm.

• Would you do an elective neck dissection for this patient?

Yes. The risk of occult metastasis in a T1–T2 SCC of the oral tongue is between 14.8% and 23% in T1 lesions and from 50% to 57% in T2 lesions (Table 107.1). It is important to identify this group of patients as the prognosis diminishes to 50% with the presence of lymph node metastasis. A neck dissection aids in accurately identifying the group of patients who may need adjuvant treatment. However, a neck dissection is not without morbidity, and in patients who present with a superficial lesion, the risks may outweigh the benefits. Various factors have been evaluated to help identify the group at highest risk for occult metastasis, and many studies have found tumor thickness or depth of invasion to correlate with the risk of occult metastasis. The cutoff point for determining the need for neck dissection, however, is controversial, with ranges from 2 to 10 mm being used. The risk of occult metastasis using various cutoff points are as follows (except for Byers *et al.*'s study, the rest of the studies quoted here looks specifically at T1–T2, N0 oral tongue SCC).

In our center, we use 4 mm depth of invasion as the cutoff point.

• Which levels of the neck should be dissected for SCC of the anterior tongue?

Ipsilateral levels I to IV. The most common lymph node levels involved in SCC tongue are levels I, II, and III. Thus, at least these three levels should be removed in a selective neck dissection. The removal of level IV lymph nodes in an N0 neck is controversial. However, for the following reasons, we would recommend resection of the level IV lymph nodes. First, skip metastasis to level III–IV may range from 1.5% to as high as 15.8%. Second, consideration would be that the demarcation between level III and IV is somewhat arbitrary, and if the level III lymph nodes return positive, there would be a question of adequacy of the neck dissection and the need for further treatment. If a metastatic lymph node is missed and becomes clinically apparent, the success of salvage treatment is poor. Lastly, in experienced hands, the resection of level IV does not add more morbidity or increase the surgical time significantly.

Table 107.1 The risk of occult cervical metastasis based on primary tumor thickness.

Author	Year	Cutoff point (mm)	Thickness or depth of invasion	Risk of occult metastasis (%)
Byers *et al.*	1998	<4	Depth	31
		4 to 8		47
		9 to 16		67
		≥17		87
Fakih *et al.*	1989	<4	Depth	8.3
		>4	Depth	66.7
Ocharoenrat *et al.*	2003	≤5	Thickness	16
		>5	Thickness	64
Sparano *et al.*	2004	<4	Thickness	0
		≥4	Thickness	40.6
		<4	Depth	0
		≥4	Depth	41.9
Ganly *et al.*	2012	<2	Depth	0
		≥2	Depth	31.2
		<4	Depth	11.8
		≥4	Depth	32.5

Case study 107.3

A 50-year-old male smoker complains of odynophagia, and clinical examination shows an ulcer limited to the suprahyoid epiglottis on the right side. Both cords are mobile. Computed tomography (CT) scan of the head and neck reveals that the mass is limited to the epiglottis, does not cross the midline, and has no enlarged cervical lymph nodes. Chest X-ray did not show any lung metastasis. He has hypertension that is well controlled and denies any exercise limitation on exertion. Biopsy of the lesion confirms moderately differentiated SCC.

• How would you stage this case?

T1 N0 M0 (AJCC 7th ed., 2010).

• **What are the treatment options for this patient?**
The treatment options would include transoral CO_2 laser resection or radiation. The local control rate for transoral laryngeal microsurgery (TLM) and radiation for T1 supraglottic squamous cell carcinoma is comparable. The local control rate for T1 supraglottic SCC treated with TLM ranges from 79.5 % to 100 % and from 77% to 100% with radiation. Thus, the decision would depend on other factors such as patient preference, the ability to visualize the tumor during microlaryngosopy, contraindications to general anesthesia, and poor pulmonary function that may put the patient at risk of aspiration after TLM. The advantage of TLM over radiation would include a shorter treatment time, lower cost, avoidance of radiation exposure to the surrounding normal tissues, and being able to save radiation for any recurrences or second primary tumors. TLM would also allow accurate assessment for the need to add adjuvant radiation if adverse features are present on the final pathology.

• **How will you manage the neck?**
Treatment of bilateral level II to IV with neck dissection or radiation. The risk of occult metastasis in supraglottic SCC with N0 neck ranges from 20% to 40%, and missing these occult metastases would decrease the survival. Thus, the neck needs to be treated. The choice of neck dissection or radiation would depend on the choice of treatment of the primary tumor. The choice of unilateral or bilateral treatment of the neck is controversial with literature supporting both approaches. In our institution, we recommend treatment of both sides of the neck because (i) studies show the presence of bilateral and contralateral neck metastasis, even in lateralized supraglottic tumors; (ii) there is no reliable method currently to predict the risk of contralateral neck metastasis; and (iii) missing an occult metastasis decreases the survival of the patient. Selective neck dissection (SND) of levels II to IV in the patient with an N0 supraglottic SCC is well accepted by most surgeons, although some surgeons recommend a more limited approach taking levels II and III only as the risk of occult metastasis to level IV is low and dissection of level IV puts the patient at risk of a chyle leak and injury to the phrenic nerve. We recommend SND taking levels II to IV as it is not clear at this point in time if a more limited neck dissection is oncologically safe, and, in experienced hands, the risk of a chyle leak and injury to the phrenic nerve is low.

Case study 107.4

A 49-year-old male nonsmoker presents with dysphagia and mild pain on swallowing. On examination, a 1.5 cm left tongue base mass was seen. He has a palpable 2 cm left level II lymph node. CT of the head and neck showed the lesion to be limited to the left tongue base without involvement of the extrinsic muscles of the tongue, and two enlarged left level II and III lymph nodes measuring 2 cm and 1.5 cm, respectively. CT chest did not reveal lung metastasis. Fine-needle aspiration cytology of the lymph node was consistent with poorly differentiated SCC. In an examination under anesthesia, direct laryngoscopy did not demonstrate any other mucosal lesions in the upper aerodigestive tract. Biopsy of the tongue mass showed poorly differentiated SCC with basaloid features that stained positive for p16.

• **What is the stage of the tumor?**
T1N2bM0 (Stage IVA).

• **What are the treatment options?**
(i) Transoral robotic surgery (TORS) with adjuvant radiation, (ii) radiation with cetuximab, or (iii) concurrent chemo-irradiation. Open transcervical surgery for resection of base of tongue tumors is morbid, and thus radiation alone or concurrent chemoradiation was often recommended in the past. However, with the advances in technology, we are able to avoid the morbidity of open surgery with transoral robotic surgery. This patient, however, has N2b disease and thus would need adjuvant radiation to the primary and both sides of the neck after resection of the primary tumor and bilateral level II to IV neck dissection. Should the lymph nodes show extracapsular spread or positive margins at the primary site, the patient would need adjuvant concurrent chemo-irradiation.

In the current NCCN guidelines (version 1.2012), concurrent chemo-irradiation with cisplatin is a category 1 recommendation for SCC of the oropharynx (OPSCC) with N2 to N3 disease and is an option for this patient. HPV-positive tumors are highly chemoradiosensitive with a 3-year overall survival rate of 82.4 versus 57.1 compared to HPV-negative tumors when treated with concurrent chemo-irradiation with cisplatin. However, in this patient with HPV-positive orophayngeal SCC with a small volume of primary and moderate neck disease, the risks of concurrent chemo-irradiation may outweigh the benefits. In the RTOG 0129 trial, the risk of acute grade 3 or 4 toxicities was about 80%, and late toxic events about 25%. Radiation with cetuximab has

(*Continued*)

been shown to be effective in the treatment of locally advanced SCC of the head and neck, with a 3-year survival rate of 55%. Adding cetuximab did not increase the acute and late toxicity of radiation, and cetuximab was well tolerated. Thus, in our institution, we would offer radiation with cetuximab to patients with HPV-positive OPSCC with low-volume disease (N2a/b with low-volume neck disease and T1/T2 primary tumors). The RTOG trial 1016 is now ongoing to study the results of radiotherapy plus cetuximab versus chemoradiotherapy in HPV-associated OPSCC.

- **How would you manage the neck?**

Bilateral level I to V needs to be treated. The risk of contralateral neck metastasis is significant in SCC of the tongue base. In patients with an N0 neck, the risk of occult metastases in the ipsilateral and contralateral neck is about 30%, and in the presence of ipsilateral neck metastasis the risk of contralateral neck metastasis is even higher with reported incidence as high as 60%. In Dzielgielewski's study, multivariate analysis shows that N2a disease in the ipsilateral neck is an independent predictor of contralateral neck metastasis independent of tumor size. Thus, even though this patient has a small primary tumor, both sides of the neck require treatment.

In Byer's study in 1988, the most common levels involved in a tongue base SCC are levels II to IV and upper posterior level V in a N0 neck (Figure 107.1). Thus, these levels should be included in the management of the neck. If a patient is receiving radiation as definitive or adjuvant treatment, level I is included in the radiation field as that would be necessary to deliver an adequate dose to the tongue base.

If the patient's primary treatment is surgical, both sides of the neck should be dissected. The conventional teaching for a node-positive neck is to perform a comprehensive neck dissection taking levels I to V. In our institution, we have found that to be unnecessary. If the patient is to receive adjuvant radiation, we would perform a selective neck dissection removing lymph nodes in levels II to IV bilaterally, sparing the level V neck dissection to reduce the morbidity from mobilizing the XI nerve in the posterior triangle. This is based on Byer's study in 1999, where he observed that in a significant proportion of patients who had node-positive disease and were treated with selective neck dissection, the recurrence was in the dissected neck and a comprehensive neck dissection would not have benefited these patients. Several studies in the last decade on SND for node-positive neck reported rates of regional recurrence that ranged from 3% to 16%. The overall survival, local control, and distant control rates were not significantly different in patients treated with selective neck dissection and comprehensive neck dissection in several studies.

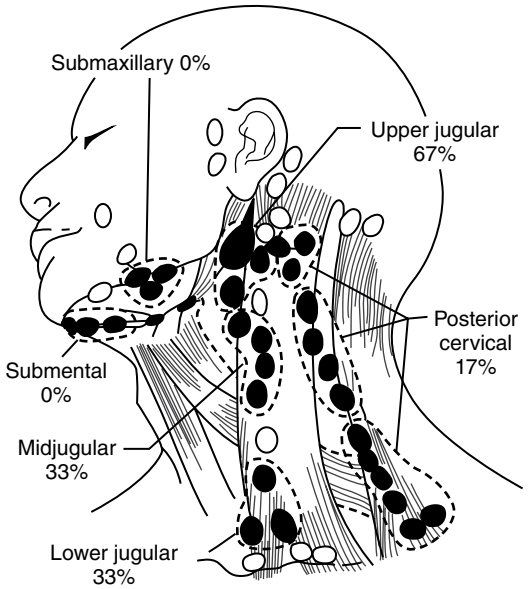


Figure 107.1 The relative percentage of nodes involved with cancer in the N0 neck when electively dissected for base of the tongue primary (Source: Byers RM *et al.* Head & Neck 1999;21:499–505. Reproduced with permission of John Wiley & Sons).

Case study answers

Case study 107.1

Question 1: Answer B, C, and D

Selected reading

Ang KK, Harris J, Wheeler R, *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35.

Dzielgielewski PT, O'Connell DA, Szudek J, *et al*. Neck metastasis in oropharyngeal cancer: necessity and extent of bilateral treatment. Head Neck 2012 Sep 25. doi:10.1002/hed.23172. [Epub ahead of print]

Ganly I, Patel S, Shah J. Early stage squamous cell cancer of the oral tongue: clinicopathologic features affecting outcome. Cancer 2012;118(1):101–11.

Givi B, Linkov G, Ganly I, *et al*. Selective neck dissection in node-positive squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg. 2012;147(4):707–15.

Karatzanis AD, Psychogios G, Zenk J, *et al*. Evaluation of available surgical management options for early supraglottic cancer. Head Neck 2010;32:1048–55.

CHAPTER 108

Surgical aspects of thoracic malignancies

Albert S.Y. Chang[1], Thomas A. D'Amico[2], and David C. White[1]

[1]Duke University Medical Center, Duke Raleigh Hospital, Raleigh, NC, USA
[2]Duke University Medical Center, Durham, NC, USA

Case study 108.1

A 65-year-old smoker presents with a spiculated, peripheral 2.5 cm right upper lobe mass. Positron emission tomography–computed tomography (PET–CT) scan reveals intense uptake in the lesion with mildly hypermetabolic hilar and paratracheal lymph nodes but no evidence of distant disease.

1. Which is the preferred treatment option?

A. Referral for induction chemotherapy and radiation due to the presence of hilar and paratracheal lymphadenopathy
B. Invasive mediastinal staging by endobronchial ultrasound (EBUS) or mediastinoscopy, followed by right upper lobe diagnostic wedge resection and possible lobectomy if the lymph nodes are benign by frozen section
C. Proceed directly to thoracoscopy for diagnostic wedge resection and lymph node sampling, followed by lobectomy if the lymph nodes are benign
D. Percutaneous needle biopsy of the right lung mass to confirm malignancy, followed by thoracotomy to ensure complete lymph node dissection

Invasive staging of the mediastinum is important to confirm suspected stage III disease, as PET–CT scan has a significant false-positive rate, particularly in areas of endemic fungal infection. Alternatively, a negative PET–CT does not rule out stage III disease, as there is a false-negative rate of up to 5–10%, particularly for larger and more central tumors. Both EBUS with fine-needle aspirate and mediastinoscopy allow access to both the left and right paratracheal lymph nodes as well as the subcarinal area. There is growing evidence that the accuracy of EBUS is comparable to mediastinoscopy, with a lower risk of significant complications. If pathologic lymph nodes are suspected or identified, mediastinoscopy may allow for larger amounts of tissue to be obtained for complete pathologic analysis, including histologic subtyping as well as mutation analysis, helping to direct treatment decisions. If the lymph nodes are benign by invasive staging, then one can proceed to diagnostic thoracoscopy for wedge resection or biopsy of the tumor if possible prior to lobectomy. Diagnostic thoracoscopy initially would allow for sampling of the paratracheal and subcarinal lymph nodes, but not the left paratracheal nodes, and is more invasive than EBUS or mediastinoscopy, which are generally outpatient procedures. Diagnostic thoracoscopy for lymph node sampling is useful in certain situations; for example, following induction therapy in a patient with previous mediastinoscopy, or in a patient with limited neck extension contraindicating mediastinoscopy. Finally, while percutaneous needle biopsy is often obtained to confirm malignancy, it is not mandatory if a high clinical suspicion exists. Hilar (N1) involvement is not a contraindication to resection provided an R0 resection can be achieved, but identification of N2 disease mandates referral for systemic therapy prior to consideration of resection. While many surgeons prefer thoracotomy for bulky lymph node disease, evidence suggests that thorough lymph node dissection can be achieved safely by experienced surgeons using a thoracoscopic approach, and that the identification of occult lymph node disease is similar whether an open or thoracoscopic approach is used.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 108.2

A 77-year-old man with 80-pack-year smoking history is referred for resection of a biopsy-proven, 1.5 cm. peripheral lingular squamous cell carcinoma. PET–CT reveals moderate uptake in the lesion, but no enlarged or PET-avid hilar or mediastinal lymph nodes and no distant disease. The patient's pulmonary function tests reveal an FEV1 of 30% predicted, with a diffusion capacity of 32% predicted, and he has a history of coronary artery bypass grafting with a patent left internal mammary artery (LIMA) graft to the left anterior descending coronary artery.

1. Appropriate treatment options include which of the following?

A. Referral for stereotactic body radiation therapy (SBRT)
B. Referral for radiofrequency ablation of the tumor
C. Referral for cardiopulmonary exercise testing and consideration of resection if his VO_2 max (maximal oxygen consumption) is acceptable with a plan for lingular segmentectomy
D. All of the above

This patient is certainly high risk and requires careful consideration for any type of treatment planning. While patients with predicted postop diffusing capacity <50% predicted and predicted postop FEV1 <50% predicted are at increased risk of mortality following lobectomy, these numbers are not absolute contraindications to surgery, particularly if sublobar resection is an option. For stage IA non-small-cell lung cancer patients with small (<2 cm) tumors, meta-analysis suggests equivalent survival with sublobar resection when compared to lobectomy. In addition, patients with upper-lobe predominant emphysema may tolerate even lobectomy relatively well. The patient's functional capacity is certainly important, and the use of minimally invasive techniques (video-assisted thoracoscopic surgery (VATS) or robotic segmentectomy–lobectomy) may help to minimize pain, reduce complications, and expedite recovery, and has been shown to reduce complications as lung function worsens. The presence of an intact LIMA graft is not an absolute contraindication to surgery, but an important consideration in operative planning. This patient should also be made aware of alternatives to resection for early-stage lung cancer. These include SBRT, which appears to achieve local control comparable to surgery with follow-up of almost 3 years, low risk of serious complications, and 3-year survival in excess of 50%. Radiofrequency ablation, which causes tumor necrosis by heating the cells, can also achieve excellent local control, although it works best for smaller tumors (<3 cm) that are away from the hilum where larger blood vessels can act as a heat sink, reducing the efficacy of the technique. Additional options, including wedge resection with placement of radioactive mesh along the staple line, are under investigation and show promise as well.

Case study 108.3

A 66-year-old woman who has never smoked and has normal lung function presents for her annual physical exam. She complains of nonspecific respiratory symptoms, and a chest X-ray is obtained, revealing a subtle right-sided lung nodule. CT scan confirms a subpleural right upper lobe ground-glass lesion (1 cm), a 1.5 cm peripheral right lower lobe nodule with both solid and ground-glass components, and a left upper lobe ground-glass lesion (8 mm), again relatively peripheral. A PET scan demonstrates very low-grade uptake in the right lower lobe nodule with a background level in the upper lobe lesion and no uptake in the left-sided lesion.

1. Which is the best treatment option?

A. Percutaneous needle biopsy of at least two lesions to confirm advanced-stage disease, with subsequent referral for cytotoxic chemotherapy
B. Wedge resection of the most peripheral lesion to confirm malignancy, followed by referral for cytotoxic chemotherapy for multifocal disease
C. Invasive mediastinal staging with plan for right lower lobectomy, right upper lobe wedge resection, and left upper lobectomy
D. Right thoracoscopy for wedge resection and/or segmentectomy to remove both right-sided lesions to ensure complete resection, while minimizing the amount of lung resected, followed by pathologic analysis including screening for epidermal growth factor receptor (EGFR) and ALK mutations, and close follow-up or resection of the left-sided lesion

This patient likely has multifocal adenocarcinoma in situ (formerly termed "bronchioloalveolar carcinoma") or minimally invasive adenocarcinoma. She has a high likelihood of having the EGFR receptor mutation, potentially making her a candidate for targeted therapy with erlotinib. Surgical resection may still be curative, however, and should be pursued with the goal of removal of gross disease with negative margins, while making an effort to preserve as much lung as possible. Complete resection of adenocarcinoma in situ or minimally invasive adenocarcinoma, even with non-anatomic resection, is associated with excellent long-term

survival. Therefore, options such as wedge resection and segmentectomy should be utilized where possible. Mediastinoscopy is not likely to be helpful, as even if there is an invasive component in one or more of the lesions, the chance of mediastinal lymph node metastases is very low (<5%) given the small size and peripheral nature of the lesions. Similarly, PET scan is often not useful, as adenocarcinoma in situ and minimally invasive adenocarcinoma tend not to have significant activity on PET scan. Percutaneous needle biopsy is often difficult for these small lesions, and often does not yield adequate tissue for diagnosis, or for analysis of EGFR mutations.

Case study 108.4

A 72-year-old smoker is referred with a large, right infrahilar mass. Bronchoscopy with brushings is diagnostic of squamous cell carcinoma of the right lower lobe. PET scan reveals significant uptake in the lesion, with low-grade uptake in right hilar lymph nodes, but no evidence of distant disease. The patient undergoes cervical mediastinoscopy with biopsies of 2R, 4R, 4L, and level 7 lymph nodes, all of which are benign. Right lower lobectomy and mediastinal lymph node sampling is performed using a thoracoscopic approach. At the time of surgery, the mass is adherent to the parietal pleura, but there is no evidence of invasion. Final pathology reveals a 4.5 cm. squamous cell carcinoma invading the visceral pleura but not extending into the parietal pleura, with negative margins, and with surrounding pneumonia and reactive lymph nodes (pT2pN0pMx).

1. How should the patient be counseled?

A. Thoracotomy would have been preferable due to the size of the mass and the ability to achieve more complete lymph node dissection

B. No further treatment is necessary as an R0 resection was achieved, and there is no evidence of lymph node involvement

C. Adjuvant chemotherapy should be strongly considered given the large size of the tumor and the significant incidence of distant recurrence

D. Chest wall resection should have been performed given the adherence of the tumor to the parietal pleura, and, in the absence of this, radiation therapy to the chest wall should be considered

While, early on, VATS lobectomy was thought to be most suited for small (<3 cm), peripheral tumors, there is growing evidence of its efficacy for larger, more central lesions. Documented advantages of thoracoscopic lobectomy include reduced postoperative pain, shorter hospital stay and chest tube duration, and better tolerance of adjuvant chemotherapy when compared to patients undergoing thoracotomy. In addition, while early opponents of VATS lobectomy questioned the adequacy of lymph node sampling, multiple studies have supported the ability to perform equivalent lymph node sampling–dissection to that achieved by thoracotomy. In addition, survival after VATS lobectomy appears to be similar to that achieved following thoracotomy. Despite the absence of lymph node involvement, this patient is at high risk for recurrent disease due to the large size of the tumor. Adjuvant chemotherapy has been associated with significant survival benefit in resected non-small-cell lung cancer, including stage IB and stage II disease. While the chest wall margin may be close, there is no indication for adjuvant radiation therapy, which currently is generally reserved for N2 disease or positive margins.

Case study 108.5

A 66-year-old smoker is referred from a chiropractor after presenting with shoulder and arm pain. MRI of the C-spine revealed no cervical disc disease, but incidentally noted was an apical lung mass. CT confirms a right apical lung mass with boney destruction of the first and second ribs posteriorly. CT-guided needle biopsy confirms adenocarcinoma, and PET–CT suggests T3N0M0 disease. The patient complains of numbness in the fourth and fifth digits of his hand as well as his forearm, but strength is completely intact in his right upper extremity.

1. What is the most appropriate treatment?

A. Chemotherapy and definitive radiation treatment, as the tumor is not resectable based on the clinical finding of numbness in his fingers and forearm

B. Invasive mediastinal staging to exclude stage III disease, followed by chemotherapy and radiation prior to en bloc resection of the right upper lobe with the first through third ribs

(*Continued*)

C. Invasive mediastinal staging to exclude stage III disease, followed by resection with a plan for adjuvant chemotherapy and radiation in the postoperative setting
D. Chemotherapy and radiation followed by an anterior approach for resection of the tumor and the first three ribs with wedge resection of adherent lung

While superior sulcus tumors may invade the lower trunk of the brachial plexus, numbness of the fingers and forearm suggests involvement of the T1 nerve root, which can be resected with impunity. Atrophy of the intrinsic hand muscles suggests involvement of the C8 nerve root, and resection could result in paralysis of the forearm and hand. Similarly, identification of the classic Pancoast syndrome of ipsilateral miosis, ptosis, and anhidrosis indicates involvement of the Stellate ganglion and unresectability. While select groups advocate surgery as initial therapy, particularly outside of North America, the more common approach in North America is induction chemotherapy and radiation in an effort to reduce the size of the apical tumor and facilitate resection of all disease. Mediastinoscopy or EBUS should be performed initially to identify patients with stage III disease who will not benefit from surgery. The anterior approach is advocated by many surgeons and is particularly helpful for tumors involving the subclavian vessels, which can be resected or grafted if necessary; however, lobectomy is preferable to wedge resection given the improved long-term survival. Superior sulcus tumors remain a difficult problem, and are often diagnosed in delayed fashion; however, with aggressive multimodality therapy, reasonable long-term results may be anticipated.

Case study 108.6

A 68-year-old female with a 55-pack-year history of tobacco abuse and good performance status underwent a screening CT scan for lung cancer. A 3.4 cm mass is noted near the right lower lobe bronchus and a 1.5 cm subcarinal lymph node. Both lesions are hypermetabolic on PET–CT scan, but no other disease is seen. Brain MRI is also negative. Bronchoscopy shows a mass in the basilar segment of the right lower lobe. Biopsy is positive for adenocarcinoma. EBUS biopsy of level 7 is positive for adenocarcinoma as well, but stations R4 and L4 are negative. As stage IIIA, she undergoes induction chemotherapy with cisplatin and etopiside without radiation. Repeat imaging studies shows a decrease in the size of the subcarinal node and a slight decrease in her lung mass. She undergoes mediastinoscopy with biopsy of five lymph node stations. Level 7 shows a persistent microscopic focus of disease on frozen section.

1. What is the best next step?

A. Palliative chemotherapy
B. Definitive chemotherapy and radiation
C. Proceed with lobectomy and thoracic lymphadenectomy.
D. Radiation alone

Patients with stage IIIA non-small-cell lung cancer previously had a very poor prognosis. The 3- and 5-year survival rates of patients with N2 ipsilateral mediastinal lymph node metastases were less than 10% with surgery or with radiation alone. Thus, combined modality therapy has become the mainstay for treatment of T1–T3 N2 M0 patients. However, the optimal treatment regimen is not known. The SWOG 8805 trial showed significantly improved survival compared to historical controls in patients undergoing concurrent cisplatin–etoposide with radiation (45 cGy) followed by surgery. Intergroup trial 0139 compared induction chemoradiation followed by surgery versus chemoradiation without surgery and demonstrated better progression-free survival in the surgical group but not overall survival. This was felt to be primarily due to the excessive mortality in patients undergoing pneumonectomy. While many centers adopted the Intergroup 0139 protocol for stage IIIA patients, others questioned the need for radiation as chemotherapy alone allowed possibly higher doses of chemotherapy, more accurate assessment of systemic biologic response during mediastinal restaging without the confounding effects of radiation, and the avoidance of interrupting radiation treatment in patients who ultimately prove to be unresectable. Furthermore, there have been few studies that directly compared induction chemotherapy followed by surgery to induction chemoradiation followed by surgery. While chemoradiation has demonstrated better downstaging of the mediastinum with significantly higher complete response rates, the overall survival between the two groups was not different. Furthermore, while studies have shown that a complete response in the mediastinum is the strongest predictor of long-term survival, the persistence of N2 disease at restaging studies may still warrant aggressive local control with surgery or radiation, as survival in carefully selected patients approaches that seen in complete responders. Thus, either treatment induction strategy can be used with similar results. Another advantage of induction chemotherapy without radiation followed by surgery is the higher likelihood of being able to perform thoracoscopic resections with all of its inherent benefits and the decreased incidence of postoperative complications.

Therefore, palliative treatment is not indicated in this patient, who should receive more aggressive treatment. In this patient with good performance status and evidence of response to induction therapy, radiation or chemoradiation alone have worse progression-free survival compared to induction therapy followed by surgical resection.

Case study 108.7

A 56-year-old female with a remote 30-pack-year history of tobacco abuse is incidentally found to have a peripheral solitary pulmonary nodule in the right upper lobe. PET–CT scan confirms hypermetabolic activity in the lung mass, but no evidence of lymphadenopathy or distant metastatic disease. A CT-guided needle biopsy is performed, demonstrating small-cell lung cancer.

1. Reasonable treatment options include all of the following EXCEPT which?

A. Wedge resection or lobectomy and no further therapy
B. Chemotherapy and radiation therapy, followed by prophylactic cranial irradiation
C. Mediastinoscopy to exclude N2–N3 disease, then lobectomy followed by chemotherapy and prophylactic cranial irradiation
D. VATS wedge resection to evaluate for mixed small-cell and non-small-cell lung cancer or carcinoid

Originally, the treatment for small-cell lung cancer included surgery. However, studies such as the Medical Research Council and the Lung Cancer Study Group trial published in 1994 suggested that chemotherapy and radiation should be the standard of care, and surgery was temporarily abandoned. Currently, the treatment for limited-stage small-cell lung cancer has been chemotherapy with cisplatin and etoposide and lung and mediastinal radiation usually followed by prophylactic cranial irradiation. Flaws in the original studies and more recent studies have spurred a renewed interest in the addition of surgery as a third arm to therapy. The rationale includes the potential for improved local control and the ability to elucidate whether a mixed histology is present (a non-small-cell component is typically less chemosensitive, and carcinoid can be misdiagnosed as small-cell lung cancer in small biopsy specimens). In addition, surgery can be beneficial in cases of chemoresistant tumors in place of second-line chemotherapy or in cases of localized tumor relapse. However, if surgery is contemplated, the key issue for long-term control and survival is thorough invasive mediastinal staging, typically with mediastinoscopy. If the medastinal nodes are negative, and a complete resection can be performed, survival can be quite good compared to concurrent chemotherapy and radiation. Lobectomy has generally been shown to have the longest survival, but even pneumonectomy and sublobar resection results are better than no surgery in properly selected patients. Even with complete resection, adjuvant treatment is still required to prevent local and distant metastatic disease, notably the brain. Thus, after resection, all patients who are medically fit must undergo adjuvant chemotherapy and, if there is no disease progression, prophylactic cranial irradiation. For patients with N2 disease, adjuvant radiation should also be used. Patients with N0 and N1 disease do not show benefit to postoperative radiation, which may even be detrimental.

Case study 108.8

A previously healthy 72-year-old man has a syncopal episode. MRI of the brain demonstrates a 1.8 cm lesion in the right frontal cortex, which is worrisome for a metastatic lesion. Further work-up included a CT scan of the chest due to a 50-pack-year history of tobacco use, and a 3.7 cm spiculated mass is found in the left lower lobe of the lung. PET–CT scan demonstrates the lung mass with a SUV of 8.2, but no distant metastatic disease. Also noted is mild hypermetabolic activity in a left paratracheal node with a SUV of 2.9.

1. What are the clinical stage and best treatment option?

A. T2aN2M1; palliative chemotherapy
B. T2NXM1; sterotactic radiotherapy for the brain and definitive chemotherapy and radiation for the lung
C. T2NXM1; craniotomy followed by VATS wedge resection and adjuvant chemotherapy and whole brain radiation
D. T2N0M1; mediastinoscopy, and if negative then craniotomy or stereotactic radiosurgery, followed by lobectomy with mediastinal lymphadenectomy
E. T2N0M1; mediastinoscopy and lobectomy with thoracic lymphadenectomy followed by whole-brain radiation and chemotherapy

While almost half of all patients diagnosed with non-small-cell lung cancer have metastatic disease at the time of presentation, about 10% will have synchronous isolated distant metastatic disease, with no evidence of mediastinal lymph node involvement. This is the key point before pursuing aggressive management in this select patient population that has demonstrated improved long-term survival compared to other stage IV lung cancer patients. Sites of isolated distant disease that have been resected in addition to the primary lung cancer include the brain, adrenal gland, and contralateral lung. Other areas, including the liver, skin, musculoskeletal system, and gastrointestinal organs, have

(*Continued*)

been reported, but generally as case reports and for metachronous tumors. The general strategy in this highly selective patient cohort of younger and medically fit patients include a PET–CT scan and additional imaging studies to look for occult sites of distant disease. If none are found, then a thorough invasive staging of the mediastinum is mandatory. Any involvement of mediastinal nodes should preclude patients from an aggressive resection strategy as outcomes are universally poor and provide little long-term benefit. Those patients should be treated with palliative chemotherapy and radiation. If the mediastinoscopy is negative for N2 or N3 disease, and the isolated distant metastatic site as well as the lung primary can both be completely resected, then the metastatic site generally should be resected first, especially if symptomatic. Following metastasectomy, the primary lung cancer should be resected. Adjuvant radiation is dependent on the site of metastatic disease, and adjuvant chemotherapy is generally at the discretion of the treating medical oncologist, as there is generally less consensus.

In terms of particular sites, the isolated M1 disease to the brain has generally been the best studied. Previously, treatment for brain metastases was whole-brain radiation. However, the overall benefit was generally short-lived, with overall survival in these patients of less than 6 months. Advances in neurosurgical techniques and perioperative care, along with a decrease in postcraniotomy complications, have significantly improved outcomes. For patients who cannot undergo surgical resection, stereotactic radiosurgery is a viable alternative. Whole-brain radiation may be given after surgery or in conjunction with stereotactic radiosurgery.

For an isolated adrenal metastasis, histologic confirmation is recommended as not all adrenal masses are malignant and imaging studies may not be conclusive. A CT-guided biopsy is generally performed, but in properly selected patients, proceeding to diagnostic laparoscopy and adrenalectomy is also a viable strategy with good outcomes and low morbidity. Even bilateral adrenalectomies followed by lung resection have been performed with good long-term survival. While the short-term results for resection of synchronous isolated adrenal metastases are not as good as those for metachronous metastases, with a median survival of 12 months, the long-term 5-year survival rates were comparable at about 25% and 26%, respectively. Local recurrence in the adrenal bed or retroperitoneum was 21% in a meta-analysis.

Contralateral lung metastases require special mention. Patients with bilateral tumors are considered to have M1 disease based upon the latest lung cancer–staging classification. However, it is not known whether these patients with a negative mediastinum are synchronous bilateral early-stage lung cancers or patients with isolated M1 disease. While the outcomes are worse when compared to a single early-stage lung cancer, the results are still better than other patients with metastatic (stage IV) lung cancer. Furthermore, the use of thoracoscopic resection techniques and the associated better outcomes with minimally invasive surgery allow more patients to be able to tolerate bilateral lung resections. Thus, aggressive surgical management for patients with a negative pathologically staged mediastinum and isolated M1 disease is warranted in selective patients.

Case study 108.9

A previously healthy 38-year-old man is re-presented at a multidisciplinary thoracic tumor board. He originally presented with cough and shortness of breath. Work-up, including CT scan with intravenous contrast and PET–CT scan, revealed a large, lobulated, anterior mediastinal mass that had central necrosis and calcification and was hypermetabolic. There was confluent tissue invading a small area of the superior vena cava (SVC) as well as a thick rim of tissue surrounding the right lung with an elevated right hemidiaphragm. CT-guided core needle biopsy diagnosed a World Health Organization (WHO) classification B2 thymic tumor. A fluoroscopic sniff test confirmed right diaphragmatic paralysis. He was considered initially unresectable as a Masaoka stage IVA and was offered induction chemotherapy with cisplatin, doxorubicin, and cyclophosphamide. Follow-up PET–CT scan shows a mild response to therapy.

1. What should be the recommendations?

A. Proceed with right extrapleural pneumonectomy and SVC reconstruction followed by hemithoracic radiation
B. Proceed with debulking surgery followed by radiation and consolidation chemotherapy
C. Radiation to 60 cGy followed by chemotherapy
D. Hospice

Thymic tumors remain a rare entity, and most recommendations for treatment are based upon single institutional studies with relatively limited patient sizes. It is well accepted that early-stage thymomas (Masaoka stage I, noninvasive and encapsulated, and stage II, capsular invasion) should be treated with surgery, and, if completely resected, no adjuvant therapy is generally considered necessary, although lifelong follow-up is necessary for this indolent tumor. For patients with Masaoka stage III (invasion to

surrounding organs) and stage IVA (pleural or pericardial dissemination), the recurrence rates are much higher, even with complete resection. Also, many of these patients are not considered resectable and have worse WHO classification histologic subtype, which correlates with poorer survival. For these high-risk patients and those considered initially unresectable, induction chemotherapy should be considered. Because of the rarity of thymomas, no large randomized trials exist to compare chemotherapy regimens, but cisplatin-based combination regimens have shown the best results. Thus, multiple regimens have been used with generally very good response rates, since thymomas are generally very chemosensitive and have led to improved resectabilty rates. Results using induction chemoradiation regimens similar to stage IIIA lung cancer treatments for advanced invasive thymomas are provocative, but overall experience is limited and primarily from small case series. In addition, large preoperative radiation fields limit its use in large bulky tumors.

Following induction chemotherapy, repeat imaging is performed, with CT scans with IV contrast to predict level of invasion and PET–CT scans to look at tumor response to chemotherapy. However, radiographic response rate does not always correlate with pathologic response (i.e., tumor necrosis), and surgical resection should still be considered, including extended resections, as long as complete extirpation is felt to be feasible. Following surgery in patients with advanced disease, patients should undergo adjuvant radiation of 45–50 Gy following complete resection and 54–60 Gy for incomplete resection. Additional chemotherapy is generally not recommended, although it has been used in patients considered high risk for recurrence, based upon higher WHO classification.

Debulking is generally not recommended unless thorough surgical exploration reveals tumor involving unresectable structures (e.g., heart and bilateral phrenic nerves). In those cases, after maximal tumor removal, clips are left in place to mark residual disease. In unresectable patients following induction chemotherapy, definitive radiation of 60–70 Gy followed by additional chemotherapy have shown notable prolonged survival rates.

In this extreme patient example presented, aggressive surgery can be offered in select patients with invasive thymomas since they are generally younger and overall quite healthy. While pleuropenumonectomy as well as vascular reconstruction are rarely necessary, they remain a good option when the tumor can be fully resected, as shown by several single-institution studies with good long-term outcomes.

Case study 108.10

A 62-year-old female with a history of a T2N1 left breast cancer (ER and PR positive) treated with lumpectomy and sentinel lymph node biopsy followed by adjuvant chemotherapy and radiation 6 years ago presents with a sudden onset of shortness of breath and was found to have a new left upper lobe lung mass and a moderate pleural effusion. She has a 15-pack-year history of tobacco use but quit 20 years ago. A thoracentesis is performed, and 400 mL of fluid is removed. Cytology shows adenocarcinoma. Additional immunohistochemical staining is inconclusive. Follow up chest X-ray 5 days later shows some reaccumulation of her pleural effusion.

1. What is the next best step?

A. Observation until patient is symptomatic, then repeat thoracentesis as needed
B. Indwelling catheter placement
C. Chest tube placement followed by talc slurry pleurodesis
D. Thoracoscopy and talc poudrage pleurodesis
E. Pleuroperitoneal shunt

The answer to this question is purposely controversial. Malignant pleural effusion is a significant problem that can adversely affect the quality of life even in patients with only several months to live. However, some pleural effusions, such as breast or mesothelioma, can have better prognosis and longer survival times. In addition, patient factors such as family support, comorbidities, and overall preferences play a role in the decision-making process and must all be factored together. Traditionally, pleurodesis was the only effective treatment for malignant pleural effusions. While talc was the primary sclerosing agent, doxycycline, bleomycin, and tetracycline have also been used. Studies have shown that talc pleurodesis is the most effective, with success rates of 50–90%. However, issues such as cost, length of stay in the hospital, pain, and respiratory complications have been noted. Newer agents such as bacterial proteins, staphylococcal superantigen, and lipoteichoic acid have also been tried in an effort to lessen toxicity while maintaining the proinflammatory effects, but they are not widely available.

Indwelling catheter placement is gaining in popularity to control pleural effusions and occasionally achieve pleural symphysis. It is particularly effective in cases of entrapped lung for which pleurodesis procedures are not effective. Also, it can be placed in the outpatient setting with minimal

(*Continued*)

in-hospital stays and has been shown to be very cost-effective. It is generally well tolerated, and success rates of 70–90% are noted. Complications such as catheter dislodgement or infection have been observed in about 22% of cases.

The reason that thoracoscopy should be considered in this case is because of the uncertainty of the cause of the pleural effusion. Thoracoscopy with pleural biopsy may provide additional tissue for analysis that can impact therapy. Estrogen and progesterone status for breast cancer as well as EGFR and ALK status for lung cancer can result in a significant change in therapy. However, in patients where the diagnosis is not in doubt and additional tissue would not impact therapy, then an indwelling catheter would be an excellent choice for this patient. Furthermore, a combined approach can also be used. Outpatient placement of an indwelling catheter followed by talc slurry pleurodesis through the catheter in 1–2 weeks with catheter removal has been reported. Also, simultaneous thoracoscopic talc poudrage pleurodesis and indwelling catheter placement with eventual catheter removal approximately one week later have also been described. In a patient population with a short life expectancy, rapid control of the effusion and improvement in breathing and quality of life are key factors. Patients' ability to manage an indwelling catheter will also impact decision making. Serial thoracentesis is not a good option, and pleuroperitoneal shunts are not frequently performed anymore.

Case study answers

Case study 108.1

Question 1: Answer B

Case study 108.2

Question 1: Answer D

Case study 108.3

Question 1: Answer D

Case study 108.4

Question 1: Answer C

Case study 108.5

Question 1: Answer B

Case study 108.6

Question 1: Answer C

Case study 108.7

Question 1: Answer A

Case study 108.8

Question 1: Answer D

Case study 108.9

Question 1: Answer A

Case study 108.10

Question 1: Answer D

CHAPTER 109

Surgical aspects of upper gastrointestinal cancers

Sabha Ganai and Mitchell C. Posner
The University of Chicago Medicine, Chicago, IL, USA

Case study 109.1

A 53-year-old male presents with severe dysphagia and weight loss. Upper endoscopy reveals a circumferential mass at 35–39 cm from the incisors. Biopsies are consistent with adenocarcinoma. He undergoes endoscopic ultrasound and positron emission tomography–computed tomography (PET–CT) imaging, demonstrating an uT3N1 gastroesophageal junction tumor without evidence of metastatic disease. The multidisciplinary team plans to begin induction chemoradiotherapy followed by surgical resection.

• Are there important considerations when discussing perioperative nutritional support?

Dysphagia is a challenging problem for patients undergoing neoadjuvant therapy for locally advanced esophageal cancer. While enteral tube feeding is often used to address nutritional consequences of dysphagia, it does not address symptom control. Self-expanding metal or plastic stents have been used on occasion to bridge patients until surgical resection while receiving neoadjuvant therapy. Although stents may cause issues related to migration, there is support that they lead to improvements in dysphagia scores and maintenance of weight, and may not cause additional surgical complications or alteration of operations (Level 3). Importantly, response to chemoradiotherapy frequently leads to relief of dysphagia.

There is some controversy about performing an esophagectomy after percutaneous endoscopic gastrostomy (PEG) placement. A majority of surgeons use the stomach as an esophageal replacement during the reconstruction phase of esophagectomy and may have concerns about compromising the viability of the gastric conduit after takedown of a prior PEG. While there is retrospective evidence that PEG does not significantly compromise perioperative outcomes (Level 4), this should be discussed in advance with the surgeon, especially if they may be performing minimally invasive approaches. Laparoscopic jejunostomy tube placement may be a better option instead of blind percutaneous approaches in light of possible injury or proximity to the right gastroepiploic artery, the essential feeding vessel to the future gastric conduit.

During the postoperative period, feeding jejunostomy tubes are recommended as a method to intervene with existing malnutrition, possible complications, and a slow transition to oral intake by providing enteral support when needed (Level 3). While having a feeding jejunostomy tube placed in the setting of esophagectomy has potential value, routine postoperative enteral feeding after esophagectomy is not recommended based on current evidence (Level 2).

• What are the surgical options for esophagectomy? Are there important differences based on approach?

Esophagectomy is generally approached by either transthoracic or transhiatal means with reconstruction using mobilized stomach (occasionally the colon or jejunum) and the creation of an anastomosis in the chest or neck. Ivor Lewis esophagectomy entails a right thoracotomy and

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

laparotomy with an intrathoracic anastomosis. A McKeown, or "three-hole," approach involves right thoracotomy and laparotomy with a left cervical anastomosis. Transhiatal esophagectomy involves blunt dissection of the esophagus through an abdominal incision with a cervical anastomosis. Minimally invasive, robotic, and hybrid approaches use a combination of laparoscopy and/or thoracoscopy to perform esophagectomy by any of the above methods.

Data encompassing two meta-analyses, four randomized controlled trials, and a large population-based study demonstrate no significant differences in overall survival between the transthoracic and transhiatal approaches (Level 1). Cervical anastomoses are associated with a higher leak rate, but avoid the devastating complications often associated with leaks from intrathoracic anastomoses. Significantly greater ICU stay and surgical costs have been noted after transthoracic approaches, while transhiatal esophagectomy has been associated with lower postoperative mortality and less pulmonary complications. The largest reported series of transhiatal esophagectomies ($n = 2007$) described an in-hospital mortality of 1% and a 9% leak rate across the most recent 944 patients. However, recent experience with 1033 minimally invasive esophagectomies (MIEs) attributes a mortality rate of 1.7% and a 5% rate of anastomotic leak requiring surgery. While a randomized trial reporting short-term data from MIE has shown decreased pulmonary infections, similar leak rates, less vocal cord paralysis, improved pain scores, and improved quality-of-life parameters in comparison to open transthoracic esophagectomy (Level 2), significant advantages in length of stay and oncologic outcomes of MIE over open esophagectomy have not yet been demonstrated. There continues to be a lack of consensus on the ideal approach to esophagectomy.

• What is the impact of hospital volume on perioperative outcomes for esophagectomy?

In 1979, Luft and colleagues suggested that regionalization of complex surgical procedures should occur based on volume–outcome relationships. Birkmeyer and the Veterans Affairs Outcomes group later demonstrated that among surgical procedures performed on Medicare recipients, esophagectomy had the highest 30-day mortality rate and strongest-observed relationship with hospital volume, with a significant correlation between mortality and surgeon volume when adjusted for hospital volume. Recent trends have shown a decrease in risk-adjusted mortality associated with esophagectomy, which may reflect a redistribution of patients from low-volume to high-volume centers, but also better training and perioperative care. Some debate exists on an approach to further regionalization, as low-volume hospitals with certain systems characteristics have been demonstrated to have outcomes similar to those of high-volume hospitals. While procedure volume has become a quality measure adopted by the Leapfrog Group and the Agency for Healthcare Research and Quality, more recent analyses with large databases have suggested that patient characteristics may better predict mortality risk than hospital volume (Level 3).

• What is the role of endoscopic ultrasound (EUS) and PET–CT in primary staging and assessing response to therapy for esophageal cancer?

EUS tumor and nodal staging correlate with the ability to perform an R0 (microscopically negative-margin) esophagectomy, with highly effective discrimination of stages T1–T2 from T3–T4. However, EUS does not retain its utility as a staging modality after neoadjuvant therapy. PET has been shown to improve the detection of metastatic disease as well as the diagnostic specificity for nodal staging of esophageal cancer, with PET–CT leading to a change management in 34% of patients, most commonly a change from curative to palliative intent. A meta-analysis examining the role of standardized uptake value (SUV) in prediction of survival among patients receiving neoadjuvant therapy demonstrated that a reduction in SUV was associated with improved survival (Level 1). While post-therapy SUV is the most accurate test to predict survival after induction therapy, it does not, however, rule out microscopic disease and cannot be used to reliably avoid esophagectomy. Recently, PET response criteria in solid tumors (PERCIST) criteria have been defined, with better reliability and correlation with outcomes than traditional size-based response evaluation criteria in solid tumors (RECIST) criteria. The optimal role and timing of PET–CT in the context of multimodality therapy are still under investigation.

• What is the role of surgery for squamous cell carcinoma (SCC) of the esophagus?

A limitation in the literature on esophageal cancer is the historical grouping of outcomes data on the management of adenocarcinoma and SCC. There is increasing evidence that esophageal SCC is similar in etiology, biology, and response to platinum-based chemoradiotherapy to SCC of the oropharynx and upper aerodigestive tract. With this rationale, a phase III randomized trial from Germany examined the role of definitive chemoradiation therapy (50–60 Gy) versus induction chemoradiation (40 Gy) followed by esophagectomy in the management of SCC of the upper and middle third of the esophagus. While the surgical arm had better progression-free survival, there was no significant difference in overall survival between groups (Level 2). Treatment-related mortality was substantially greater in the surgical arm (12.8% vs. 3.5%) and may have blunted any potential improvement in survival in the surgery arm. Deaths from cancer were markedly reduced

in the surgery arm compared to the chemoradiation arm. The FFCD-9102 trial used a novel randomization scheme in which patients with resectable SCC were randomized to surgery or further chemoradiotherapy if there was an initial treatment response after initial chemoradiotherapy. There were no significant differences noted in overall and recurrence-free survival or quality-of-life outcomes, while patients undergoing surgery had greater therapeutic mortality (attributed to perioperative deaths) and hospital length of stay, but less locoregional recurrences and need for esophageal stents (Level 2). As in the German trial, deaths from cancer were markedly reduced in the surgery arm compared to the chemoradiation arm. While it has still been argued that induction therapy followed by esophagectomy remains the standard of care for resectable SCC, definitive chemoradiation may be an acceptable decision reserving esophagectomy for instances of documented residual or recurrent disease.

Case study 109.2

A 72-year-old female presents with a 3 cm antral lesion discovered during work-up for anemia. Biopsies are positive for adenocarcinoma, and she is clinically staged by EUS as uT2N1. She has been otherwise asymptomatic and has an excellent performance status. Computed tomography reveals no evidence of metastatic disease. The multidisciplinary team plans to begin perioperative chemotherapy.

- **What are the roles of diagnostic laparoscopy and peritoneal washings in gastric cancer?**

Positive peritoneal cytology has been demonstrated to have prognostic value in patients with advanced gastric cancer undergoing curative resection. In patients staged preoperatively without evidence of gross metastatic disease or ascites who underwent an R0 resection with positive cytology, 61% recurred locally or with peritoneal disease. While it is compelling evidence as a predictor of mortality, some authors have debated its added prognostic utility in patients with serosal-positive disease. While there is a lack of consensus surrounding the role of gastrectomy for curative intent in patients with positive cytology or the role of repeat cytology after neoadjuvant therapy, the added value of gastrectomy in either of these scenarios has not been demonstrated (Level 4). At this time, we would advise against gastrectomy in cytology-positive patients and suggest that diagnostic laparoscopy with peritoneal washings is a reasonable strategy to stage patients with locally advanced disease prior to administration of perioperative chemotherapy.

- **Does it matter how much of the stomach is resected?**

A French cooperative group randomized patients with antral gastric carcinoma to either subtotal gastrectomy with Billroth II reconstruction versus total gastrectomy with roux-en-Y esophagogastrostomy. This was followed by a multicenter Italian trial randomized trial in patients who could achieve 6 cm margins to the cardia to either total or subtotal gastrectomy with D2 lymphadenectomy. Both groups were unable to find survival differences between the two procedures (Level 2). Perhaps of greater controversy is the management of lesions of the gastric cardia and gastroesophageal junction. Examining nonrandomized outcomes of surgical therapy of cardia (type II) lesions, Siewert and colleagues demonstrated no significant differences in long-term survival between extended total gastrectomy and esophagectomy, although 30-day mortality was worse after esophagectomy (Level 3).

- **What about the extent of lymphadenectomy?**

The extent of nodal dissection for gastric cancer has been a source of controversy for years. Much of the impetus for studying this topic in the Western world came from numerous reports from East Asia showing consistent benefit from extended lymphadenectomy. In 1998, the German Gastric Cancer Study group reported prospectively collected multicenter data on the role of standard D1 versus extended D2 lymphadenectomy (Level 3). They found that the number of nodes dissected was a predictor of survival in stage II and IIIA disease, and that lymph node ratio and resection status were important independent predictors of outcome. The Medical Research Council (MRC) Gastric Cancer Surgical Trial was a randomized comparison between standard D1 versus extended D2 lymphadenectomy (including distal pancreatectomy and splenectomy) for resectable gastric cancer. Their study suffered from noncompliance and contamination of the randomization protocol, where similar numbers of resected nodes and D2 nodal stations were seen in both groups. They found similar rates of overall survival between groups, although distal pancreatectomy and splenectomy were found to be an independent predictor of poor outcome. The Dutch Gastric Cancer Trial also confirmed problems with adherence to protocol when they randomized patients to limited D1 versus extended D2 lymphadenectomy despite instruction by all surgeons by an expert Japanese surgeon. D2 lymphadenectomy included routine distal pancreatectomy and splenectomy, with a concurrent increase in complications and in-hospital mortality. The Dutch group recently reported extended follow-up that demonstrates significantly higher gastric-cancer-specific survival in the D2 group at 15 years, with a marked reduction in loco-regional recurrence (Level 2). While the importance of extended lymphadenectomy is still controversial, further evidence supporting routine use of D2 lymphadenectomy can be

gleaned from another well-designed randomized trial demonstrating survival benefit. National Comprehensive Cancer Network (NCCN) guidelines now recommend that D2 lymphadenectomy should be considered the standard of care during gastrectomy for localized gastric cancer.

Selected reading

Mariette C, Piessen G, Briez N, *et al*. Oesophagogastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol. 2011 Mar;12(3):296–305.

National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. gastric cancer (version 2.2012). http://www.nccn.org (accessed January 28, 2013).

Orringer MB. Esophageal mythology. J Am Coll Surg. 2008 Aug;207(2):151–63.

Rice TW, Blackstone EH, Rusch VW. A cancer staging primer: esophagus and esophagogastric junction. J Thorac Cardiovasc Surg. 2010 Mar;139(3):527–9.

Songun I, Putter H, Kranenbarg EM, *et al*. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010 May;11(5):439–49.

CHAPTER 110

Surgical aspects of pancreatic cancer

Amanda B. Cooper[1], Ching-Wei D. Tzeng[2], and Matthew H.G. Katz[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]University of Kentucky, Lexington, KA, USA

Case study 110.1

A jaundiced 64-year-old woman presents with a computed tomographic (CT) scan showing a 3 cm hypoattenuating pancreatic head mass with a tumor–portal vein interface measuring 270°. The superior mesenteric vein (SMV) appears patent. The tumor also abuts the hepatic artery at the level of the gastroduodenal artery (GDA). Peripancreatic lymph nodes are not enlarged. Endoscopic ultrasound (EUS)–guided biopsy of the mass is consistent with pancreatic adenocarcinoma.

• What would you tell her about her stage and prognosis?

Several clinical staging systems exist for pancreatic adenocarcinoma. The American Joint Commission on Cancer (AJCC) system stages patients' disease based on physical examination findings and the results of cross-sectional imaging. According to the AJCC system, this patient has a potentially resectable cancer. The final pathologic AJCC stage might be either T3N0 (IIA) or T3N1 (IIB) following resection, however, because CT may underestimate lymph node involvement. Under the current (7th edition) system, stages I–II denote potentially resectable disease (irrespective of lymph node status), whereas stages III–IV indicate unresectable and/or metastatic cancer. A large study using the National Cancer Database validated the current AJCC staging system's ability to predict 5-year survival and showed that patients with pathologic stage IIA disease have a 15.7% 5-year survival rate after successful resection.

According to National Comprehensive Cancer Network (NCCN) guidelines, this tumor would be anatomically staged as borderline resectable based on portal vein encasement (with reconstruction potential) and GDA abutment up to the hepatic artery. At the MD Anderson Cancer Center, clinical staging assesses the primary tumor anatomy ("A"), the tumor biology ("B"), and the patient's condition ("C") (Figure 110.1). Within this system, this woman's disease would be borderline resectable type A unless she has an elevated CA 19-9 level or extensive comorbidities.

By definition, patients with anatomic borderline resectable disease have a high risk of positive surgical margins and early treatment failure with a surgery-first approach. The general consensus is that these patients should receive chemotherapy and/or chemoradiation before surgical resection. In a retrospective study of borderline resectable patients treated with a neoadjuvant approach, 38% completed multimodality therapy and resection with a 40-month median overall survival (OS), comparable to that of patients with "potentially resectable" anatomy who received multimodality therapy and resection. Figure 110.1 illustrates the distinction between borderline resectable and potentially resectable tumors using the MD Anderson system.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

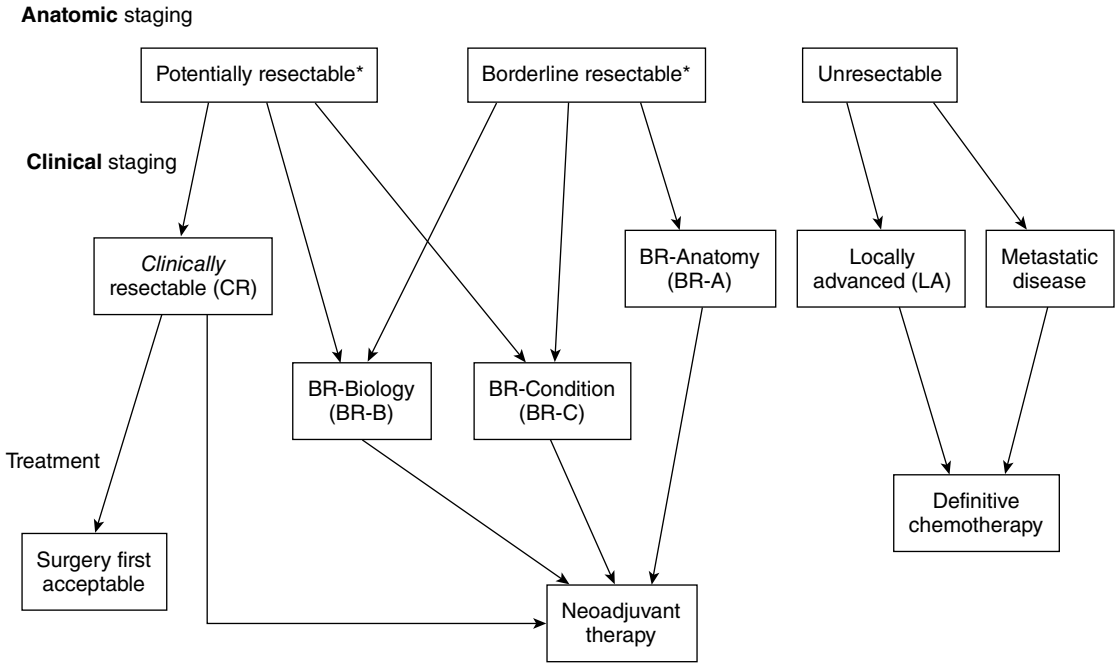


Figure 110.1 The MD Anderson clinical-staging and stage-specific treatment algorithm for pancreatic cancer patients. Patients with "clinically resectable" tumors have resectable tumor anatomy, no elevated suspicion for metastatic disease, and a performance status suitable for a major abdominal operation. Either surgery or neoadjuvant therapy is a rational treatment option for such patients. Three categories of patients have "borderline resectable" tumors: type A patients have borderline tumor anatomy, typically consisting of venous occlusion or arterial abutment; type B patients have borderline biology due to a significantly elevated CA 19-9 level and/or radiologic findings indeterminate for metastatic disease; and type C patients have borderline physiology, such as frailty or potentially reversible comorbidities requiring either prolonged work-up or intervention prior to major surgery. Patients with borderline resectable tumors are routinely treated with neoadjuvant therapy before resection. Patients with locally advanced or metastatic disease are treated palliatively.
*Previously defined MDACC (not AJCC or NCNN) criteria for potentially resectable and borderline resectable anatomy.

Case study 110.2

A 68-year-old man presents with a 2.1 cm hypodense mass in the uncinate process of the pancreas and a bilirubin level of 13.8 mg/dl. A CT scan shows no obvious extrapancreatic disease or vascular involvement.

• **What would you recommend to this patient? Would you obtain a tissue biopsy? Refer to a gastrointestinal specialist for endobiliary decompression? Refer to a pancreatic surgeon? Start chemotherapy immediately?**

If not already performed, a "pancreatic protocol" CT scan (triple-phase—noncontrast, portal venous, pancreatic parenchymal, and arterial phase—with water as an oral contrast agent with 2–3 mm cuts through the pancreas) allows for optimal assessment of resectability. This patient appears to have resectable tumor anatomy by NCCN criteria and should be referred to a multidisciplinary group that includes a pancreatic surgeon for consideration of resection. Although administration of neoadjuvant therapy to patients with resectable cancers is a valid option at many centers, particularly within a clinical trial, primary surgical resection remains the standard of care. If the surgeon believes the patient is an appropriate candidate for resection, confirmatory biopsy is unnecessary if clinical evidence favors a diagnosis of pancreatic cancer.

Multiple randomized controlled trials (RCTs) have explored whether preoperative biliary stenting benefits

patients with obstructive jaundice scheduled for imminent surgery. The best designed of these was a 2010 multicenter Dutch trial, limited to patients with pancreatic head cancer and bilirubin levels of 2.3–14.6 mg/dl. Patients randomized to preoperative biliary drainage underwent drainage 4–6 weeks before surgery. Drainage was performed endoscopically, with percutaneous transhepatic drainage reserved for endoscopic failures. No significant difference was found between the two groups in mortality, length of hospital stay, or postoperative complications, but a significantly higher rate of serious complications occurred in the biliary drainage group (74% vs. 39% in the immediate surgery group) when including procedure-associated complications. The authors concluded that routine preoperative biliary drainage for jaundiced pancreatic cancer patients undergoing surgery-first sequencing increases complication rates. Two meta-analyses reported similar findings.

A 2012 Cochrane Review summarizing the results of RCTs of preoperative biliary drainage included six trials with 520 patients with biliary obstruction from benign or malignant causes. Four trials included percutaneous transhepatic biliary drainage, and two used exclusively endoscopic biliary stenting. Although the Cochrane group felt all included trials had a high risk of bias, they found no significant difference between the drained and undrained groups with respect to mortality or length of stay. Preoperatively drained patients, however, had a higher overall serious morbidity rate. The Cochrane group concluded that with the limitations of the existing studies, the evidence was insufficient to recommend routine preoperative biliary drainage in jaundiced patients.

Although these studies suggest preoperative biliary drainage is unnecessary for jaundiced pancreatic cancer patients who undergo immediate surgery, in practice, patients often present after diagnostic endoscopic retrograde cholangiopancreatography and have had a biliary stent placed as prophylaxis against cholangitis due to instrumentation of an obstructed biliary system.

Case study 110.3

A 72-year-old woman is referred to you with a 3 cm biopsy-proven pancreatic head adenocarcinoma. A soft tissue plane is visible between the tumor and the portal vein. Her CA 19-9 level is 1000 U/ml (with normal bilirubin), and her CT scan shows two low-density liver lesions too small to characterize.

- **How would you treat this patient?**

Although this patient has resectable tumor anatomy by NCCN criteria, an experienced clinician should strongly suspect metastatic disease based on the elevated CA 19-9 and indeterminate liver lesions. These factors make her a borderline resectable type B (biology) patient within the MD Anderson classification. As such, she would be an appropriate candidate for neoadjuvant sequencing. Although good prospective data are lacking, neoadjuvant therapy has several purported advantages in this setting. First, the preoperative therapy period provides a window to observe the patient's tumor biology (i.e., 3–4 months of neoadjuvant therapy allows time for the liver lesions to "declare themselves" as benign or metastatic and for the CA 19-9 level to trend up or down). If metastatic disease manifests during that window, the patient will be spared the morbidity and mortality associated with pancreatic resection. Second, neoadjuvant administration of chemotherapy ensures that all resected patients receive this vital modality. Up to 30–50% of patients undergoing surgery first do not receive timely postoperative systemic therapy (arguably the most important component of this patient's therapy) because of surgical complications, poor postoperative recovery, or personal preference. In a study reporting outcomes of neoadjuvant treatment sequencing in patients similar to this one, 46% of patients had metastases detected before surgery and 46% of patients ultimately underwent resection. For patients who completed both neoadjuvant therapy and resection, the median overall survival approached 29 months.

If this patient undergoes surgery first, then a rational therapeutic strategy would include staging laparoscopy before laparotomy. A selective approach to laparoscopy based on either CA 19-9 levels $\geq$150 U/ml or tumor size $\geq$3 cm significantly decreases nontherapeutic laparotomy rates (3% vs. 18%) and detects occult metastases in 31% of patients. If laparoscopy confirms metastatic disease, a shorter recovery time (compared to postlaparotomy recovery) allows more rapid initiation of systemic therapy.

Case study 110.4

• A patient is referred to you with a bilirubin of 10 mg/dl and a CT scan showing a hypodense pancreatic head mass causing short-segment portal vein–SMV occlusion just below the splenic vein junction (with adequate vein for reconstruction above and below). You and the patient discuss treatment options and agree on a neoadjuvant approach. What additional procedures are needed before initiating therapy?

This patient's tumor is borderline resectable by NCCN criteria (short-segment portal vein–SMV occlusion with reconstruction potential) and MD Anderson criteria. The case should be referred to a surgical oncologist for multidisciplinary treatment planning. With a tumor occluding the portal vein–SMV, this patient's risk of a positive superior mesenteric artery (SMA) margin after surgery alone is high; however, with neoadjuvant chemoradiation and meticulous surgical technique, only about 17% of SMA margins should be close ($\leq$1 mm).

For patients undergoing neoadjuvant therapy, a tissue diagnosis is often required to initiate chemotherapy and/or chemoradiation. EUS-guided fine-needle aspiration is the preferred method for obtaining a tissue diagnosis because of an approximately 85% sensitivity, a 98% specificity, and a lower risk of biopsy track recurrence relative to CT-guided biopsy (since in patients who undergo pancreaticoduodenectomy, the duodenal wall containing the biopsy track is resected).

Before beginning neoadjuvant therapy, this patient will need biliary stenting for his or her obstructive jaundice because a bilirubin $<$2 mg/dl is needed prior to initiation of chemotherapy. Although no RCTs have specifically compared use of plastic versus self-expanding metal stents in patients with malignant biliary obstruction undergoing neoadjuvant therapy, the combined evidence from several trials compellingly favors use of metal stents for these patients. First, randomized trials of plastic versus metal stents in patients with malignant biliary obstruction have demonstrated longer median stent patency rates (3.5–9 months) for metal stents versus plastic stents (1.1–5.4 months). Additionally, a retrospective analysis of pancreatic cancer patients treated with neoadjuvant therapy compared time-to-stent-complication rates for plastic and metal biliary stents, revealing a nearly 7-times-higher complication rate, a 3-times-higher hospitalization rate due to stent-related complications, and a nearly 5-times-shorter time-to-stent-complications rate with plastic stents. Finally, a prospective study examined the safety and efficacy of self-expanding metal stents in pancreatic cancer patients undergoing neoadjuvant treatment. This study reported a 3.4-month median time from neoadjuvant therapy initiation until surgery, during which 88% of metal stents maintained patency. Over the whole follow-up period, 13% of the cohort experienced stent occlusion and 2% experienced stent migration. The authors also reported no complications from metal stents in the 49% of patients who ultimately underwent pancreaticoduodenectomy, which they attributed to their use of the shortest stent necessary to cross the stricture. This practice maintains the maximal length of normal bile duct above the stent for reconstructive hepaticojejunostomy.

• Would you recommend anticoagulating this patient?

Yes. Although no studies have specifically addressed this question, the physiologic rationale behind anticoagulation is prevention of clot propagation rendering the patient's tumor unresectable due to inadequate length of vein below the occlusion for successful reconstruction. In addition to a high risk of portal venous clot propagation, this patient has a high risk of pulmonary embolism. Low-molecular-weight heparins are the preferred therapeutic anticoagulation for such patients based on results from previous studies in cancer patients. A 2003 multicenter RCT compared the efficacy of dalteparin, a low-molecular-weight heparin, and an oral vitamin K antagonist (warfarin or acenocoumarol) in the prevention of recurrent venous thrombosis in oncology patients. This study demonstrated a lower probability of recurrent venous thromboembolism without a significant difference in rates of any bleeding, major bleeding, or mortality for the dalteparin group. A second study, to date reported only in abstract form, reported preliminary results from the multicenter CONKO 004 Trial, which prospectively randomized patients with advanced pancreatic cancer to palliative chemotherapy $\pm$ enoxaparin. This study closed early, but showed a significant absolute risk reduction (approximately 10%) for symptomatic venous thromboembolism for patients randomized to receive enoxaparin, without a significant difference in major bleeding, fatal tumor-related hemorrhage, or overall survival rates (preliminary data).

Case study 110.5

• A 70-year-old woman is referred to you after margin-negative resection of a 1.8 cm pancreatic tail cancer with 0/6 lymph nodes involved. The patient's preoperative CA 19-9 level was 190 U/ml with a normal bilirubin level. Her baseline postoperative CA 19-9 level was 60 U/ml. What does the CA 19-9 trend tell you about this patient's prognosis?

A retrospective review from the Massachusetts General Hospital evaluated CA 19-9 levels in pancreatic cancer patients before and after resection and found that patients with preoperative CA 19-9 levels <1000 U/ml, postoperative CA 19-9 levels <200 U/ml, and decreased postoperative CA 19-9 levels all had significantly longer median overall survival, respectively, than those with higher preoperative levels, higher postoperative levels, and CA 19-9 levels that did not decrease postoperatively. In a multivariate analysis, a postoperative CA 19-9 decrease, negative lymph nodes, lower T-stage, and a postoperative CA 19-9 level <200 U/ml all significantly correlated with improved survival. With all of these positive predictors, a relatively favorable prognosis might be expected for this patient.

A second study from the University of Heidelberg analyzed preoperative and postoperative CA 19-9 levels in 1543 patients and found an inverse association between preoperative CA 19-9 levels and overall survival. Furthermore, a significantly higher proportion of tumors in patients with CA 19-9 levels <250 U/ml were resectable at exploration compared with those in patients with a CA 19-9 level >250 U/ml. In a multivariate analysis, CA 19-9 levels <250 U/ml were the most useful independent predictor of resectability. The authors also found a correlation between postoperative CA 19-9 levels and survival, with the shortest survival observed in patients with postoperative increases. However, in contrast to the earlier study, a significant survival difference was observed between patients with a normal postoperative CA 19-9 level (<37 U/ml) and those with an elevated value. Based on these data, a more guarded prognosis might be expected.

• Can you draw any meaningful conclusions about this patient's prognosis based on the pathologically negative lymph nodes?

Six lymph nodes are insufficient for properly staging pancreatic cancer. Although multiple studies have found that negative lymph node status is correlated with improved survival, other studies have shown that the number of lymph nodes examined is also a critical consideration. These studies have shown that node-negative patients with fewer than 12–15 nodes in the specimen have a lower survival rate than those with higher lymph node counts. One of these studies showed no difference between the survival curves of patients with stage N1 disease and ≥12 lymph nodes examined and those with stage N0 disease and ≤12 lymph nodes examined.

• Is there a role for surgical consultation in patients receiving palliative treatment for locally advanced, unresectable pancreatic cancer?

If a patient with symptomatic biliary or gastric outlet obstruction is found to have locally advanced disease precluding resection, then surgical palliation will likely provide substantial benefit. For patients with a life expectancy ≥6 months, surgical palliation of biliary and/or gastric outlet obstruction (GOO) with or without celiac plexus block provides durable palliation. For patients with biliary obstruction but no clinical GOO, prophylactic gastrojejunostomy in combination with biliary bypass should be considered since it may prevent symptoms in the 10–20% of patients who would otherwise develop GOO, and can be performed without increasing postoperative morbidity rates or length of hospital stay. For patients with life expectancies <6 months (typically those with metastatic disease or a declining performance status), endoscopic biliary stenting, and if necessary duodenal stenting, is preferable because it is associated with superior quality of life, decreased hospital stay, and likely decreased cost.

A prospective double-blinded RCT studied surgical palliation of pain associated with advanced pancreatic cancer. In this study, patients with unresectable tumors found at exploration for potentially resectable pancreatic cancer were randomized to celiac plexus injection with either 50% alcohol or saline placebo. The study included both patients with and without significant preoperative pain and found improved pain scores in the alcohol group at 2, 4, and 6 months as well as at last follow-up before death. The study showed a benefit with alcohol injection even for patients without significant preoperative pain since it reduced their overall pain scores and delayed the onset of pain (and, in some cases, altogether prevented subsequent development of pain) relative to the placebo group. Perhaps the most surprising finding in this study was that patients with substantial preoperative pain in the alcohol injection group also lived significantly longer than those in the control group. For patients experiencing pain who do not undergo surgical exploration, substantial benefit can often be achieved with a CT- or EUS-guided celiac plexus block.

Selected reading

Adams MA, Anderson MA, Myles JD, *et al*. Self-expanding metal stents (SEMS) provide superior outcomes compared to plastic stents for pancreatic cancer patients undergoing neoadjuvant therapy. J Gastrointest Oncol. 2012 Dec;3:309.

Katz MH, Pisters PW, Evans DB, *et al*. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Amer Coll Surg. 2008 May;206:833.

Katz MH, Wang H, Balachandran A, *et al*. Effect of neoadjuvant chemoradiation and surgical technique on recurrence of localized pancreatic cancer. J Gastrointest Surg. 2012 Jan;16:68.

Tzeng CW, Fleming JB, Lee JE, *et al*. Defined clinical classifications are associated with outcome of patients with anatomically resectable pancreatic adenocarcinoma treated with neoadjuvant therapy. Ann Surg Oncol. 2012 Jun;19:2045.

van der Gaag NA, Rauws EA, van Eijck CH, *et al*. Preoperative biliary drainage for cancer of the head of the pancreas. New Engl J Med. 2010 Jan 14;362:129.

CHAPTER 111

Surgical aspects of hepatobiliary tumors

Subhasis Misra[1] and Leonidas Koniaris[2]

[1]Texas Tech University Health Sciences Center, Amarillo, TX, USA
[2]Indiana University School of Medicine, Indianapolis, IN, USA

Case study 111.1

A 50-year-old male, a chronic alcoholic with a recent diagnosis of 2 cm hepatocellular carcinoma (HCC), is referred to you. His alpha-fetoprotein (AFP) level is 200 ng/ml, and he has a low model for end-stage liver disease (MELD) score reflecting well-preserved liver function.

1. What would be the best modality to treat this patient?

A. Chemotherapy
B. Radiation
C. Resection
D. Transplantation
E. Ablative therapies

The curative therapies to treat patients who develop HCC with the best long-term survival rates are liver resection or transplantation. Unfortunately, because of intrinsic liver dysfunction (limiting resection), lack of liver donor availability (limiting transplant), and late detection (limiting both), only a small subset of patients are candidates for either of these curative therapies. Increasingly, a role for hepatic ablative therapies has been recognized, but such therapies in Western series have not been universally associated with equivalent patient outcomes. Nonetheless, determination of which curative intent therapies to provide patients remain poorly defined.

Ablative therapies have generally been restricted as a bridge therapy before transplantation, or as palliative therapy for patients who are not candidates for either resection or transplantation. Chemotherapy and radiation are not first-line agents for cure in HCC.

A recent study by Koniaris *et al.* (2011) showed that, overall, patient survival for resection versus intent-to-transplant (ITT) patients was similar (5-year survival of 53.0% vs. 52.0%, not significant). However, for HCC patients who had MELD scores less than 10 and radiologically met Milan or UCSF (University of California, San Francisco) criteria, 1-year and 5-year survival rates were significantly improved in resected patients. For patients with MELD scores less than 10 who met Milan criteria, 1-year and 5-year survival were, respectively, 92.0% and 63.0% for resection ($n = 26$) versus 83.0% and 41.0% for ITT ($n = 73$; $P = 0.036$). For those with MELD scores less than 10 who met UCSF criteria, 1-year and 5-year survival were, respectively, 94.0% and 62.0% for resection ($n = 33$) versus 81.0% and 40.0% for ITT ($n = 78$; $P = 0.027$).

Given that there are robust data from many studies that show similar 5-year survival rates with resection and transplantation, the authors suggest that the onus should be on transplantation to prove superiority. If there are two therapies with equivalent 5-year survival rates, one costing $750,000 after 5 years and the other costing $40,000, the $750,000 therapy needs to prove superiority. As well, using limited livers from the donor pool to treat patients with HCC who could equivalently be treated with resection prevents another potential patient from receiving a liver for transplantation. That being said, many patients are not candidates for surgical resection, and those patients may suitably be treated with liver transplantation. So, for known HCC patients with preserved low-MELD-score liver function, surgical resection should be the first line of therapy. Transplantation may be considered for HCC recurrence.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 111.2

You discussed the above data with the patient, and you recommended that he sees a surgical oncologist. While he is trying to make up his mind, his health gradually declines. He develops worsening ascites and decompensated liver function. Unfortunately, a donor liver is not available for him to undergo transplant.

1. What does the best course of treatment now become?

A. Chemotherapy
B. Radiation
C. Resection
D. Transplantation
E. Bridging therapies

We know that liver transplantation offers the advantage of both eradicating the tumor and treating the underlying liver disease in HCC patients. However, donor organs are limited and the time on the transplant waiting list is up to 6 or 12 months in Europe and the United States, with up to 30–40% dropouts per year. It has been demonstrated that patients with untreated HCC while on the waiting list longer than 6–10 months do not have any benefit in survival after liver transplantation.

Multiple choice and discussion questions

1. What are the various forms of bridging therapies?

Bridging therapies commonly used to treat HCC while awaiting transplant include chemoembolization (transcatheter arterial chemoembolization (TACE) and hepatic arterial therapy (HAT)), alcohol ablation, and radiofrequency ablation. Combination bridging therapies have also been utilized.

2. What are the clinical outcomes of bridging therapies?

Adjuvant treatment with TACE, percutaneous ethanol injection, and/or radiofrequency ablation (RFA) in T1- and T2-staged HCC resulted in tumor-free survival after transplantation of 95.2% after 4 years and ITT survival of 94%, 85%, and 79% at 1, 2, and 3 years, respectively. Percutaneous therapies carry risks of tumoral seeding between 0.1% and 0.6%. There use is somewhat controversial, however. To date, there is no high-level evidence that waiting-list HCC treatment with these modalities is effective in (i) achieving improvement of post–liver transplant survival, (ii) achieving downstaging of advanced HCC to within Milan criteria, and (iii) preventing waiting list dropout.

Often, combinations of these therapies are utilized to achieve high rates of tumor necrosis, which has been shown to improve recurrence-free survival in posttransplant patients. None of the macromorphological HCC features, but only the absence of increased (18)F-fluoro-deoxyglucose (FDG) uptake on pretransplant positron emission tomography (PET), was identified as an independent predictor of postinterventional tumor response ($P < 0.001$). Hence, pretransplant PET assessment may identify those patients with advanced HCC who will benefit from postinterventional bridging therapy (IBT) tumor response and may, thereby, achieve excellent posttransplant outcome.

Case study 111.3

A 55-year-old female with complaints of generalized abdominal pain underwent evaluation with colonosocopy, ultrasound (US), and CT scan, and was diagnosed with synchronous colorectal liver metastases. Her carcinoembryonic antigen (CEA) level is 250 ng/ml. She has a solitary lesion on the liver. Colonoscopy showed a non-obstructing lesion in the right colon.

1. In the general population, what percentage of patients with colorectal cancer will have synchronous colorectal liver metastases?

A. 15%
B. 25%
C. 35%
D. 45%
E. 55%

Colorectal cancer is the third most common cancer arising in American patients, and the disease is the second leading cause of cancer deaths. Approximately 15% of patients will have synchronous liver metastases at the time of treatment of the primary tumor. Within 5 years of treatment of the primary tumor, liver metastases will develop in another 15% of patients. The overall 5-year survival for patients with colorectal liver metastases ranges from 3% to 6%. However, for patients who undergo curative intent treatment of the metastatic lesions with complete eradication of all documented tumor tissue, the 5-year survival improves and ranges from 37% to 58%.

3. Given the above numbers, are there scoring systems to predict survival in these patients with colorectal liver metastases?

Yes. There are several scoring systems that have been proposed. Fong and colleagues (2001) have presented a clinical scoring system that applied one point for each of the following patient and lesion characteristics: (i) nodal status of the primary colorectal malignancy, (ii) interval between treatment of the primary tumor and diagnosis of liver metastasis <12 months, (iii) number of liver lesions >1, (iv) serum CEA level >200 ng/mL, and (v) size of the largest liver lesion >5 cm. Application of the scoring system to a group of 1001 patients showed that the actuarial 5-year survival was 60% for patients with a score of 0. No patient with a score of 5 survived for 5 years.

4. Can one use these scoring systems to predict use of and/or benefit with chemotherapy?

No. Zakaria and coauthors (2007) examined the utility of four prognostic scoring systems with their patient database of hepatic metastasis resections. After multivariate analysis, only intraoperative blood transfusion and involvement of hepatoduodenal lymph nodes were associated with survival and recurrence. Since these are intraoperative findings, the authors concluded that scoring systems are of limited value for choosing preoperative chemotherapy strategies. However, these scoring systems can be used to assist in counseling patients about the use of postoperative therapies.

5. What is the best way to manage a solitary liver lesion measuring approximately 2.5 cm in maximum dimension?

A. Chemotherapy
B. RFA
C. Resection with microscopically negative margins (R0 resection)
D. Radiation

This is a highly controversial area, and there are strong proponents of both RFA and resection. Current literature provides the following main recommendations: (i) resection remains the gold standard of therapy for patients who meet criteria for operability, (ii) complete ablation with good local control is obtained with RFA of lesions 3 cm in diameter or less,(iii) treatment with multimodality strategies is superior to single-modality treatment for hepatic metastases from colorectal carcinoma, (iv) RFA combined with resection and other treatments is preferred to RFA alone, and (v) margin following surgical resection remains somewhat controversial, but generally margins of at least 0.5 cm are ideal.

There is a higher local recurrence rate with RFA alone, and this should normally be reserved for patients who are not good candidates for surgery.

6. With synchronous colorectal liver metastases, should patients undergo a single simultaneous colon and liver surgery or staged surgery if they are good operative candidates?

The approach to treating synchronous metastases has to be individualized to the patient. Traditionally, the primary tumor has been treated first in order to preclude a complication of the primary tumor (bleeding, obstruction, and/or perforation). Others, however, have advocated to treat the metastatic liver disease first and have performed an interval colectomy following chemotherapy. With marginally resectable liver lesions, a staged hepatectomy can be performed and remains the approach used most frequently. With stage IV disease, chemotherapy is the mainstay initially. When patients present with near-obstruction symptoms, especially with primary distal sigmoid or rectal lesions, patients may need an urgent diversion colostomy prior to proceeding with chemotherapy and chemoradiation. Laparoscopic diversion, if feasible, may make subsequent definitive cancer operations easier.

The extent of the liver resection, the surgeon's experience and comfort, and consideration to incisions needed for access to the operating sites all should be considered if simultaneous liver and colon resection rather than a staged resection is considered. Most surgeons will avoid doing a major hepatectomy (formal lobectomy) and extensive colon resection in the same setting, although certain centers of excellence have extolled the virtues of the combined approach. Patient safety as well as the opportunity to observe the biological response to chemotherapy are always considerations in choosing approach. If single-stage approaches are considered, we suggest that careful patient selection is warranted.

7. Is there a role for chemotherapy in the neoadjuvant setting?

Yes. Here again, the approach has to be individualized to the patient and clinical circumstances. We believe that patients with small, localized disease limited to a single lobe, easily amenable to resection, may be referred for surgery first without additional therapy. In the setting of multiple, bilobar liver metastases, there is general consensus that patients may benefit more by an approach that uses neoadjuvant chemotherapy (NAC). The controversy arises regarding whether patients with initially resectable lesions should be offered chemotherapy. Advantages of chemotherapy include the following: (i) evaluating biological aggressiveness of the tumor—certain patients will progress to extrahepatic metastatic disease despite

chemotherapy and hence would be spared an operation that would not provide benefit; (ii) NAC allows defining the responsiveness of the lesions to chemotherapy, and this data could guide postoperative chemotherapy choices; and (iii) with adequate response, unresectable lesions can potentially become resectable.

8. Potential side effects of chemotherapy for colorectal liver metastases that can have an impact on surgical management include which of the following?

A. Renal failure
B. Steatosis
C. Sinusoidal obstruction
D. Both A and B
E. None of the above

Both production and progression of steatosis as a toxic side effect of chemotherapy have been documented, especially after treatment with 5FU and irinotecan. Treatment with oxaliplatin has been associated with sinusoidal obstruction syndrome. This can lead to increased perioperative complications but not mortality. A recent study suggested that steatosis is not related to chemotherapy but to the Body Mass Index of the patients.

One potential drawback with very good response to NAC is that it could render some patients inoperable with initially resectable liver metastases because of the absence of visible residual tumor on imaging. Hence, a study recommended that patients undergo surveillance imaging during NAC to be sure that those rapidly responding patients have resection while the lesions can be identified by imaging and intraoperatively.

Case study 111.4

A 55-year-old male presents with weight loss and abdominal pain. CT scan demonstrates that the right liver lobe appears atrophied while the left hepatic lobe is enlarged. There is a mass encasing the right portal pedicle.

1. What is the best modality of treatment of this condition?

A. Resection of the tumor
B. Orthotopic liver transplant
C. Chemotherapy
D. Radiation

Cholangiocarcinoma is the second most common primary hepatobiliary malignancy. The cell of origin for his tumor is the cholangiocyte. This can be both intra- and extrahepatic in origin. Patel *et al.* in *Nature Reviews Gastroenterology and Hepatology* (2011) elucidated that there are two basic phenotypes of cholangiocarcinoma, extrahepatic and intrahepatic. The extrahepatic phenotype includes the classic Klatskin tumor that is usually located in the hepatic hilum and is the most common type of cholangiocarcinoma. Other subtypes of extrahepatic cholangiocarcinoma include tumors located in the distal common bile duct and ampulla of Vater, and these are the second most common types of cholangiocarcinomas. These tumors tend to spread proximally and distally along the common bile duct, and nodal and extrahepatic spread are frequently present at the time of diagnosis. Intrahepatic cholangiocarcinoma is the least common subtype of cholangiocarcinoma and usually presents as a liver mass.

This patient has the unusual clinical presentation of perihilar cholangiocarcinoma with the "hypertrophy-atrophy" complex, where there is unilobar biliary obstruction with vascular encasement. This results in atrophy of the involved liver lobe and hypertrophy of the other hemiliver.

9. Risk factors for development of cholangiocarcinoma include all EXCEPT which of the following?

A. Primary sclerosing cholangitis
B. Infestation with liver fluke
C. Hepatitis C infection
D. Exposure to thorium dioxide (Thorotrast)
E. HIV infection

The above-mentioned risk factors are present in only 30% of the diagnosed cases. One of the most important steps in the imaging process is to attempt to determine whether the intrahepatic mass is metastasis, hepatocellular carcinoma, or cholangiocarcinoma. If there is no obvious history of an extrahepatic primary malignancy, dynamic CT or magnetic resonance imaging is done to assess the contrast enhancement of the hepatic lesion during the arterial and venous phases of imaging. HCCs are characterized by intense arterial phase enhancement followed by prompt venous phase washout of contrast. Cholangiocarcinomas display continuous uptake of contrast throughout the arterial and venous phases in more than 80% of lesions. PET scans are useful for differentiating HCC from cholangiocarcinoma in lesions 1 cm or larger and are also helpful in diagnosing extrahepatic disease. If the lesion is resectable, proceed with surgery. If not, then biopsy the lesion to rule out HCC and determine appropriate chemotherapy.

For perihilar and distal ductal cholangiocarcinomas, an useful algorithm was created by Blechacz and coauthors (2011), as shown in Figure 111.1.

Petrowsky and Hong (2009) noted that for patients who achieve R0 resections status, 5-year survivals of 40–50%

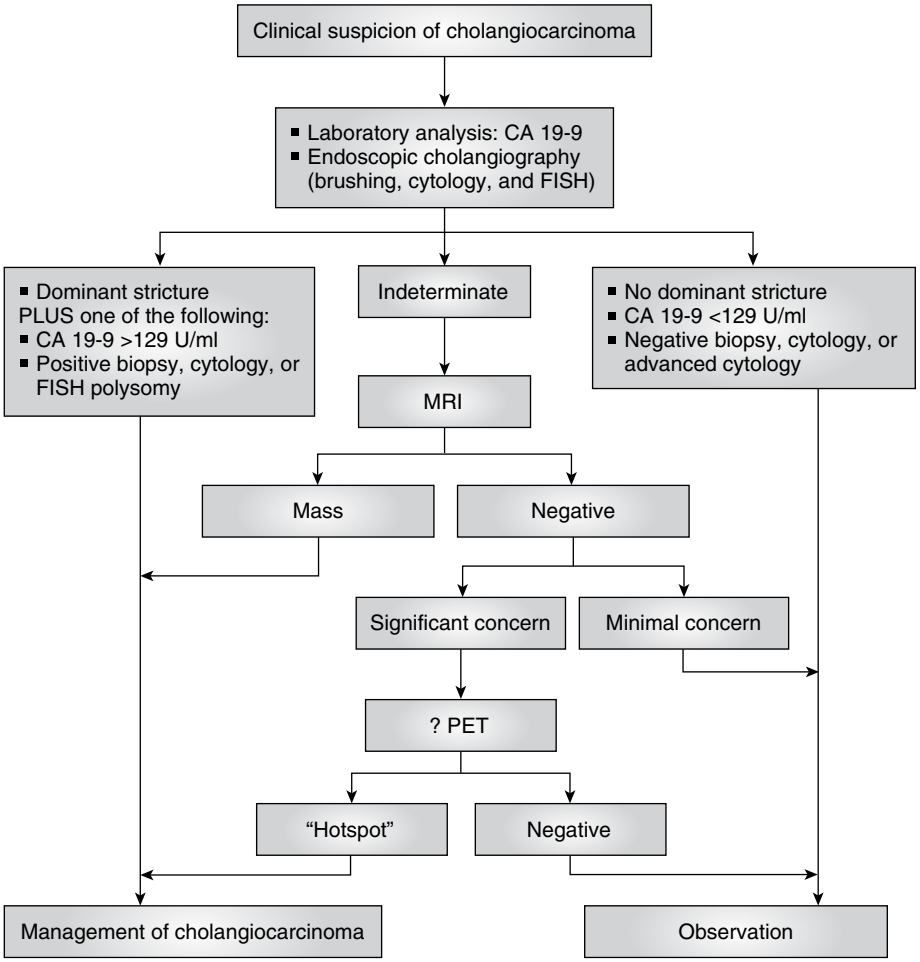


Figure 111.1 Diagnostic criteria for perihilar and distal extrahepatic cholangiocarcinoma. FISH, fluorescent in situ hybridization; PET, positron emission tomography (Source: Blechacz B *et al*. Nat Rev Gastroenterol Hepatol. 2011;8(9):512–522. Reproduced with permission of the Nature Publishing Group).

have been reported. The authors stress that no patients with R2 resections achieve 5-year survival and, therefore, there is no role for tumor debulking in perihilar cholangiocarcinoma. They also noted that preoperative radiation and chemotherapy followed by liver transplantation have resulted in improved outcomes for a carefully selected group of patients with perihilar cholangiocarcinoma, and this is done under protocol.

Nonoperative therapies for cholangiocarcinoma include stereotactic radiation therapy, transarterial chemoembolization, and photodynamic therapy. These can be offered as adjuvant therapy following curative intent resection or as palliative therapy for patients who cannot be treated with resection.

Beltran and coauthors in *Cancer Treatment Review* (2012) noted that patients undergoing resectional therapy for perihilar cholangiocarcinoma were frequently referred for radiation therapy if they had positive lymph nodes discovered at operation or positive resection margins. In this group of patients who received postoperative radiation therapy, there was a 38% increase in overall survival at 5 years.

Case study answers

Case study 111.1

Question 1: Answer C

Case study 111.2

Question 1: Answer E

Case study 111.3

Question 1: Answer A

Case study 111.4

Question 1: Answer A

Multiple choice answers

Question 5: Answer C
Question 8: Answer D
Question 9: Answer E

Selected reading

Ashoori N, Bamberg F, Paprottka P, *et al.* Multimodality treatment for early-stage hepatocellular carcinoma: a bridging therapy for liver transplantation. Digestion 2012;86(4): 338–48.

Blechacz B, Komuta M, Roskams T, *et al.* Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011 Sep;8(9):512–22.

Flint L, McGillicuddy J, Prabhakar Baliga P. Liver, Part II. ACS. Selected Readings in General Surgery. 2012;38(4). www.facs.org/srgs/

Grundmann RT. Current state of surgical treatment of liver metastases from colorectal cancer. World J Gastrointest Surg. 2011 Dec 27;3(12):183–96.

Koniaris LG, Levi DM, Pedroso FM, *et al.* Is surgical resection superior to transplantation in the treatment of hepatocellular carcinoma? Ann Surg. 2011 Sep;254(3):527–38.

Petrowsky H, Hong JC. Current surgical management of hilar and intrahepatic cholangiocarcinoma: the role of resection and orthotopic liver transplantation. Transplant Proc. Dec 2009; 41(10):4023–35.

CHAPTER 112

Surgical aspects of lower gastrointestinal cancers

Anthony J. Senagore
Central Michigan University School of Medicine, Mount Pleasant, MI, USA

Case study 112.1

A 65-year-old healthy female patient presents with a non-obstructing sigmoid colon adenocarcinoma found on screening colonoscopy. During her preoperative work-up, a 3 cm lesion consistent with metastasis is found near the surface of the right lobe of the liver.

1. What is the best therapeutic option for this patient?

A. Laparoscopic sigmoid colectomy and laparoscopic wedge resection of the metastasis followed by chemotherapy
B. Initial 3-month course of neoadjuvant chemotherapy followed by surgical resection of the primary and metastasis
C. Laparoscopic sigmoid colectomy and radiofrequency ablation of the liver metastasis followed by adjuvant chemotherapy
D. A 12-month course of chemotherapy followed by restaging of the lesions and consideration for surgery only if the disease is stable or regresses in the liver

This scenario and similar situations with initial presentation as stage IV colon cancer have evolved in recent years with proponents of a liver-first strategy typically prevailing in more extensive involvement of the liver. The current data support a strategy of combined colon and liver surgery when the extent of the liver resection is more modest (especially when a limited wedge resection of a surface metastasis is possible). It is probably optimal to perform intraoperative ultrasound examination of the liver to confirm the absence of other deposits. This approach effectively renders the patient tumor free and avoids any potential risk of chemotherapy-induced liver damage. Conversely, in more advanced single-lobe disease, the approach remains more controversial. There are strong advocates for both of the following options: (i) colon resection followed by chemotherapy and restaging with anticipation of a delayed hepatic resection; or (ii) a combined colon and hepatic resection followed by postoperative chemotherapy. The former is advocated in units with strong outcomes in liver resection and in cases where the primary colon resection is not complex (i.e., a large bulky lesion or cases requiring multivisceral resection). A recent analysis using a large US administrative data set suggested that this approach is associated with a significantly higher morbidity and mortality rate compared to a staged resection approach. There are a number of single center cohort studies, however, which demonstrate excellent outcomes and similar complication rates with either approach. The colon-first approach is also advocated on the basis that a major liver resection (i.e., formal lobectomy or trisegmentectomy) may confer an unreasonable operative risk for the patient. In addition, successful completion of the colectomy followed by a 3-month course of chemotherapy will allow time to assure that the patient does not manifest disease advancement in other locations of the liver, possibly to the extent that resection is futile. Unfortunately, no solid prospective randomized data suggest the superiority of either strategy, and the existing data are fraught with

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

selection biases that are difficult to control for with retrospective data sets. Although the modern chemotherapy regimens have shown improved response rates, irinotecan has been associated with steatohepatitis and oxaliplatin with sinusioidal endothelial injury and presinusiodal scarring. These disorders can limit the amount of liver resected.

The final scenario of unresectable liver disease and a nonobstructing, non-bleeding primary colon lesion has largely been resolved in favor of a liver-first approach. The goal of therapy is to hopefully render the liver disease resectable over time. The perceived risk of advancement of the colon primary leading to emergency colectomy for obstruction, hemorrhage, or perforation has been demonstrated to be a rare event in these patients. In addition, an often unappreciated advantage of this approach by surgeons is the fact that surgical complications of the colectomy may actually delay or deprive this patient group of the ability to begin chemotherapy and the chance for a survival advantage.

Case study 112.2

A 59-year-old male patient presents with a 3 cm adenocarcinoma at 8 cm from the dentate line. A metastatic work-up demonstrates no evidence of disease outside the rectum. Ultrasound demonstrates an uT3N0Mx primary lesion, and on magnetic resonance imaging (MRI), the closest margin is 7 mm from the fascia propria of the rectum.

1. What is the most appropriate management of this patient?

A. Short-course radiation therapy followed by restorative proctectomy
B. Long-course neoadjuvant chemoradiation therapy followed by restorative proctectomy
C. Transanal resection of the primary using the TAMIS technique followed by chemoradiotherapy
D. Restorative proctectomy followed by adjuvant chemotherapy

This scenario represents a complex and evolving clinical scenario that should be addressed by a multidisciplinary tumor board. According to existing NCCN guidelines, the technique of preoperative radiotherapy followed by formal restorative proctectomy is the current standard therapy. The former is more generally accepted in Europe and has the benefit of limiting the neoadjuvant treatment cycle to 1 week. It has the disadvantage of providing limited size reduction of the primary lesion, which may improve the opportunity for a negative circumferential margin and avoidance of a permanent colostomy for low-lying tumors. The best available data are from the Dutch TME trial, which demonstrated significant improvement of local recurrence rates with the use of short-course radiotherapy (2500 cGy) followed by total mesorectal excision by trained surgeons. The overall reduction of local recurrence was 11% versus 5% with the combined therapy. However, caution was raised by the final 12-year follow-up data, in which patients' overall survival was similar between the groups. A lower cancer death rate was offset by earlier-stage patients who died more frequently from cardiovascular disease and other malignancies. Although the authors determined that T3 patients with negative circumferential margins and radiotherapy had a survival advantage, the absolute risk reduction was only 10% (50% vs. 40%; $P = .032$). This study was disadvantaged because it predated the concept of MRI-predicted margins and the potential role of nonthreatened margins in guiding decisions related to the risk–benefit ratio of radiotherapy. The extensive work by Dr Gina Brown has refined the definitions and diagnostic criteria related to the use of local staging of rectal cancer. The surgical outcomes related to these criteria are embodied in the MERCURY trial, which demonstrated favorably low local recurrence rates with total mesorectal resection even in T3 l lesions without threatened margins (i.e., >5 mm from the fascia propria of the rectum). There are a number of single-center retrospective studies confirming the fact that local recurrence rates can be very low when high-quality surgery is employed in the pelvis. Similarly, the risk associated with nodal disease may also ultimately be challenged using similar criteria with MRI. The significant benefit of a well-performed total mesorectal excision as defined by scoring of the integrity of the mesorectum is clear. The recognition of the relative contribution of excellent surgery with or without supplementation by radiotherapy will be the next major task in the improvement of rectal cancer outcomes. The major reason for this is not only the specter of increased non-cancer-related death rates due to radiation, but also the significant impairment of functional results (increased incontinence rates) and the greater need for diverting stomas due to the risk of early anastomotic leakage. Finally, there is a growing interest in the role of neoadjuvant chemotherapy without radiation. which carries the potential for tumor shrinkage, an improvement in the predicted negative margin rate, and the avoidance of radiation-related reductions in clinical outcome.

Case study 112.3

A 65-year-old female patient presents with an ultrasound-confirmed T3N1MX adenocarcinoma at the top of the anorectal ring. A distant metastatic work-up is negative. She returns 8 weeks after completing a neoadjuvant long-course chemoradiotherapy regimen and has no evidence of the primary lesion other than a scar. Mucosal biopsies are negative for neoplasia.

1. What is the optimal therapy at this point?

A. Transanal excision of the scar
B. Boost brachyradiotherapy
C. Observation
D. Abdominoperineal resection

The wide use of neoadjuvant chemoradiotherapy has produced the clinical conundrum of what to offer the patient who apparently has had a completed pathologic regression of a rectal cancer. The issue hinges on several issues. First, how accurate is clinical assessment of the rectum in assuring patient and physician that an apparent complete clinical response is actually a complete pathologic response warranting a nonoperative approach? Second, how to resolve the fact that significant tumor regression is a predictor of a significant improvement in both local recurrence and overall survival when coupled with a well-performed total mesorectal excision. Third is the lack of any significant body of data confirming the long-term risk of locoregional recurrence in the face of an apparent complete pathologic response. Finally, what is the ability to salvage the patient who initially presents with an apparent complete pathologic response only to ultimately present with recurrent tumor in the rectum?

Case study 112.4

A 45-year-old male patient is diagnosed with an ascending colon cancer on colonoscopy performed for iron-deficiency anemia. There is no family history of colorectal cancer, and the completed staging work-up does not demonstrate distant metastatic disease.

1. Which family cancer syndrome should be principally considered in this patient?

A. Attenuated familial polyposis
B. Hereditary nonpolyposis colon cancer (HNPCC)
C. Syndrome X
D. Hyperplastic polyposis syndrome

This patient is under the age of 50, and HNPCC should be strongly considered in this patient because of the right-sided location. The pathologist should be queried regarding other suspicious histologic criteria, such as mucinous histology or significant tumor infiltrating lymphocytes (so-called Crohns-like response). In addition, strong consideration should be given to performing microsatellite instability testing on the biopsy specimen. A finding of high or unstable microsatellite should raise suspicion regarding this diagnosis and warrants formal consultation with a genetic counselor. Final testing requires assessment of the potential site of mutations for accurate decision making for the patient and his family members. The most common mutation occurs in MLH1; however, reduction in this protein is also very common in association with BRAF mutation unassociated with HNPCC kindreds. Although not part of this discussion, BRAF and KRAS mutational assessment may lead to directed biologic treatments related to the presence of one or both mutations. Although accuracy may be limited compared to assessing a larger specimen, this distinction is important for the operating surgeon to make the important determination of deciding to perform an oncologic right hemicolectomy (MLH1 and BRAF positive) versus a subtotal colectomy. If he is indeed HNPCC at any of the four potential sites (MLH1, MLH2, HMSH2, and PMSH6), his lifetime risk of a metachronous colon cancer approaches 50%. In addition, female relatives of patients with PMSH6 are at significant risk for uterine cancer and need to be counseled regarding surveillance versus prophylactic hysterectomy. If this had been a female patient, then a discussion regarding concomitant hysterectomy would have been a consideration. This risk can be more safely managed by reducing the amount of colon that needs to be assessed and allowing ongoing surveillance to be performed by flexible sigmoidoscopy. Conversely, diagnosis of a BRAF mutation is effectively managed by a right hemicolectomy and standard lifelong surveillance of the colon for new polyps and potentially a metachronous colon cancer.

Case study answers

Case study 112.1

Question 1: Answer A

Case study 112.2

Question 1: Answer A or B

Case study 112.3

Question 1: Answer D

Case study 112.4

Question 1: Answer B

Suggested reading

Buecher B, Cacheux W, Rouleau E, *et al*. Role of microsatellite instability in the management of colorectal cancers. Dig Liver Dis. 2012 Nov 26;45(6):441–9.

van Gijn W, Marijnen CA, Nagtegaal ID, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011 Jun;12(6):575–82.

Viganò L. Treatment strategy for colorectal cancer with resectable synchronous liver metastases: is any evidence-based strategy possible? World J Hepatol. 2012 Aug 27;4(8):237–41.

Win AK, Lindor NM, Winship I, *et al*. Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome. J Natl Cancer Inst. 2013 Feb 20;105(4):274–9.

CHAPTER 113

Surgical aspects of renal cancer

Michael E. Woods and Matthew C. Raynor

University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

Case study 113.1

A 52-year-old female was diagnosed with an incidental left renal mass discovered during evaluation for abdominal pain (see Figure 113.1).

• What is the best imaging study for evaluation of a suspected renal mass?

Currently, computed tomography (CT) without and with intravenous contrast is the gold standard imaging study for the evaluation of a renal mass. Standard cross-sectional scans without and with contrast are sufficient to evaluate for mass enhancement, measured in Hounsfield units, and to evaluate vascular anatomy. Coronal and 3D reconstructions can also be useful for surgical planning by allowing for visualization of tumor complexity (nearness to collecting system or renal hilum), depth of penetration, and regional metastatic disease. Alternatively, magnetic resonance imaging (MRI) without and with gadolinium can be used with excellent anatomic detail, as well.

In patients with chronic kidney disease or a contrast allergy, CT and/or MRI can be performed without contrast. Suspicious renal lesions can be further characterized with ultrasound to better delineate solid or cystic components. However, cross-sectional imaging is essential for staging and for surgical planning.

• What is the likelihood of an enhancing renal mass being malignant?

The likelihood of malignancy increases with increasing renal mass size. Close to one-half of all renal masses less than 1 cm and approximately 20% of renal masses 2–4 cm in size are benign. Conversely, only about 6% of renal masses 7 cm or greater are benign. Additionally, high-grade tumors and negative prognostic features are more frequently identified in larger tumors. Other than fat-containing angiomyolipoma, current imaging modalities are unable to distinguish benign from malignant renal tumors.

• What is the role of renal mass biopsy for small renal masses?

Historically, renal mass biopsy was not routinely utilized in the management of small renal masses due to tissue inadequacy. This led to frequent inability to accurately assess tumor histology and grade. However, historical studies of renal mass biopsy utilized fine-needle aspiration (FNA). The current standard of renal mass biopsy involves utilization of core biopsy specimens (preferably, 18-gauge cores). Contemporary studies of renal mass biopsy with core biopsy specimens demonstrate diagnostic rates of greater than 80%. Additionally, concordance of renal mass biopsy with final surgical pathology was greater than 90%. Tumor heterogeneity and necrosis can affect accuracy rates for histology and grade on biopsy.

Indications for renal mass biopsy continue to change. Historically, biopsy was utilized to confirm metastatic disease to the kidney from a nonrenal primary malignancy or renal involvement of lymphoma. Currently, biopsy is frequently performed prior to ablative therapies and for further risk stratification in order to determine treatment or surveillance strategies.

In practice, renal mass biopsy is offered to all patients with an incidental renal mass. However, results of biopsy do not frequently alter treatment decisions of intervention or surveillance. This may be, in part, due to the low incidence of benign pathology (<20%) or, more commonly, patient preference.

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

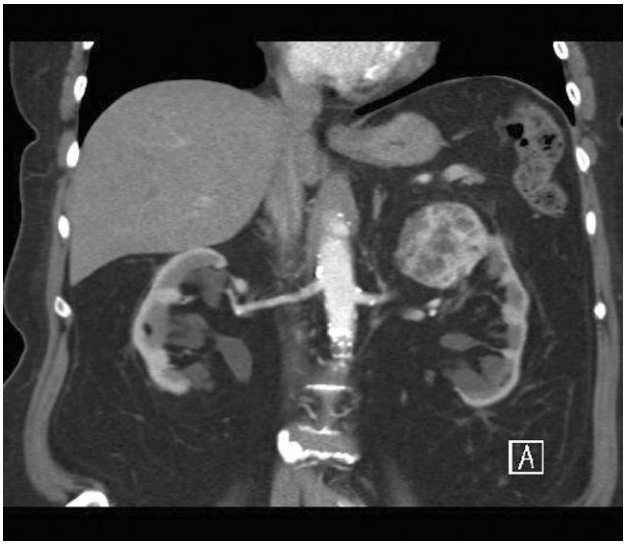


Figure 113.1 Left renal mass found in a 52-year-old female patient.

• **What are management options for small renal masses?**
Management options include active surveillance, ablation, or surgical excision. Active surveillance has been recommended for some due to the slow growth rate of small renal masses (~0.3 cm/year) and low risk of metastatic disease (<2%). Active surveillance of a small renal mass should be the initial management strategy for elderly patients with decreased life expectancy and those patients with extensive comorbidities considered high risk for intervention. Active surveillance is generally not recommended for younger patients or those with a longer life expectancy (>10 years) due to the small risk of progression. Unfortunately, the natural history of small renal masses has yet to be accurately elucidated, but disease progression to metastatic disease represents an incurable condition. Active surveillance generally involves serial imaging with CT, MRI, or ultrasound every 3 to 6 months initially. The interval between subsequent imaging studies can be varied based on observed growth rates. Intervention after an initial period of active surveillance still carries similar excellent oncologic outcomes as primary intervention.

Ablative therapies include cryoablation (CA) or radiofrequency ablation (RFA). These techniques represent minimally invasive treatment options for small renal masses. Each procedure can be performed via a percutaneous or laparoscopic approach and has the added benefit of treating the tumor in a nephron-sparing manner, thus potentially reducing the risk of long-term chronic kidney disease (CKD). Renal mass biopsy should be performed prior to ablation in order to guide future surveillance strategies.

Surveillance after ablation typically involves frequent cross-sectional imaging to evaluate for complete tumor ablation. However, there remains controversy regarding radiographic appearance post ablation and histologic success. Local recurrence has been shown to be higher for ablative techniques compared to surgical excision. Initial incomplete ablation of the target lesion is more common with percutaneous approaches, but repeat ablation can be performed. Surgical salvage of ablation failures can be quite challenging due to extensive perinephric fibrosis. Currently, ablative therapies are considered an option for masses smaller than 4 cm in patients considered higher risk for surgical intervention or in elderly patients. The risks of incomplete ablation and complications significantly increase in tumors larger than 4 cm. Ablation is generally not recommended for younger patients.

Surgical excision remains the gold standard management option for small renal masses. Specifically, partial nephrectomy has become the gold standard treatment. Oncologic outcomes are similar between partial and radical nephrectomy. However, there has been a significant accumulation of evidence that radical nephrectomy increases the risk of long-term chronic kidney disease when compared to partial nephrectomy. Evidence has also shown that CKD increases the risk of hospitalizations, cardiovascular events, and death as GFR decreases. Therefore, partial nephrectomy should be performed when technically feasible in order to preserve as much overall renal function as possible. Partial nephrectomy is an absolute indication in patients with preexisting CKD, bilateral renal masses, genetic predisposition (VHL, BHD, etc.), or solitary kidney.

Only one randomized controlled trial evaluating radical versus partial nephrectomy for small renal masses (<5 cm) has been performed. However, the study was terminated early due to poor accrual. Interestingly, overall survival was slightly lower in the nephron-sparing cohort versus the radical nephrectomy cohort (75.7% vs. 81.1%, respectively, at 9-year median follow-up). When patients with pathologically confirmed renal cell carcinoma (RCC) were analyzed, there was no difference in survival. Despite the findings of this study, the accumulation of other evidence suggests that partial nephrectomy should be the gold standard for management of small renal masses.

Partial or radical nephrectomy can be performed via open or laparoscopic approaches. More recently, robotic partial nephrectomy has become more common due to its shorter learning curve over laparoscopic partial nephrectomy. Partial nephrectomy does have a higher risk of perioperative complications compared to radical nephrectomy. Hemorrhage and urinary fistula are specific complications more commonly occurring after partial nephrectomy. Hemorrhage can occur at the time of surgery or present postoperatively as a delayed bleed, usually resulting from arterio-venous fistula or renal pseudoaneurysm. However, the rates of re-intervention after partial nephrectomy remain very low overall.

• **How is renal function affected by intervention?**

As stated, radical nephrectomy increases the risk of long-term development of CKD. Additionally, patients with small renal masses tend to be older (over 60) and have comorbidities such as diabetes or hypertension that may further increase the risk of CKD. In fact, one study demonstrated that approximately one-quarter of patients undergoing surgical excision of a small renal mass had pre-existing CKD (epidermal growth factor receptor (EGFR) <60 mL/min/1.73m2). In this study, the risk of CKD (EGFR < 60) at 3 years was 65% for patients undergoing radical nephrectomy versus 20% for patients undergoing partial nephrectomy.

Even though partial nephrectomy can preserve overall renal function, several factors can affect ultimate renal function. Patient age and baseline renal function remain the most important factors in determining postoperative renal function. Tumor size and complexity are also important factors, as this will determine the amount of renal parenchymal volume loss after partial nephrectomy.

The main surgically modifiable factor affecting ultimate renal function is ischemia time, in which blood supply to the kidney is temporarily interrupted to allow for tumor excision and reconstruction. Renal ischemia is typically induced by clamping the main renal artery and/or vein. Historically, cold ischemia was used through an open incision by placing ice slush around the kidney after hilar clamping to allow cooling of kidney to ~20°C. Cold ischemia allows for prolonged ischemia time (>60 minutes) without permanent renal injury. However, current minimally invasive surgical techniques such as laparoscopy and robotic surgery make it difficult to induce cold ischemia. Typically, warm ischemia is utilized during tumor excision. Prolonged warm ischemia has been shown to negatively impact renal function. Therefore, the goal is to ensure adequate tumor resection with minimal ischemic time. Current evidence suggests that a warm ischemia time of less than 30 minutes produces minimal impact on overall renal function. However, this cutoff continues to be debated. Recent surgical innovations have allowed for more precise vascular dissection allowing for segmental renal ischemia only to the desired area of the planned resection, while preserving perfusion to the remainder of the kidney. In fact, recent series have demonstrated success with microvascular dissection to vessels supplying only the tumor. Long-term data on ultimate renal function are still needed to determine the allowable time of warm ischemia to minimize renal damage. However, current ideology recommends minimizing warm ischemia as much as possible to allow for adequate tumor resection.

Case study 113.2

This patient is a 64-year-old female with a history of Crohn's disease who underwent a metastatic evaluation that was negative. Her baseline estimated GFR was 51 mL/min/1.73m^2 (CKD stage III). She underwent robot-assisted partial nephrectomy and was discharged home on postoperative day 2. Warm ischemia time during the procedure was 22 minutes. Final pathology demonstrated grade 2 renal cell carcinoma, clear cell type, with negative surgical margins (pT1bNxM0). At one year follow-up, her estimated GFR was 45 mL/min/1.73m^2 with no evidence of disease.

This patient underwent imaging with a CT scan for abdominal pain and diarrhea. An incidental 8×8 cm left renal mass suspicious for neoplasm was discovered without any evidence of retroperitoneal lymphadenopathy or distant metastases. Given the size and location of the mass, a left nephrectomy was recommended. (See Figure 113.2.)

• **Should this patient undergo ipsilateral adrenalectomy at the time of nephrectomy?**

Historically, a radical nephrectomy, including removal of the kidney, all contents of gerota's fascia, the regional lymph nodes, and the adrenal gland, was the standard treatment for RCC. This was reported in the 1960s by Robson and colleagues (1969). Over time, some of these surgical principles began to be challenged, one of which was routine adrenalectomy. The equivalent oncologic outcomes of partial and laparoscopic nephrectomy (both procedures often spare the adrenal gland) compared to radical nephrectomy questioned this practice. A large, retrospective series of over 4000 patients was recently published from the Mayo Clinic evaluating the role of routine adrenalectomy at the time of nephrectomy. Approximately 1500 patients underwent adrenalectomy with 2.4% having synchronous adrenal involvement, and this rate increased to approximately 10% in the highest risk group (tumor >7 cm, T3, T4, and upper pole location). On a multivariate analysis accounting for all tumor characteristics, there was no difference in cancer-specific survival (CSS) if an ipsilateral adrenalectomy was performed. Of the patients who did not undergo adrenalectomy at the time of nephrectomy, 91 developed a subsequent adrenal metastasis at a mean follow-up of approximately 5.5 years. Thirty-seven recurrences occurred in the ipsilateral gland, and 37 occurred in the contralateral gland, while 17 patients experienced bilateral recurrences. This finding

(*Continued*)

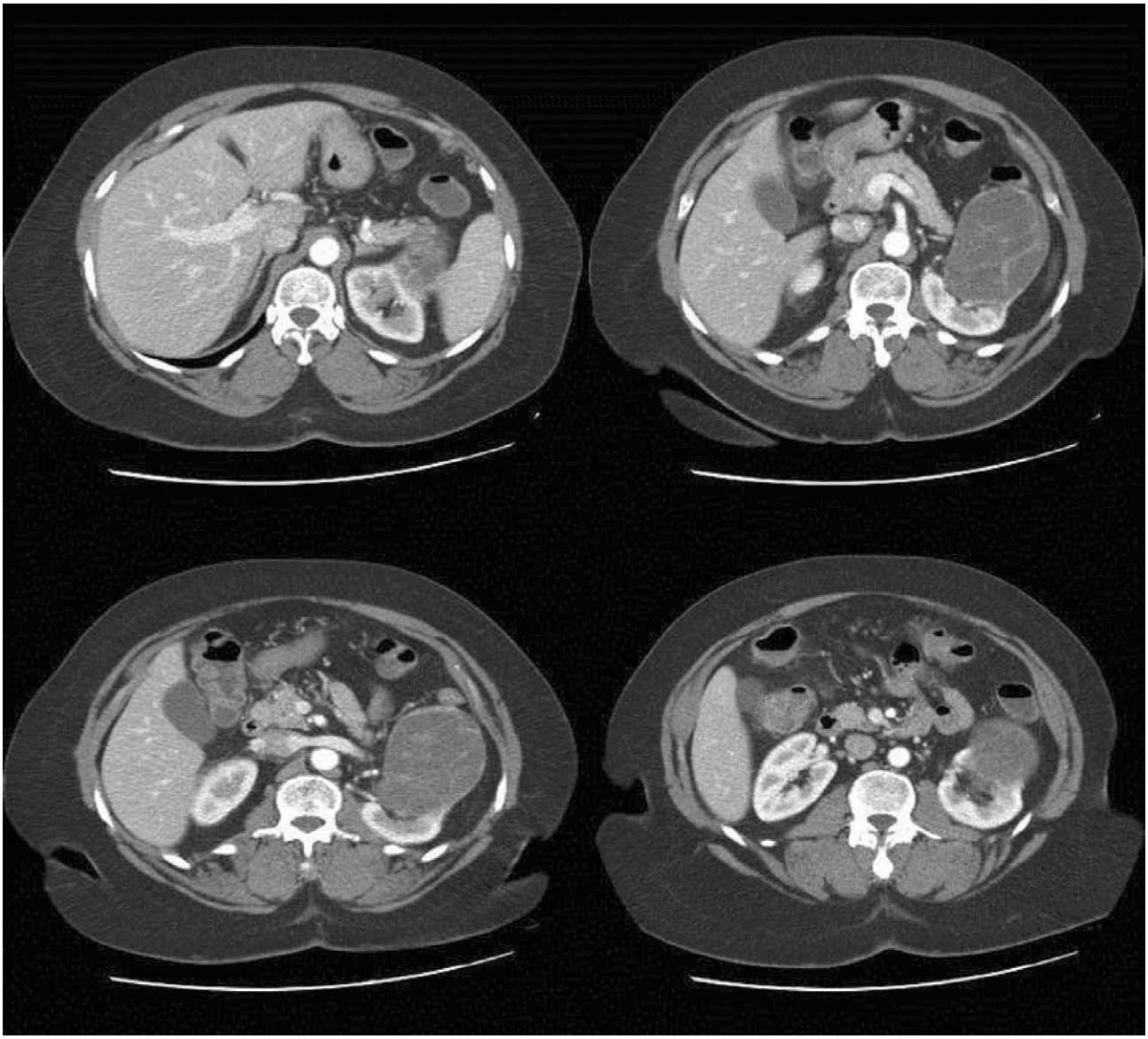


Figure 113.2 Incidental left renal mass found in a 64-year-old female patient.

brings into question if the ipsilateral adrenal gland should be spared in all cases if radiologic and operative evaluations do not demonstrate any evidence of disease, as a significant number of recurrences will develop in a contralateral solitary adrenal gland and would require adrenal replacement therapy if metastasectomy is performed. Some have advocated the removal of the ipsilateral adrenal gland based on renal tumor size and location (>7 cm and upper pole). Kutikov *et al.* (2011) challenged this modified approach to the adrenal gland in a retrospective analysis of 179 patients treated with surgery for RCCs greater than 7 cm. Ninety-one patients underwent concurrent adrenalectomy at the time of nephrectomy, and involvement by RCC was seen in four patients (4.4%). At a median follow-up of 12 months, no asynchronous adrenal metastases developed in the non-adrenalectomy group, and there was no difference in survival between the two groups. Interestingly, all four adrenal glands harboring RCC had been identified on preoperative imaging as abnormal (out of 12 total radiographically abnormal adrenal glands). Preoperative adrenal imaging performed fairly well in this series, with a 33.3% positive predictive value and a 100% negative predictive value. It was also noted by the authors that upper pole location did not predict adrenal involvement. Some recent data exist that suggest ipsilateral adrenalectomy may negatively impact survival in this patient population. Yap *et al.* (2012) reviewed a large cancer registry of nearly 6000 radical nephrectomies to evaluate the impact of adrenalectomy on overall survival

(OS). They focused on the patients with small (<4 cm) masses who would have the least likelihood of cancer-related death and evaluated the outcomes of patients undergoing ipsilateral adrenalectomy (490) versus an adrenal-sparing procedure (1161). There was no difference in OS or CSS at 5 years, but at 10 years there was significantly worse OS for patients with adrenal removal (74.1% vs. 79.8%). These data have some limitations as they are retrospective and derived from an administrative data set, but they nonetheless suggest there may be detrimental impact to unnecessarily removing an adrenal gland in the RCC population. In summary, ipsilateral adrenalectomy is not indicated at the time of nephrectomy if the gland is normal radiographically and on intraoperative evaluation.

• **Should this patient undergo a lymph node dissection (LND) at the time of nephrectomy?**

There is significant variability in the lymphatic drainage of the kidney. The most common landing site for the right kidney is the paracaval and retrocaval nodes, and for the left kidney is the para-aortic and pre-aortic nodes, and the interaortocaval region is a landing zone for both kidneys. The rates of lymph node metastases have been reported to be between 4% and 14.6% in modern series. Lymph node involvement is directly related to stage and grade. The reported rates for T1, T2, T3, and T4 are 1.1–3.9%, 4.5–8.6%, 12.3–19.8%, and 36%, and for grades I, II, III, and IV are 3.2%, 6.5%, 17.2%, and 30%, respectively. For nonmetastatic patients, lymph involvement has a significant impact on outcome, which results in a three times greater risk of cancer-specific mortality. Current imaging techniques (CT and MRI) perform fairly well in detecting enlarged lymph nodes, but they are still unable to reliably detect small (<5 mm) nodes or micrometastatic disease. Retroperitoneal lymph nodes are often enlarged secondary to reaction from renal tumors, resulting in a significant rate of false-positive imaging. In a large European study, the false-positive rate was 58%, but importantly the false-negative rate was only 4.1%. It is recommended that all patients undergo a lymph node dissection if preoperative imaging demonstrates abnormal retroperitoneal lymph nodes. But what is the best approach for a clinically node-negative patient, such as this patient? Level 1 evidence now exists addressing this question. The European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized phase III study comparing radical nephrectomy alone to radical nephrectomy with LND. A total of 772 patients (383 LND, 389 no LND) were enrolled from 1988 to 1991 and followed for progression-free (PFS) and overall survival (OS). It is important to note that all patients were deemed lymph node negative and metastasis free on preoperative imaging. There was only a 4% rate of lymph node positivity in the node dissection group with no increased morbidity for patients undergoing LND. With a medium follow-up of 12.6 years, there was no difference in PFS or OS. This study has been criticized for evaluating a lower-risk population (median tumor size ~6 cm, LN+ rate of 4%) who would be the least likely to benefit from a lymph dissection or, more importantly, would not be harmed by omitting it. There was an interesting finding in the nondissection group. Fifty-one patients had enlarged lymph nodes at the time of surgery, 20% of which were confirmed metastases, leaving only 4/311 (1%) with lymph node metastases in nonpalpable lymph nodes with normal preoperative imaging. Despite the limitations of this study, it remains the highest-quality data to date and applies well to the patient in this scenario, clinical stage T2N0, allowing for the omission of a lymph node dissection. Several retrospective, nonrandomized studies have suggested a benefit to LND in high-risk populations (cT3-T4N0 and N1). There are even some limited retrospective data that imply some potential benefit to LND at the time of cytoreductive nephrectomy in the setting of metastatic disease. It must be kept in mind that these studies are limited by their retrospective design as well as the potential selection bias of which patients received an LND. In summary, a LND does not appear to provide any advantage in T1–T2N0 RCC and may be omitted, but should be considered in high-risk (T3–T4N1) or metastatic patients undergoing cytoreductive nephrectomy when technically feasible.

Selected reading

Alasker A, Williams SK, Ghavamian R. Small renal mass: to treat or not to treat. Curr Urol Rep. 2013 Feb;14(1):13–18.

Margulis V, Wood CG. The role of lymph node dissection in renal cell carcinoma: the pendulum swings back. Cancer J. 2008 Sep–Oct;14(5):308–14.

Pierorazio PM, Hyams ES, Mullins JK, *et al*. Active surveillance for small renal masses. Rev Urol. 2012;14(1–2):13–19.

Volpe A, Cadeddu JA, Cestari A, *et al*. Contemporary management of small renal masses. Eur Urol. 2011 Sep;60(3):501–15.

Wang R, Li AY, Wood DP, Jr. The role of percutaneous renal biopsy in the management of small renal masses. Curr Urol Rep. 2011 Feb;12(1):18–23.

CHAPTER 114

Surgical aspects of bladder cancer

Michael B. Williams
Eastern Virginia Medical School, Virginia Beach, VA, USA

Case study 114.1

A 65-year-old male presents with gross painless hematuria. Diagnostic bladder tumor resection demonstrates muscle invasion, exam under anesthesia suggests a three-dimensional (3D) mass, and imaging demonstrates unilateral hydronephrosis with an epidermal growth factor receptor (EGFR) of >50.

1. What is the best treatment option in this otherwise healthy patient?

A. Radical cystectomy with urinary diversion
B. Neoadjuvant methotrexate, vinblastine, adriamycin, and cisplatin (M-VAC) followed by radical cystectomy and urinary diversion
C. Definitive radiation
D. Radiation + gemcitabine
E. Palliative chemotherapy

In 2003, Grossman *et al*. published the Southwest Oncology Group (SWOG) randomized trial that was initiated in 1987. This paper demonstrated a dramatically increased survival in patients with locally advanced disease. As compared to cystectomy alone, patients who had neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin had a 31-month improved survival. Further, patients who had a complete response to neoadjuvant chemotherapy (i.e., pT0) had the longest survival, with the median not being reached for the study. Since this publication, a non-inferiority trial was published with regard to a gemcitabine and cisplatin combination as an alternative therapy with fewer reported adverse side effects. Further, a dose-dense regimen of M-VAC has also been found to have similar outcomes with less adverse events and imaging demonstrates unilateral hydronephrosis with an estimated glomerular filtration rate (eGFR) >50 ml/min.

Case study 114.2

A 54-year-old male presents with gross painless hematuria. Diagnostic bladder tumor excision demonstrates a superficial non-invasive (i.e., cTa) bladder cancer. Imaging demonstrates no evidence for disease.

1. What is the best treatment option for this patient?

A. Radical cystectomy with urinary diversion
B. Intravesical mitomycin C
C. Intravesical bacillus Calmette–Guerin (BCG) induction only
D. Observation with cystoscopy and repeat resection as warranted
E. Intravesical BCG induction + maintenance

Since the discovery of the decreased incidence of bladder cancer recurrence by Morales *et al*. in 1976, BCG has been the preferred regimen for the management of superficial bladder cancers. This immunotherapy is administered intravesically, is held within the bladder for 1–2 hours, and is given once a week for 6 weeks ~4 weeks after transurethral resection of bladder tumor (TURBT). In 2000, SWOG published the results of a maintenance regimen trial, which demonstrated a dramatic increase in recurrence-free survival in the maintenance arm (36 vs. 77 months). Maintenance is described as a 3-week course of BCG given at 3, 6, 12, 18, 24, 30, and 36 months. Routine cystoscopy is performed prior to each of the administrative doses to ensure no development of tumor recurrence.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 114.3

A 74-year-old male with an Eastern Cooperative Oncology Group (ECOG) PS 2 presents with cT2N0M0 HG UC of the bladder. His eGFR is ~30 ml/min, and he is not felt to be a surgical candidate.

1. What other treatment option is available to him for definitive therapy?

A. None; palliation is the only option
B. Radiotherapy ± chemotherapy
C. TURBT as needed
D. Radical TURBT + radiotherapy ± chemotherapy
E. Chemotherapy only

In the setting of poor performance status and inability to undergo definitive surgical resection, radiotherapy in conjunction with or without chemotherapy has demonstrated the best response rates. Since the initial report by Duncan *et al*. in 1986 of nearly 1000 patients who received definitive radiotherapy for ≥T2 disease, many factors have been noted to best predict poor response rates to this treatment strategy. Of these, the most common factors are multiplicity (several primary tumors within the bladder), Stage T4, and large tumors (i.e., >8 cm).

There have been multiple trials performed by the RTOG with the utilization of combination chemoradiation therapy yielding, at times, similar results to cystectomy. Many different regimens have been applied with similar success rates. The best approach is to have an excellent genitourinary oncology team with the urologist, radiation oncologist, and medical oncologist who together understand the timing and complexity of these types of regimens. For example, RTOG 9906 required induction chemotherapy with Taxol and cisplatin with twice daily radiotherapy (40 Gy) for the first 3 weeks. Response was then evaluated in the operating room at ~week 7. If a complete response was found, then completion of radiotherapy was performed (~60 Gy) over the next 2 weeks. However, if ≥T1 disease was demonstrated, then the patient went straight to cystectomy and then received adjuvant chemotherapy.

Multiple choice questions

1. How many lymph nodes are required to be removed at the time of cystectomy in order to predict a better outcome?

A. 2
B. 5
C. 15
D. 30
E. 50

There have been several retrospective studies that have suggested that the minimum number of lymph nodes needed to be removed in order to improve staging assessment and outcome is 15. The largest to date is by Leissner *et al*., who evaluated 447 patient outcomes with respect to lymph node number. The mean number of lymph nodes removed was 15, and this demonstrated an improved cancer-specific survival. Further, this held true if the patients were found to have either T1 or T2 disease and if they were found to have between 1 and 5 lymph nodes positive. There are many studies evaluating the extent of lymphadenectomy and improved outcomes with most major centers performing a lymph node dissection extending from the obturator fossa to the bifurcation of the aorta, with some extending to the inferior mesenteric vein.

2. True or false? As compared to the ileal conduit urinary diversion, the ileal neobladder has the best quality of life at one year.

A. True
B. False

Multiple studies have been reported in regard to quality of life at one year for patients undergoing either ileal conduits or bladder substitutions. No study has demonstrated a difference in the health-related quality of life (HRQOL) for this population between the two types of urinary diversion. However, there are certain indications where a urinary neobladder diversion should be cautiously discussed (e.g., baseline creatinine of >2.0 with eGFR <40 ml/min). Ultimately, all studies have stated that there is not a best type of diversion for all, and this should be discussed fully along with the patient's overall health and individual preferences.

Case study 114.4

A 66-year-old female presents with gross hematuria and is found on CT urogram to have a filling defect in the renal pelvis without evidence of lymphadenopathy. Ureteroscopy and biopsy are performed that demonstrate a high-grade Ta urothelial carcinoma. She has a normal eGFR and normal functioning contralateral renal unit.

1. What is the best treatment course of action?

A. Observation
B. Intravesicle BCG therapy after stenting
C. Intravesicle mitomycin C therapy
D. Radical nephroureterectomy with regional lymph node dissection
E. Chemotherapy

Patients who present with upper-tract tumors are notoriously understaged. This means that although this particular patient is found to have a non-invasive lesion, the likelihood of having a more advanced lesion on final pathology is higher, and thus removal of the entire renal unit and ureter to the level of the bladder is warranted. There is an appropriate rationale behind the utilization of chemotherapy in a neoadjuvant strategy based on the data obtained from the RCTs in bladder cancer. The primary reason is based on the removal of one renal unit, rendering further chemotherapy in an adjuvant strategy with platinum-based agents difficult to administer.

Case study answers

Case study 114.1

Question 1: Answer B

Case study 114.2

Question 1: Answer E

Case study 114.3

Question 1: Answer D

Case study 114.4

Question 1: Answer D

Multiple choice answers

Question 1: Answer C
Question 2: Answer B

Selected reading

Grossman HB, Natale RB, Tangen CM, *et al*. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349:859–66.

Kaufman DS, Winter KA, Shipley WU, *et al*. Phase I-II RTOG study (99-06) of patients with muscle invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, twice daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. Urology. 2009;73(4):833–37.

Lamm DL, Blumenstein BA, Crissman JD, *et al*. Maintenance bacillus calmette-guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163:859–66.

Leissner J, Hohenfeller R, Thuroff JW, *et al*. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Intl. 2000;85:817–23.

Somani BK, Gimlin D, Fayers P, *et al*. Quality of life and body image for bladder cancer patients undergoing radical cystectomy and urinary diversion—a prospective cohort study with a systematic review of the literature. Urology. 2009;74(5):1138–43.

CHAPTER 115

Surgical aspects of prostate cancer

Peter Pinto

Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Case study 115.1

Low-risk disease

A 65-year-old male with an elevated prostate-specific antigen (PSA) of 5.7 ng/dl underwent a prostate biopsy revealing one core Gleason 6 disease in the right midprostate and one core Gleason 6 left base; both cores are <50% involved.

1. What treatment should this patient undergo?

A. Brachytherapy
B. External-beam radiation with hormone therapy
C. Radical prostatectomy
D. Active surveillance

It is important for the clinician to discuss the necessity for intervention with patients before discussing details of different treatment modalities, hence the consideration for active surveillance among the answer choices. The recently published Prostate Intervention versus Observation (PIVOT) trial is a good place to begin this discussion. This study evaluated over 700 men with PSA-detected locally confined prostate cancer and randomized them to treatment versus observation with a primary endpoint of all-cause mortality. The authors concluded that in men diagnosed with prostate cancer in the early PSA era, at 12 years of follow-up, prostatectomy did not improve all-cause or prostate cancer–specific mortality over observation. However, to apply the findings of the overall study to this patient, one must delve further, which we will consider again in another vignette in this chapter. The lack of treatment effect from the PIVOT trial most strongly applies to patients with Gleason grade (GG) <7 and PSA ≤10 who were ≥65 years of age, as seen visually when looking at the forest plots from the study. These findings are in concert with other studies showing that in many men with low-risk prostate cancer, active surveillance should be the treatment of choice. There are slight variations for inclusion criteria and definition of progression, but all stress the concept that men with low-grade disease should be offered a trial of active surveillance with the ability to intervene at the first signs of progression.

The patient and his wife were extensively counseled about active surveillance; however, they were both very uncomfortable with this option, each having witnessed family members die from cancer. They are having a hard time believing that you can just "watch" cancer.

2. What minimally invasive treatment options exist for this patient besides the more standard options of radiation or surgery?

A. Focal cryoablation
B. Focal high-intensity focused ultrasound (HIFU)
C. Focal laser therapy

Any of the above focal treatments is an option in the setting of an Institutional Review Board–approved clinical trial. This patient does have multifocal, bilateral disease, and thus the appropriateness of a focal approach depends on the goal of treatment and the ability to determine the most clinically significant lesion.

There are centers offering focal treatment for prostate cancer outside the setting of a clinical trial; however, with low patient numbers, limited follow-up, and nonstandardized methods for determining effectiveness, it must be carefully applied. This is best accomplished through the confines of a clinical trial, and this is especially true for focal HIFU in the United States as it is not currently approved by the US Food and Drug Administration (FDA).

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

This patient would not necessarily be excluded from focal treatment because of its multifocality. If utilizing improved imaging (e.g., endorectal magnetic resonance imaging (MRI) or color Doppler ultrasound) and biopsy targeting, a clinician can determine which of the lesions within the prostate is clinically significant, in which case focal treatment may be a sound option. The determination of the "index" lesion might be based on tumor size, grade, or growth rate. Studies evaluating tumor volume have estimated an increased risk of disease progression in a lesion 5 mm, and have correlated positive surgical margins and extraprostatic extension to the "index" or largest lesion. Therefore, an argument can be made for treating an index lesion with focal therapy while continuing active surveillance of smaller, clinically low-risk or very-low-risk lesions. This would allow for minimizing side effects, with the possibility of future treatments if needed. If, in contrast, the treatment goal is complete disease eradication, then a patient with multifocal bilateral disease would represent poor patient selection.

• If you are going to treat this patient with a focal treatment, how can you be sure that his disease is accurately staged and graded?

This is a very real concern for those treating prostate cancer. When using most preoperative nomograms, the most important prognostic variable is the Gleason grade (GG). These nomograms are important tools for physicians and patients in counseling; however, some patients are not appropriately counseled as to the risk of upgrading from the biopsy results. Estimates of the rate of upgrading after radical prostatectomy are between 24% and 61% and upstaging at 7–19% for extracapsular extension and 2–9% for seminal vesicle invasion. One potential way to improve these results is through better imaging, including functional and molecular modalities. Multiple studies, including several from our center, have identified multiparametric MRI's (mpMRI) ability to improve prostate cancer detection compared to grayscale transrectal ultrasound (TRUS) biopsy, correlate suspicion level with D'Amico risk group, localize imaged lesions to true disease burden on whole-mount pathology sections, and potentially decrease the rate of upgrading or upstaging at prostatectomy. There have also been advances in grayscale ultrasound, including color Doppler and contrast-enhanced modalities that have shown promise in early trials.

Case study 115.2

High-risk disease

A 63-year-old male with an initial PSA screening showing an elevated PSA of 8.0 ng/dl. He was therefore referred to an urologist for a prostate biopsy. His PSA 3 months later was 13.0 ng/dl. The patient had a normal rectal exam. A biopsy at the time showed Gleason $4 + 3 = 7$ disease in 4/12 cores. He had a multiparametric endorectal MRI (eMRI) that showed a high-suspicion lesion with extracapsular extension (ECE).

1. How would you stage this patient?

A. D'Amico intermediate risk (organ-confined T2 disease)
B. D'Amico high risk (non-organ-confined T3a disease)
C. Locally advanced disease.(T4 disease)

Based on the AJCC 6th edition, this patient with cT1c Gleason 7 disease would be considered D'Amico intermediate risk, considering only the digital rectal exam. However, the most recent AJCC 7th edition staging system does take into account imaging findings. Therefore, one must consider the findings for this patient on MRI of extracapsular extension. A recent study from Harvard showed an increased risk of ECE and seminal vesicle invasion (SVI) in patients who had undergone radical prostatectomy with a preoperative endorectal MRI (eMRI) prediction of T3 disease. The eMRI had a negative predictive value for T3 disease of 79%; however, the positive predictive value for ECE was only 51%. In another study evaluating the predictive ability of MRI, researchers from the Memorial Sloan Kettering Cancer Center (MSKCC) reviewed the area under the curve for the predictive capability of their prostate cancer nomogram and whether or not it could be improved with eMRI. They found a significant benefit when adding eMRI, especially as it related to extracapsular extension. The interpretation of prostate MRI is still based on subjective interpretation without a current standardized approach across centers. For example, in the Harvard study, they included patients who had possible, probable, and definite ECE in their eMRI T3 group, thus making their positive predictive value lower. The clinician must be familiar with his or her institution and their expertise in the arena of prostate MRI. There is evidence that MRI can predict ECE and SVI if the radiologists who are interpreting the studies are well versed in this arena. In this patient's case, he should be counseled for treatment options based on T3a disease.

2. Are there preoperative predictive tools that can aid in the counseling of this patient?

A. Yes
B. No

The answer is both "Yes" and "No," depending on the incorporation of his imaging findings. Appropriate and thorough pretreatment counseling for prostate cancer relies on a clinician's ability to accurately stage the disease and then utilize commonly available predictive nomograms (e.g., Partin tables, Kattan nomograms, and D'Amico risk groups) to give patients information about their chance for potential cure and clinicians with the information required to make decisions about appropriate treatment options. Utilizing an online nomogram from the MSKCC website, this patient has a predicted chance of organ-confined disease of 57%, ECE 33%, and SVI 21%. Already, we can see how the addition of the MRI might change our counseling for this patient, with MRI evidence of ECE and no evidence of SVI. The prediction of postoperative pathology may be less useful than more clinically relevant information such as biochemical recurrence-free survival (BRFS), cancer-specific survival (CSS), and overall survival (OS). The two most widely utilized tools in regard to predicting PSA recurrence are the D'Amico risk groups and the Kattan nomogram. Based on AJCC 6th edition or earlier, this patient would be a D'Amico intermediate-risk patient with a 76.6% chance of BRFS at 5 years. If one utilized the Kattan nomogram, his risk of BRFS at 5 and 10 years would be 83% and 76%, respectively. We are unable to alter these nomograms as they currently stand for the change in his clinical stage based on imaging, as these tools are not currently able to incorporate findings on imaging. However, if you did incorporate the imaging findings, then the Partin tables or D'Amico risk groups would not be applicable as he would have T3a disease and the Kattan nomogram would predict his 5- and 10-year BRFS at 69% and 57%, respectively, which is significantly decreased from above. The above online nomogram from MSKCC increases his chance of lymph node involvement to 17% from 3%. It is obvious from this patient's example that the currently utilized predictive nomograms have a potentially more limited utility in patients with high-quality imaging that significantly alters their clinical stage from that of the digital rectal exam.

3. What preoperative imaging studies would be needed for accurate staging of this high-risk patient?

A. Pelvic computed tomography (CT) and bone scan
B. Pelvic CT and NaF (sodium fluoride) positron emission tomography (PET)–CT
C. No additional imaging over pelvic MRI already received with prostate MRI

In the majority of patients with clinically localized disease, currently available imaging modalities provide little additional information. CT and MRI have low probabilities of detecting metastatic disease in patients without a high PSA or GG. However, National Comprehensive Cancer Network (NCCN) guidelines recommend pelvic CT or MRI for all patients with clinical T3 or T4 disease, as well as T1 or T2 patients with nomogram-predicted lymph node invasion (LNI) >10%. The recommendations for bone scan include all patients PSA >20 ng/dl, GG ≥8, or T3, T4, and symptomatic.

There are significant limitations to these imaging tools. Pelvic CT and MRI are best at detecting enlarged nodes; however, many patients with lymph node–positive prostate cancer will not have enlarged nodes. Patients with metastatic prostate cancer may also have no soft tissue disease, with bone metastasis only.

Bone scan provides a limited 2D view and is not specific for bony metastatic lesions. If an area is positive on bone scan, it is customary to get plain films or a CT–MRI to confirm the presence of a lesion in that area. Therefore, NaF PET has several advantages in that it has a higher affinity for bone tissue, provides better imaging quality in 3D, with the addition of CT scan findings to correlate any areas of increased uptake. However, currently, bone scan is still the first-line study in most centers owing to increased experience and decreased cost.

Other imaging modalities utilizing C11 choline, F18 choline, F18FDHT, and so on are still in trial format and are being investigated as to their clinical utility. There is also much interest in the use of nanoparticles for both improved imaging accuracy and treatment delivery. Ferumoxytran-10 is an ultrasmall superparamagnetic iron oxide (USPIO) particle that was felt to improve imaging accuracy for patients with lymph node–positive disease, even without enlarged lymph nodes. However, this agent did not gain FDA approval in the United States secondary to safety concerns. Our center is currently evaluating a newer agent from the same company, Ferumoxytol, for its utility in improving detection of lymph node–positive disease.

4. Now that this patient is considered to have clinical T3a disease, what are his treatment options?

A. The *only* appropriate option is radiation
B. Radical prostatectomy is a viable option

There is strong opinion in the urologic community about whether or not high-risk patients, such as this one, should be considered for surgery. One of the main difficulties is the lack of level 1 evidence comparing surgery to radiation for these patients. It is also extremely difficult to compare as BRFS is the most utilized metric, and is measured differently in the two treatment approaches. Also BRFS does not

(*Continued*)

always lead to cancer-specific mortality, as this is a disease generally in men older than 60 years and is a slow-growing malignancy. For example, researchers from the Mayo Clinic found a 99.7%, 97%, and 95% 10-year cancer-specific survival for patients with D'Amico low-, intermediate-, and high-risk disease after undergoing radical prostatectomy for curative intent. Boorjan and colleagues (2012) reviewed a group of over 1500 patients with high-risk disease undergoing radical prostatectomy with a 10-year CSS of 95%, with approximately 30% receiving adjuvant therapy. Another potential benefit of surgery in this population is accurate staging that might direct adjuvant treatments as well as the avoidance of hormone therapy. Patients receiving radiation for high-risk disease will be treated with long-term hormone deprivation therapy, and surgery could potentially avoid that treatment and its side effects (both morbidity and possible increased non-cancer-specific mortality). There is a significant percentage of patients who will be predicted to have non-organ-confined disease, but on final pathology after surgery will in fact have organ-confined disease and not require additional treatment. I would inform this patient that there is a risk that he may need multimodal treatment for his prostate cancer but that surgery is a good and viable option.

5. The patient elects for surgery to treat his prostate cancer. At the time of his prostatectomy:

A. A limited lymph node dissection (limLND) should be performed that includes obturator nodes only
B. An extended bilateral pelvic lymph node dissection (eLND) should be performed
C. No lymph node dissection is necessary

An extended bilateral pelvic lymph node dissection, which would include dissection along the obturator, external iliac, and internal iliac up to the bifurcation of the common at the level of the ureteric crossing, should be performed for this patient with D'Amico high-risk disease. A limLND would include the external iliac vein laterally to the obturator vessels posteriomedially.

For those performing radical prostatectomy, deciding who should be offered and the extent of pelvic lymph node dissection (PLND) to offer is an issue without unanimous agreement. The American Urological Association (AUA) consensus statement on management of prostate cancer published in 1987 argued a PLND was a tool for staging of high-risk patients before a potential prostatectomy and without therapeutic benefit. Unfortunately, in the last 25 years, there have been no prospective trials comparing outcomes in patients with and without PLND, and therefore no definitive conclusions can be drawn.

There does appear to be clear evidence of benefit with eLND versus limLND in terms of improved staging. In an elegant study, Mattei and colleagues (2008) evaluated the drainage pattern of prostate cancer in node-negative patients (thus preventing the theoretic risk of drainage alterations in nodes infiltrated with cancer) and showed that the primary lymphatic landing sites could include the internal iliac, external iliac, obturator, inguinal, perirectal, or presacral nodes. In a study of 122 patients by Schumaker and colleagues (2011) of node-positive patients, only 16% of patients who underwent an extended lymph node dissection were positive in the obturator fossa alone, with 21% positive in the internal iliac chain only and 9% positive in the external iliac chain only. Therefore, the current NCCN guidelines argue that an ePLND should be used whenever a dissection is to be undertaken.

- **Some clinicians argue that a clear benefit in the arena of staging, with potential to improve decision making in regard to adjuvant therapy or potential trial enrollment, is an adequate reason to include PLND for patients with a risk for LNI. However, is there a potential therapeutic benefit?**

A study often cited in this debate utilizing SEER data demonstrated a survival advantage to both node-positive and node-negative patients when greater than four lymph nodes were removed. This survival advantage could simply be secondary to improved staging of patients in both categories. In contrast, clinicians from the Mayo Clinic published a series of over 7000 patients undergoing radical prostatectomy and PLND with pTxN0 disease between 1987 and 1999. The PLND changed during the time of this study, with a decreasing number of LNs removed toward the later years; however, there were no differences in BRFS in patients on multivariate analysis examining the year of surgery or number of lymph nodes removed. In contrast, there are multiple studies showing a prolonged BRFS in men with LNI who have undergone PLND, with fewer positive nodes equaling a better prognosis. This indirect evidence seems to support that a percentage of men with limited nodal involvement may benefit from PLND.

In reality, the patient and clinician must weigh the advantages and potential morbidity in order to determine a threshold risk they will utilize for LNI before including PLND. The current NCCN guidelines argue that an ePLND should be used when the predicted percentage of LNI for the patient is $\geq$2%. This was recently validated in a SEER study showing the nomogram to be highly accurate; however, the number of patients avoiding a PLND was smaller than the group had predicted. If the threshold was increased to $\geq$3%, then 58% of patients with node-negative disease would have avoided an unnecessary PLND; however, 15% of patients with LNI would have been missed. Our recommendations to this patient would be to undergo a bilateral extended pelvic lymph node dissection.

7. The patient did well after his uncomplicated surgery. His final pathology was Gleason 4 + 3 = 7. The patient had focal extracapsular extension in the left side with negative surgical margins and lymph node–negative disease (0/16). His PSA at 3 months postop was undetectable. What is the appropriate treatment for this patient?

A. Adjuvant radiation therapy
B. Continued close observation with salvage radiation if there is a PSA recurrence
C. Observation with hormone therapy if the patient develops symptomatic metastatic disease

There are currently three randomized trials (Southwest Oncology Group (SWOG) 8794, European Organization for Research and Treatment of Cancer (EORTC) 22911, and Arbeitsgemeinschaft Radiologischer Onkologie (ARO) 9602) that have compared adjuvant radiotherapy versus observation in patients with high risk for disease recurrence after radical prostatectomy. It is important to remember that these trials were comparing radiation to observation and not salvage treatments. A recent update of the EORTC 22911 trial with a median of 10 years of follow-up continued to show improved BRFS for adjuvant radiotherapy; however, there was no difference in clinical progression-free survival, distant metastasis-free survival, or overall survival compared with observation. The authors further concluded that patients with negative margins might not benefit and those over age 70 might be harmed by adjuvant radiation. The long-term update of the SWOG 8971 trial showed an improvement in BRFS with adjuvant radiation over observation, but, different from the EORTC trial, it showed an improved metastatic-free survival and overall survival as well. The authors argue that this difference was seen despite one-third of the patients in the observation arm receiving salvage therapy. The problem is that the salvage therapy delivered in the trial is vastly different from that considered appropriate by today's standards. First, most salvage radiation today is offered with early rising PSA post-surgery; however, only 56% of the men received salvage radiotherapy because of a rise in PSA alone. Second, the PSA trigger for salvage therapy with ultrasensitive PSA can be as low as .02 or .03 ng/dl; the median PSA before initiation of radiation in the SWOG trial observation arm was 1.0 ng/dl. Therefore, to draw conclusions about the effectiveness of adjuvant versus a modern salvage treatment is not possible in this study. There are currently two trials, RADICALS and RAVES, that are attempting to accrue to answer the question of salvage versus adjuvant therapy; however, results are not yet available.

It is important that the clinician and patient discuss the available evidence for adjuvant therapy, including its limitations, for patients with pT3N0 disease. Yes, there is level I evidence that adjuvant therapy improves outcomes in patients with high risk for recurrence versus observation, but there is no such evidence comparing adjuvant to modern salvage therapy. It has been our practice to discuss these difficult issues with patients so they can make an informed clinical decision. For those patients who elect surveillance, we offer continued close PSA monitoring with ultrasensitive PSA. The AUA consensus panel defined PSA recurrence as $\geq$0.2 ng/ml; however, it is important to note that this is not a guideline for when to deliver therapy. In our practice, we would intervene on two consecutive rises in PSA on ultrasensitive PSA.

Case study 115.3

A 53-year-old male was referred to your clinic for continued rising PSA over the past 6 years in the setting of five prior negative biopsies. His most recent PSA is 9.8 ng/dl.

1. What is the management for a patient with multiple prior negative biopsies and continued clinical concern for prostate cancer?

A. Repeat 12-core ultrasound-guided biopsy
B. Saturation biopsy
C. Multiparametric MRI and guided biopsy
D. Transurethral resection of the prostate

The management of men with continued clinical concern for prostate cancer (i.e., rising PSA, DRE changes, etc.) after a negative biopsy is controversial. Initial prostate biopsy is estimated to miss up to one-third of cancers, and therefore repeat biopsy in this setting is warranted. However, the consensus in the urologic literature ends there. The NCCN guidelines recommend a repeat extended biopsy in patients with one prior negative and continued clinical concern for prostate cancer, only recommending a saturation biopsy in the setting of multiple prior negatives. However, many studies, in the setting of one prior negative, have shown increased prostate cancer detection with saturation versus extended biopsy. These studies are difficult to compare owing to differences in the method of biopsy (e.g., transrectal, transperineal, and with or without template), number of biopsies (e.g., 20 cores or >50 cores), and prostatic location of additional biopsies (e.g., apical, anterior, or laterally directed). Importantly, both of these approaches have limited

(*Continued*)

utility after multiple prior negatives, as is the case for our patient. The NCCN and EUA guidelines on repeat prostate biopsy state that multiparametric MRI may be valuable in these patients. As can be seen by these updated guidelines, the advent of improved imaging within the field of prostate cancer has started to change this paradigm. Vourganti *et al*. (2012), from our center, recently published an article examining the utility of mpMRI in this subset of patients. We found an overall improved prostate cancer detection rate compared to extended 12-core TRUS biopsy, including men with high-risk prostate cancer, 55% of whom were missed on standard 12-core biopsy. In stark contrast to other published reports, our detection rate did not significantly decrease with increasing number of biopsies. Also we noted that the percentage of men with high-risk disease detected by mpMRI increased as the number of prior negative biopsies increased; both of these findings are obviously highly relevant in this specific patient. The utilization of mpMRI of the prostate is an incredibly valuable tool and offers clinicians and patients an alternative to saturation or standard TRUS biopsy.

The patient underwent a multiparametric MRI of the prostate with endorectal coil showing a lesion of concern that was biopsied as Gleason 3 + 4 in 4/18 cores.

2. What treatment options would be available for this patient?

A. Neoadjuvant hormones plus surgery
B. Active surveillance
C. Whole gland HIFU
D. Radical prostatectomy with obturator-only lymph node dissection
E. Radical prostatectomy with extended lymph node dissection

This patient has locally confined D'Amico intermediate-risk prostate cancer. Therefore, any of the standard treatment modalities for prostate cancer, radiation or surgery, would be an option for this patient.

Again, as discussed in this chapter, the PIVOT trial concluded that in men diagnosed with prostate cancer in the early PSA era, at 12 years of follow-up, prostatectomy did not improve all-cause or prostate cancer–specific mortality over observation. However, only 10% of the men in the PIVOT study were under the age of 60, and only about half of patients overall had no other comorbid conditions. To enroll in the study, patients supposedly had to have a life expectancy greater than 10 years, yet approximately 50% of patients were dead at 10 years of follow-up, signifying a much less healthy population than was intended for study inclusion. In other words, it appears that the majority of patients in this study were not candidates for surgery (i.e., they had a life expectancy less than 10 years) and should have been relegated to observation, yet in this study half of them were randomly assigned to surgical intervention. In contrast, our patient is 53 years old and has no other medical comorbidities or competing causes of death, and thus is more likely to benefit from treatment. Another limitation is in the overall enrollment of only 731 patients, making it an underpowered study to evaluate effectively many of the conclusions drawn. When reviewing the forest plots of subgroup analysis, it is readily apparent that the largest contributors favoring the lack of observed difference between surgery and observation are patients greater than 65 years old with <GG 7 disease. This relatively young, healthy patient has multiple cores of Gleason 7 disease with a rising PSA, making active surveillance a risky treatment option and one we would not favor.

HIFU has been used to treat prostate cancer since the early 1990s and has undergone a continued evolution. However, this is still a newer treatment modality with only limited short-term follow-up. There are currently no trials, to this author's knowledge, comparing it to standardized treatments for prostate cancer in a prospective fashion. The majority of patients that this treatment has been utilized for is also those who were considered unfit for surgery or in the salvage setting. With these limited data, it should not be considered in a young healthy patient who has no contraindication for surgery or radiation. Multiple trials have shown no benefit to neo-adjuvant hormone therapy prior to surgery for patients at high risk for recurrence.

Therefore, I would counsel this patient that both surgery and radiation are excellent treatment options. There are currently no published prospective trials comparing surgery versus radiation in men with clinically localized disease. Patients must carefully consider the risks and benefits to each treatment and decide accordingly. It is imperative that patients consider the specific outcomes of their treating provider (whether it be their radiation oncologist or surgeon) as opposed to published outcomes from tertiary-care centers.

This patient elected for surgical resection of the prostate and did very well from the procedure. He had an extended lymph node dissection as well as prostatectomy showing GG 3 + 4 disease with node-negative disease.

Case study answers

Case study 115.1

Question 1: Answer D
Question 2: Answer "Any of the above"

Case study 115.2

Question 1: Answer B
Question 2: Answer A and B
Question 3: Answer A
Question 4: Answer B
Question 5: Answer B
Question 7: Answer A or B

Case study 115.3

Question 1: Answer C
Question 2: Answer E

Selected reading

Bolla M, Van PH, Tombal B, *et al.* Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018.

Boorjian SA, Eastham JA, Graefen M, *et al.* A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. Eur Urol. 2012;61:664.

Godoy G, Chong KT, Cronin A, *et al.* Extent of pelvic lymph node dissection and the impact of standard template dissection on nomogram prediction of lymph node involvement. Eur Urol. 2011;60:195.

Wilt TJ, Brawer MK, Jones KM, *et al.* Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367:203.

Zaytoun OM, Moussa AS, Gao T, *et al.* Office based transrectal saturation biopsy improves prostate cancer detection compared to extended biopsy in the repeat biopsy population. J Urol. 2011;186:850.

CHAPTER 116

Surgical aspects of melanoma

Thomas Velancia
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction

Although melanoma represents only 10% of skin cancers, it accounts for at least 65% of skin cancer-related deaths. Because current systemic therapy fails to offer durable complete response, surgical intervention remains central to the treatment of melanoma. Optimizing surgical interventions rests upon accurate histologic assessment of the primary tumor and staging. To this end, the American Joint Committee on Cancer (AJCC) Melanoma Staging Committee, a multinational collaboration of melanoma researchers from North America, Australia, and Europe, has worked to pool staging and outcome data to provide staging and treatment recommendations. The most current AJCC *Cancer Staging Manual*, published in 2009, demonstrated that the strongest prognostic indicators of survival are tumor thickness (Breslow depth), mitotic rate, and the presence of ulceration in the primary tumor. Though improvements in disease-free survival have been achieved with various surgical and systemic interventions, significant improvement in survival has not been consistently achieved. As a result, there is continued open discourse regarding the utility of certain treatment practices in the contexts of disease-free survival and overall survival.

Histologic subtypes of melanoma

Although the pathogenesis is unclear, melanoma is commonly thought to arise from epidermal melanocytes that have undergone oncogenic transformation. One widely accepted model for growth describes an initial, intraepidermal growth phase followed by a more aggressive vertical growth phase. Cutaneous melanomas may present histologically as a number of different subtypes, with the most prevalent summarized by the AJCC as follows: superficial spreading, lentigo maligna, nodular, acral-lentiginous, desmoplastic, childhood, or unclassified types. Melanomas can arise in the background of preexisting nevi, as described in up to 25% of cases, although most commonly melanomas arise de novo.

Shared by all histologic subtypes of melanoma is the malignant melanocyte. These cells can present as round (epithelioid) or flat (spindled) cells with a prominent nucleus, occasional nuclear pseudo-inclusions, cytologic atypia, mitoses, and blue-gray cytoplasm on routine hematoxylin and eosin staining. Melanomas tend to display poor nesting, with single cells predominating over nested architecture as it invades into the surrounding tissue. The use of immunostaining has been critical in the separation of melanomas from their benign counterparts, the nevomelanocellular nevus, and the histologically atypical but benign possible precursor lesion, the dysplastic nevus. These immunostains have included S-100, MART-1 (Melan-A), and HMB-45. Additional immunostains, including tyrosinase and Ki67 (MIB-1), have also been crucial in the diagnosis of melanoma. These immunostains have also been included in the most recent AJCC as an acceptable tool in the detection of microscopic nodal disease. Unfortunately, however, there is no one stain that defines malignant melanocyte behavior. The diagnosis of melanomas, as a result, is an art best left to skilled dermatopathologists and pathologists experienced in the assessment of melanocytic lesions.

Superficial spreading melanoma, the most common subtype, appears classically on the thigh of a woman or on the back of a man. Lentigo maligna melanoma, the next most common subtype, tends to arise on chronically sun-damaged skin. It is worth mentioning that the nomenclature for melanomas confined to the epidermis, the in situ

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

melanomas, is confusing. These non-invasive tumors are superficial and, as a result, are not given a Breslow depth. At times, melanomas in situ arising in chronically sun-damaged skin, commonly in individuals of advanced age, are referred to as "lentigo malignas" without explicit mention of the words "melanoma in situ." This can lead to confusion, however, because there exists a lentigo maligna melanoma, an invasive tumor with an intraepidermal component of lentigo maligna overlying invasive disease. There also exists a subtype of melanoma, "superficial spreading melanoma in situ," which may also be termed simply "melanoma in situ." In ambiguous cases, the pathologist can provide critical information as to the nature of the tumor. Nodular melanomas are melanomas that tend to be identified during an expansive vertical-growth phase early in the life of the melanoma. In people of Asian and African descent, acral-lentiginous melanomas predominate, occurring on the hands and feet. Desmoplastic melanomas, although they represent only 1–4% of the overall melanomas, are notoriously difficult to diagnose clinically and histologically. Clinically, they can be amelanotic, presenting only as an innocuous, erythematous papule or patch. Histologically, this lesion is characterized by a population of spindled melanocytes within a fibrotic stroma resembling a scar and demonstrates an unusual staining profile with negative staining for the most sensitive melanoma markers (MART-1 and HMB-45).

There have been efforts to clarify a group of melanocytic tumors of unclear malignant potential (MELTUMP) that plague the dermatopathology world. These tumors encompass the precursor and borderline lesions that may have features of both benignity and malignancy. One of the classic atypical melanocytic lesions is the so-called benign juvenile melanoma, the Spitz nevus. These lesions have many histologic features of melanoma, although, in children, these nevi classically follow a benign course. Unfortunately, however, unusual lesions with Spitzoid features have been described that have behaved as melanomas. Atypical lesions have been recently referred to as atypical Spitz tumors, some of which represent true Spitzoid melanomas. These tumors are an example of the melanomas that belong to the "unclassified" subtype or, if clinically appropriate, the melanoma of childhood.

Melanoma staging

The AJCC staging rests upon the TNM classification system to define stage 0 through IV disease. The tumor thickness cutoffs for T1, T2, T3, and T4 disease are defined as in situ disease, with a Breslow depth less than or equal to 1 mm, between 1 and 2 mm, between 2 and 4 mm, and greater than 4 mm, respectively. The "a" and "b" designations are defined as the presence or absence of ulceration for any T or mitoses greater than 1 in T1 disease. The nodal status, "N," is defined as 0, 1, 2–3, and 4 or more nodes for N0 through N4 disease, respectively. Finally, metastases, M, are defined as M0, M1a, M1b, and M1c based on the absence of metastases; distant skin, subcutaneous, or nodal metastases; lung; or other visceral or distant metastases. The staging system is thus defined as stage I or II if there is absence of nodal involvement, stage III disease if there is nodal involvement in the absence of metastases, and stage IV disease if metastases are present.

Stage I and II nonulcerated melanoma carries a 10-year survival of 95%. With a single mitosis per square millimeter, however, survival decreases to 88%. The inclusion of the mitotic index in the current AJCC is a new addition, and it replaces the Clark level, a histologic description of invasion based on anatomic structures, as an important indicator of survival and lymph node status. Patients with stage III nodal disease demonstrate great variability in outcome based on the tumor burden. Micrometastases in one node carries approximately a 56% 5-year survival rate, while microscopic disease in greater than four nodes carries an approximately 34% survival rate. Stage IV disease, defined as disease-displaying distant metastasis, carries a 5-year survival rate of less than 10%. For this group, chemotherapy and emerging therapies may provide increased survival benefits.

Case study 116.1

A 52-year-old previously healthy woman presents with a superficial spreading melanoma, Breslow depth 0.6 mm, Clark level IV, no ulceration, and mitotic index of <1 per mm^2 on the left thigh as determined by an excisional biopsy. Clinically, regional lymph node basins have no evidence of disease.

1. Would a sentinel lymph node biopsy (SLNB) be helpful in staging this patient?

A. No: the primary tumor characteristics support this being a stage I tumor with a low risk of nodal involvement

B. Yes: Clark level IV, invasion into the reticular dermis, is a feature of aggressive tumor behavior

C. No: clinical assessment of the nodal status is sufficient for all stage I and II tumors

D. Yes: SLNBs are always helpful

Clark level is not a strong predictor for aggressive behavior, as was thought to be true in prior staging manuals. As a result, the patient can be classified as clinical T1N0M0 (stage IA) and thus has a low risk of nodal involvement.

Primary management

The management of melanoma, in general, includes complete removal of the primary tumor with or without additional therapy for regional or distant disease. The initial step in the management of melanoma is the histologic confirmation of disease. The ideal biopsy provides a complete sample of the tumor, whether through a saucerization or an excisional biopsy. A saucerization, also known as a tangential shave biopsy, is a deep biopsy to the level of the deep, reticular dermis, or superficial fat, with an intent to remove the entire lesion. This sampling technique differs from the superficial shave biopsy in that the superficial shave biopsy does not allow for proper evaluation of the underlying dermis, which is critical in the assessment of invasion. Complete biopsy specimens enable the pathologist to assess the subtype of disease, the Breslow depth of invasion, the mitotic index, presence of ulceration, and other prognostic indicators such as regression, lymphovascular invasion, and the presence of tumor-infiltrating lymphocytes. When complete biopsies are not possible, a sample of the most clinically concerning area of the lesion may be performed. This sample is inherently limited and suboptimal due to sampling error, however, and it is best to communicate to the pathologist that only a partial biopsy was performed. It is likely that a complete biopsy will be required at a later date before definitive treatment is undertaken for these types of biopsies.

Case study 116.2

A 16-year-old girl with a giant congenital nevus (34×27 cm) on the back was noted to have a proliferative nodule measuring 0.6 cm in the central aspect of the lesion.

1. What is the most appropriate clinical action?

A. Perform a punch biopsy of the nodule
B. Refer the patient for complete removal of the giant congenital nevus on the back
C. Perform a shave biopsy of the lesion
D. Monitor the lesion clinically

The nodule likely has a dermal component given the background of a giant congenital nevus. A biopsy that removes the entire lesion while allowing for the adequate assessment of the dermis for invasion is best. Given the presence of a giant congenital nevus, which is known to occasionally develop melanoma, clinical follow-up may not be prudent.

Surgical intervention

Proper resection margins are required to provide complete tumor extirpation while minimizing the risk of local recurrence. The National Comprehensive Cancer Network guidelines, based on past, extensive, multinational studies on melanoma surgical outcomes, recommend a margin of 0.5 cm for in situ melanomas, 1 cm margins for invasive melanomas 1 mm or less, 1 to 2 cm margins for melanomas between 1 and 2 mm, and 2 cm margins for melanomas greater than 2 mm in depth. In situ melanomas require excision to the depth of at least the mid- to deep fat to ensure that the adnexal structures lined with epidermis are completely excised, while invasive melanomas are excised to the level of the muscle fascia. There have been emerging data that Mohs-assisted excisions, excisions that utilize intraoperative frozen sections to provide assessment of 100% of a tumor margin, may be useful in the treatment of in situ melanoma. Although processing artifacts may obscure full melanocyte assessment, the employment of immunostains has been shown to increase the accuracy of the procedure.

Although stage I and II disease carry a 95% 10-year survival with wide local excision (WLE) alone, deeply invasive tumors greater than 4 mm in depth, ulcerated tumors, and tumors displaying lymphovascular invasion, perineural invasion, or satellitosis are at risk for local recurrence. For these tumors, as well as desmoplastic melanomas that are notoriously difficult to excise, some authorities offer adjuvant radiation therapy. Radiation can also be utilized after a tumor recurs at the primary site.

For stage I and II individuals with no clinical evidence of nodal involvement, SLNBs (discussed in this chapter) can provide critical staging information. Preliminary studies support the possible use of ultrasound for improved detection of metastases as compared to palpation alone, but this method has yet to be rigorously tested against current practices. If an SLNB is positive, the patient undergoes treatment for stage III nodal disease, which includes a complete lymph node dissection. The complete removal of the nodal basin is carried out to help decrease the tumor burden, assess the number of involved nodes, and assess for extracapsular extension. Basins at high risk for recurrence include greater than three to 10 positive nodes, a single node greater than 3 cm, extracapsular disease, or palpable disease. Recurrences of up to 50% have been reported in basins demonstrating extracapsular extension or the involvement of greater than two nodes. As with high-risk stage I and II melanomas, radiation therapy may be offered as an adjunctive therapy. Further therapy with systemic agents may also be pursued (see Chapter 100).

Stage III disease in the absence of nodal involvement occurs when in-transit metastases or satellitosis is present. Approximately 21% of primary recurrences will present as in-transit metastases. Metastasectomy may be performed if the in-transit lesions are few in numbers. The recurrence rate is high, however, and chemotherapeutic measures may offer greater relief. For some individuals with in-transit

disease localized to the extremities, hyperthermic isolated limb perfusion (HILP) and isolated limb infusion (INI) may offer a greater opportunity for cure. With HILP, femoral or subclavian vessels are cannulated, an Esmarch tourniquet is placed, and high-flow, heated, melphalan-based persulfate is introduced to the limb. Roughly 50% to 80% of patients achieve a complete response. This procedure uses a high dose of melphalan, has a longer treatment time, and is associated with a low but realistic risk of treatment-related limb loss. A new, less invasive procedure, isolated limb infusion (ILI), is an alternative that involves percutaneous catheterization of arteries and veins, placement of the Esmarch tourniquet, and melphalan. ILI can be repeated if necessary. Response rates of HILP and ILI have been reported to be 79% versus 64%, although there is no clear consensus of the treatment algorithm. Although melphalan is the most widespread chemotherapeutic agent used with HILP and ILI, other agents such as temozolamide, sorafenib, dasatinib, and bevacizumib are under investigation.

Stage IV melanoma carries a poor prognosis. Primary management is based upon a multifaceted approach, oftentimes combining surgery, radiation, and chemotherapy as no one modality significantly alters long-term survival. Metastasectomy may be considered in stage IV disease when a complete resection of all tumors is possible or for palliation. This practice is supported by a number of studies that demonstrated improved long-term survival in stage IV patients who underwent a metastasectomy as compared to those in the observation group (25% vs. 6%; $n = 4426$; $P < .001$).

Case study 116.3

A 62-year-old man presents with a desmoplastic melanoma with perineural invasion, Breslow depth 1 mm, with lymphovascular invasion on the right dorsal wrist.

1. When counseling the patient, what do you inform him?

A. His treatment will likely include an amputation of the hand at the wrist

B. His treatment will likely include a WLE with an SLNB and adjuvant radiation

C. His treatment will likely include radiation only to the site

The current standard of care is to excise the tumor to the level of the muscle fascia. The SLNB and radiation may be indicated given the aggressive melanoma subtype and the presence of lymphovascular invasion.

Sentinel lymph node biopsy

With significant survival differences between stage I and II disease as compared to stage III disease, much effort has been devoted to the proper assessment of lymph node status. The clinical assessment of microscopic nodal disease in clinical stage I and II tumors has been the basis of much study. It has been estimated that subclinical, nonpalpable, microscopic nodal disease may be present in up to 20% of patients at the time of WLE. Prior to the early 1990s, stage I and II melanoma patients with clinically uninvolved lymph nodes could be offered clinical observation versus an elective lymph node dissection (ELND). Although removing a potential site of tumor metastasis could potentially offer a decrease in clinical recurrence, multiple studies from the 1970s onward failed to establish an overall survival advantage in patients with ELND as compared to observation alone. In 1992, Morton *et al*. described a minimally invasive lymph node biopsy technique as an alternative to the ELND. Using the hypothesis that dermal drainage patterns mimic the potential route of melanoma metastasis to regional lymph nodes, vital blue dye is injected into the dermis of the primary tumor with or without lymphoscintigraphy and the first afferent lymph node, the sentinel lymph node (SLN), is identified and evaluated for potential metastasis.

Over the last 20 years, the SLNB has been proven to be a critical staging tool that has replaced the ELND in the assessment of microscopic disease. Identification rates up to 85% with vital dye alone and up to 99% with the use of high-resolution lymphoscintigraphy allow for the accurate detection of the SLN. In a study of 105 patients with at least one positive SLN, 86 were found to have regional node metastases with a false-positive rate of approximately 5% as observed in prior studies. Based on the AJCC *Staging Manual*, T1b tumors, thin primary tumors with a mitotic index of 1 mm^2 or greater, have a 10% incidence of occult nodal metastasis. Temporally, lymph node biopsies can be performed up to 40 days after the initial biopsy without adversely affecting the biopsy results, or one month after the excision of the primary melanoma without significant alteration of the lymphatic draining patterns.

Significant controversy surrounds whether SLN biopsies are an appropriate practice given the risk of complication and the failure to improve survival outcomes. Complications from lymphadenectomy include lymphedema at a rate of 60% when inguinal nodes are involved and 17% for axillary nodes, cellulitis, and scarring. The data on SLNBs have largely been based upon the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1). There was no significant treatment-related difference in the 10-year melanoma-specific survival rate in the overall study population. Mean (±SE) 10-year disease-free survival rates were significantly improved in the biopsy group, as compared with

the observation group, among patients with intermediate-thickness melanomas, defined as 1.20 to 3.50 mm (71.3 ± 1.8% vs. 64.7 ± 2.3%; hazard ratio [HR] for recurrence or metastasis, 0.76; $P = 0.01$), and those with thick melanomas, defined as >3.50 mm (50.7 ± 4.0% vs. 40.5 ± 4.7%; HR, 0.70; $P = 0.03$). Among patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1 ± 4.8% among those with metastasis versus 85.1 ± 1.5% for those without metastasis (hazard ratio for death from melanoma, 3.09; $P < 0.001$); among patients with thick melanomas, the respective rates were 48.0 ± 7.0% and 64.6 ± 4.9% (HR, 1.75; $P = 0.03$). Biopsy-based management improved the 10-year rate of distant disease-free survival (HR for distant metastasis, 0.62; $P = 0.02$) and the 10-year rate of melanoma-specific survival (HR for death from melanoma, 0.56; $P = 0.006$) for patients with intermediate-thickness melanomas and nodal metastases. Based on the significant survival difference between stage I–II disease and stage III disease, consideration of SLNB is currently recommended by the AJCC for stage I and II tumors displaying aggressive features.

Case study 116.4

A 75-year-old man presents with a lentigo maligna melanoma on the back, Breslow depth 1.2 mm, and mitotic index 2, without ulceration.

1. Which intervention provides the most significant survival benefit?

A. WLE only
B. WLE with SLNB
C. WLE with ELND
D. All of the above treatments result in similar rates of long-term survival

Given the lack of support for improved survival outcomes with either SLNB or lymphadenectomy, all treatments listed will result in the same overall survival.

Case study answers

Case study 116.1

Question 1: Answer A

Case study 116.2

Question 1: Answer A

Case study 116.3

Question 1: Answer B

Case study 116.4

Question 1: Answer D

Selected reading

Morton DL, Thompson JF, Cochran AJ *et al*. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014 Feb 13;370(7):599–609.

Dickson PV, Gershenwald JE. Staging and prognosis of cutaneous melanoma. Surg Oncol Clin N Am. 2011;20:1–17.

Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localized primary cutaneous melanoma. Lancet Oncol. 2005;6(8):608–21.

Manola J, Atkins M, Ibrahim J, *et al*. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. J Clin Oncol. 2000;18:3782.

Ott PA, Berman RS. Surgical approach to primary cutaneous melanoma. Surg Oncol Clin N Am. 2011 Jan;20(1):39–56.

PART 10

Multidisciplinary Approach: Consultation with Radiation Oncology Team

CHAPTER 117

Radiotherapy for head and neck cancers

Shiyu Song
Virginia Commonwealth University Health System, Richmond, VA, USA

Multiple choice questions

1. Induction chemotherapy is increasingly used in patients with advanced-stage head and neck cancers (HNCs). To which of the following patients would you LEAST likely recommend induction chemotherapy?

A. T4bN0Mx unresectable bulky oropharyngeal cancer
B. T1N3Mx oropharyngeal cancer
C. T2N2bMx oropharyngeal cancer with three positive lymph nodes in ipsilateral level II neck
D. T2N2b with supraclavicular nodal involvement

The use of induction chemotherapy is one of the most controversial topics in HNC management. Many clinical trials and meta-analyses failed to show significant benefit of adding induction chemotherapy to radiation. For a period of time, few oncologists would view induction as an option. This view has gradually changed since the publication of the TAX 324 and European Organization for Research and Treatment of Cancer (EORTC) 24971–TAX 323 trial results. These trials demonstrated excellent tumor response in patients treated with TPF (Taxol, cisplatin, and 5FU) induction chemotherapy as compared with PF (cisplatin and 5FU), the standard induction regimen at that time. Survival also improved. For patients with a bulky tumor and a high risk for distant metastasis, including large primary or nodal disease and lower neck involvement, induction chemotherapy seems a reasonable treatment option. For practical and technical reasons, in patients having difficulty tolerating radiation treatment due to pain, breathing difficulty, or the pooling of saliva requiring consistent spitting or suction, neo-adjuvant chemotherapy reduces tumor size and improves patient functional status before they start radiation therapy.

We need to realize that the current standard of care for locally advanced HNCs is still concurrent chemoradiation therapy. Two trials directly compared induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone: the DeCIDE (American Society of Clinical Oncology (ASCO) 2012 meeting, abstract 5500) and the PARADIGM (ASCO 2012, abstract 5501) studies. Preliminary results of the two trials were reported during the 2012 ASCO annual meeting in Chicago. Both studies showed no survival advantage with induction chemotherapy. In most cases with stage III and IV HNCs, concurrent chemoradiation should remain the choice.

2. Postoperative chemoradiation therapy is shown to improve survival in patients only with positive surgical margins and/or extranodal extension. Now you see a middle-aged patient with oral cavity cancer for postoperative consultation. He has good performance; pathology showed a poorly differentiated 5 cm tumor with mandibular invasion, clear but close margins, 0/24 nodes from bilateral supraomohyoid neck dissection, and perineural invasion. What do you recommend?

A. Radiation alone
B. Concurrent chemotherapy and radiation therapy
C. Further surgery for better surgical margin
D. Observation

Combined analysis of the Radiation Therapy Oncology Group (RTOG) 9501 and EORTC 22931 studies showed a clear survival benefit of concurrent chemoradiation therapy over radiation alone in patients with positive-margin or extranodal involvement. In a regular postoperative case without positive-margin and/or extranodal extension, postoperative radiation alone is the treatment of choice. In this particular case, however, it is oral cavity cancer with a cluster of risk factors; it is a high-risk case requiring

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

aggressive treatment. Furthermore, recurrent oral cavity cancer can be highly aggressive, and further surgery would cause significant morbidity when tumor recurs. Concurrent chemoradiation therapy is thus recommended for this patient. The treatment target of radiation should include primary sites and bilateral neck, although the neck dissection is negative.

Case study 117.1

A 40-year-old, nonsmoking, nondrinking patient presents with T2N2bM0 left tonsil cancer that is human papilloma virus (HPV) positive. His primary tumor is 3 cm with multiple lymph nodes in the range of 2–3 cm.

1. Given the excellent cure rate in HPV-positive patients, would you still recommend combined chemotherapy and radiation therapy?

A. Yes
B. No

The cure rate is excellent in patients with HPV-positive HNCs, with a 3-year overall survival of more than 90%. This survival rate is achieved with concurrent chemoradiation therapy. There are discussions about de-escalating treatment to reduce long-term complications. Possible options include reduction of radiation dose, elimination of chemotherapy, or switching to a less toxic chemotherapy regimen. Currently, there are two clinical trials waiting for results. One is the ECOG 1308 study that has completed its accrual. This is a phase II trial evaluating the efficacy of induction chemotherapy with paclitaxel, cisplatin, and cetuximab followed by a low-radiation dose of 54 Gy if CR is achieved versus a standard dose (70 Gy) of intensity-modulated radiation therapy (IMRT) plus concurrent cetuximab. The result of this study is expected to be available in 2015. The other is a phase III RTOG study (RTOG 1016), which is halfway through its enrollment. All patients receive the standard dose of 70 Gy with IMRT. The patients are randomized to receive either concurrent cisplatin or cetuximab. Cetuximab is considered a less toxic alternative to cisplatin, but the study is hardly a less intense treatment from a radiation point of view because all patients will receive 70 Gy. Until the results of these or other similar studies are available, chemoradiation therapy probably should remain as the standard of care for stage III–IV HPV-associated HNCs.

Case study 117.2

A middle-aged man presented with a 4 cm right neck mass of unknown primary. He underwent direct laryngoscopy and right neck dissection. Pathology showed poorly differentiated cell carcinoma in the right neck with extracapsular extension. Biopsy of nasopharynx, bilateral tonsils, and base of tongue showed no malignancy.

1. What treatment option would you recommend at this time?

A. Radiation to the right neck only
B. Radiation to bilateral neck and mucosal sites, including the nasopharynx and oropharynx
C. Radiation to neck and mucosal sites (as described in B) plus cisplatin chemotherapy
D. Radiation to neck and mucosal sites plus cetuximab
E. Surgery alone without postoperative treatment

There is no consensus on the management of neck metastatic squamous cell carcinoma of unknown primary sites. Practice varies among institutions after initial work-up and neck surgery. There are no clinical trials addressing this particular question. Patients treated with neck dissection alone can have a primary tumor emergence rate as high as 54%, and this is rarely recommended as the only treatment. Radiation only to the neck is an option; the emergence rate of the primary tumor is in the range of 5–44%. Therefore, radiation therapy to the bilateral neck and potential primary sites in the nasopharynx, oropharynx, and hypopharynx is recommended for most patients. While radiation is typically the treatment choice, adding chemotherapy might be reasonable in this case because of extracapsular extension (ECE). ECE is a high-risk feature for this group of patients and decreases tumor control and survival. The RTOG and EORTC postoperative studies (as discussed in this chapter) showed significant improvement of disease-free survival (both studies) and overall survival (EORTC) with concurrent chemotherapy in patients with this risk feature; the data should apply to this patient.

Case study 117.3

A 65-year-old man presented with left pre-auricular mass that is about 3 cm in diameter. The patient has a history of kidney transplant 10 years ago and is still on low-dose immunosuppression. He did have multiple skin lesions in the scalp that were treated with Mohs surgery. Fine-needle aspirate (FNA) of the nodule showed squamous cell carcinoma. He underwent left total parotidectomy that showed three parotid nodes positive for cancer; the largest is 3 cm. Neck scan showed no adenopathy.

1. What will be the most appropriate treatment after surgery?

A. Postoperative radiation to the left parotid area and left neck
B. No further treatment
C. Concurrent chemoradiation therapy

Skin cancers in immunosuppressed patients are more aggressive in nature and tend to metastasize to regional lymph nodes. The parotid nodes are the most commonly involved. While the skin cancers rarely cause fatality, the skin cancers with nodal metastasis could decrease patient survival. There is no consensus on postoperative treatment. The standard initial treatment is parotidectomy and its nodal dissection. Radiation therapy is commonly recommended. Radiation fields usually include the parotid region and ipsilateral neck, to a dose of 50–60 Gy. The use of chemotherapy is not common, and the benefit is not certain.

Case study 117.4

A 35-year-old male patient presents with a large mass in the nasopharynx with involvement of the left parapharyngeal space, extending to the left base of the skull. There was a left level II node about 5 cm in greatest diameter. Biopsy of the nasopharyngeal mass revealed poorly differentiated carcinoma, World Health Organization (WHO) type IIa. The patient will be treated with concurrent radiation and chemotherapy.

1. Would you recommend adjuvant chemotherapy in this case?

A. Yes
B. No

Since the results of the Intergroup 0099 study were published, the standard of care has been concurrent radiation and cisplatin followed by three cycles of chemotherapy with cisplatin and 5FU. However, the benefit of an adjuvant component of chemotherapy has been constantly questioned. Meta-analysis of HNC clinical trials as well as meta-analysis of nasopharyngeal cancer trials showed minimal benefit of adding adjuvant chemotherapy in patient survival. A large recent randomized clinical trial from China showed no survival benefit of adding adjuvant chemotherapy. Because the Chinese study was not designed to test the inferiority of the adjuvant chemotherapy regimen, concurrent radiation and chemotherapy without adjuvant chemotherapy have not been accepted as the standard of care, but adjuvant chemotherapy is rarely given to patients in China.

Case study 117.5

A middle-aged male with a history of tobacco and alcohol abuse is diagnosed with T3N2b right tonsillar cancer. His hemoglobin (Hb) is 9.5 mg/dl.

1. Because anemia is associated with poor treatment outcome and may exacerbate hypoxia in tumor and decrease radiation cell killing, which of the following would you do for this patient before starting radiation therapy?

A. Transfusion to correct anemia
B. Use of erythropoietin to increase his Hb level
C. Hyperbaric oxygen to correct hypoxia in tumor
D. None of the above

It has long been recognized that anemia in patients with HNCs is associated with poor tumor control and poor survival. Attempts to increase Hb level by transfusion or erythropoietin injection have been tried. Multiple clinical trials failed to show the benefit of blood transfusion. Some even reported worse treatment outcomes in the patients who received transfusion. Two major clinical trials examining the use of erythropoietin showed no effects or even detrimental effects on tumor control and survival. The biological mechanism of such a detrimental effect is not clear, but is possibly related to the existence of erythropoietin receptors in the HNC cells. Erythropoietin could act as an autocrine or paracrine factor to promote growth in these cells.

Case study 117.6

A 65-year-old male presents with a right retromolar trigone mass; a biopsy showed moderately differentiated carcinoma, and computed tomography (CT) of the chest demonstrated a 2.5 cm left upper lung nodule. CT-guided biopsy revealed squamous cell carcinoma, consistent with metastatic disease from primary HNC. Positron emission tomography (PET) showed hypermetabolic activity in both the right retromolar trigone mass and left lung nodule; no other metastatic lesion was noted.

1. How do you manage this patient?

A. Chemotherapy alone
B. Concurrent radiation therapy and chemotherapy for head neck tumor and stereotactic body radiation therapy to the left lung lesion, both aiming for tumor control
C. Palliative radiation therapy to both the head neck lesion and lung lesions
D. Low-dose palliative radiation plus chemotherapy

The standard of care in patients with metastatic HNCs is chemotherapy, but in patients with solitary metastasis or oligometastases, aggressive local treatment is warranted. Progression of disease in the head and neck region will cause severe pain and suffering. It may serve as the source for more metastasis. When a patient has good performance, aggressive treatments may help to extend life by controlling the advanced local disease. The metastatic lesions should also be treated with a curative dose as well. Some small clinical series have reported that long-term survival is achievable in patients after definitive treatment.

Case study 117.7

A patient with node-positive oropharyngeal cancer received concurrent chemoradiation therapy a month ago. He comes for follow-up. The oropharyngeal mass is no longer visualized or palpable, but a 2 cm residual neck node is palpable, and it is mobile. The initial adenopathy at this site was 4.5 cm.

1. What do you recommend at this time?

A. PET scan now
B. Plan for neck dissection
C. FNA to confirm the residual disease
D. PET scan in 2 months

Historically, patients with initial adenopathy >2.5 or 3 cm undergo planned neck dissection after radiation treatment. The necessity of the planned dissection is now debatable. When clinical exam and CT show no residual disease, the treatment outcomes are excellent without neck dissection. There were still studies that showed that postradiation neck dissection improved survival, especially when there are residual neck nodes.

In the last few years, PET scans have been increasingly used for restaging after treatment, with high sensitivity and specificity. The negative predictive value of PET scans is consistently >90%. If a PET scan is negative, postradiation neck dissection is not necessary. This is true even in those with residual nodes on physical exam or neck CT scans. The timing of PET scans is important. The radiation-induced mucositis may affect the interpretation of the PET images. There is an increase in false-positive PET if it is done early. Besides, the neck masses usually regress much slower than the primary tumors and may continue to decrease in size a month after radiation. We recommend PET to be done at least 3 months after radiation therapy.

Case study 117.8

A 70-year-old patient is diagnosed with locally advanced oropharyngeal cancer, but due to multiple comorbidities he is deemed not a candidate for cytotoxic chemotherapy.

1. If radiation is the primary treatment, which of the dose fractionation schedules listed below is least favorable for loco-regional control?

A. Standard dose and fractionation: 70 Gy in 35 fractions over 7 weeks
B. Accelerated radiation with concomitant boost with twice-daily treatments in the last 2 ½ weeks, with the entire treatment given over 6 weeks
C. Accelerated radiation with 1.2 Gy twice daily over 6 weeks
D. Accelerated radiation with six fractions per week instead of the standard five fractions per week
E. Standard radiation dose and fractionation to 70 Gy plus cetuximab

Although chemoradiation therapy is the standard treatment for locally advanced HNCs, many patients could not tolerate conventional chemotherapy due to other comorbidities. Alternative agents such as cetuximab can be the treatment choice. An RTOG phase III trial showed a significant survival advantage with concurrent radiation plus cetuximab over radiation alone. Median overall survival for patients treated with radiation and cetuximab was 49.0 months versus 29.3 months in the radiotherapy-alone group. 5-year overall survival was 45.6% versus 36.4%, favoring cetuximab.

If the patient is treated with radiation alone, alternative fractionations have been shown to provide better tumor control. A landmark study (RTOG 9003) demonstrated significant improvement of loco-regional control when patients were treated with accelerated radiation fractionations, including twice-daily treatment and concomitant boost techniques. Treatment acceleration by giving six treatments instead of five fractions per week also improves tumor control as well as disease-free survival.

Case study 117.9

A 67-year-old female patient presents with a history of right nasal obstruction, facial pain, and paresthesia. Initial MRI showed a large mass involving the right maxillary sinus, the right nasal cavity, and the floor of orbit. She is status post–right radical maxillectomy with orbital exenteration. Pathology showed adenoid cystic carcinoma with microscopic positive margins.

1. What do you recommend?

A. Radiation to the surgical bed
B. Radiation to surgical bed with radiation field extending to the base of the skull
C. Radiation as in B, plus neck nodes
D. Radiation as in B, plus chemotherapy

A group of HNCs requires special attention. These include major and minor salivary gland tumors and sinonasal cancers. Certain rare types of cancer present with special biological behaviors. For example, adenoid cystic carcinoma is a neurotropic disease and can spread by perineural invasion. Radiation treatment should treat the entire nerve tracks, especially when there are symptoms indicating nerve involvement. In this case, the patient has facial paresthesia that is indicative of cranial nerve V involvement. Lymph node involvement is not common, and prophylactic nodal radiation is usually not necessary. Due to the positive surgical margin, adding chemotherapy is reasonable, although data supporting its use are sparse in this particular entity. The choice of drugs is limited by the lack of data. Biologically, adenoid cystic carcinomas mimic neuroendocrine tumors. Cisplatin and etoposide might be effective. Currently, an RTOG clinical trial (RTOG 1008) is enrolling patients with high-grade salivary gland tumors. Patients on this study will be treated with either postoperative radiation alone or radiation plus 40 mg/m^2 weekly cisplatin (RTOG.ORG). If successfully completed, this study might help to define the role of chemotherapy in the management of these cancers.

Case study 117.10

A patient with T3N1 laryngeal cancer wishes to have larynx preservation therapy, but he is not a candidate for larynx preservation surgery.

1. In discussion with the patient about larynx preservation chemoradiation, all the following findings may affect his functional outcome and therefore may exclude the patient from larynx preservation therapy, EXCEPT which of the following?

A. Tracheostomy before treatment
B. Tumor-related dysphagia requiring feeding tube placement
C. Invasion of arytenoid cartilage
D. Recurring pneumonia due to aspiration, requiring hospitalization

For T2–T3 laryngeal cancer, partial laryngectomy for preservation is recommended as the first choice if feasible. If larynx preservation surgery is not possible, efforts should be made to preserve the larynx with radiation or radiation plus chemotherapy. The ultimate goals are to control the tumor and to preserve good laryngeal function. If the function of the larynx is severely compromised before treatment, the functional outcome is poor. Pretreatment work-up should include speech and swallow tests, and breathing and voice assessment. All the findings listed except for answer C predict unsatisfactory functional results. An international consensus panel recommended the exclusion of patients with these risk factors from future larynx preservation clinical trials.

Case study answers

Case study 117.1

Question 1: Answer A

Case study 117.2

Question 1: Answer C

Case study 117.3

Question 1: Answer A

Case study 117.4

Question 1: Answer A

Case study 117.5

Question 1: Answer D

Case study 117.6

Question 1: Answer B

Case study 117.7

Question 1: Answer D

Case study 117.8

Question 1: Answer A

Case study 117.9

Question 1: Answer D

Case study 117.10

Question 1: Answer C

Multiple choice answers

Question 1: Answer C
Question 2: Answer B

Selected reading

al-Sarraf M, Pajak TF, Cooper JS, *et al*. Chemo-radiotherapy in patients with locally advanced nasopharyngeal carcinoma: a radiation therapy oncology group study. J Clin Oncol. 1990;8(8):1342–51.

Ang KK, Harris J, Wheeler R, *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35.

Bernier J, Vermorken JB, Koch WM. Adjuvant therapy in patients with resected poor-risk head and neck cancer. J Clin Oncol. 2006;24(17):2629–35.

Forastiere AA. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845–52.

Haddad R, O'Neill A, Rabinowits G, *et al*. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013;14(3):257–64.

CHAPTER 118

Radiotherapy for ductal carcinoma in situ (DCIS)

Beryl McCormick
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Multiple choice questions

1. Why does the appropriate treatment recommendation for a woman diagnosed with duct carcinoma in situ (DCIS) remain controversial?

A. Unlike invasive breast cancer treatment options, there is a lack of well-designed clinical trials and evidence to guide the physician in the treatment of DCIS
B. DCIS, much like lobular carcinoma in situ (LCIS), is more of a marker of breast cancer risk than a "cancer disease entity"
C. Local treatment options for DCIS result in different local recurrence risks in the index breast, but have no impact on survival of the DCIS patient, which remains extremely high

For almost all clinical trials that evaluate treatment options for cancer, "survival" and "cancer-free survival" are endpoints that matter the most to both the patients and the trial investigators. Because only the risk of developing a local failure is modified with a given DCIS treatment, the decision to treat or not to treat is perceived differently by women and their doctors, resulting in much more controversy than the management of invasive early breast cancer. A study from the University of Michigan demonstrates this issue.

2. Which of the following statements are true about DCIS in women in the United States?

A. In mammography screening programs, DCIS accounts for about 25% of all newly diagnosed breast cancers
B. The most common presentation of DCIS on mammography is microcalcifications
C. If taken as a separate entity, DCIS is the fourth leading cancer, after invasive breast, lung, and colon cancer
D. All of the above

Because of the number of women in the United States who undergo screening mammography on a regular basis, DCIS is diagnosed far more commonly than in countries without a screening program in place.

3. If a woman is found to have suspicious calcifications on mammogram, according to the American College of Radiology guidelines, what is the preferred technique for obtaining a tissue diagnosis?

A. Fine-needle aspiration
B. Stereotactic core biopsy
C. Surgical biopsy using wire localization

Multiple professional organizations, including pathologists and surgeons, endorse stereotactic core biopsy as the preferred method of obtaining tissue from a mammographic abnormality; the core specimen provides good architectural information and avoids surgery until the diagnosis is established.

4. True or false? With the exception of the definition of a clear surgical margin as "no tumor on ink," surgical margin definitions are difficult to consistently produce agreement about, in part because the processing of the specimen actually only samples a small proportion of the total volume of tissue submitted.

A. True
B. False

The NSABP Cooperative Group has consistently used the definition of "no tumor on ink" as their definition

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

of a clear margin. When looking at pathology slides, this definition is workable and clear. But there are little consistent data supporting other "ideal" margin widths for DCIS. In part, this is because the processing of the tissue in the pathology lab, meticulous as it is, actually samples only a small proportion of each submitted block. Thus, hypothetically, a "2 mm margin" in a given slide could be measured as "1 mm" or "3 mm," for example, in different cuts from the same block.

Case study 118.1

A 41-year-old woman has a core biopsy of new microcalcifications on her mammogram, yielding high-nuclear-grade DCIS.

1. She is referred to her local breast surgeon, who offers her which of the following treatment options?

A. Wide excision or lumpectomy followed by external-beam radiation
B. Simple mastectomy
C. Simple mastectomy with sentinel lymph node evaluation
D. A and B only

DCIS is an in situ lesion that does not have the biological capability to invade the draining lymph nodes. Thus, evaluation of the sentinel lymph nodes for DCIS is not appropriate. In special cases where the patient opts for mastectomy, and invasion is suspected based on pathologic characteristics of the core biopsy specimen, a sentinel node biopsy may be considered, because the ability to "map" the sentinel nodes is usually lost after a mastectomy is performed.

This patient decides to have a simple mastectomy as her surgical treatment for her DCIS. The final pathology report shows a 1.4 cm intermediate-high-grade DCIS; the lesion is unifocal, but DCIS is seen less than 1 mm from the posterior margin.

2. Is a referral to a radiation oncologist for consideration of postmastectomy radiation appropriate for this patient?

A. Yes
B. No

An experienced breast surgeon will remove the deep pectoral fascia at the time of mastectomy, which forms a natural boundary at the posterior aspect of the breast. Retrospective studies looking at patients who have close margins posteriorly have not found the risk of local recurrence to be high enough to justify giving postmastectomy radiation in this clinical situation.

5. Three large, prospective randomized trials comparing radiation to no radiation, after breast-conserving surgery, have been reported with long-term outcomes. They include the NSABP B-17 Study, the European EORTC 10853 Study, and the SweDCIS Study from Sweden. Which of the following statements is true about these trials?

A. The radiation dose for the women randomized to treatment was 50 Gy to the whole breast with a boost dose of 12 Gy
B. The local recurrence rate in the ipsilateral breast was reduced by at least 50% with the addition of radiation
C. The breast cancer–specific survival was improved by 8% for the women assigned to receive radiation

None of these trials specified that a "boost" or additional radiation to the lumpectomy cavity should be used. And there was no impact on survival, although long-term follow-up of the B-17 Trial combined with the B-24 Trial from the NSABP Cooperative Group did demonstrate an increased mortality risk for that subset of women who developed an invasive recurrence after primary treatment for DCIS. The primary benefit from the radiation in all three trials was a marked reduction in the risk of ipsilateral local recurrence.

6. True or false? For those women with DCIS who do develop a local recurrence in the treated breast, the proportion demonstrating invasive breast cancer, of the total with local recurrence, is about 50% in most studies.

A. True
B. False

This pattern of about 50% invasive and 50% DCIS recurrences is consistent through almost every published study on DCIS. Several groups are working on a way to identify which DCIS patients are destined to get an invasive recurrence.

7. True or false? DCIS is a heterogeneous process, much like invasive ductal cancer. Studies of gene expression profiles for DCIS lesions demonstrate similar patterns of Luminal A and B, Her-2 positive and basal-like profiles as are expressed in invasive ductal carcinoma.

A. True
B. False

Several centers have demonstrated this molecular heterogeneity of DCIS lesions, which suggests early differentiation in DCIS lesions, which then likely progress to invasive cancers with a similar gene expression profile.

Case study 118.2

A 61-year-old woman presented with new calcifications on a recent screening mammogram. On biopsy, she was found to have a low-grade DCIS lesion, with minimal necrosis. She opts for breast conservation surgery, and the final surgical pathology report reveals atypical ductal hyperplasia and biopsy site changes from the core biopsy, which appears to have removed the entire DCIS lesion. The DCIS tested ER receptor (+).

1. Although not the "standard of care," offering this patient observation only, or observation plus anti-estrogen therapy, is a reasonable alternative to prescribing radiation.

A. Yes
B. No

Multiple prospective and retrospective studies of DCIS treatment identify patients to be at lowest risk of local recurrence, based on older age, small size, generous margins, and low-grade disease. So although this patient would benefit from a course of radiation, which would decrease her local recurrence risk by about 50%, her baseline risk is quite small to start with. Use of an anti-estrogen further reduces the risk of local recurrence, although the prospective trial investigating the use of tamoxifen for DCIS in the United States (NSABP B24) combined radiation and tamoxifen.

8. As longer follow-up data become available for women treated with breast conservation surgery for DCIS, which of the following is true about nuclear grade and recurrence?

A. High-grade lesions are associated with local recurrence, which usually appears within 5 years of diagnosis
B. Low-grade lesions are associated with a low local recurrence rate within 5 years of diagnosis
C. After about 7 years of follow-up, the recurrence rate of the high-grade lesions levels off, while the low-grade lesions continue to recur out to and past 10 years, almost "catching up" with the high-grade lesions in one long-term study
D. All of the above

Both the Solin Collaborative DCIS study, where all patients were treated with radiation, and the more recent ECOG study, where no radiation was given but tamoxifen was "allowed," showed this pattern of recurrence over time, within the different grades of DCIS studied.

9. The role of tamoxifen alone in DCIS management is addressed in the UK/ANZ DCIS trial, which has a modified 2 × 2 factorial design comparing various combinations of whole-breast radiation and tamoxifen. This study of 1700 women, now followed a median of 12.7 years, showed which of the following findings?

A. Radiation had no impact on contralateral breast events
B. Radiation reduced the risk of both ipsilateral DCIS and invasive cancer recurrences; hazard ratios were 0.38 and 0.32 for the use of radiation
C. Tamoxifen reduced the risk of contralateral breast cancer (HR: 0.44) and ipsilateral DCIS (HR: 0.70), but had no effect on ipsilateral invasive disease
D. All of the above

Although the first report from this trial with 4.4 years of follow-up showed tamoxifen was only "weakly associated with a reduction in all new breast cancers," the longer follow-up time shows more of an impact of tamoxifen therapy (20 mg daily for 5 years). However, in those women randomized to tamoxifen who also received radiation, "there was no apparent benefit."

Case study 118.3

A 35-year-old patient opts for breast conservation surgery and whole-breast radiation, after receiving a diagnosis of ER^+ DCIS following her first screening mammogram.

1. After completing the radiation, her doctor advises her to do which of the following?

A. Take tamoxifen for 5 years because it has been shown to further reduce the risk of ipsilateral breast recurrence following whole-breast radiation
B. Maintain her yearly screening with a mammogram, but no further treatment
C. Tamoxifen for 5 years because she is at increased risk to develop a contralateral breast cancer, and tamoxifen will reduce that risk
D. Either B or C, depending on patient preference

A recent analysis of the patients treated on the NSABP B24 DCIS Trial, comparing tamoxifen to placebo after whole-breast radiation, concluded that only patients whose DCIS tested positive for the estrogen receptor had a benefit from tamoxifen, in terms of treating the diagnosed DCIS. So for this patient, either no further treatment or an option to take tamoxifen because of her young age and increased risk for future new breast cancer development, as a prevention agent, would be appropriate.

Case study answers

Case study 118.1

Question 1: Answer D
Question 2: Answer B

Case study 118.2

Question 1: Answer A

Case study 118.3

Question 1: Answer D

Multiple choice answers

Question 1: Answer C
Question 2: Answer D
Question 3: Answer B
Question 4: Answer A
Question 5: Answer B
Question 6: Answer A
Question 7: Answer A
Question 8: Answer D
Question 9: Answer D

Selected reading

Allred DC, Anderson SJ, Paik S, *et al*. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol. 2012;30:1268–73.

Bijker N, Meijnen P, Peterse JL, *et al*. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24:3381–7.

Chan LW, Rabban J, Hwang ES, *et al*. Is radiation indicated in patients with ductal carcinoma in situ and close or positive mastectomy margins? Int J Radiat Oncol Biol Phys. 2011;80:25–30.

Cuzick J, Sestak I, Pinder SE, *et al*. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21–9.

National Comprehensive Cancer Network (NCCN). NCCN guidelines for treatment of breast cancer. https://subscriptions.nccn.org/gl_login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed February 25, 2014).

CHAPTER 119

Radiotherapy for early-stage invasive breast cancer

Julia White

The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH, USA

1. What is the appropriate method for postlumpectomy breast radiotherapy?

Case study 119.1

A 63-year-old postmenopausal female has an abnormal screening mammogram of a new 8 mm spiculated mass and is found to have a grade 2 infiltrating ductal carcinoma on ultrasound core biopsy. Her entire clinical exam is normal without any palpable abnormality in the breast or axilla. She desires breast conservation and undergoes a lumpectomy and sentinel node biopsy. On pathology review, a 12 mm grade 2 infiltrating ductal carcinoma is found with negative surgical resection margins. The estrogen receptor is positive (90%), the progesterone receptor is positive (90%), and the HER2 is 2+ on immunohistochemistry (IHC) and negative by fluorescent in situ hybridization (FISH). An Oncotype DS™ is done for systemic therapy decision making and returns with a score of 8. She is recommended to take 5 years of anastrazole for systemic therapy.

It is well acknowledged that breast conservation with lumpectomy and radiotherapy yields local control and overall survival that is equivalent to mastectomy in appropriately selected women. For over two decades, there was a nearly uniform approach to breast radiotherapy delivered post lumpectomy for breast conservation. Typical radiotherapy delivered approximately 50 Gy in 25–28 treatments (fractions) of 1.8–2.0 Gy each to the entire breast and in many cases was followed by additional or "boost" irradiation of 10–16 Gy in 5–8 fractions of 2 Gy each concentrated on the breast tissue immediately adjacent to the surgical cavity, for a cumulative total of 60–66 Gy. This meant nearly every patient received a total of 30–34 treatments over 6–7 weeks. This approach to breast radiotherapy has a long track record of success, yielding excellent in-breast cancer control, low overall toxicity rates, and high rates of acceptable cosmetic appearance of the breast. This conventional method of breast radiotherapy is still commonly recommended and in fact is an appropriate approach for this patient. However, more recent developments in our understanding of breast cancer failure patterns, radiobiology, radiotherapy delivery principles, and technology have allowed the development of alternative methods of postlumpectomy breast radiotherapy for which this patient is also a good candidate.

Hypofractionated whole-breast irradiation (HWBI) shortens the treatment course by the delivery of larger daily radiation doses of 2.67 Gy to a total of 40 or 42.67 Gy with 15 or 16 treatments over approximately 3 weeks' duration. The radiation effect in tumor and normal tissues has both a linear (α) and quadratic (β) component in response, and the ratio of these two components is unique to specific normal tissue and tumors. Initial models examining the ratio of α and β influences on radiation response for breast cancer supported standard radiation fractionation of 1.8 to 2.0 Gy per day. Newer research and clinical trials have now established a model of α–β that supports altered fractionation to the entire breast of up to 3–4 Gy daily to yield comparable outcomes. Four randomized clinical trials have demonstrated that the in-breast local control and overall survival with HWBI are not inferior to those of conventional whole-breast irradiation (WBI) (Table 119.1). In 2010, the American Society of Radiation Oncologists (ASTRO) generated an evidenced-based clinical guideline supporting the use of HWBI as appropriate for postlumpectomy treatment in patients older than 50 years of age with

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 119.1 Phase III randomized controlled trials of hypofractionated versus conventional fractionated whole-breast irradiation after lumpectomy.

Phase III clinical trial	*n*	Follow-up (years)	Method	Total dose (Gy)	Fraction dose (Gy)	Number of fractions	In-breast recurrence (%)
GMH Pilot (2006)	1410	9.1	Hypofractionated	42.9	3.3	13	9.6
			Hypofractionated	39	3	13	14.8
			Conventional fraction	50	2	25	12.1
START A (2008)	2215	5.1	Hypofractionated	41.6	3.2	13	3.5
			Hypofractionated	39	3	13	5.2
			Conventional fraction	50	2	25	3.6
START B (2008)	2215	6	Hypofractionated	40	2.67	15	2.2
			Conventional fraction	50	2	25	3.3
OCOG	1234	10	Hypofractionated	42.56	2.67	16	6.25
			Conventional fraction	50	2	25	6.7

OCOG, Ontario Clinical Oncology Group.

pathologic stage T1–T2, N0 breast cancer who would not be treated with chemotherapy and for whom a homogeneous dose for the radiotherapy treatment plan could be achieved. The patient in this clinical scenario has numerous good clinical-pathologic risk features associated with her breast cancer—small tumor size, intermediate histology grade, hormone receptor responsive, low Oncotype score, age >60 years, and negative surgical margins—and she is committed to 5 years of an aromatase inhibitor for systemic therapy. Postlumpectomy treatment with 42.56 Gy in 16 fractions of HWBI, analogous to that of the Ontario Clinical Oncology Group (OCOG), is a reasonable and appropriate treatment option for this patient. In the OCOG study, none of the patients received a tumor bed boost, but the 10-year rate of in-breast recurrence was only 6.2% in the HWBI arm, suggesting that the potential benefit of a tumor-bed boost is small in this case. None of the randomized trials of HWBI studied the optimal boost delivery method, so no strong evidence exists for specific dose fractionation schemes in this setting. However, guidelines recommend that a sequentially delivered boost should be used if indicated and a dose of 10–16 Gy in 2 Gy fractions is reasonable.

Accelerated partial breast irradiation (APBI) focuses a short hypofractionated course (typically, 5–10 treatments over 5–8 days) of postlumpectomy radiotherapy solely to the vicinity of the lumpectomy cavity. Analysis of in-breast recurrences following lumpectomy alone or with subsequent breast radiotherapy reveals that it more frequently occurs geographically within the vicinity of the original surgical cavity and much less frequently in other breast quadrants. This effectively defines a more focused target such that radiation aimed at this highest-risk region may account for the preponderance of radiation benefit in securing in-breast cancer control post lumpectomy. The findings from the European Organization for Research and Treatment of Cancer (EORTC) boost trial emphasize the importance of adequate radiation dose to the vicinity of the surgical cavity. A 40% relative reduction of in-breast recurrence was found when an additional boost dose to the lumpectomy cavity region to a cumulative amount of 66 Gy is given versus when just the whole-breast dose of 50 Gy is delivered. There are multiple methods for delivery APBI, including external-beam radiotherapy with 3DCRT or intensity-modulated radiation therapy, as well as brachytherapy with single-entry devices (e.g., MammoSite®, Contura®, or Savi®) or multicatheter implants. Numerous prospective phase II studies and retrospective case review data have demonstrated acceptable in-breast recurrence rates using APBI in select patients. However, evidence from randomized controlled trials comparing APBI to WBI (conventionally or hypofractionated) is not yet available. Three large multi-institutional randomized controlled trials have completed accrual, and two are still open for accrual. Until this level I evidence becomes available from clinical trial outcomes, numerous groups have issued statements and recommendations regarding which breast cancer patients can be safely treated post lumpectomy with APBI based on the existing data (Table 119.2). There is consistent agreement that breast cancer patients with positive nodes and tumor sizes >3 cm should not be treated with APBI. There is less agreement on whether younger women, triple-negative receptor status, and/or DCIS should be treated post lumpectomy with APBI prior to the outcome data from randomized clinical trials becoming available. McHaffie *et al*. (2011) studied 322 women who had received APBI with a multicatheter implant and who had been followed for a median of 60 months, and analyzed loco-regional recurrence rates (LRRs) by ASTRO consensus guideline

Table 119.2 ASTRO suitable, GEC ESTRO low risk, ABS and ASBS recommended criteria for treatment with APBI.

Statement	Age	T-size	pN-stage	ER/PR	Histology	Margins	DCIS
ASTRO	>60	≤3 cm	N-0	Pos.	No ILC/EIC	Neg.	No
GEC-ESTRO	>50	≤3 cm	N-0	—	No ILC/EIC	Neg.	No
ABS	>50	≤3 cm	N-0	—	No ILC/EIC	Neg.	Yes
ASBS	>45	≤3 cm	N-0	—	—	Neg.	Yes

ABS, American Brachytherapy Society; ASBS, American Society of Breast Surgeons; ASTRO, American Society of Radiation Oncology; GEC-ESTRO, Groupe European de Curiethérapie—European Society for Therapeutic Radiology and Oncology.

Table 119.3 Randomized controlled trials evaluating radiotherapy benefit of "low-risk" invasive breast cancer post lumpectomy.

Clinical trial	*n*	Follow-up yrs	Age >50 years (%)	ER/PR+ (%)	Tam or AI (%)	Grade 1–2 (%)	In-breast recurrence (%)	
							RT	No RT
NSABP B21	1009	8	80	56.5	67	67	9.3[1] 2.8[2]	16.5
PMH	769	5.6	100	80.5	100	68.3	0.6	7.7
ABCSGStudy 8a	869	4.48	99	100	100	95	0.4	5.1
CALGB 9343	626	10.5	100[3]	97	100	—	2	8
GBSG-V	347	9.9	91.4	88	50	97.2	6	20
BASO II	1172	4.5	—	—	25	100[5]	1.3	3.6
PRIME	255	5	100[4]	—	—	94.5	0	6

ABCSG, Austrian Breast and Colorectal Cancer Study Group; AI, aromatase inhibitor; BASO, British Association of Surgical Oncology; CALGB, Cancer and Leukemia Group B; ER, estrogen receptor; GBSG, German Breast Cancer Study Group; NSABP, National Surgical Breast and Bowel Program; PMH, Princess Margaret Hospital; PR, progesterone receptor; PRIME, Postoperative Radiotherapy in a Minimum Risk Population; RT, radiation therapy; Tam, tamoxifen.

[1]RT + placebo.

[2]RT + tamoxifen.

[3]All were >70 years of age.

[4]All were age >65 years of age.

[5]All were grade 1.

groups. The 5-year LRR was as follows: suitable, 1.6% (95% CI: 0.0–4.8%); cautionary, 4.8% (95% CI: 0.7–8.9%); and unsuitable, 8.7% (95% CI: 3–14.4%). Among 104 patients with stage I or II invasive carcinoma, the actuarial LRR rate for patients considered cautionary by virtue of being age 50–59 alone is 0%, versus 12.7% in those deemed cautionary due to clinical or pathologic factors ($P = 0.018$). A suggestion of worse outcomes with adverse pathologic features is further supported by a recent update from the American Society of Breast Surgeons MammoSite® registry of single-entry balloon-based brachytherapy APBI for 1255 breast cancer cases. With a median follow-up of 60 months, ER-negative status was the only factor associated with in-breast recurrence for all patients with invasive carcinoma as well as for failures that occurred outside the treated APBI index region or "elsewhere" in the breast ($P < 0.001$). For patients with invasive malignancies, trends for increased rates of "elsewhere" recurrences in the treated breast were noted for increased tumor size ($P = 0.067$) and an extensive intraductal component ($P = 0.087$). Similarly, Pashtan *et al*. (2012) reported that of 98 women treated on a prospective trial of 3DCRT APBI at Massachusetts General Hospital with a 71-month median follow-up, 3 of 10 patients with triple-negative breast cancers experienced an in-breast recurrence, for a 5-year actuarial ipsilateral breast tumor recurrence rate of 33% (95% CI: 0–57%) compared to two of 88 patients without the triple-negative feature for a 5-year actuarial in breast recurrence rate of 2% (95% CI: 0–6%; $P < .0001$). Therefore, while the outcomes of randomized controlled trials are awaited, a conservative use of APBI in ASTRO consensus "suitable" patients is recommended with perhaps some accommodation of those aged

50–59 years, provided all other criteria are met. Therefore, this patient would also be a reasonable candidate for APBI as her sole radiotherapy modality post lumpectomy.

A survey in 2008–2009 of 1806 women from a mammography database from three hospitals (Wright-Patterson Medical Center, Wright-Patterson Air Force Base, Ohio; Clarian Health/Indiana University, Indianapolis, Indiana; and Wilford Hall Medical Center, Lackland Air Force Base, Texas) and 363 radiation oncologists from the ASTRO database evaluated patient and physician preferences regarding breast radiotherapy post lumpectomy. The patients' order of preferences for radiotherapy was hypofractionated WBI (61.7%), followed by APBI (28.1%) and conventional fractionated WBI (10.1%). In contrast, the physician order of preferences was conventional WBI (81%), single entry brachytherapy APBI (55.5%), hypofractionated WBI (43.8%), 3DCRT APBI (35.9%), and multicatheter brachytherapy APBI (10.9%). With multiple choices of radiotherapy post lumpectomy, it is important for physicians to engage patients in selecting treatment approaches that maximize local control of the cancer and meet the patient's individual needs.

2. Can postlumpectomy breast radiotherapy be omitted for some breast cancer patients?

Case study 119.2

A healthy 71-year-old woman is found to have a breast cancer detected by screening mammogram. She undergoes lumpectomy and sentinel node biopsy for a 9 mm grade 2 infiltrating ductal cancer; her estrogen receptor is positive (90%), her progesterone receptor is positive (90%), and the HER2 is 2+ on IHC and negative by FISH. She is active, performs all of her own activities of daily living, is on only a hypertensive medication daily, and has a Karnofsky Performance factor of 100 or ECOG 0. She is planning to take 5 years of anti-endocrine therapy and has already been given a prescription of Ariamidex. She is a compliant patient who has undergone annual mammogram screening since the age of 50.

Breast radiotherapy after lumpectomy is considered standard for nearly all invasive breast cancer. However, there is recognition that for some cases of invasive breast cancer, near-optimal cancer control in the breast is achieved with lumpectomy alone. Breast cancers with lower risks of recurrence are less likely to derive benefit from breast radiotherapy, and in these cases the question of whether the radiotherapy can be omitted arises. For invasive breast cancer, the goals of breast radiotherapy after lumpectomy are to maximize in-breast cancer control so it is equivalent to that achieved by mastectomy; minimize risk of breast cancer mortality; preserve a sensate, cosmetically appealing breast; and avoid mastectomy. The benefit of breast radiotherapy after lumpectomy has been studied in numerous clinical trials that have randomized women post lumpectomy to breast radiotherapy versus observation, and a consistent, highly significant relative reduction in cancer recurrence (typically, 70–75%) in the treated breast with the addition of breast radiotherapy is achieved. In 2005, the Early Breast Cancer Trialists Group (EBCTCG) reported on a meta-analysis of 7311 patient-level data from 10 randomized clinical trials that examined the relationship of loco-regional recurrence at 5 years and breast cancer mortality at 15 years. The 5-year local recurrence was 7% among those randomized to radiotherapy post lumpectomy and 26% among those observed, corresponding to an absolute reduction of 19%. The 15-year risk of death from breast cancer was 30.5% among those allocated postlumpectomy radiotherapy and 35.9% among those observed (corresponding to a modest but significant absolute breast cancer mortality reduction of 5.4%; SE: 1.7). Of particular interest, analyses that divided absolute local recurrence risk reduction after lumpectomy or mastectomy into three categories of $<10\%$, 10–20%, or $>20\%$ demonstrated that for those with less than 10% absolute reduction in local recurrence by 5 years from radiotherapy, no improvement in breast cancer mortality by 15 years is seen. A more recent meta-analysis from the EBCTCG of 10,801 women in 17 trials further explored the impact of postlumpectomy breast radiotherapy on 10-year overall breast cancer recurrence rate (loco-regional or distant) and 15-year breast cancer mortality effects. The 10-year risk of any (loco-regional or distant) first recurrence was 19.3% in women allocated to radiotherapy and 35.0% in women allocated to breast-conserving surgery only, corresponding to an absolute risk reduction of 15.7% (95% CI: 13.7–17.7; $2P < 0.00001$). Radiotherapy also reduced breast cancer death at 15 years by a moderate amount: 25.2% without and 21.4% with radiotherapy, respectively, for a 15-year absolute risk reduction of 3.8% (95% CI: 1.6–6.0; $2P = 0{\cdot}00005$). A similar analysis demonstrated that in a low-risk group, defined as having a $<10\%$ absolute reduction in loco-regional or distant breast cancer recurrence risk by 10 years, the risk with and without radiotherapy was 18.9% versus 12% for a 6.9% absolute reduction of in-breast cancer recurrence. The corresponding absolute reductions in a 15-year risk of breast cancer death in the low-risk group were 0.1% (from -7.5 to 7.7). These analyses suggest that breast cancer patients with an anticipated $\leq 10\%$ absolute reduction in risk of locoregional recurrence by 5 years and overall recurrence (loco-regional and distant) by 10 years can omit breast radiotherapy without risking excess breast cancer mortality.

Table 119.3 lists several randomized controlled trials designed to evaluate the benefit of breast radiotherapy in patients considered to be at low risk of recurrence post

lumpectomy. The breast cancer populations in these trials were all node negative and typically >50 years in age, and they had received anti-endocrine therapy for cancers that were <2 cm in size, ER and PR positive, and grade 1–2. The rate of loco-regional recurrence without radiotherapy can be as high as 20% in this relatively low-risk group selected by standard clinical pathologic features. Patients in the group can have variable risks of in-breast recurrence post lumpectomy, which underlines the need for better tests to predict an individual's risk so that optimal treatment decisions can be made. However, for elderly women there are two trials that support omission of radiotherapy post lumpectomy when 5 years of anti-endocrine therapy is planned.

CALGB 9343 randomized, post lumpectomy, 626 women >70 years old with hormone receptor–positive breast cancer who intended to take 5 years of tamoxifen, to breast radiation versus observation. The most recent reporting of this trial at 12.6 years of follow-up demonstrated an absolute reduction in local regional recurrence of 8% from radiotherapy post lumpectomy; local regional recurrence of 10% without versus 2% with radiotherapy. Notably, 43% of women participating in this study had died, but only 7% due to breast cancer, indicating that in this older population comorbidity was more frequently the primary health risk rather than the breast cancer. There was statistically similar freedom from mastectomy after lumpectomy alone: 96% versus 98% with the addition of breast radiotherapy. A SEER–Medicare database that identified 8724 women >70 years of age who were treated with lumpectomy for small, lymph node–negative, hormone receptor–positive breast cancer demonstrated good agreement with CALGB 9343 results. In this study, by 8 years of follow-up, women who received breast radiotherapy post lumpectomy had a 5.7% absolute benefit; 8% had an ipsilateral breast cancer event without versus 2.3% with treatment. Healthy women ages 70–79 years were more likely to experience the benefit associated with radiation therapy. However, a separate study of the SEER–Medicare observational cohort showed that omission of radiotherapy resulted in higher rates of mastectomy in 7074 women age 70–79 with receptor-positive, node-negative breast cancer <2 cm in size. Overall, the 10-year risk of mastectomy without radiotherapy was 6.3% and 3.2% with radiotherapy ($P < 0.001$). In particular, women 70–74 years of age and those with high-grade breast cancer had a 10-year absolute reduction in mastectomy rates of 3.8% and 6.7%, respectively.

The PRIME trial examined 255 women >65 years of age with negative nodes and <3 cm size breast cancer treated with lumpectomy and anti-endocrine therapy to evaluate quality of life in those randomized to observation versus radiotherapy. More breast symptoms were noted at 15 months of follow-up in the irradiated group, but it was no longer significant by 5 years of follow-up.

In summary, for most patients with invasive breast cancer who undergo lumpectomy, radiotherapy is needed to maximize local control and minimize breast cancer mortality. For woman age 70 or older, competing health risks may influence outcomes more thant intrinsic risk features of the breast cancer. For this group of patients, the absolute reduction in loco-regional recurrence with radiotherapy post lumpectomy at 10 years is expected to be 7% and may not be clinically meaningful in the presence of other serious comorbidity. For the patient presented in the clinical scenario, who has a history of compliance for taking her medication and undergoing surveillance imaging, observation is a reasonable option. An in-depth conversation is recommended to explain to this patient that the omission of radiotherapy does place her at some additional risk of cancer recurrence in the breast, but with ongoing surveillance it should not impact her risk of developing distant disease or undergoing mastectomy. Additional studies are warranted in younger postmenopausal woman to further identify patients for whom the radiation therapy might be safely omitted.

3. Does the plan for radiotherapy change post lumpectomy for breast cancer patients who have a positive sentinel node biopsy without completion axillary node dissection (AND)?

Case study 119.3

A 58-year-old woman underwent a lumpectomy and sentinel node biopsy for a clinical stage 1 breast cancer that, on core biopsy, demonstrated a grade 2 infiltrating ductal cancer that was estrogen and progesterone receptor positive, and HER2 nonamplified. Pathology from her surgery reveals a 1.8 cm, grade 2 infiltrating ductal cancer with negative surgical margins; one of two sentinel nodes had a macrometastasis of 3 mm in size without any extra capsular extension.

Sentinel lymph node biopsy (SLNB) is now routinely used in women with early-stage breast cancer without clinical suspicion of axillary metastases for staging of the axilla. The avoidance of AND for early-stage breast cancer patients has been an important achievement in breast cancer care. Axillary lymph node dissection (ALND) can compromise patients' quality of life with higher incidences of lymphedema, pain, restriction of shoulder movement, and/or anesthesia in comparison to SLNB alone. Approximately 20–40% of breast cancer patients will be found to have metastases in the sentinel nodes (SNs). Two phase III trials have reported excellent local control and survival in

selected sentinel node biopsy–positive patients who did not undergo completion AND. ACOSOG Z-11 randomized 891 women who had undergone lumpectomy for T1 or T2 breast cancers and were found to have a positive sentinel node to completion AND versus no further axillary treatment. Many of the patients enrolled had T-1 tumors (67.4%), were grade 1 or 2 (71.2%), were ER or PR positive (83.6%), and were older than age 50 (67.4%). Seventy percent had only one positive sentinel node, and in 40% this was a micrometastasis. The prevalence of lower-risk features in the enrolled population likely explains why the rate of additional positive nodal metastases in the arm receiving completion AND was only 27%. In comparison, the rate of additional positive axillary nodal metastases reported from the ACOSOG Z10 clinical trial was 36.2% and from the NSABP B32 trial was 38.6%. At a median follow-up of 6.3 years, loco-regional recurrence was seen in only 29 (3.4%) patients of the entire ACOSOG Z11 population. There was no significant difference in the rate of regional or local in-breast recurrence by treatment arm. Regional recurrences in the ipsilateral axilla were uncommon in either arm: 0.9% for those who underwent SLND alone compared with 0.5% in the ALND group. Similarly, in-breast recurrence was 1.8% in the SN alone group compared with 3.6% in the ALND arm. Overall survival was statistically similar at 5 years: 91.8% (95% confidence interval (CI): 89.1–94.5%) with ALND and 92.5% (95% CI: 90.0–95.1%) with sentinel lymph node dissection (SLND) alone. The International Breast Cancer Study Group (IBCSG) clinical trial 23-01 randomized 934 breast cancer patients with tumors <4 cm in size who were found to have axillary nodal micrometastases (≤2 mm in size) at SLNB to completion axillary node dissection versus no further axillary treatment. The enrolled patients mostly had T-1 tumors (69%), were estrogen receptor positive (90%), and had grade 1–2 histology (72%). The rate of additional nodal metastases at completion axillary node dissection was 13%. At a median follow-up of 5 years, the group randomized to further axillary surgery did not have inferior outcomes compared to those who underwent completion axillary node dissection. The local, regional, and distant recurrence of those randomized to completion axillary dissection was 2%, 1%, and 7%, respectively, versus 2%, 1%, and 5%, respectively, for those who did not receive any further axillary surgery.

There has been considerable debate regarding the degree to which these findings can be broadly generalized to all breast cancer patients with positive SLNBs. It has been suggested that the good cancer control outcomes in these trials are related to the enrollment of a population of breast cancer patients with mostly low-risk disease. Therefore, the findings are not generalizable to those features not well represented in either clinical trial, including triple-negative breast cancer, HER2-positive disease, age <50, or patients not treated with radiotherapy after breast-conserving surgery. Additionally, there is some evidence that the high rates of axillary control may reflect that the fields for breast irradiation can include a significant portion of the lower axilla that would have been targeted for removal by the completion axillary dissection. It is recognized from other studies that irradiation can achieve comparable local control to axillary dissection in clinically node-negative breast cancer. The EORTC is addressing this question further in the After Mapping of the Axilla, Radiotherapy or Surgery (AMAROS) clinical trial. The AMAROS trial is a phase III study comparing completion axillary dissection with axillary radiotherapy in sentinel node–positive patients. Patients enrolled on the trial must have an operable breast cancer >5 mm and <3 cm, and without clinically suspect regional nodes. The main objective of the trial is to prove equivalent loco-regional control and reduced morbidity for patients with proven axillary node metastases by SLNB if treated with axillary RT instead of dissection.

Numerous investigators have used three-dimensional CT volumes to evaluate the dose delivered to the axillary nodes with standard breast irradiation, demonstrating that up to 50% of the axilla can receive the prescribed radiation dose without intentionally targeting the low axilla. For those patients with positive sentinel nodes, the breast fields can be modified to target close to 90% of the level 1 and level 2 axilla below the axillary vessels that would normally be resected with the completion axillary dissection. This requires careful delineation by the radiation oncologist of the level 1 and level 2 nodes below the level of the axillary vessel to be included in the fields in addition to targeting the breast post lumpectomy. For patients with higher risk factors, whose disease is more advanced than that of the patients who were typically enrolled onto Z0011 or IBCSG 23-01 trials, targeting the remaining undissected nodes in addition to level I and II is an alternative to completion axillary node dissection.

Two studies in particular have sought to predict which patients with a positive SLNB will have ≥4 positive nodes involved at the time of completion and therefore would benefit from more comprehensive regional nodal irradiation. A University of Kentucky study reviewed 126 cases that had positive SLNB to identify the variables that predicted for patients with N1 versus N2–N3 stage disease. They found that three factors predicted for >3 positive axillary nodal metastases at completion axillary dissection: LVI in the primary tumor ($P < 0.025$), ENE in the sentinel node ($P < 0.01$), and a sentinel node tumor deposit of >5 mm ($P < 0.001$). A similar study from Brigham and Women's and the Massachusetts General Hospitals examined 402 breast cancer cases that had completion AND for a positive SLNB to identify factors predictive for ≥4 positive axillary nodal metastases. On multivariate analysis, increasing primary tumor size ($P = 0.04$), invasive lobular

histology ($P = 0.02$), the presence of LVI in the primary tumor ($P = 0.003$), ENE in SNs ($P = 0.001$), increasing number of positive SNs ($P = 0.001$), macroscopic size of SN metastasis ($P = 0.02$), and decreasing number of uninvolved SNs ($P = 0.01$) correlated with an increased probability of having $\geq$4 axillary nodal metastases following completion AND. The authors developed a nomogram based on these seven pathologic factors from the primary tumor and SLNB to calculate the probability of having $\geq$4 involved axillary nodes, and they demonstrated that it could predict those with three or less positive nodes in 94.7% of cases and those with $\geq$4 positive nodes in 97.5% of cases. Patients with primary tumor and SLNB pathologic features at high risk for N-2 disease or $\geq$4 positive axillary nodal metastases should be considered for axillary and supraclavicular radiation using a separate field matched to the breast or chest wall fields.

The breast cancer patient in the clinical scenario has clinical pathologic features consistent with those enrolled on the ACOSOG Z-11 trial and therefore is anticipated to be a good candidate for omission of a completion AND. Standard whole-breast irradiation is recommended. The level 1 and portion of the level 2 axilla distal to the axillary vessels can be delineated on the treatment-planning CT scan in addition to the breast to be included in modified breast irradiation fields. Typically, this modification does not add significant morbidity in comparison to standard breast irradiation.

Selected reading

Beitsch PD, Wilkinson JB, Vicini FA, *et al*. Tumor bed control with balloon-based accelerated partial breast irradiation: incidence of true recurrences versus elsewhere failures in the American Society of Breast Surgery MammoSite® Registry Trial. Ann Surg Oncol. 2012;19:3165–70.

Early Breast Cancer Trialists Collaborative Group, Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomized trials. Lancet 2011;378:1707–16.

Vicini FA, Winter K, Wong J, *et al*. Initial efficacy of RTOG 0319: three dimensional conformal radiation therapy (3D-CRT) confined to the region of the lumpectomy cavity for the stage I/II breast carcinoma, Intl J Radiation Oncol Biol Phys. 2010;77(4):1120–7.

Whelan TJ, Pignol J-P, Levine MN, *et al*. Long-term results of hypofractionated radiation therapy for breast cancer. New Engl J Med. 2010;362:513–20.

Williams LJ, Kunkler IH, Prescott RJ, *et al*. A randomized controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population: the PRIME trial. Health Technol Assess. 2011;15(12):1–59.

CHAPTER 120

Radiotherapy for thoracic malignancies

Meredith E. Giuliani and Andrea Bezjak

University of Toronto, Princess Margaret Cancer Center, Toronto, ON, Canada

Case study 120.1

A 84-year-old man presents with a T1N0M0 non-small-cell lung cancer (NSCLC) in the periphery of the right upper lobe. His FEV1 is 0.8 L, and he is medically inoperable according to his thoracic surgeon.

• He would like to know: what are his options for treatment?

This patient has several options for treatment, including stereotactic body radiotherapy (SBRT), hypofractionated radiotherapy, conventionally fractionated radiotherapy, and observation.

We do not recommend observation in this patient population unless the patient is estimated to have an extremely limited life expectancy from his comorbidities, as the median survival in patients with untreated stage I NSCLC is 9 months, and the majority die of lung cancer.

It is our institutional practice to offer radiotherapy to patients who are well enough and agreeable to treatment. Our preference for treatment in this patient population is for SBRT in all eligible patients. SBRT may be considered for T1–2N0M0 and select <5 cm T3N0M0 chest wall NSCLC. The dose and fractionation of SBRT depend on the lesion size and location. It is our practice to deliver 54 Gy in three fractions for peripheral tumors, away from organs at risk (OARs); 48 Gy in four fractions for peripheral tumors <3 cm in diameter, and close to the ribs or OARs; and 60 Gy in eight fractions for centrally located tumors (i.e., tumors within a 2 cm radius of the airway or great vessels). The optimal dose for centrally located tumors is the subject of an ongoing Radiation Therapy Oncology Group (RTOG) study. SBRT for early-stage NSCLC is associated with 3-year 98% tumor control, 91% local control, and 56% overall survival (OS).

If the risks of SBRT are considered too high for the given tumor and/or patient—usually, that is due to the size of the tumor, its proximity to critical structures, or previous high-dose radiotherapy (RT)—we would consider hypofractionated RT. Common regimens used at our institution that have acceptable efficacy, have 20% local failure at 5 years, and are well tolerated are 60 Gy in 20 fractions and 50 Gy in 20 fractions.

For patients with early-stage lung cancer not suitable for SBRT or hypofractionated regimens, conventional regimens include 60 Gy in 30 fractions, 66 Gy in 33 fractions, and 70 Gy in 35 fractions. They have the advantage of conventional dose per fraction, with potentially less late normal tissue injury but a lower biological dose, and thus would be expected to have lower rates of long-term local control.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 120.2

A 79-year-old man presents with a 1.4 cm adenocarcinoma (T1N0M0) located 1 cm from the right main stem bronchus; he is medically inoperable.

• He would like to discuss the option of SBRT; how would you respond?

For the purposes of SBRT, tumors are considered centrally located if they are "within or touching the zone of the proximal bronchial tree defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi)," per the RTOG 0236 study. The RTOG 0813 trial also defines central tumors as those "tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura)." Some institutions consider central tumors to also be any tumor within 2 cm of any mediastinal structure.

In a retrospective study by Timmerman (2006), an excess of toxicity was reported in patients who receive 54 Gy in three fractions to centrally located tumors. Patients with central tumors had a 2-year freedom from severe toxicity of 54%, significantly lower than patients with peripheral tumors (84%). This practice-changing report has resulted in caution when using SBRT for central tumors.

There is currently significant heterogeneity in institutional practices for SBRT dose and fractionation for centrally located tumors. In a patterns-of-practice survey, the majority of clinicians preferred a protracted fractionation schedule ($\geq$4 fractions) for centrally located tumors. It is our institutional practice, as well as that of other institutions, to deliver 60 Gy in eight fractions. Other institutions have reported 50 Gy in four fractions, 48 Gy in four fractions, 48 Gy in six fractions, or 60 Gy in five fractions.

The RTOG is conducting a dose-finding study in patients with centrally located tumors. This study explored various five-fraction regimens starting with 10 Gy per fraction and ending with 12 Gy per fraction for 60 Gy in five fractions. This study will establish a safe and efficacious dose fractionation for central tumors and will also provide novel data on the radiation tolerance of mediastinal structures.

Case study 120.3

A 75-year-old woman, an ex-smoker with significant medical problems that include mild chronic obstructive pulmonary disease, coronary artery disease, diabetes, and a recent mild stroke, was found to have a T2N1 large cell carcinoma, with a 3.5 cm primary tumor in the right lower lobe of the lung and a 2 cm right hilar lymph node. Both areas are fluorodeoxyglucose (FDG) avid on positron emission tomography (PET) scan. The remainder of the metastatic work-up is negative. Her performance status is ECOG1; she has no respiratory symptoms and has not lost weight.

• How should she be managed?

This patient has a clinical stage II (T2N1M0) NSCLC. If she were medically operable, the standard treatment would be mediastinal nodal assessment, and, if that is negative for N2 disease, lobectomy with lymph node dissection followed by adjuvant chemotherapy. This patient, however, is at high risk for surgery, particularly due to the recent stroke. Her risk of perioperative and postoperative vascular events is significant. Thus, she should be considered for nonsurgical treatment with curative intent. This clinical scenario is not common, and thus treatment recommendations are not based on randomized trials specific to this question, but are extrapolations of evidence from nonsurgical treatments of N2 disease, and a known natural history of surgical N1 disease.

Radical radiotherapy would be the main local treatment, and discussion would be around whether the patient is fit enough for combined chemoradiotherapy. Her age, diabetes, and vasculopathy are risk factors that put her at a higher risk of chemotherapy complications, including arterial thrombotic events, although they are not absolute contraindications to chemotherapy. If the patient is deemed well enough to tolerate chemotherapy, it could be considered concurrently with radiation, or sequentially to minimize toxicity.

Radiation volumes would need to consider the risk of this patient having occult mediastinal nodal disease. Ideally, sampling of mediastinal lymph nodes through endobronchial ultrasound (EBUS) biopsy (which would avoid the risk of general anesthesia) would be performed prior to commencing treatment, and if they are indeed computed tomography (CT), PET, and EBUS negative, they may be excluded from the radiation field. However, in the presence of gross N1 disease, mediastinal nodes are at a risk of harboring microscopic disease, and consideration would be given to including at least first-eschalon nodes (e.g., the subcarinal and ipsilateral lower paratracheal nodes) in the RT volumes if pathological information was unavailable.

(*Continued*)

Typical doses would be in the range of 60 Gy in 30 fractions to the known cancer, and lower doses to the areas thought to be at risk of microscopic disease. If chemotherapy is not being considered, more hypofractionated RT regiments (e.g., 60 Gy in 20 fractions) could be considered. Although SBRT could deliver a much higher dose, currently it is not a consideration for nodal disease, except as part of an experimental protocol.

It is likely that this patient would tolerate radical radiotherapy well, with some esophagitis, tiredness, and likely a relatively small risk of symptomatic radiation pneumonitis. Although local control with RT is considerably less than with surgery, the morbidity and mortality risks from treatment are also considerably less, and the potential for cure is probably around 50–60%.

Case study 120.4

A 45-year-old man presented with right shoulder and back pain, progressive cough, and increasing shortness of breath. Staging investigations (PET–CT, magnetic resonance imaging (MRI) brain, MRI brachial plexus, and EBUS) reveal a right-sided T4N0M0 superior sulcus squamous cell carcinoma with involvement of the vertebral body at one level with no involvement of the brachial plexus.

- **How should he be managed?**

This patient should be discussed in a multidisciplinary tumor board. The resectability of the tumor must be discussed with a thoracic surgeon and neurosurgeon or spinal surgeon as needed. Superior sulcus tumors present unique challenges due to involvement of the brachial plexus, vertebral body, neural foramen, and/or epidural tumor extension. With advances in surgical techniques and the use of MRI scans to accurately delineate the extent of tumor infiltration, some patients can now undergo curative surgical resection. It is our policy to discuss all such cases in a multidisciplinary tumor board and to offer neo-adjuvant chemoradiotherapy followed by surgical resection to patients with resectable tumors. Prior to starting preoperative chemoradiotherapy (CRT), patients must undergo mediastinal staging via mediastinoscopy or EBUS to confirm N0 or N1 disease. Patients receive two cycles of cisplatin and etoposide chemotherapy concurrent with 45 Gy in 25 fractions of radiotherapy followed by surgical resection. Radiotherapy volumes typically encompass the gross tumor with a margin. The supraclavicular fossa may be electively irradiated; however, the hilar and mediastinal nodal regions are not frequently electively included. Patients then proceed with surgical resection (provided there has been no disease progression), with an en-block resection of lung and the involved verterbal body, and spinal stabilization), if well enough, they would be considered for two further cycles of chemotherapy. This protocol was tested in a phase II study in Pancoast tumors, which reported 17% local failure, 67% distant failure, and a 54% OS at 5 years in patients with R0 resection.

Patients who are not candidates for surgical resection after complete staging investigations and discussion with the multidisciplinary team are offered concurrent CRT. Radiation is 60–66 Gy in 30–33 fractions given 2 Gy per day with concurrent cisplatin and etoposide chemotherapy. This scenario represents a significant radiotherapy challenge due to the proximity of the spinal canal. Planning techniques such as intensity-modulated radiotherapy (IMRT) may allow the target dose to be delivered to the gross tumor with dose painting in areas approaching the organ at risk, while sparing the spinal cord.

In conclusion, patients with superior sulcus tumors represent a unique subset of locally advanced NSCLC patients. They must be discussed in a multidisciplinary setting prior to commencing therapy. A decision about the surgical resectability of the tumor is essential to management planning.

Case study 120.5

A 60-year-old ex-smoker with minimal comorbidities (mild hypertension and high cholesterol) is diagnosed with a T2N2M0 squamous cell carcinoma of the left upper lobe (LUL), with multiple bulky and FDG-avid lymph nodes (LNs) seen on CT and PET scan, including a 3 cm left hilar LN, 2.5 cm station 5 LN just lateral to the aortic arch, 3.5 cm subcarinal LN, and 1.5 left paratracheal LN. EBUS confirms levels 10L, 5, 7, and 4L are positive; they appeared quite bulky and matted; and the contralateral paratracheal LN (4R) was biopsy negative. There are no metastases, no weight loss, excellent performance status, and no contraindications to any treatment.

- **What is the optimal treatment for this patient?**

The recommended treatment would be concurrent CRT with platinum-based CRT. Given that the patient has multistation bulky mediastinal involvement, trimodality treatment with neo-adjuvant therapy followed by surgery would not be recommended; the only randomized phase III study that showed a disease-free survival benefit (but not overall survival benefit) to trimodality treatment over CRT alone for N2 disease focused only on patients with initially potentially resectable disease. This is not the case for this patient.

Issues for consideration in the management of this patient include:

• *Type of concurrent chemotherapy:* Cisplatin-based doublets are generally considered most effective but have toxicity, including fatigue, anemia, peripheral neuropathy, and renal impairment. Carboplatin regiments are widely used, at reduced doses, but are associated with more bone marrow suppression. What the second agent should be is not clearly established and may depend on the histological subtype of NSCLC.

• *Radiotherapy dose:* The standard RT dose is 60–66 Gy in 30–33 fractions over 6–6.5 weeks (once daily). Although some phase III studies suggested that a higher dose to involved disease is superior to a standard dose to elective volumes, a large phase III study of 74 Gy in 37 fractions versus 60 Gy in 30 fractions with concurrent carboplatin and taxol ± cetuximab showed superior outcomes with standard RT, despite the absence of obvious grade 5 toxicity.

• *Radiotherapy volumes:* Current guidelines suggest that known disease be encompassed and that fields not be expanded to include elective regions unless they can be included with a minimal increase in toxicity. PET scans can be helpful in delineating target volumes, although care should be taken regarding the timeliness of PET scans as evidence is emerging that FDG PET scans repeated in a 3–4-week interval may show disease progression. If conformal RT is utilized, adjacent lymph node regions receive incidental irradiation. However, if IMRT is utilized, in order to conform better to a complex volume, spare critical organs at risk, or provide better coverage of the target, the identification of target volumes becomes far more critical as dose dropoffs are steeper and beam arrangements are more complex.

• *Whether consolidative chemotherapy should be utilized:* This is controversial as phase III trials were not able to replicate the advantage to consolidative chemotherapy seen in initial phase II trials. Considering that evidence points to the advantage of four cycles of chemotherapy for resected stage II and stage III patients, and that concurrent chemotherapy is frequently given either at reduced doses (e.g., Carbo Taxol) or with less effective doublets (e.g., cisplatin–etoposide), many experts argue that consolidative chemotherapy may indeed benefit a proportion of patients with unresectable N2 disease, although studies performed to date have not been able to demonstrate that.

• *Should prophylactic cranial irradiation (PCI) be given?* The role of PCI in patients with locally advanced NSCLC was investigated in several randomized trials, including an RTOG study that was closed early due to poor accrual. Analysis of the accrued patients demonstrated no improvement in overall survival (OS) or progression-free survival (PFS) in patients who received PCI; however, there was a significantly reduced rate of brain metastases at 1 year (7.7% vs. 18.0%; $P = 0.004$).

Case study 120.6

A 45-year-old man with T2N2M0 squamous cell carcinoma involving his right upper lobe and a positive right lower paratracheal (4R) node on EBUS is considered a candidate for surgical resection.

• **Should he receive neo-adjuvant CRT?**

Patients with single-station N2 disease have for many decades been considered for surgery, with the knowledge that best outcomes are seen in patients managed with combined-modality treatment. Two small randomized trials demonstrated that in patients known to have N2 disease, preoperative chemotherapy followed by surgery produces superior results to surgery alone. A large Intergroup randomized trial utilized preoperative CRT with 45 Gy in 25 fractions and concurrent cisplatin and etoposide, and demonstrated superior disease-free survival in comparison to patients treated with CRT without surgery. However, overall survival was no better, and this was in part related to high postoperative mortality in the surgical arm, most of which was attributable to pneumonectomy patients. One possible explanation was that radiation may have contributed to the risks of postsurgical complications—a question that a subsequent Intergroup phase III trial attempted to answer by randomizing patients to neo-adjuvant chemotherapy or chemoradiotherapy followed by surgery for fit, potentially resectable N2 patients. This study failed to accrue and was closed prematurely, as oncologists, surgeons, and centers had a strong preference for one or the other arm of the study. Although induction treatment that includes radiation may have more toxicity, including potential concerns about surgical healing, it results in a higher rate of surgical downstaging, including mediastinal nodal complete pathological clearance, which is one of the strongest predictors of survival in trimodality studies. Patients in such a situation who will require a lobectomy, not a pneumonectomy, are considered for trimodailty therapy at our institution.

(*Continued*)

In selected cases, patients who were not resectable or marginally resectable are treated with chemoradiotherapy to 60 Gy (or 66 Gy) and reassessed for surgical resection. A series of 28 such patients reported a 64% response rate to induction treatment and a 43% gross total resection rate. They concluded that "full-course radiotherapy can be administered before surgical resection without additional surgical morbidity or mortality"; however, they also reported a 19% perioperative death rate. These deaths occurred in three patients, two of whom underwent pneumonectomy. The RTOG conducted a phase II trial of full-dose neoadjuvant CRT followed by surgical resection in patients with stage III NSCLC with N2 or N3 disease. This study reported a 3% 30-day postoperative mortality, 63% of patients achieved mediastinal nodal clearance with this regimen, and the 2-year OS was 54%. It is our institutional practice to select cases for resection following full-dose CRT on a highly selected basis.

Case study 120.7

A fit 60-year-old man, a smoker, presents with a seizure and is diagnosed with a solitary brain lesion on MRI, in keeping with a metastasis. Diagnostic workup reveals a 3 cm lung lesion compatible with a primary NSCLC, ipsilateral mediastinal lymphadenopathy, and no disease elsewhere. He has no thoracic symptoms and has good performance status. Discussion ensues regarding optimal management and if the goal of care should be curative or palliative.

- **Is there any role for high-dose radiation to his intrathoracic disease?**

Lung cancer commonly presents with symptoms and signs of metastases (e.g., it is already stage IV at the time of diagnosis). Typically, patients with stage IV NSCLC are considered incurable and are treated with nonradical approaches—chemotherapy, targeted therapy if appropriate, or palliative or moderate-dose radiotherapy, but the intent is not to eradicate all known disease. However, if the patient is otherwise fit and the burden of metastatic disease is very low, such as a solitary metastasis, consideration is given to a radical approach to both the local and/or regional disease and the metastases. This is most commonly done for patients with a solitary brain metastasis, especially since surgical resection and/or stereotactic brain radiotherapy ("radiosurgery" if delivered in a single fraction) can provide very high chances of control of that metastasis, and whole-brain RT, either immediately or as salvage, can reduce risks of other brain metastases. There are numerous reports of prolonged survivals and apparent cures of patients with either synchronous or metachronous brain metastases; most are seen if patients have only a lung primary, without nodal disease. However, the patient described in this scenario would be a candidate for chemoradiotherapy for his locoregional thoracic disease, after appropriate management (surgery or stereotactic RT ± whole-brain RT) to brain metastasis. The risk of developing further metastases would be high but is not universally seen, and the combination of local RT and effect of chemotherapy on any other micrometastases may be sufficient to render the patient cured, or at least to prolong his life, prolong disease-free survival, and reduce risks of local complications related to thoracic disease.

Whether such an approach is worthwhile for patients with solitary lesions in other organs (e.g., adrenal, bone, or liver) is far less clear. From the current reports in the literature and clinical experience, a solitary extracranial metastasis is less likely than a solitary intracranial metastasis to remain the isolated site of metastatic disease. Even less clear is whether a fit patient with a few metastases ("oligometastases") would benefit from an aggressive approach that would include local therapy (radiation or surgery) to eradicate all known sites of disease. There are relatively few patients who remain in the oligometastatic state for a prolonged time, but some do, especially those who have more slowly proliferating tumors, and/or response to systemic therapy and/or certain host characteristics that are currently poorly understood. As the biological understanding of the various subtypes of NSCLC increases, it is likely that patients with more prolonged solitary or oligometastatic states will be discovered to harbor certain mutations and tumor profiles that may distinguish them and in the future allow for the identification of patients in whom radical treatment of their metastatic disease will indeed be worthwhile in rendering them disease free for prolonged periods of time; some of them may remain free of cancer progression indefinitely.

In summary, well-selected patients managed in a multidisciplinary setting may derive prolonged disease control and survival from radical treatment with radiotherapy in the setting of limited metastatic disease.

Case study 120.8

A 49-year-old woman has biopsy-proven small cell lung cancer (SCLC) involving the mediastinum (levels 2R, 4R, 2L, 4L, and 7) as well as a left lower lobe 4 cm mass. She is suitable for and has agreed to chemotherapy and radiotherapy.

• **When is the optimal timing for radiotherapy?**
Thoracic radiotherapy improves OS in addition to chemotherapy for limited stage SCLC. A randomized trial of early (cycle 1) versus late (last-cycle) concurrent chemoradiotherapy reported improved OS and progression-free survival in patients who receive early-cycle radiotherapy. In a meta-analysis, 5-year OS was improved in patients when the interval from the first day of chemotherapy and the last day of chest radiation was less than 30 days.

In two major randomized trials in patients with limited-stage SCLC (LS_SCLC), radiotherapy was to be delivered with cycle 1 of chemotherapy. The Turrisi trial required radiation with cycle 1. This study has the best reported outcomes in LS-SCLC. The US Intergroup phase III trial also recommends radiation be given with cycle 1 of chemotherapy. CONVERT study recommends radiation to start with day 22 of cycle 1. This study is exploring the optimal dose of thoracic radiation with concurrent chemotherapy (45 in 30, twice daily, vs. 66 in 33, once daily).

Case study 120.9

A 67-year-old man presents with limited stage (LS) SCLC. He is planned to start concurrent chemoradiotherapy with cycle 1.

• **What dose of thoracic radiotherapy should be given?**
The optimal dose of thoracic radiotherapy remains a topic under study. A Canadian trial randomizing patients to early versus late radiotherapy used a dose of 40 Gy in 15 fractions delivered in 267 cGy once daily. The Intergroup 0099 trial randomized patients to 45 Gy in 30 fractions delivered in 1.5 Gy per fraction twice daily compared to 45 Gy in 25 fractions delivered in 1.8 Gy per fraction once daily. This study demonstrated 45 Gy in 30 fractions was associated with increased OS and reduced local failure. It did have significantly increased esophagitis compared to 45/25. This trial has been criticized for the biologically lower radiotherapy dose in the 45 Gy in 25 fractions arm. The international CONVERT study is an ongoing randomized controlled trial comparing 45 Gy in 30 fractions to 66 Gy in 33 fractions in 2 Gy fractions delivered once per day and the US Intergroup is conducting a similar large phase III study to determine the best RT fractionation schedule.

A pattern-of-practice survey from Japan reported a significant increase in the use of twice-daily radiotherapy for the treatment of LS-SCLC; however, there is still heterogeneity in clinical practice.

In summary, the current randomized evidence suggests 45 Gy in 30 fractions delivered, daily has superior outcomes to 45 Gy in 25 fractions. Although this twice-daily regimen has not been compared in a randomized fashion to other hypofractionated treatments such as 40 Gy in 15 fractions, it is our policy to offer twice-daily radiotherapy to eligible patients. The results of the current phase III studies are eagerly awaited.

Case study 120.10

A 55-year-old man presents with limited-stage lung cancer involving a 4 cm mass in the right upper lobe with involved lymph nodes in levels 2R, 4R and 2L (i.e. upper right, lower right and upper left paratracheal). Following six cycles of cisplatin and etoposide chemotherapy with concurrent thoracic radiation (45 Gy in 30 fractions delivered in 1.5 Gy twice daily), he has had a complete response.

• **What dose of prophylactic cranial irradiation (PCI) should be given?**
PCI improves survival in patients with LS-SCLC. The RTOG conducted a randomized study to compare 25 Gy in 10 fractions of PCI with a higher dose of 36 Gy delivered in either 18 fractions (2 Gy once per day) or 24 fractions (1.5 Gy fractions delivered twice daily). Patients who received 25/10 had higher OS and equivalent brain control. The current recommended dose of PCI is 25/10. This should be derived 4 weeks following chemotherapy.

The RTOG 0212 was conducted in patients with LS-SCLC. It is our institutional practice to use the same dose for PCI in patients with extensive-stage SCLC.

Case study 120.11

A 60-year-old woman with good performance status completed six cycles of chemotherapy for extensive-stage SCLC. She presented with a bulky mediastinal mass as well as metastasis to the T6 vertebral body and the right adrenal gland. There has been a complete response at the metastatic sites and a partial response in the mediastinum.

- **The patient has agreed to PCI and would like to know if there would be benefit from radiotherapy to the chest.**

Thoracic radiotherapy in addition to chemotherapy increases the OS in patients with LS-SCLC. With the introduction of PET scans for staging of SCLC and improved diagnostic imaging, patients with a minimal burden of metastatic ES-SCLC are being identified. These patients represent a clinical challenge, and the role of thoracic RT is unclear.

The patient population with ES-SCLC who may benefit from this more aggressive approach is controversial and is the subject of ongoing studies. This topic is currently the subject of two prospective clinical trials, RTOG 0937 and the CREST study in Europe. These studies will explore the benefits to local control and survival with consolidative thoracic RT and RT to a limited number of metastatic sites. In a retrospective review, consolidative RT in this patient population has been shown to have an acceptable toxicity profile.

It is currently our institutional practice to enroll all eligible patients on existing clinical trials. If a patient is not eligible, and he/she presented with very bulky or symptomatic thoracic disease, the potential role of consolidative thoracic radiation, its toxicity and current lack of high quality evidence would be discussed with them.

Selected reading

Albain KS, Swann RS, Rusch VW, *et al*. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379–86.

Curran WJ, Jr., Paulus R, Langer CJ, *et al*. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452–60.

Rusch VW, Giroux DJ, Kraut MJ, *et al*. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol. 2007;25:313–8.

Slotman B, Faivre-Finn C, Kramer G, *et al*. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007;357:664–72.

Timmerman R, Paulus R, Galvin J, *et al*. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.

CHAPTER 121

Radiotherapy for gastrointestinal malignancies

Manisha Palta[1], Christopher Willett[2], and Brian Czito[2]

[1]Duke Regional Hospital, Durham, NC, USA
[2]Duke University Medical Center, Durham, NC, USA

Case study 121.1

A 65-year-old female presents with painless jaundice and diarrhea for 1 month. Labs show an elevation in liver function tests and total bilirubin of 13.4. Computed tomography (CT) scan reveals a 2 cm lesion in the pancreatic head. Endoscopic retrograde cholangiopancreatography demonstrates a common bile duct stricture, and a metal stent is placed. Endoscopic ultrasound demonstrates a 1.9 cm pancreatic head mass and fine-needle aspiration shows adenocarcinoma. CT scan confirms no involvement of major vessels and no evidence of distant metastases. The patient undergoes pancreaticoduodenectomy, revealing pT1N0 poorly differentiated adenocarcinoma with negative margins.

1. Which of the following would be the most appropriate next step in management?

A. Gemcitabine
B. 5FU-based chemotherapy
C. Chemoradiotherapy (CRT) with a 5FU-based regimen
D. No adjuvant therapy

Although surgical resection remains the cornerstone of treatment, local and distant failure rates are high, and debate continues as to the appropriate adjuvant therapy. Retrospective analyses indicate high rates of both local and distant failure. 50–80% local failure rates following surgery alone prompted evaluation of optimized adjuvant therapy. The Gastrointestinal Tumor Study Group (GITSG) laid the foundation for the adoption of CRT in the United States, showing an improvement in disease-free (DFS) and overall survival (OS). In Europe, the use of adjuvant CRT underwent further assessment, with the European Organization for Research and Treatment of Cancer (EORTC) and European Study Group for Pancreatic Cancer-1 (ESPAC-1) trials showing no benefit and, in the case of the ESPAC-1 trial, a possible detriment with adjuvant CRT.

In parts of Europe, the EORTC and ESPAC-1 trials were judged to provide sufficient evidence to exclude the routine use of adjuvant CRT in favor of adjuvant CT. Further trials in Europe have focused on identifying the optimal adjuvant CT regimen. The CONKO-001 trial evaluated the role of gemcitabine after Whipple and found an improvement in DFS and OS with adjuvant gemcitabine compared to observation. The ESPAC-3 trial compared adjuvant gemcitabine to 5FU with folinic acid after surgery. No differences were seen in DFS or OS, but gemcitabine had a more favorable toxicity profile and remains the standard adjuvant regimen in parts of Europe. The ongoing ESPAC-4 trial is currently randomizing patients with pancreatic and periampullary tumors to adjuvant gemcitabine or gemcitabine–capecitabine therapy.

While adjuvant CT has remained the standard in parts of Europe, CRT has remained a standard in the United States. In addition to the GITSG trial, two large retrospective series compared outcomes with CRT compared to no adjuvant therapy after surgical resection, showing a survival benefit with CRT. Further insight as to the role of radiation therapy will be gained through the ongoing Radiation Therapy Oncology Group (RTOG) 0848–EORTC trial, which randomizes patients with resected pancreatic head adenocarcinoma (stratified based on CA 19-9, nodal, and margin status) to gemcitabine or gemcitabine–erlotinib for five cycles. If no progression is seen on restaging after completion of CT, patients are further randomized to receive an additional cycle (for a total of six cycles) of previously administered CT versus CRT (50.4 Gy) using modern techniques and central

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

RT quality assurance, with concurrent capecitabine or 5FU. Although options 1–3 are supported by available data, given the high rates of local failure and the data from the GITSG and large retrospective series, the authors advocate for adjuvant CRT.

2. If this patient was initially found to have encasement of the celiac axis with abdominal pain despite narcotics, which of the following would be the most appropriate next step in management?

A. Gemcitabine
B. 5FU-based CT
C. CRT with a 5FU-based regimen
D. Attempted surgical resection
E. FOLFIRINOX

Data regarding the appropriate management of patients with locally advanced pancreatic cancer are conflicting. A number of randomized trials have compared CT and CRT. The GITSG trial found a 2-month OS improvement with CRT when compared to CT alone, while an Eastern Cooperative Oncology Group (ECOG) and Fédération Francophone de Cancérologie Digestive (FFCD) trial showed no difference and survival detriment, respectively, with CRT. A more contemporary publication from the ECOG randomized patients to CT or CRT, with both arms utilizing gemcitabine. Despite failing to meet accrual goals, this trial showed a statistically significant improvement in median OS from 9 to 11 months in patients receiving CRT. Data from a randomized trial in the metastatic setting compared treatment with gemcitabine to a regimen of oxaliplatin, irinotecan, leucovorin, and 5FU (FOLFIRINOX). Median survival was 6.8 months in the gemcitabine group and 11.1 months in the FOLFIRINOX group. Median survival in this randomized trial is the longest seen in the published literature for patients with metastatic pancreatic cancer. There are, as of yet, no randomized data evaluating the efficacy of FOLFIRNOX in patients with locally advanced disease although this may be reasonable in select situations. In this case, options 1–3 are reasonable and supported by available data. In many situations, a course of CT upfront, followed by CMT in patients who do not progress, is reasonable. The authors advocate for option 3 given local tumor-related symptoms.

Case study 121.2

A 57-year-old male presents with a 1-month history of dysphagia, initially to solids and then progressing to liquids. Barium swallow indicates a stricture at the lower esophagus. Endoscopy demonstrates a fungating, nearly circumferential mass at 37–40 cm from the incisors (GE junction at 40 cm). Biopsy shows invasive adenocarcinoma, endoscopic ultrasound shows T3N1 disease, and PET–CT shows no evidence of distant metastases.

1. Which of the following is your initial treatment recommendation?

A. Neo-adjuvant CT
B. Neo-adjuvant CRT
C. Upfront surgery
D. Stent placement

Early initiation of therapy should provide improvement in tumor-related symptoms and potentially obviate the need for stent placement. Both neo-adjuvant CT and neo-adjuvant CRT have been compared to upfront surgical resection. The majority of randomized trials of neo-adjuvant CT compared to upfront surgical resection indicate superior OS in patients receiving neo-adjuvant CT. Similarly, the majority of data comparing outcomes of neo-adjuvant CRT compared to initial surgical resection shows superior OS in the trimodality arm.

To date, only one phase III randomized trial has evaluated the optimal neo-adjuvant regimen, comparing CT with CRT prior to surgery. One hundred and twenty-six patients (of a planned 354) with locally advanced esophageal and gastric cardia adenocarcinoma were randomized to CT followed by surgery versus CT, then CRT (radiation dose of 30 Gy), followed by surgery. As expected, the pathologic complete response (pCR) rate was higher in the trimodality arm compared with preoperative CT (15% vs. 2%). There were significantly higher rates of R0 resections and fewer patients with node-positive disease in the CRT cohort. However, the study's primary endpoint was OS, and, given the limited accrual, the study was underpowered to detect a difference. However, 3-year OS was 47% in the CRT–surgery arm compared with 28% in the CT arm—a clinically significant difference. An updated meta-analysis of nearly 4000 patients accrued to 24 randomized trials evaluated the role of neo-adjuvant CRT versus neo-adjuvant CT in patients with resectable esophageal cancer. An all-cause mortality benefit of 8.7% at 2 years was seen in patients receiving neo-adjuvant CRT. The authors advocate for neo-adjuvant CRT prior to surgical resection.

Case study 121.3

A 56-year-old male presents with a 3-month history of early satiety and abdominal pain. Upper endoscopy demonstrates a 5 cm mass in the gastric antrum. Biopsy shows invasive adenocarcinoma. Endoscopic ultrasound reveals uT3N1 disease, and PET–CT imaging shows no evidence of metastatic disease.

1. What of the following is the most appropriate next step in management?

A. Neo-adjuvant CRT
B. Neo-adjuvant CT
C. Surgical resection with adjuvant CRT
D. Surgical resection with adjuvant CT

Three randomized trials have compared neo-adjuvant CT to upfront surgical resection in esophagogastric cancers, with two showing a 13% improvement in OS with neo-adjuvant CT. The third trial randomized patients with locally advanced cancer of the stomach-cardia to neo-adjuvant CT followed by surgery or surgery alone. The trial closed prematurely due to poor accrual and did not demonstrate an OS difference; however, higher rates of R0 resections were seen with neo-adjuvant chemotherapy. The Intergroup 0116 trial demonstrated a 10% improvement in OS with the addition of CRT to surgical resection. The ARTIST trial randomized patients with resected gastric cancer (D2 dissection) to adjuvant CT with capecitabine–cisplatin with or without the addition of CRT. This trial, which was powered for DFS, showed no differences at 3 years; however, in a subset analysis of node-positive patients, a benefit to CRT was seen. Many trials of resected gastric cancer randomized patients to adjuvant chemotherapy or observation. Although most of these trials showed no benefit with adjuvant chemotherapy, a large randomized trial from Japan demonstrated an almost 10% improvement in OS with the addition of S-1 (tegafur, gimeracil, and oteracil). Similarly, a Korean study randomized 1000 patients undergoing D2 gastrectomy to adjuvant CT with capecitabine and oxaliplatin versus surgery only. Three-year DFS was improved in the adjuvant CT group (74% vs. 59%). The aforementioned data support answer choices B–D.

In other gastrointestinal malignancies (i.e., rectum and esophagus), the use of neo-adjuvant CRT has become standard practice. Given the potential for significant delays in the delivery of adjuvant therapy following surgical resection and the modest survival gains associated with adjuvant therapy, delivery of neo-adjuvant therapy offers a potentially attractive alternative. Advantages of preoperative therapy include an undisrupted tumor vasculature, allowing for improved chemotherapy delivery and radiosensitizing oxygenation. Downstaging may occur, potentially allowing the resection of more advanced lesions and sterilization of the operative region, which may reduce the risk of spread during surgical manipulation. Preoperative treatment also avoids delay in adjuvant therapy delivery due to postoperative recovery and, importantly, avoids potentially morbid radical resection in patients with rapidly progressive disease. The use of neo-adjuvant CRT in gastric cancers is an emerging approach. A phase II study, RTOG-9904, prospectively evaluated 49 patients with localized gastric cancer who received preoperative CRT with 5FU–paclitaxel. The primary study endpoint was pCR (26% in this trial).

Ongoing trials are attempting to clarify the optimal approach to gastric cancer. The CRITICS trial randomizes patients to adjuvant CT or CRT with cisplatin–capecitabine, and the ARTIST II trial is randomizing resected, node-positive gastric cancers to adjuvant CT or CRT. The TOPGEAR trial, the only trial evaluating a neo-adjuvant approach, is randomizing patients with gastric-junctional adenocarcinoma to neo-adjuvant CT or CRT followed by surgical resection. Although any of the above options are supported by the aforementioned data, the authors recommend surgical resection followed by adjuvant CRT.

Case study 121.4

A 62-year-old female presents with a 3-month history of hematochezia and narrow-caliber stool. Colonoscopy reveals a mass 7 cm from the anal verge. Biopsy shows moderately differentiated adenocarcinoma. Rigid proctoscopy measures the lesion as 6 cm from the verge, and staging CT shows no evidence of metastatic disease. Endoscopic ultrasound demonstrates T3N1 disease.

1. Which of the following is the most appropriate next step?

A. Total mesorectal excision
B. Neo-adjuvant CT
C. Short-course neo-adjuvant radiotherapy (RT) (5 Gy ×5)
D. Long-course neo-adjuvant CRT (45–50 Gy)

The results of the German Rectal Cancer Trial resulted in a subsequent paradigm shift to preoperative CRT. Two randomized controlled trials from Poland and Australia have compared long-course CRT with short-course RT. Neither trial showed a difference in local control, DFS, OS, or sphincter preservation. The median follow-up in the Polish and Australian trials is 4 and 5.9 years, respectively.

The primary concern of short-course RT utilization is potential late effects. Basic radiobiologic principles dictate

(*Continued*)

that larger fraction size carries a higher risk of late toxicities. Although there was no difference in late effects in the Polish and Australian trials, the median follow-up of roughly 6 years is not sufficient to fully appreciate late toxicities. Long-term data from European randomized trials of short-course RT highlight some concerns for late effects, with higher rates of small bowel obstruction and abdominal pain admissions, chronic neuropathy, femoral neck and pelvic fractures, fecal incontinence, and more patient-reported bowel and sexual dysfunction. Additionally, given that surgery is typically performed within one week following short-course RT, no significant downstaging is observed. The authors recommend neo-adjuvant long-course CRT.

2. If this patient had Crohn's disease which of the following is the most appropriate next step?

A. Total mesorectal excision
B. Neo-adjuvant CT
C. Short-course neo-adjuvant RT (5 Gy ×5)
D. Long-course neo-adjuvant CRT (45–50 Gy)

Optimization of medical management and symptoms as well as radiation technique is key in treating such patients. Several small retrospective series indicate higher rates of acute toxicities in patients with inflammatory bowel disease undergoing RT. In a series from Massachusetts General Hospital, 20% of patients ceased RT treatments due to enteral toxicity. Rates of late toxicity (i.e., small bowel obstruction) were as high as 30%. Both acute and late toxicity can be reduced with specialized planning techniques and patient positioning, including prone positioning or the use of intensity-modulated radiotherapy to minimize bowel dose. The authors generally advise long-course CRT with techniques to reduce bowel dose.

3. This patient has an uT1N0 rectal cancer 2 cm from the anal verge and undergoes local excision with pathology demonstrating pT2Nx disease. The patient is not felt to be a candidate for radical resection. Which of the following is the most appropriate next step?

A. No further therapy
B. Adjuvant CT
C. Short-course neo-adjuvant RT (5 Gy ×5)
D. Long-course neo-adjuvant CRT (45–50 Gy)

Local excision alone is reasonable in T1 lesions that measure less than 4 cm in size, involve <40% of the lumen circumference, are moderately or well differentiated, and have no perineural, lymphovascular invasion, or other adverse histologic features. Patients with T2 disease could be treated with total mesorectal excision with abdominoperineal resection, with long-course CRT as an alternative, although long-term local failure rates in the RTOG 89-02 and Cancer and Leukemia Group B (CALGB) 8984 studies after local excision and adjuvant CRT were approximately 20%.

Case study answers

Case study 121.1

Question 1: Answer C
Question 2: Answer C

Case study 121.2

Question 1: Answer B

Case study 121.3

Question 1: Answer C

Case study 121.4

Question 1: Answer D
Question 2: Answer D
Question 3: Answer D

Selected reading

Cunningham C, Allum WH, Stenning SP, *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11.

Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725.

Ngan SY, Burmeister B, Fisher RJ, *et al*. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with t3 rectal cancer: trans-tasman radiation oncology group trial 01.04. J Clin Oncol. 2012;30:3827.

Russell AH, Harris J, Rosenberg PJ, *et al*. Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. Intl J Radia Oncol Biol Phys. 2000;46:313.

Sauer R, Liersch T, Merkel S, *et al*. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30:1926.

Sjoquist KM, Burmeister BH, Smithers BM, *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12:681.

CHAPTER 122

Radiotherapy for genitourinary malignancies

Christina H. Chapman[1] and Curtiland Deville[2]

[1]University of Michigan Health System, Ann Arbor, MI, USA
[2]University of Pennsylvania, Philadelphia, PA, USA

Case study 122.1

A 61-year-old is diagnosed with nonmetastatic prostate adenocarcinoma and informed of radical prostatectomy.

• **He heard some may undergo radiotherapy (RT) after surgery and wants to know the risk factors.**

Prostatic fossa RT may occur in the adjuvant (no clinical evidence of disease) or salvage (clinical evidence of disease) setting. Risk factors are:

1. pT3 disease—extracapsular extension or seminal vesicle invasion
2. Positive margins
3. Biochemical (prostate-specific antigen (PSA)) persistence or recurrence
4. Persistent or recurrent local disease after surgery, including radiographically visible disease or biopsy-proven disease, often from the vesico-urethral junction.

Case study 122.2

A 62-year-old was diagnosed with T1c, a Gleason score of 7, PSA 8.9 prostate adenocarcinoma. He underwent radical prostatectomy with positive margins and had an undetectable PSA at 3 months postop. He is lost to follow-up and returns 2 years later with a PSA of 1.2.

• **Which features suggest he is likely to benefit from salvage RT?**

Patients who are most likely to benefit from salvage RT to the prostatic fossa are those at low risk of micrometastases, as demonstrated by multiple large retrospective series. Favorable features include:

1. Pre-prostatectomy low-risk disease and PSA velocity <2 ng/ml in the year before initial diagnosis
2. Gleason score ≤ 7 (less aggressive histology with lower risk of metastatic disease)
3. Positive margins (suggesting local residual tissue)
4. Negative lymph nodes (less evidence of metastatic spread)
5. No seminal vesicle invasion (less invasive disease, suggesting lower risk of metastases)
6. Time to PSA failure >3 years after radical prostatectomy
7. Low PSA at the time of salvage (<0.4–1 ng/ml).

Ongoing cooperative group trials (e.g., NCT00541047 and NCT00567580) are evaluating whether concurrent androgen deprivation therapy (ADT) and/or pelvic nodal RT may improve outcomes, and therefore currently may also be considered for patients with high-risk features: a Gleason score of 8 or greater, seminal vesicle invasion, and/or a PSA doubling time of less than 6 months.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 122.3

• A patient with T2b, PSA 9, Gleason 4 + 3 = 7 in 7 out of 12 total biopsy cores wants to undergo external-beam RT and asks whether you think he should receive ADT as well.

The addition of ADT in intermediate-risk patients is a topic of ongoing debate. D'Amico *et al*. (2008), in a single-institution randomized trial of RT with or without short-term (6 months) ADT, demonstrated an overall survival benefit using RT doses since shown to be suboptimal. Castle *et al*. (2012) retrospectively investigated dose-escalated RT with or without ADT in intermediate-risk patients, finding that while unfavorable patients (defined as GS 4 + 3 or T2c) benefited from ADT (freedom from failure (FFF): 74 vs. 94%; $P = 0.005$), favorable patients (defined as GS 6, ≤T2b or GS 3 + 4, ≤T1c) did not (FFF: 94 vs. 95%; $P = 0.85$). Radiation Therapy Oncology Group (RTOG) 0815 (NCT00936390) is currently, prospectively addressing this question in the setting of dose escalation.

1. What are the potential external-beam RT options for a patient with low-risk prostate cancer?

Three-dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), proton therapy, and stereotactic body RT (SBRT).

1. 3DCRT, developed in the 1990s, incorporated computed tomography (CT)-based treatment planning and decreased the risk of toxicity compared to conventional 2D techniques, allowing for dose escalation and improved biochemical control.

2. IMRT uses CT-based inverse treatment planning, permitted by the invention of the multileaf collimator, to modulate the intensity of the radiation beam over small surface areas. This allows for steep dose gradients, further reduces dose exposure to adjacent organs at risk (bowel, bladder, rectum, penile bulb, and femoral heads), and is currently considered the standard of care.

3. SBRT uses larger doses per fraction (also known as "extreme hypofractionation") with the advantage of a higher biologic effective dose (BED) and a lower total number of treatments, generally five (compared to 8–9 weeks of IMRT). Limited data, primarily in the low-risk setting, are available with relatively short follow-up. Most studies show >93% biochemical control rates with acceptable acute toxicity. Late and extended follow-up toxicity rates are awaited, particularly in the collaborative group setting.

4. Loma Linda has published its long-term results of patients treated with proton therapy, showing comparable treatment outcomes to IMRT. A multi-institutional trial (NCT01617161) is currently assessing whether there are any clinically relevant differences compared to IMRT that are of particular interest due to the higher cost of proton therapy compared to IMRT.

All of the above technologies are employed with daily image-guided RT (IGRT) techniques to verify patient and prostate positioning, such as cone beam CT, ultrasound, an endorectal balloon, or fiducials implanted in the prostate prior to treatment initiation with daily kilovoltage orthogonal imaging.

Case study 122.4

• A 60-year-old is diagnosed with cT3a, Gleason 4 + 5, PSA 21 prostate cancer, and he asks whether there is any advantage to undergoing RT in addition to ADT.

The standard of care for patients with locally advanced, high-risk prostate cancer with no evidence of distant metastases is RT with long-term (28–36 months) ADT based on multiple randomized trials showing an overall survival advantage to RT with ADT over RT alone. The overall survival benefit of RT with ADT over ADT alone was demonstrated in the Widmark trial, where after a median follow-up of 7.6 years, 79 men in the ADT alone group versus 37 men in the ADT plus RT group had died of prostate cancer. Cumulative 10-year prostate-cancer-specific mortality was 23.9% for ADT alone versus 11.9% for ADT plus RT (95% CI: 4.9–19.1%), for a relative risk of 0.44 (0.30–0.66).

2. What treatments should men be offered with node-positive prostate cancer?

Both immediate ADT and pelvic RT may be considered. Prospective randomized evidence has established the overall survival benefit of immediate ADT over delayed ADT at detection of distant metastases or symptomatic recurrence. Regarding RT, RTOG 85-31 included patients with positive lymph nodes and randomized them to RT and ADT or RT alone. The 10-year absolute survival rate was greater in the ADT arm: 49 versus 39% ($P = 0.002$). Local failure, distant metastasis, and disease-specific mortality showed a statistically significant benefit in favor of ADT.

Case study 122.5

A 58-year-old male is diagnosed with T1c, Gleason 3 + 3, PSA 9 prostate adenocarcinoma. Because of the nature of his work, he does not want to undergo external-beam RT, but will consider radical prostatectomy or brachytherapy.

• **Which patients are optimal candidates for prostate radioactive seed brachytherapy?**
American Brachytherapy Society relative contraindications include: prostate size >60 mm in width and 50 mm in height, severe urinary irritative or obstructive symptoms, extensive transurethral resection of the prostate defect, substantial median lobe hyperplasia, severe pubic arch interference, gross seminal vesicle involvement, prior pelvic RT, inflammatory bowel disease, and pathologic involvement of pelvic lymph nodes. Absolute contraindications include distant metastases and life expectancy <5 years.

3. How is treatment failure defined after RT versus radical prostatectomy?

Following prostatectomy, biochemical failure is defined as PSA of 0.2. Because noncancerous prostate is retained, the PSA does not generally become undetectable after RT and a failure is defined as a PSA rise ≥2 ng/ml above the nadir (with or without hormone therapy).

Bladder cancer

4. A patient with muscle-invasive bladder cancer wants to avoid cystectomy. She wants to know if she is a good candidate for bladder preservation and if it is inferior to cystectomy.

No randomized trials have compared cystectomy to bladder preservation. Good preservation candidates will have no hydronephrosis or hydroureter, good bladder function, and unifocal disease <5 cm. Preservation includes a "visibly complete" transurethral resection of the bladder tumor → chemotherapy concurrent with 40–45 Gy RT → second-look cystoscopy with multiple biopsies and urine cytology → complete response (70–80%) will receive consolidation chemoradiation to 60–65 Gy versus a residual tumor that is managed with salvage cystectomy. Follow-up consists of surveillance cytology and cystoscopies. Bladder preservation 5-year overall survival is 50–60%, comparable to cystectomy.

Testicular cancer

5. Which patients with testicular cancer are most likely to receive RT in the nonpalliative setting?

Early-stage seminoma (Royal Marsden Stage I–IIB) patients are candidates for RT following orchiectomy.

Case study 122.6

A 28-year-old undergoes radical orchiectomy with high ligation of the spermatic cord for 5 cm seminoma with lymphovascular and rete testis invasion, staged as pT2N0M0.

• **What are his management options?**
Management options for stage I seminoma are surveillance, para-aortic RT, and chemotherapy. The relapse rate after radical inguinal orchiectomy alone is ~16%; however, in this case, it may be greater than 30% due to >4 cm primary and rete testis invasion. Single-dose carboplatin has also emerged following a randomized trial comparing it to adjuvant RT, showing similar 3-year relapse-free survival rates for RT and carboplatin (95.9% vs. 94.8%).

Renal cell carcinoma

Case study 122.7

A patient has a mass highly suspicious for renal cell carcinoma found incidentally on magnetic resonance imaging.

• **He wants to know whether there is any role for RT before or after surgery.**
There is no widely accepted role for neo-adjuvant or adjuvant RT. Limited retrospective data suggest reduced recurrence risk and disease-free survival with positive surgical margins, locally advanced disease, positive lymph nodes, and unresectable disease. Stereotactic techniques, including SBRT and stereotactic radiosurgery, are emerging for unresectable primaries and oligometastases, particularly brain.

Selected reading

Bolla M, Collette L, Blank L, *et al*. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet. 2002 Jul 13; 360(9327):103–6.

Castle KO, Hoffman KE, Levy LB, *et al*. Is androgen deprivation therapy necessary in all intermediate-risk prostate cancer patients treated in the dose escalation era? Int J Radiat Oncol Biol Phys. 2012 Jul 24;85(3):693–9.

D'Amico AV, Chen MH, Renshaw AA, *et al*. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA. 2008 Jan 23;299(3):289–95.

Trock BJ, Han M, Freedland SJ, *et al*. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA. 2008 Jun 18;299(23):2760–9.

Widmark A, Klepp O, Solberg A, *et al*. Scandinavian Prostate Cancer Group Study 7; Swedish Association for Urological Oncology 3. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet. 2009 Jan 24; 373(9660):301–8.

PART 11

Hereditary Cancer Syndromes and Genetic Testing in Oncology

CHAPTER 123

When to suspect hereditary cancer syndromes

Emily Dalton[1] and Kathy Schneider[2]

[1]Ambry Genetics, Aliso Viejo, CA, USA
[2]Dana-Farber Cancer Institute, Boston, MA, USA

Multiple choice questions

1. What percentage of all cancer is considered to be hereditary?

A. 50%
B. 20–25%
C. 5–10%
D. 75%

All cancer is considered to be *genetic* because it is caused by the accumulation of mutations in the genes that control cell growth, death, and/or repair. However, only 5–10% of cancers are *hereditary* (i.e., caused by an inherited mutation in a cancer predisposition gene).

The two main types of cancer predisposition genes are tumor suppressor genes, which include mismatch repair genes, and proto-oncogenes. Tumor suppressor genes regulate cell division, promote apoptosis in abnormal cells, and signal repair mechanisms. Proto-oncogenes that are damaged (mutated) and become permanently activated are termed oncogenes. Oncogenes can trigger cell overgrowth and potentially cancer development.

In cases of sporadic cancer, individuals have acquired somatic mutations in both copies (alleles) of one or more tumor suppressor genes or proto-oncogenes. In cases of hereditary cancer, individuals are born with one allele of a tumor suppressor gene or proto-oncogene that contains a mutation. This mutation is present in every cell in the body, including germ cells, and in most cases can be passed on to one's children. The second, normal allele can acquire a mutation over time, rendering the cell without a working copy of the gene. Since a second mutation, or "hit," is necessary for the formation of a malignant tumor, inherited cancer genes are considered cancer predisposition genes. Inheriting a cancer predisposition gene increases the risk of certain cancers, but it is not sufficient to cause cancer. This helps explain why in most hereditary cancer syndromes, the associated cancer risks are less than 100%.

Inherited mutations in specific tumor suppressor genes or proto-oncogenes are rare, yet as a whole, they account for roughly 5–10% of all cancers. However, this estimate can vary greatly depending on the tumor type. For example, up to 25% of medullary thyroid cancers are due to germline mutations in the *RET* oncogene, while 50–80% of childhood adrenocortical carcinomas are due to germline mutations in the *TP53* tumor suppressor gene.

2. True or false? Hereditary cancer syndromes can skip a generation.

A. True
B. False

Inherited gene mutations do not skip generations. However, the risks of cancer associated with a specific inherited gene mutation may be less than 100%.

Most hereditary cancer syndromes are inherited in an autosomal dominant manner. Everyone carries two alleles of each gene, one inherited from each parent. Individuals who carry a germline mutation in one allele of a cancer predisposition gene have a 50% risk of passing on the allele containing the mutation and a 50% risk of passing on the normal allele to each child. Individuals who inherit two normal alleles can only pass on a normal allele to their children.

Sometimes, in assessing the pattern of cancer in the family, it may appear that the cancers have skipped a generation given the principle of reduced penetrance. Penetrance is defined as the likelihood that an individual carrying a mutated gene will express the associated phenotype (i.e., cancer). Most hereditary cancer syndromes display reduced or incomplete penetrance. For example, a

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

patient and her maternal grandmother both developed premenopausal breast cancer, and both were found to carry a *BRCA* mutation. Since the patient's mother never developed cancer, does this mean that the gene mutation "skipped" a generation? No, actually it means that the gene mutation was present in the patient's mother, but it never led to the associated phenotype due to incomplete penetrance.

In addition, some cancer syndromes have gender-specific penetrance. Using the example of *BRCA* mutations again, the risk of breast cancer associated with *BRCA* mutations is about 50–85% for women and about 6–10% for men. Thus, the vast majority of men with *BRCA* mutations will not develop an associated cancer, although they can still pass on the *BRCA* mutations to their children.

Another genetic mechanism that can affect the penetrance of disease is imprinting. This is the genetic mechanism whereby the genetic information resets or nullifies certain alleles depending on whether they were maternally or paternally inherited. For example, *SDHD* mutations, which are associated with hereditary paraganglioma–pheochromocytoma syndrome, are paternally imprinted. Therefore, individuals who inherit an *SDHD* mutation from their fathers are at risk for developing the rare endocrine tumors associated with this syndrome, while individuals who inherit an *SDHD* mutation from their mothers are not. Once again, regardless of if the individual with the *SDHD* mutation develops any associated tumors, the risk of passing on the *SDHD* mutation to their offspring remains at 50%.

Certain hereditary cancer syndromes, such as *MUTYH*-associated polyposis (MAP) syndrome, are inherited in an autosomal-recessive manner. This means that an individual must be born with both *MUTYH* alleles containing mutations in order to have the condition. Individuals who are born with one mutated MUTYH allele and one normal allele are considered carriers. Carriers tend to have no increased risk of cancer themselves, but if their partner also carries an MUTYH mutation, then they would have a 25% risk of having a child with MAP syndrome. If the carrier's partner does not carry an MUTYH mutation, then there is zero risk of having a child with MAP syndrome.

When assessing a family for a hereditary cancer syndrome, keep in mind that autosomal dominant syndromes would display a vertical pattern of cancer through consecutive generations of the family, while autosomal recessive syndromes tend to occur in one generation, often among siblings.

Case study 123.1

A 45-year-old woman comes to clinic given her family history of colon cancer. Her brother was diagnosed at age 35 and is now 41, and their mother was diagnosed at age 55 and is now 70. Their father was diagnosed with testicular cancer at age 30 and is now age 70. You discuss the option of Lynch syndrome (HNPCC) testing for the family.

1. Who is the best person in this family to test for a hereditary cancer syndrome?

A. The patient
B. The patient's brother
C. The patient's mother
D. The patient's father

In order to obtain the most informative results in a family, it is best to test an affected individual (i.e., an individual who has had cancer). This allows for better interpretation of other family members' results.

When more than one person in a family is affected and living, it is best to test the individual who has the history most concerning for a hereditary predisposition (e.g., the person diagnosed with bilateral disease or at an unusually young age). In this scenario, the best person to test for Lynch syndrome is the brother, who was diagnosed with colon cancer at the younger-than-average age of 35. If the brother's genetic test results are negative, then one can assume that Lynch syndrome is not the underlying cause of his colon cancer. Therefore, the likelihood of identifying an alteration in an unaffected family member would be very low. If the brother's test results do reveal the presence of a mutation in a mismatch repair gene, then it would confirm that he has Lynch syndrome, and other relatives (including your patient) would be at risk for having this condition as well.

If you were to test the unaffected patient without first identifying a specific mutation in her brother, then the genetic test results may be less informative. If the patient tests negative in this situation, then it is considered an "indeterminate negative" result. The family history of cancer still has not been explained, and one cannot rule out the possibility that a gene mutation could be present in other relatives. If the patient's brother tests positive for a specific gene mutation, and the patient tests negative for the familial mutation, then this is considered a "true negative" result. Unaffected relatives who test positive for a familial mutation would need to follow enhanced screening guidelines, and those who test negative for the familial mutation could follow general population guidelines for cancer screening.

When assessing a family history for a possible hereditary cancer syndrome, it is important to be aware of the various types of cancers that could be explained by the same inherited gene mutation. For example, in Lynch syndrome, the family history may display a pattern of colon, rectal, uterine, transitional cell kidney, or small intestine cancers.

3. In individuals or families that have adult-onset hereditary cancers, at what age are they typically diagnosed?

A. Before age 50
B. After age 75
C. Before age 65
D. Between the ages of 15 and 25

One of the strongest predictors of hereditary risk is a younger-than-average age at diagnosis.

Sporadic cancers are caused by multiple acquired gene alterations over time, likely due to environmental carcinogens, lifestyle factors (such as tobacco use), and random cellular errors. Individuals with a hereditary predisposition to cancer start out with one mutated allele of a tumor suppressor or proto-oncogene in every cell of their body. Therefore, it takes less accumulated DNA damage to start the development of a malignant tumor.

Many population-based studies have confirmed that individuals diagnosed with cancer at younger ages are more likely to have hereditary cancers. For instance, the likelihood for a woman with breast cancer, diagnosed at any age, to carry a *BRCA* alteration is 1 in 50 (2%), while the likelihood for women diagnosed under 40 is 1 in 10 (10%). About half of *BRCA1*-related breast cancers occur before age 50, which is significantly younger than age 61, which is the average age of breast cancer in the general population.

In Lynch syndrome, which is the most common hereditary cause of colon cancer, the average age of diagnosis of colon cancer is 44 to 52 years, compared to 71 years in the general population. In another rare colon cancer syndrome termed familial adenomatous polyposis (FAP), 95% of affected individuals develop hundreds of colorectal adenomas by age 35 and develop colorectal cancer, on average, at age 38, unless prophylactic colectomies have been performed.

4. Your patient has a family history of cancer, which includes several individuals with breast cancer, soft tissue sarcomas, and brain tumors. Could the pattern of different cancers in this family be due to the same inherited gene mutation?

A. Yes
B. No
C. Only the breast cancers
D. Impossible to determine

Most hereditary cancer syndromes are associated with more than one type of cancer. When assessing a family history for a possible hereditary cancer syndrome, it is important to be aware of the spectrum of cancers that could be explained by the same inherited gene mutation.

In determining the risk for a hereditary cancer syndrome, it is important to assess whether the cancers in the family could be due to the same underlying genetic cause. Genetic counselors are trained to be familiar with the spectrum of cancers associated with various hereditary syndromes, but it is also important for oncologists to be familiar with the related cancers of the more common hereditary cancer syndromes, so that these individuals will be recognized and referred to genetics. As examples, the *BRCA* genes and mismatch repair genes confer increased risks of several different forms of cancer. The *BRCA1* and *BRCA2* genes are associated with hereditary breast and ovarian cancer syndrome, and they increase the risk for breast, ovarian, male breast, pancreatic, and prostate cancer. Lynch syndrome, the most common hereditary cause of colon cancer, is due to inherited alterations in the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *EPCAM*, and *PMS2*) and also confers risks for endometrial, ovarian, and other gastrointestinal and urinary tract cancers. Generally speaking, if there is a clustering of close family members with the same or similar cancers, it is usually safe to assume they at least have a risk for hereditary cancer and should be evaluated.

In considering the above scenario, a family history that includes individuals with breast cancer, soft tissue sarcomas, and brain tumors may have a rare hereditary cancer syndrome termed Li–Fraumeni syndrome, which is associated with germline mutations in the *TP53* gene. Of course, more information is needed to determine the exact likelihood that the family could have Li–Fraumeni syndrome. About half of Li–Fraumeni syndrome cancers occur before age 30, and about one-third of the cancers occur in childhood, so determining the ages of diagnosis in this scenario would help determine the likelihood that the family could have Li–Fraumeni syndrome.

Also, it is helpful to determine how closely the affected individuals are related. If the individuals with cancer are first-degree relatives (e.g., parents, siblings, or children) or second-degree relatives (e.g., nieces, nephews, grandparents, or grandchildren) rather than more distant relatives, then it is more likely that there could be a *TP53* mutation in this family. In addition, *TP53* mutations are dominantly inherited, so that the presence of cancer in consecutive generations—for example, the patient, her parent, and her grandparent—would be more compelling than cancers in a single generation or scattered among great-aunts, great-uncles, and distant cousins. And finally, it may seem obvious, but patterns of cancer in a family are more concerning if they occur among blood relatives within the same lineage (i.e., the maternal side of the family or the paternal side of the family).

5. One of your patients develops a rare type of thyroid cancer termed medullary thyroid carcinoma. No one else in his family has developed this type of cancer. Would you recommend that this patient be evaluated for a possible hereditary cancer syndrome?

A. Yes, if the patient plans to have children
B. Yes, if the patient was diagnosed under age 30

C. Yes, in all cases
D. No; a genetics evaluation is not necessary.

Another hallmark of hereditary cancer syndromes is that they can include rare or unusual cancer types. Therefore, the presence of a rare tumor may be sufficient to justify a referral for genetic counseling and testing.

Examples of rare tumors that should warrant a genetics evaluation include diffuse gastric cancers, adrenocortical carcinomas, paragangliomas, pheochromocytomas, retinoblastomas, and wild-type gastrointestinal stromal tumors. While it is true that rare tumors can (and do) occur sporadically, it is often important to rule out an underlying genetic predisposition. If two members of the same family develop similar rare (or even less common) tumors, then this greatly increases the likelihood that they have a shared genetic risk factor (i.e., inherited gene mutation). However, even a seemingly isolated case of a rare tumor can turn out to have an underlying inherited genetic predisposition.

In the scenario listed above, the patient has medullary thyroid cancer (MTC), which is a rare form of thyroid cancer. It is estimated that up to 25% of MTCs, regardless of other family history, are due to a germline *RET* mutation. Since MTC is an aggressive tumor and can be prevented through prophylactic surgery, it is recommended that all patients diagnosed with MTC, regardless of other family history, be referred for genetic counseling and testing. Although the age at diagnosis is always a useful factor, for many of the rare tumors, there is still a possibility of an inherited gene mutation regardless of the age of the patient at diagnosis.

The lack of significant family history may be due to incomplete penetrance. Therefore, other family members may be at increased risk for developing the associated cancers or for having children who develop the associated cancers. Once an inherited cancer predisposition gene has been identified, it is recommended that all close relatives be tested. It is especially helpful for the parents of the individual who tested positive to be tested in order to establish which set of extended relatives are at increased risk.

In addition, it is possible for an individual to carry a germline mutation that has occurred as a *de novo* (new) genetic event. This would also explain the lack of cancers in the family. However, the individual who carries the de novo mutation will pass on the mutation to his or her children in a standard Mendelian fashion: there is a 50% risk if passing on a dominant mutation, and a 25% risk if passing on a recessive mutation *and* his or her partner also carries a mutation in the same gene.

In hereditary cancer syndromes, it is also possible for more common cancers to occur in an unusual subgroup. Examples include lung cancer in a 30-year-old nonsmoker or an adult cancer that has occurred in a child or adolescent. Another example of this is male breast cancer. Breast cancer itself is, of course, one of the most common cancers in women, with the average lifetime risk quoted as 12% in the general population. The risk for breast cancer in men is significantly less than 1%, but may be up to 6–10% in men who carry *BRCA* mutations. Therefore, male breast cancer, regardless of contributing family history, is enough to warrant genetic evaluation.

6. True or false? Individuals with hereditary cancer syndromes are more likely to have bilateral or multifocal disease.

A. True
B. False

In general, individuals with bilateral disease or multiple primaries have a greater likelihood of testing positive for a hereditary cancer syndrome.

Individuals with a hereditary cancer syndrome are typically at increased risk for developing bilateral disease and/or more than one cancer. We often describe the "two-hit hypothesis" when discussing hereditary cancer. We all have two copies of every gene, including the tumor suppressor genes and proto-oncogenes, which are involved in protecting our cells from tumor development. Individuals who have a dominantly inherited cancer syndrome are born with one normal allele and one mutated or nonworking allele, which is the "first hit." The "second hit" occurs when the DNA of the normal allele becomes somatically damaged, usually due to environmental carcinogens. Because individuals with hereditary cancer are starting out with one nonworking allele in all their cells, they are more susceptible to developing that second hit more than once, and thus developing multifocal, bilateral, or multiple primary cancers.

The cancer risks associated with hereditary cancer syndromes are not mutually exclusive. For example, if a woman with a *BRCA* alteration develops breast cancer, then that does not preclude her or reduce her chances for developing ovarian cancer or contralateral breast cancer. For women with *BRCA* alterations, their lifetime risk of developing a first breast cancer is said to be 50–85%, yet the risk for ovarian cancer may be as high as 40% and the risk of a second primary breast cancer is up to 50%. Similar numbers exist for Lynch syndrome; the lifetime risk for colon cancer in a patient with Lynch syndrome is up to 80%, yet without screening, their risk for a second primary colon cancer is significantly increased over the general population.

7. What other features, besides cancer, might suggest a hereditary cancer syndrome?

A. Benign tumors or characteristics
B. Absence of environmental factors
C. Tall stature
D. Both A and B
E. All of the above

Several hereditary cancer syndromes are associated with benign tumors or characteristic physical features. Cowden syndrome, which is a syndrome diagnosed by clinical features or the presence of a germline *PTEN* alteration, has many benign yet pathognomonic features associated with it. These include macrocephaly, characteristic skin findings (trichelimommas, papillomatous papules, and acral keratoses), and hamartomatous polyps. The macrocephaly and skin findings in particular are strongly linked with a diagnosis of Cowden syndrome, and suspicion should be very high if an individual has them.

Another example of a syndrome with benign features is Peutz–Jegher syndrome, which is due to inherited alterations in the *STK11* gene. Individuals with PJS will typically have dark freckling in and around their oral mucosa, although this can fade with age. They can also have a specific subtype of hamartomatous gastrointestinal polyp known as a Peutz–Jegher polyp. Looking out for these benign features of rarer cancer syndromes can assist clinicians in making diagnoses that may not have been picked up otherwise.

It is well known that environmental carcinogens and other exposures are highly linked with certain types of cancer: asbestos and mesothelioma, the HPV virus and cervical cancer, and the *Helicobacter pylori* virus and stomach cancer. However, when these or other malignancies are present in the absence of environmental risk factors, it may be more important to consider a possible inherited genetic risk factor. For example, many diseases increase colon cancer risk (colitis, inflammatory bowel disease, etc.), so it would not be unexpected to see a younger-than-average diagnosis of colon cancer in an individual with a long history of such a disease. However, if a young individual is diagnosed with colon cancer in the absence of any known risk factors, then it is much more concerning that an inherited predisposition is present.

Case study answers

Case study 123.1

Question 1: Answer B

Multiple choice answers

Question 1: Answer C
Question 2: Answer B
Question 3: Answer A
Question 4: Answer A
Question 5: Answer C
Question 6: Answer A
Question 7: Answer D

Selected reading

Hampel H, Frankel WL, Martin E, *et al*. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352(18):1851–60.

Libé R, Bertherat J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. Eur J Endocrinol. 2005;153: 477–87.

Newman B, Mu H, Butler LM, *et al*. Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. JAMA. 1998;279(12):915–21.

CHAPTER 124

Hereditary breast cancer syndromes

Kathy Schneider[1] and Emily Dalton[2]

[1]Dana-Farber Cancer Institute, Boston, MA, USA
[2]Ambry Genetics, Boston, MA, USA

Multiple choice questions

1. Hereditary breast-ovarian cancer syndrome is associated with germline mutations in which of the following two genes?

A. *MSH2* and *MSH6*
B. *BRCA1* and *BRCA2*
C. *BRCA2* and *TP53*
D. *BRCA1* and *PTEN*

Hereditary breast-ovarian cancer syndrome is associated with germline mutations in the *BRCA1* and *BRCA2* genes.

BRCA1 and *BRCA2* mutations are identified in about 15–20% of individuals with family histories of breast cancer and about 60–80% of those with family histories of breast and ovarian cancers. Therefore, *BRCA* mutations are, by far, the most frequent cause of hereditary breast and ovarian cancers. Keep in mind that the majority of breast and ovarian cancers (90–95%) are not hereditary (i.e., not due to an underlying inherited gene mutation).

In the general population, it is estimated that 1 in 800 individuals carry a *BRCA* mutation. Among individuals of Eastern European (Ashkenazi) Jewish descent, about 1 in 50 individuals carry one of three specific mutations in the *BRCA* genes. The three Ashkenazi Jewish *BRCA* founder mutations are the 187delAG and 5385insC mutations in the *BRCA1* gene and the 6174delT mutation in the *BRCA2* gene. *BRCA* mutations have been identified in every ethnic group, and founder mutations have been identified in several other ethnic groups, including the Dutch, Icelanders, and French-Canadians.

2. What are the four major types of cancer associated with *BRCA1* and *BRCA2* mutations?

A. Breast, uterine, colon, and prostate cancers
B. Breast, ovarian, colon, and prostate cancers
C. Breast, uterine, pancreatic, and colon cancers
D. Breast, ovarian, pancreatic, and prostate cancers

The four major forms of cancer associated with *BRCA1* and *BRCA2* mutations are cancers of the breast, ovary, pancreas, and prostate. Women with *BRCA* mutations are at risk for developing breast cancer, often at younger-than-average ages. The risk of contralateral breast cancer is also increased. Women with *BRCA1* mutations have an estimated 57–65% risk of breast cancer to age 70 and a 90% risk of breast cancer to age 80. Women with *BRCA2* mutations have an estimated 41–49% risk of breast cancer to age 70. When compared with sporadic breast cancers, *BRCA1*-associated breast cancers are more likely to be medullary, to be of a higher grade, and to be "triple-negative" tumors (i.e., negative for estrogen receptors, progesterone receptors, and the Her2neu growth factor). *BRCA2*-associated breast cancers do not appear to have a specific phenotype.

Women with *BRCA1* mutations have an estimated 24–40% risk of ovarian cancer. Women with *BRCA2* mutations have an estimated 11–18% risk of ovarian cancer. *BRCA*-associated ovarian cancers are more likely to be serous adenocarcinomas. Women with *BRCA* mutations also have increased risks of fallopian tube and primary peritoneal cancers.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Men with *BRCA* mutations have an increased risk of prostate cancer. The relative risks for prostate cancer are 1.8 for men with *BRCA1* mutations and 4.6 for men with *BRCA2* mutations. When compared to sporadic prostate cancers, *BRCA2*-associated prostate cancers may occur at younger-than-usual ages and may have a more aggressive phenotype. Men with *BRCA2* mutations also have a 6% risk of breast cancer. Breast cancers have also been reported in men with *BRCA1* mutations.

Men and women with *BRCA2* mutations may have as high as a 10% risk of developing pancreatic cancer. Cases of pancreatic cancer have also been reported in people with *BRCA1* mutations.

3. All of the following features increase the likelihood of a *BRCA* mutation EXCEPT:

A. Family history of pancreatic cancer
B. Triple-negative breast tumor
C. Lobular carcinoma in situ
D. Ashkenazi Jewish heritage

Lobular carcinoma in situ (LCIS) is not a feature of Hereditary Breast-Ovarian Cancer syndrome. The presence of LCIS does not increase the likelihood of a *BRCA* mutation. In contrast, ductal carcinoma in situ (DCIS) is a feature of hereditary breast-ovarian cancer syndrome. However, the likelihood of a *BRCA* mutation in women with DCIS is lower than for women with invasive breast cancers.

Indications for *BRCA* genetic counseling and testing include the following:

- Women with premenopausal breast cancer, typically before age 50
- Women with triple-negative breast cancer diagnosed at any age
- Women with serous ovarian cancers, fallopian tube cancers, or primary peritoneal cancers, diagnosed at any age
- Women who have developed bilateral breast cancer or have developed two separate malignancies (e.g., breast and ovarian cancers, or breast and pancreatic cancers)
- Men with breast cancer diagnosed at any age
- Men with prostate cancers that have an aggressive phenotype *and* have occurred at a younger-than-usual age (typically under age 55)
- Individuals with pancreatic cancer who also have a family history of breast, ovarian, prostate, or pancreatic cancer
- Individuals who are cancer-free but have family histories that include any of the cancers listed above
- Individuals of Ashkenazi Jewish heritage who have any personal or family history of breast, ovarian, and/or pancreatic cancers diagnosed at any age.

Several empiric risk models have been developed to help calculate the likelihood that an individual carries a *BRCA* mutation. These models base their calculations on the number of breast and ovarian cancers among the patient and his or her first- and second-degree relatives, as well as the ages at diagnosis and the family's ethnicity (Ashkenazi Jewish or not). The most widely used models for *BRCA* estimation are BRCAPRO and Myriad II.

Case study 124.1

Mrs. Smith, who developed breast cancer at age 40 and now has ovarian cancer at age 60, undergoes ***BRCA*** genetic testing. She is found to have a novel variant of uncertain significance in the ***BRCA2*** gene.

1. How should this variant result be interpreted?

A. Positive result
B. Suspected positive result
C. Inconclusive result
D. Negative result

A novel variant result in the *BRCA2* gene is considered to be an inconclusive result. A variant of uncertain significance is a simple substitution of one nucleotide for another in the lengthy DNA coding of the gene. If a particular variant result has not been seen before, then the lab does not know whether it is a damaging change that renders the gene nonfunctional (deleterious mutation) or if it represents normal DNA variation with no clinical significance (benign polymorphism). The likelihood of obtaining a variant of uncertain significance on the *BRCA* test is about 10–15%.

The genetics laboratory will gather additional evidence from multiple sources, including family studies, prevalence estimates, and evolutionary data, in order to reclassify the variant result as either a positive or negative result. Over time, most variants are able to be reclassified, with the majority representing benign polymorphisms.

Identification of a deleterious mutation is a positive *BRCA* result, which means that the individual has Hereditary Breast-Ovarian Cancer syndrome and the associated cancer risks. If no *BRCA* mutations or inconclusive variants are detected, then it is a negative result. A negative result is considered to be a "true negative" result if a *BRCA* mutation has previously been identified in the family and an "indeterminate negative" result if this is not the case.

(*Continued*)

2. Mr. Jones is found to carry a *BRCA1* gene mutation. What is the probability that he will pass on the *BRCA1* mutation to his daughter?

A. 0
B. 25%
C. 50%
D. 100%

Hereditary Breast-Ovarian Cancer syndrome is an autosomal dominant genetic condition. Thus, there is a 50% risk of passing on a *BRCA* mutation to one's offspring. Both men and women can pass on a *BRCA* mutation to their children.

Everyone has two copies (alleles) of the *BRCA1* and *BRCA2* genes. *BRCA* mutations are dominantly inherited, meaning that inheriting one mutated allele (along with one normal allele) is sufficient to cause the syndrome and increased cancer risks. This is in contrast to recessive conditions in which both inherited gene alleles must contain mutations.

If a *BRCA* mutation is identified in the family, then the risks to relatives are as follows:

- 50% for first-degree relatives (siblings, children, and parents)
- 25% for second-degree relatives (nieces, nephews, aunts, uncles, grandparents, and grandchildren)
- 12.5% for third-degree relatives (cousins, great-aunts, and great-uncles).

Individuals who test positive for *BRCA* mutations are encouraged to inform their relatives that they may also be at risk and that they have the option of targeted genetic testing and increased cancer monitoring. It is especially helpful to test the parents of an individual who tests positive for a *BRCA* mutation in order to determine which set of relatives (maternal or paternal) are at risk.

4. True or false? A woman who tests positive for a *BRCA* mutation is recommended to undergo prophylactic salpingo-oophorectomies, even if there is no ovarian cancer in the family.

A. True
B. False

A woman who tests positive for a *BRCA* mutation is recommended to undergo prophylactic salpingo-oophorectomies, even if there is no ovarian cancer in the family. The risk of ovarian cancer associated with *BRCA* mutations is greatly increased over the general population risk of 1–2% in the United States, and to date, there is no effective screening modality for ovarian cancer. Therefore, it is recommended that women with *BRCA* mutations undergo surgical removal of their ovaries and fallopian tubes once their families are complete. Prophylactic salpingo-oophorectomy reduces the risk of ovarian cancer by at least 90%. The use of oral contraceptives reduces the risk of ovarian cancer by about 50%. Current screening strategies, such as the CA-125 blood test and transvaginal ultrasounds, do not appear to affect ovarian cancer mortality and also have a high rate of false positives, especially among premenopausal women.

Women with *BRCA* mutations also have high risks for developing breast cancer. It is recommended that women with *BRCA* mutations be monitored every 6 months with clinical breast exams and alternating mammograms and breast magnetic resonance imaging exams beginning at around age 25. Women with *BRCA* mutations also have the option of undergoing prophylactic bilateral mastectomies, which reduces the risk of breast cancer by at least 90%. Chemoprevention, such as tamoxifen or raloxifene, may cut the risk of breast cancer in half. Prophylactic oophorectomy, if performed on a premenopausal woman, also appears to reduce the risk of breast cancer by about 50%.

Men with *BRCA* mutations should initiate prostate cancer screening at age 40 years, which is 10 years earlier than standard recommendations. Prostate cancer screening should include an annual exam and prostate-specific antigen blood test. It is also suggested that clinicians have a low threshold for recommending follow-up tests, because *BRCA*-associated prostate cancers may be more aggressive than sporadic cases.

There is currently no effective method for screening for pancreatic cancer, although several groups are searching for better screening modalities to offer to high-risk populations.

5. Individuals who test negative for *BRCA* mutations might have a different hereditary cancer syndrome. All of the following syndromes are associated with increased breast cancer risks EXCEPT:

A. Cowden syndrome
B. Von Hippel–Lindau syndrome
C. Li–Fraumeni syndrome
D. Hereditary Diffuse Gastric Cancer syndrome

Von Hippel–Lindau syndrome is not associated with increased risks of breast cancer. Individuals who test negative for *BRCA* mutations could potentially be tested for Cowden syndrome, Li–Fraumeni syndrome, or hereditary diffuse gastric cancer syndrome if they have any of the other features of these rare hereditary cancer syndromes.

Cowden syndrome is associated with increased risks of cancer of the breast, thyroid, uterine, and kidney. In addition, people with Cowden syndrome typically have a larger-than-average head circumference (macrocephaly) and may also have skin manifestations such as lipomas and facial trichilomomas or acral keratoses. Genetic testing for Cowden syndrome involves looking for mutations in the *PTEN* gene.

Li–Fraumeni syndrome is associated with increased risks of diverse cancers, including breast cancers, sarcomas, brain tumors, adrenocortical carcinomas, acute leukemias, and gastrointestinal cancers. Individuals with Li–Fraumeni syndrome have an estimated 90% risk of developing cancer, often at younger than average ages. For example, breast cancer cases may occur in women in their 20s or 30s, as well as at older ages. Genetic testing for Li–Fraumeni syndrome involves looking for mutations in the *TP53* gene. Li–Fraumeni syndrome–associated breast tumors are more likely to be positive for estrogen receptors, progesterone receptors, and/or Her2neu growth factor. This is in contrast to *BRCA1*-associated tumors, which are more likely to be triple negative for estrogen, progesterone, and Her2neu.

Hereditary Diffuse Gastric Cancer syndrome is associated with increased risks of diffuse gastric cancer and breast cancers, especially lobular breast cancers. Genetic testing for Hereditary Diffuse Gastric Cancer involves looking for mutations in the *CDH1* gene.

6. For patients who have striking personal and family histories of breast, ovarian, and pancreatic cancers, yet test negative for *BRCA* mutations, which additional genetic test might be considered?

A. *APC*
B. *PALB2*
C. *RET*
D. *VHL*

Patients with striking personal and family histories of breast, ovarian, and pancreatic cancers, who test negative for *BRCA* mutations, can be offered testing to look for mutations in the *PALB2* gene.

Individuals with *PALB2* mutations are at increased risk for developing breast, ovarian, and pancreatic cancers. Mutations in the *PALB2* gene (i.e., the "Partner and Localizer of BRCA2") are much less common than *BRCA* mutations, which is why *BRCA* mutations are generally ruled out first.

In addition to the genes listed above, other genes, when mutated, can lead to a moderate or high risk of breast and ovarian cancer. These include other genes in the *BRCA* pathway, such as *ATM*, *BARD1*, *BRIP1*, *MRE11A*, *NBN*, *RAD50*, *RAD51C*, and *CHEK2*. Hereditary ovarian cancer has also been linked with Lynch syndrome, which is due to inherited alterations in the mismatch repair genes termed *MLH1*, *MSH2*, *MSH6*, *EPCAM*, and *PMS2*.

As clinical genetic testing moves toward exome-wide and genome-wide sequencing, it is likely that multiple other breast and ovarian cancer susceptibility genes will be identified.

7. Children who are born with two mutated *BRCA2* alleles have which of the following recessive genetic disorders?

A. Fanconi anemia
B. Bloom syndrome
C. Gaucher disease
D. Tay–Sachs disease

Children who are born with two mutated *BRCA2* alleles have Fanconi anemia, type D_1. Fanconi anemia, type D_1 is a rare chromosome breakage syndrome, which is associated with severe anemia and bone marrow failure, growth retardation, and increased risks of leukemia, lymphoma, hepatocellular cancer, and skin cancer. Many, but not all, children with Fanconi anemia have characteristic facies (small head, eyes, and mouth) and absent or deformed thumbs. Fanconi anemia, type D1 is an autosomal recessive genetic condition, meaning that it is caused by inheriting bi-allelic *BRCA2* mutations (one mutated *BRCA2* allele from each parent). Inheriting two mutated *BRCA1* alleles does not appear to be compatible with life and likely leads to an early spontaneous abortion.

It is possible for an individual to inherit both a *BRCA1* mutation and a *BRCA2* mutation. An individual who carries both a *BRCA1* mutation *and* a *BRCA2* mutation appears to have similar cancer risks as an individual who has a single mutated *BRCA* allele. However, the risk to other relatives, especially the individual's siblings and children, is increased (and may be more complicated to sort out).

Case study answers

Case study 124.1

Question 1: Answer C
Question 2: Answer C

Multiple choice answers

Question 1: Answer B
Question 2: Answer D
Question 3: Answer C
Question 4: Answer A
Question 5: Answer B
Question 6: Answer B
Question 7: Answer A

Selected reading

Clarke-Pearson DL. Screening for ovarian cancer. N Engl J Med. 2009;361:170–7.

Daly MB, Axilbund JE, Buys S, *et al*. Genetic/familial high-risk assessment: breast and ovarian. J Natl Compr Canc Netw. 2010 May;8(5):562–94.

Schneider K. Breast cancer syndromes. In: Counseling about cancer: strategies for genetic counseling. 3rd ed. Hoboken, NJ: Wiley-Blackwell; 2012. p. 171–84.

CHAPTER 125

Genetic testing in gastrointestinal tumors

Kristen M. Shannon[1] and Daniel C. Chung[1,2]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA
[2]Harvard Medical School, Boston, MA, USA

Case study 125.1

A 76-year-old man undergoes hemicolectomy for colorectal adenocarcinoma. Immunohistochemistry (IHC) performed on his tumor demonstrates loss of MLH1 and PMS2 protein in the tumor sample. Genetic counseling reveals that he has no prior personal history of cancer and no family history of cancer.

1. What is the most likely reason for the absence of protein in the tumor?

A. *MLH1* germline mutation
B. *PMS2* germline mutation
C. Hypermethylation of the *MLH1* gene promoter
D. *BRAF* mutation

IHC to detect loss of DNA mismatch repair (MMR) protein expression is used to screen for Lynch syndrome. Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited cancer syndrome characterized by early-onset colorectal cancer as well as endometrial, urinary tract, small bowel, ovarian, gastric, pancreatic, hepatobiliary, brain, and skin tumors. Individuals with germline mutations in one of the MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EpCAM*) are defined as having Lynch syndrome. Nearly all colon tumors in individuals with Lynch syndrome will exhibit loss of expression of one or more of these DNA MMR genes as well as DNA microsatellite instability (MSI). The correlation between abnormal MSI and IHC results is generally good. Loss of expression of MLH1 is almost always accompanied by loss of PMS2 expression. This specific pattern can indicate the presence of a germline mutation in the *MLH1* gene but is also observed in approximately 15% of sporadic colorectal cancers due to nonheritable *MLH1* promoter hypermethylation. Thus, when MLH1 and PMS2 are absent on IHC, *MLH1* promoter methylation testing of the tumor sample helps to distinguish sporadic from hereditary tumors. In this case, the clinical phenotype of the patient is not suggestive of a diagnosis of Lynch syndrome (due to lack of family history of Lynch syndrome cancers and late age at diagnosis of cancer). Thus, it is more likely that his tumor is a sporadic tumor and that the loss of MLH1 protein is due to somatic *MLH1* hypermethylation.

Case study 125.2

A 45-year-old man presents with five tubular adenomas on colonoscopy. His next colonoscopy 1 year later reveals an additional five tubular adenomas. He has no family history of cancer or polyps.

1. What genetic tests should be considered?

A. *APC*
B. *MYH*
C. *MSH2*, *MLH1*, *MSH6*, and *PMS2*
D. A + B
E. B + C
F. A + B + C

When a patient presents with multiple adenomas at a young age, one must consider the spectrum of inherited polyposis syndromes. The primary adenomatous polyposis syndromes are familial adenomatous polyposis (FAP), attenuated FAP (AFAP), or MYH-associated polyposis (MAP). FAP and AFAP are caused by mutations in the *APC* gene, and they are inherited in an autosomal dominant fashion.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

MYH-associated polyposis results from bi-allelic mutations in the *MYH* gene, and the syndrome is inherited in an autosomal recessive manner. If a patient with a suspected polyposis syndrome undergoes genetic testing and is not found to have an *APC* gene mutation, *MYH* gene testing should be performed to assess for MAP, as 10–20% of polyposis patients who do not have an *APC* gene mutation have bi-allelic *MYH* gene mutations. The clinical phenotype of MAP is often indistinguishable from FAP or AFAP. The typical polyp burden is usually 10–100 polyps, but sometimes more than 100 polyps can be seen. Family history often does not help to distinguish MAP from FAP. Consistent with the autosomal recessive inheritance pattern, there is often no family history of cancer in individuals with MAP. Of note, approximately 20–25% of individuals with FAP–AFAP have the disease as the result of a de novo (new) *APC* gene mutation and therefore do not have a family history of the disease. Because of the inability to rely on family history for cases such as these, genetic testing for *APC* and *MYH* is often performed concurrently.

Case study 125.3

A 35-year-old, nulliparous woman is diagnosed with a germline mutation in the *MSH6* gene (Lynch syndrome).

1. What tumor is she most likely to develop in her lifetime?

A. Colon cancer
B. Endometrial cancer
C. Stomach cancer
D. Ovarian cancer

A germline mutation in any of the DNA mismatch repair genes (MLH1, *MSH2*, *MSH6*, *PMS2*, or *EpCAM*) establishes a diagnosis of Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC). Individuals with Lynch syndrome are typically counseled that they have a 50–80% lifetime risk of developing colon cancer. However, colon cancer risk estimates are gene dependent and are notably lower for *MSH6* mutation carriers; the lifetime risk is estimated at 44% for males and 20% for females. Although *MSH6* mutations are associated with a lower risk for colon cancer when compared to *MLH1* or *MSH2*, female *MSH6* carriers have a significantly increased (44%) risk for endometrial cancer. Thus, women with an *MSH6* mutation are more likely to develop endometrial cancer than colon cancer. It is essential to recognize the spectrum of extracolonic tumors that are associated with Lynch syndrome.

Case study 125.4

A 40-year-old female is diagnosed with gastric cancer. Pathologic exam reveals signet ring cells (diffuse gastric cancer). Her family history is significant for a mother with breast cancer (lobular type) diagnosed at age 45 and a father with colon cancer at age 70.

1. What genetic test should be considered?

A. *BRCA1/2*
B. Lynch
C. *CDH1*
D. *APC*

Diffuse gastric cancers can occur in the setting of the hereditary diffuse gastric cancer (HDGC) syndrome, an autosomal dominant condition caused by an underlying germline mutation in the *CDH1* (E-cadherin) gene. The lifetime risk of diffuse gastric cancer is estimated to be as high as 70%, and women have up to a 40% lifetime risk of lobular breast cancer. Prophylactic total gastrectomy is considered the standard of care, as microscopic foci of signet ring cancer cells are identified in over 90% of gene carriers. The age at which to perform gastrectomy is not standardized, but consideration should start in the early 20s. The median age of clinically detectable gastric cancer is 38 years. *CDH1* testing identifies fewer than half of gene carriers who fulfill the following International Gastric Cancer Linkage Consortium (IGCLC) criteria: any family with two or more documented cases of diffuse gastric cancer in first- or second-degree relatives with one case under the age of 50, or three documented diffuse gastric cancers in first- or second-degree relatives at any age. In the absence of a positive *CDH1* gene test, prophylactic gastrectomy is generally not recommended. Because conventional mammography may not be sensitive for lobular breast cancers, MRI or prophylactic mastectomy should be offered. Several other hereditary syndromes are associated with an increased risk for gastric cancer (Lynch, Li–Fraumeni, and Peutz–Jeghers), but the gastric cancers seen are typically intestinal-type cancers and not diffuse gastric cancers.

Case study 125.5

The family shown in Figure 125.1 is seen for genetics consultation. Testing performed on the proband's colon cancer reveals a microsatellite high (MSI-H) tumor with loss of MSH2 and MSH6 by IHC. Germline genetic testing on the proband reveals no mutation in the *MSH2* or *MSH6* gene.

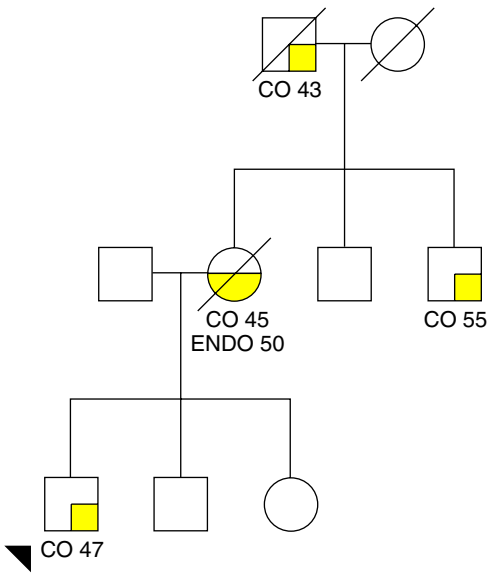


Figure 125.1 Pedigree for Case study 125.5

1. What is the appropriate medical management for the proband's sister?

A. Genetic testing for *MSH2* and *MSH6* mutations
B. Increased surveillance for colon cancer only
C. Increased surveillance for all Lynch-associated tumors
D. Surveillance as if she has general-population risks for cancer

The diagnosis of Lynch syndrome can be made by clinical criteria (Amsterdam criteria) or genetic testing (germline DNA testing for *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EpCAM*). Genetic testing is considered to be more definitive regardless of the family history. However, genetic testing is not 100% sensitive. The Amsterdam criteria are defined as:

- Three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer;
- Two successive affected generations; and
- One or more colon cancers diagnosed before age 50 years.

In this case, the family history fulfills the Amsterdam criteria and the tumor exhibits characteristic molecular features of Lynch syndrome tumors: MSI and loss of staining for a DNA MMR protein. However, no germline mutation in a mismatch repair (MMR) gene is identified. In such cases, mutations may exist that are not detectable using current technology. When such a high-risk family tests negative for germline mutations in a MMR gene, genetic testing is said to be "uninformative." It is not considered to be a "negative" test, as negative test results are considered "true negatives" only when there is a known positive test result within the family. Consequently, the family is considered to have Lynch syndrome based upon clinical criteria, and germline genetic testing cannot be used to distinguish those members with Lynch syndrome from those without the disease. In these cases, all blood relatives in the family should be screened as if they are at significant risk for developing cancer and adhere to Lynch syndrome screening recommendations.

Case study 125.6

A 25-year-old woman presents with the family history shown in Figure 125.2. Her father is known to carry a mutation in the *MSH2* gene. Your patient tests negative for the familial mutation.

1. What does the appropriate screening for her include?

A. Increased surveillance for colon cancer
B. Increased surveillance for all Lynch-associated tumors
C. Surveillance as if she has general-population risks for cancer

In a family where a Lynch syndrome mutation (e.g., *MSH2* mutation) has already been identified, a negative test in a blood relative may be considered a "true negative." This means that the person does not have the high risks for developing cancer associated with Lynch syndrome. However, since cancer is a common disease and most cancers have no known cause, a negative genetic test does not provide any assurance that a person won't develop cancer in his or her lifetime. In this case, the chances of developing cancer are similar to those of the average woman. It is important to note that other risk factors may become more important contributors. For that reason, she must review her personal medical history (e.g., whether or not she has a prior history of colon adenomas) with her physicians and be followed accordingly.

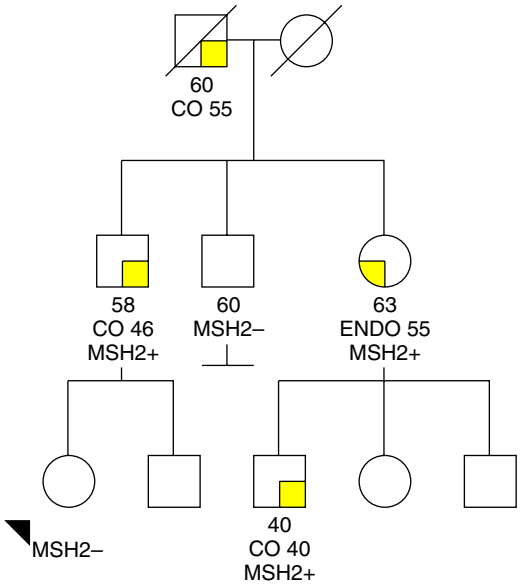


Figure 125.2 Pedigree for Case study 125.6.

Case study 125.7

A male presents with a diagnosis of classic FAP. Genetic testing reveals a mutation in the *APC* gene.

1. In accordance with most other hereditary cancer syndromes, should genetic testing be offered to his children when they reach adulthood?

A. Yes
B. No

Experts agree that genetic testing of children for inherited cancer syndromes needs to be considered carefully. Before testing of children can be performed, there must be some potential benefit from the testing that can be reasonably viewed as outweighing the disadvantages of testing. Since most inherited cancer predisposition syndromes are considered adult-onset diseases (i.e., predisposing to cancer in adulthood), most concede that genetic testing of minors should be deferred until adulthood. However, the classic form of FAP is an exception to this general rule.

In classic FAP, hundreds to thousands of polyps can develop in the colon. These polyps often begin to develop by the age of 12 years (range: 7 to 36 years). Colonoscopy to screen for colonic polyps every 1 to 2 years should begin at age 10 to 12 years, or 10 years prior to the earliest cancer diagnosis in the family, whichever is earlier. Because intervention with colonoscopy would begin at age 10, genetic testing at that age is indicated so that those children who do not have the familial *APC* mutation can avoid the costly and invasive procedure. Genetic testing in infancy may also be considered. The risk for childhood hepatoblastoma in FAP is 750 to 7500 times higher than in the general population, although the absolute risk is estimated at less than 2%. Although no screening recommendations for hepatoblastoma have been standardized for children with FAP, screening may be considered every 3 months from infancy to age 4–5 years.

Case study 125.8

A 30-year-old male presents with carpeting of adenomatous polyps in his colon. Genetic testing reveals a mutation in the *APC* gene.

1. What do his risks for cancer include?

A. Duodenal or ampullary cancer
B. Thyroid cancer
C. Desmoid tumors
D. All of the above

The FAP syndrome results from a germline mutation in the *APC* tumor suppressor gene. This is associated with diffuse colonic polyposis and a nearly 100% risk of colon cancer without prophylactic colectomy. Following colectomy, it is important to recognize the risks of other extracolonic cancers that will require lifelong surveillance. Duodenal adenomas develop in up to 90% of FAP patients, and there is a lifetime risk of 10% of duodenal cancer. The ampulla and periampullary regions are particularly susceptible. Duodenal cancer is the second leading cause of cancer-related deaths in FAP. Papillary thyroid cancer is observed in as many as 12% of FAP families. We recommend upper endoscopy with a side-viewing examination of the duodenum at the time of colectomy or by age 30 and then at 1–3-year intervals depending upon the findings. Thyroid ultrasound examinations should be performed every 1–2 years once the diagnosis of FAP is established. Clinically significant intra-abdominal desmoids tumors are seen in approximately 10% of FAP patients, and these typically occur postoperatively.

Case study 125.9

A 35-year-old male presents with 50 adenomatous polyps on colonoscopy. Genetic testing reveals that he has MYH-associated polyposis.

1. What is the risk to his siblings for also having MAP?

A. 50%
B. 33%
C. 100%
D. 25%

MYH-associated polyposis (MAP) is a newly recognized form of inherited colonic polyposis. The key distinguishing feature when compared to FAP is that MAP is inherited in an autosomal recessive manner. Consequently, an affected individual may not have a compelling family history of polyposis or colon cancer in his or her parents. Each parent is typically a heterozygous carrier of an *MYH* allele, and there is a 25% chance that a child will inherit a mutant *MYH* allele from both parents. The management mirrors that for FAP. The spectrum of extracolonic manifestations of MAP is being defined, and, similar to FAP, upper intestinal polyps are frequently observed. There are some reports of a higher incidence of breast cancer, but these require confirmation. The risk of colon cancer in heterozygous *MYH* carriers may be slightly increased (odds ratio = 1.4), but this is not firmly established.

Case study 125.10

A 45-year-old female presents with adenocarcinoma of the colon. No colon polyps are seen. Her family history is depicted in the pedigree in Figure 125.3. MSI and IHC testing performed on the adenocarcinoma reveals an MSS (microsatellite stable) tumor with MLH1, MSH2, MSH6, and PMS2 proteins present in the tumor.

1. What is the most likely diagnosis for this family?

A. Lynch syndrome
B. MYH-associated polyposis
C. Syndrome X
D. Attenuated familial adenomatous polyposis

A subset of families with a strong family history of colon cancer in the absence of polyposis and MSI has been recognized. These families do not have Lynch syndrome or a polyposis syndrome and have been tentatively designated "syndrome X." The genetic basis of syndrome X remains elusive. A working clinical definition for syndrome X entails the fulfillment of the Amsterdam criteria with the absence of MSI. It is estimated that the colon cancer risks associated with syndrome X are not as high as with Lynch syndrome, and surveillance is recommended at 3–5-year intervals. Exclusion of Lynch syndrome is critical in the evaluation of these families, and this can be accomplished by a combination of MSI testing, IHC staining for DNA mismatch repair proteins, and/or germline genetic testing. Importantly, there does not appear to be an increased risk of extracolonic malignancies as seen in Lynch syndrome. Enrollment of such families into registries is recommended.

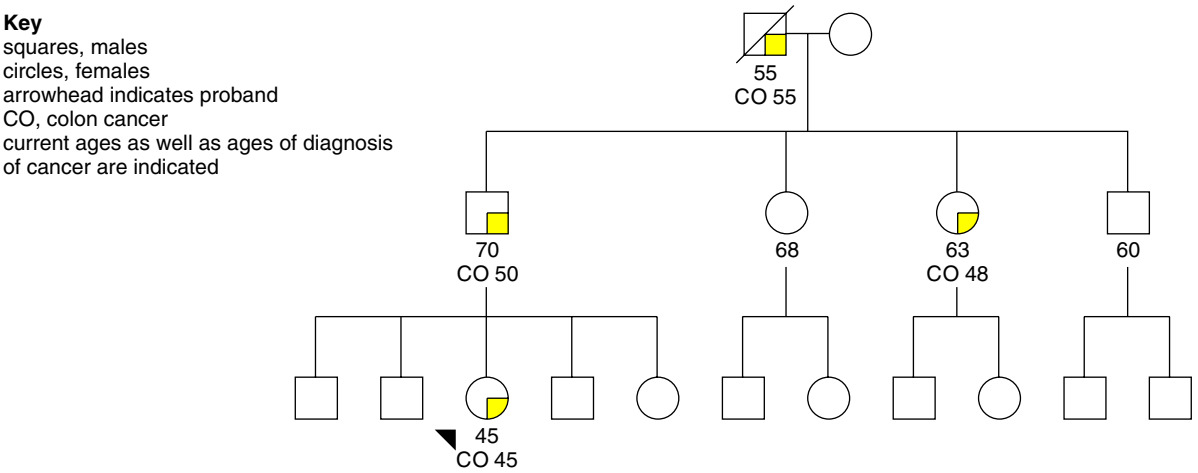


Figure 125.3 Pedigree for Case study 125.10.

Case study answers

Case study 125.1

Question 1: Answer C

Case study 125.2

Question 1: Answer D

Case study 125.3

Question 1: Answer B

Case study 125.4

Question 1: Answer C

Case study 125.5

Question 1: Answer C

Case study 125.6

Question 1: Answer C

Case study 125.7

Question 1: Answer B

Case study 125.8

Question 1: Answer D

Case study 125.9

Question 1: Answer D

Case study 125.10

Question 1: Answer C

Selected reading

Bedeir A, Krasinskas AM. Molecular diagnostics of colorectal cancer. Arch Pathol Lab Med. 2011;135(5):578–87.

Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138(6):2073–87.

Engel C, Loeffler M, Steinke V, *et al*. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012 Dec 10;30(35):4409–15.

Kaurah P, MacMillan A, Boyd N, *et al*. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA. 2007;297(21):2360–72.

Moreira L, Balaguer F, Lindor N, *et al*. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012 Oct 17;308(15):1555–65.

CHAPTER 126

Hereditary urogenital cancer syndromes

Melanie Corbman[1] and Eric Fowler[2]

[1]Eastern Regional Medical Center, Cancer Treatment Centers of America, Philadelphia, PA, USA
[2]Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA

Urogenital malignancies are in the cancer spectra of multiple hereditary cancer syndromes. Some diagnoses are strongly associated with inherited risks for cancer, while others are less predictive of a mutation. This chapter will utilize case presentations to emphasize the importance of personal and family histories in cancer genetics risk assessments, explore some of the challenges and uncertainties associated with genetic counseling and testing, and highlight selected controversies in urogenital cancer genetics.

Case study 126.1

The urological oncologist on staff asks you to meet with a 45-year-old male patient who has been diagnosed with bilateral multifocal, extensive chromophobe and oncocytic renal cell tumors and underwent bilateral partial nephrectomies. The patient had multiple skin-colored papules on his face and reported a large lipoma under his right arm. The patient has a history of smoking. The patient reports the following family history:

- Sister, age 42, was recently diagnosed with bilateral renal cell cancer and had similar papules on her face.
- Sister, age 45, is unaffected with cancer but reported that she had testing for Von Hippel–Lindau (VHL) syndrome due to family history and tested negative.
- Father died at age 48 from complications of a collapsed lung. Father had similar skin lesions and a history of smoking.
- Paternal grandfather had renal cell cancer.
- There are no cancers reported in the maternal family.

1. Considering the patient's personal and family history, what genetic syndromes would be in your differential?

A. VHL syndrome
B. Birt–Hogg–Dubé syndrome (BHDS)
C. No genetic syndrome, since smoking can explain risk for renal cell cancer and pneumothorax

One of the primary features of BHDS is skin-colored papules on the face, neck, and trunk that typically develop in the 20s–30s, and become larger and more numerous with age. Histologically, fibrofolliculomas are the most predictive of and associated with BHDS. Bilateral and multiple cystic pulmonary lesions, pneumothorax, and renal tumors such as chromophobe and oncocytoma (or hybrids of the two) further characterize the syndrome. BHDS can be diagnosed based on clinical findings or molecular genetic testing, with mutations in the FLCN gene being detected in almost 90% of people with the condition. BHDS is an autosomal dominantly inherited condition, with children and siblings of an affected individual having a 50% chance of being affected. Significant intra- and interfamilial variation has been documented.

2. The patient has limited medical insurance. The patient was referred to the dermatologist, who confirmed the diagnosis of BHDS. Would there be any reason for the patient to have genetic testing?

A. Yes, to confirm the diagnosis
B. Yes, to provide information to family members
C. No; the patient already has his diagnosis

With the information provided by the dermatologist to confirm the patient's diagnosis, the patient is more likely

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

to get coverage for the molecular genetic testing. The results of the testing will enable him to get coverage to screen for the other manifestations of BHDS and for his family members to have testing. If a mutation is identified in the patient, family members can have site-specific testing for the identified mutation.

3. If the patient's sons and sister, who have no symptoms, have genetic testing and find out that they test positive, should they have any screening for BHDS?

A. Yes; there are recommended evaluations for individuals who test positive
B. No; they have no symptoms, so they do not need to have unnecessary tests
C. No; a person who has annual medical exams does not need to have any additional testing

Individuals who have been diagnosed with BHDS or those who have been found to carry a FLCN mutation should be monitored by physicians familiar with the syndrome. The following evaluations are recommended:
- Dermatologic evaluation and punch biopsies of skin lesions
- High-resolution computed tomography (HRCT) or computed tomography (CT) of the chest and lungs to monitor for pulmonary cysts. A clinical suspicion of pneumothorax should result in immediate chest X-ray and CT and subsequent management.
- Abdominal and pelvic CT scan or magnetic resonance imaging (MRI) to monitor for renal tumors. Consideration of renal ultrasound to differentiate between cystic and solid lesions.

Case study 126.2

A 52-year-old African American and Native American female patient presented with iron deficiency anemia (large submucosal and extrinsic mass in the fundus with ulceration) and weight loss. CT of the abdomen was concerning for renal cell carcinoma with primary carcinoma of the pancreas versus renal cell carcinoma, and cystic adenoma of the pancreas. The patient underwent left-sided nephrectomy and tolerated the procedure well. The pathology showed clear cell carcinoma with sarcomatoid features (30%), stage III T3N0M0.

The patient reported the following family history:
- Brother, age 60, recently diagnosed with pancreatic cancer, with a son who died of a hemangioblastoma of the spinal cord at age 40
- Sister, age 57, with a history of three strokes and nephrectomy
- Brother with nephrectomy at age 53 for renal cell carcinoma
- Sister, age 45, recently diagnosed with an abdominal mass
- Brother died at age 29 of a cerebrovascular accident
- Mother died at age 67 of a brain stem tumor
- The patient has two sons, 26 and 21, and one daughter, 25, who are unaffected.

1. What hereditary cancer syndromes would you consider based on this patient's personal and family history?

A. VHL syndrome
B. Lynch syndrome
C. Hereditary leiomyomatosis and renal cell cancer (HLRCC)

VHL is associated with hemangioblastomas of the central nervous system and retina, clear cell renal cell carcinoma and renal cysts, endolymphatic sac tumors, and pheochromocytoma. Hemangioblastomas in the cerebellum can be the cause of such signs and symptoms as headaches, gait abnormalities, vomiting, and ataxia. Some people with VHL present initially with vision loss due to retinal hemangioblastomas. The leading cause of mortality in people with VHL is clear cell renal cell carcinoma, occurring in about 70% of affected individuals. Pheochromocytomas should be suspected as a possible cause of hypertension in people with VHL. Mild to severe hearing loss can be caused by endolymphatic sac tumors.

VHL is an autosomal dominant condition. Children and siblings of an individual who tests positive have a 50% risk to have the condition. Approximately four out of five of people with VHL have an affected parent, while one in five affected individuals are the first case in their families.

2. The patient stated that her family has been given a clinical diagnosis of VHL. Since the family already has the diagnosis, is there a benefit to performing genetic testing in this family?

A. There is no need to test this patient since she has already been diagnosed with cancer
B. The patient should concentrate on her cancer diagnosis and not have additional testing
C. Identification of the mutation in this family can enable unaffected family members to have testing and screening

(*Continued*)

The family has been given a clinical diagnosis of VHL, so each family member who is then diagnosed with any of the features of VHL is given the diagnosis of VHL. VHL is the only gene in which mutations are known to cause the condition. The detection rate for mutations is nearly 100%. Unaffected family members can have testing and then be screened for early manifestations of disease. Affected family members can pursue screening for other features of the syndrome. Family members who test negative do not have to pursue screening.

3. The patient's children are reluctant to have genetic testing since they have seen so many members of the family who have been affected with cancer. Why should they consider testing?

A. Since they have a 50% chance of inheriting the mutation, by having testing they can learn the risks for themselves and for passing the mutation onto offspring

B. Individuals who test positive can then begin screening for the associated cancers and manifestations of VHL

C. Individuals who test negative do not have to screen

D. All of the above

With the information provided by genetic testing, family members can define their risks and take steps for tumor screening. The screening recommendations for individuals with VHL, those with a VHL disease-causing mutation, and at-risk relatives who have not been tested include:

- Annual ophthalmologic, blood pressure, and neurological examinations starting at age one year;
- Annual measurement of blood–urinary metanephrines beginning at age 5 years; audiology evaluation every 2–3 years starting at age 5 or as needed if hearing loss is suspected; and
- Annual ultrasound and biennial MRI of the abdomen starting at age 16 years; biennial MRI of the spine starting at age 16 years.

Case study 126.3

A 48-year-old male of English and Norwegian ancestry is referred by a urologist with a recent diagnosis of prostate cancer. He is concerned about cancer risks for his three sons. A review of his family history reveals:

- Father: prostate cancer at age 55
- Paternal grandfather: prostate cancer at age 71
- Mother: breast cancer at age 35, died at age 38
- Maternal aunt: breast cancer at age 39, died at age 39

1. What hereditary cancer syndromes should be considered?

A. Hereditary breast-ovarian cancer syndrome

B. Familial or hereditary prostate cancer

C. Both A and B

This patient's personal and family histories are concerning for a *BRCA1/2* mutation because of the maternal history of early-onset breast cancer, and for familial or hereditary prostate cancer because of the paternal family history.

Prostate cancer is the second most common cancer in men worldwide. In the United States, the lifetime risk for a man to develop prostate cancer is one in six. Risk factors for prostate cancer are age, ethnicity, genetic factors, and possibly diet. Prostate cancer is rarely seen in men under the age of 40, but the risk increases dramatically with age. Prostate cancer has the highest incidence and earliest age of onset in African American men.

The features of hereditary prostate cancer are three or more affected men in one family, at least one affected man in each of three generations, or two men diagnosed under the age of 55. Hereditary prostate cancer appears to follow a pattern of autosomal dominant inheritance. Several prostate cancer candidate genes have been identified, and a recent study found a rare but recurrent mutation in the HOXB13 gene.

In familial prostate cancer, multiple genetic variants contribute to prostate cancer risk along with factors such as diet and environment. Having a brother or father diagnosed with prostate cancer doubles a man's risk for prostate cancer. The risk increases with the number of affected relatives and younger ages at diagnosis. Men in families with hereditary or familial prostate cancer have a 1.5–7.0-fold increased risk for prostate cancer. Men with BRCA1 and BRCA2 mutations and African American men have a 2–5-fold increased risk for prostate cancer.

Screening for prostate cancer is recommended to start at age 35–40 in men with BRCA mutations, men in families with a strong history of prostate cancer, and African American men. Screening for prostate cancer includes digital rectal exam, PSA (prostate-specific antigen), PSA velocity, and percentage of free PSA.

The patient in this case has BRCA1/2 testing and has no mutations identified. The patient wants his sons to have a genetic test for prostate cancer that he has found online. The patient provides you a website, and the requested test evaluates several genetic markers that have a minimal impact on prostate cancer risks in certain populations.

2. What is the most appropriate response to the patient's request?

A. To offer his sons the online test
B. To deny the patient's request, stating the testing is unnecessary
C. To explain the limitations of the proposed testing and how the results would not impact his sons' medical management

Genome-wide association studies (GWAS) evaluate the statistical impact of genetic variants (called polymorphisms and usually involving a single base pair change in the DNA sequence) on diseases in populations and groups of people. Unlike high-risk mutations in genes associated with inherited cancer syndromes, most of the variants that have been identified with GWAS have a small impact on actual risks for disease, and risks may be further modified by polymorphisms in other parts of the genome. Due to the complex and multifactorial etiology of most diseases, such testing currently does not provide an accurate measure of personalized risk.

Direct-to-consumer marketing of these tests is ongoing, testing can be initiated without physician orders, and patients self-pay for testing. In this case, the family history of prostate cancer warrants more intensive and earlier prostate cancer screening for the patient's sons, regardless of the results of the proposed testing.

3. What additional testing could be offered to this patient?

A. Research studies that include genetic testing for prostate cancer–specific susceptibility genes
B. Clinical genetic testing for prostate cancer–specific susceptibility genes
C. There are no additional testing options

Prostate cancer susceptibility genes have been identified, areas of chromosomal interest have been localized, and testing is available on a research basis. Research studies are searching for new prostate cancer risk genes, identifying genes that modify prostate cancer risks, and evaluating high-risk genes already linked with prostate cancer susceptibility. Eligibility criteria for enrollment in prostate cancer genetics research studies include the age at diagnosis of the patient (early-onset, typically <age 55) and/or the family history of prostate cancer (multiple cases). Some studies will provide genetic test results to participants, and enrolling in research studies gives some patients a sense of making a meaningful contribution to medical science. Cancer genetics research studies can be located at http://www.clinicaltrials.gov.

Case study 126.4

A 42-year-old African American female presents with carcinoma of the renal pelvis. She reports a 2-year history of blood in her stool, presumably because of hemorrhoids. The family history is as follows:

- Sister: endometrial cancer at age 50
- Sister: breast cancer at age 52
- Father: colon cancer at age 55

1. What hereditary cancer syndrome should be considered in this family?

A. Hereditary breast-ovarian cancer syndrome
B. Cowden syndrome
C. Li–Fraumeni syndrome
D. Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC)

This family history meets Amsterdam II criteria for Lynch syndrome (LS), which is defined as:

- Three or more family members, one of whom is a first-degree relative of the other two, with HNPCC-related cancers
- Two successive affected generations
- One or more of the HNPCC-related cancers diagnosed before age 50 years.

Cancers in the LS spectrum to which these criteria apply include colorectal, endometrial, stomach, small intestinal, hepatobiliary, renal pelvis, and ureter cancers. The rectal bleeding in the patient, especially since Amsterdam II criteria are met, is concerning for colorectal cancer.

LS is inherited in an autosomal dominant manner and is caused by mutations in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* and by deletions in the *EPCAM* gene. Lynch syndrome is the most common cause of hereditary colorectal and endometrial cancer, accounting for 2.7% and 2.1% of all cases, respectively. The prevalence of LS in the general population is estimated to be 1 in 300. Lifetime cancer risks for people with LS are: colon, 52–82% (average age: 44–61 years); endometrial, 25–60% (average age: 48–62 years); gastric, 6–13% (average age: 56 years); and ovarian, 4–12% (average age: 42.5 years, with 30% <age 40). There are lower, yet still increased, risks for cancers of the small intestine, urinary tract, hepatobiliary tract, brain, and skin.

(*Continued*)

2. According to National Comprehensive Cancer Network (NCCN) guidelines, how should patients with LS be screened for urinary tract cancers?

A. Annual urinalysis
B. Annual ultrasound
C. Annual CT or MRI
D. All of the above
E. None of the above

NCCN guidelines for screening for urinary tract cancers in patients with LS state, "Consider annual urinalysis starting at age 25–30." Urinalysis, regardless of the findings, is nonspecific for malignancy. Some European centers are recommending more intensive screening starting at age 30–35, including annual or biennial abdominal ultrasounds, and urine cytology in addition to urinalysis. Family history and genotype should be considered when developing a screening regimen, with more intensive screening offered to patients with family histories of urinary tract cancers.

Patients with LS are at increased risk for cancers of the renal pelvis and ureters, with some studies demonstrating an increased risk for bladder cancer. The lifetime risk for urinary tract cancers in people with LS is generally quoted as between 1% and 4%, but there is evidence that risks are impacted by patient genotype and gender. One study found men with MSH2 mutations have up to a 27% lifetime risk for urinary tract cancers, whereas women with MLH1 mutations have only a 1% chance for urinary tract cancers.

Case study answers

Case study 126.1

Question 1: Answer B
Question 2: Answer B
Question 3: Answer A

Case study 126.2

Question 1: Answer A
Question 2: Answer C
Question 3: Answer D

Case study 126.3

Question 1: Answer C
Question 2: Answer C
Question 3: Answer A

Case study 126.4

Question 1: Answer D
Question 2: Answer A

Selected reading

Ewing CM, Ray A, Lange E, *et al*. Germline mutations in HOXB13 and prostate-cancer risk. NEJM 2012;366:141–9.

Klein, C, Lohmann, K, Ziegler, A. The promise and limitations of genome-wide association studies. JAMA 2012;308(18): 1867–8.

National Comprehensive Cancer Network (NCCN). NCCN practice guidelines in oncology: prostate cancer early detection version 2.2012; Genetic/familial high risk assessment: breast and ovarian version 1.2012; and Colorectal cancer screening, version 2.2012. http://www.nccn.org (accessed February 15, 2014).

National Center for Biotechnology Information. Bookshelf [review of Gene reviews]. http://www.ncbi.nlm.nih.gov/books/NBK1116/ (accessed February 15, 2014).

Rybak C, Hall J. Interpretation of genetic testing for Lynch syndrome in patients with putative familial colorectal cancer. JNCCN 2011;9(11):1311–20.

PART 12

Special Issues in Hematology and Oncology

CHAPTER 127

Carcinoma of unknown primary (CUP)

Isabella C. Glitza and Gauri R. Varadhachary
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Multiple choice questions

1. Carcinomas of unknown primary (CUP) pose a challenge for the treating oncologist, given the heterogeneous presentations. Which of the following clinical scenarios is associated with a "favorable" outcome in CUP patients?

A. Multiple brain metastases
B. Adrenal metastases
C. Cervical adenopathy with squamous cell carcinoma presentation
D. Liver metastases

The working definition for carcinoma of unknown primary is a biopsy-proven metastatic cancer with no identifiable primary source by history, physical examination, chest radiography, complete blood count, chemistry panel, computed tomography (CT) of chest, abdomen and pelvis, prostate-specific antigen (PSA) in men, and mammography in women.

It is important to recognize patients that fit the favorable subgroups, because specific treatments may significantly extend survival. In addition, the prognosis largely depends on chemosensitivity of the tumor; therefore, it is crucial not to miss more favorable presentations like extragonadal germ cell tumors or patients presenting with isolated single small metastases, papillary peritoneal or isolated axillary adenocarcinoma in women, cervical adenopathy with squamous cell histology, and neuroendocrine histology. Patient and tumor-specific factors are also associated with outcome, and male sex, adenocarcinoma subtype on histologic evaluation, and metastatic involvement of liver, lungs, bone, pleura, and brain have been shown to be associated with worse outcomes.

In general, in retrospective studies, median survival of these patients ranged from 11 weeks to 11 months, with a 5-year overall survival (OS) rate at the University of Texas MD Anderson Cancer Center of 11%.

Case study 127.1

A 57-year-old male patient presents to your clinic. His work-up reveals CUP adenocarcinoma with lung metastases, a performance status of 2, albumin 3 g/dl (3.5–4.7), alkaline phosphatase 158 IU/L (38–126), CA 19–9 300 U/ml (<37), and his lactate dehydrogenase (LDH) 1.5 times the upper normal limit. The patient is asking about your prediction for length of survival in his case.

1. When using a validated prognostic model to predict the length of survival in CUP patients, the combination of which following two factors has shown to have the shortest overall survival?

A. Poor performance status and LDH
B. Decreased albumin and elevated alkaline phosphatase
C. Poor performance status and elevated CA 19-9
D. Elevated CA 19-9 and elevated alkaline phosphatase

Based on a simple but validated prognostic model published by Culine *et al*. in 2002, poor performance status and elevated LDH were associated with significant decrease in length of survival. When evaluating clinical variables, only poor performance status and liver metastases were identified as adverse prognostic variables on multivariate analysis. After adding biological markers to the analysis, only elevated serum LDH levels showed influence on survival length.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Case study 127.2

A 59-year-old white woman is being referred for right-sided isolated axillary lymphadenopathy. Excisional biopsy is positive for moderately differentiated adenocarcinoma. Chest X-ray, bilateral mammogram and a breast ultrasound are negative for any suspicious lesions in the breasts. CT scan of the chest and abdomen and pelvis is within normal limits as well, with no evidence of metastases.

1. What would be your next best step to managing the care of a woman with CUP and isolated axillary adenopathy?

A. Positron emission tomography CT (PET)–CT
B. Magnetic resonance imaging (MRI) of both breasts
C. Random biopsies from ipsilateral breast
D. Mammogram in 6 months

Occult breast cancer is the most likely differential diagnosis in any woman presenting with isolated axillary lymphadenopathy and adenocarcinoma, although it is important to rule out lung cancer, adnexal gland tumors, and other cancers because of their different therapeutic approaches. First-tier immunoperoxidase stains include estrogen receptor (ER), progesterone receptor (PR), GCDFP-15, mammoglobin, Her2neu, CK7, CK20, TTF1, and Napsin A. She should get additional tests to evaluate for a primary breast cancer. In general, women with this presentation fall into a subset with a more favorable prognosis and are often managed as stage II breast cancer.

Most guidelines and experts would recommend, after mammogram and ultrasound being negative, to continue the work-up with a dedicated breast MRI. The sensitivity to detect small primary breast tumors has been reported to be 75–90%, while carrying a very low false-negative rate. The yield of random biopsies is minimal. In light of negative MRI, most experts would recommend against mastectomy or treatment with breast irradiation, but treatment would consist of taxane- and anthracycline-based chemotherapy.

2. What is the frequency of adenocarcinoma presentation as CUP cancer—additionally, what are the different histological subtypes in CUP?

A. 2–3%
B. 5%
C. 20%
D. 65%

Adenocarcinoma is the most common histologic subgroup on light microscopy. It can be subdivided into well-, moderately, and poorly differentiated adenocarcinoma. Together, they comprise about 65% of all CUP. Poorly differentiated or undifferentiated carcinomas compose about 20% of the group, while squamous cell carcinomas are observed in 5%. Neuroendocrine and mixed histology forms about 2–3%. Adequate biopsy material and close communication with the pathologist are essential to the work-up.

Case study 127.3

A 54-year-old female presents to your office with a history of a growing "lump" in her right neck for the last 5 months. She admits to heavy smoking (a 60-pack-year history) as well as moderate alcohol intake. Currently, she has some dyspnea on exertion from her known chronic obstructive pulmonary disorder and some unintentional weigh loss. Examination of the oral cavity reveals no lesions, but you can palpate two (2–2.5 cm) enlarged neck lymph nodes high in the right posterior cervical triangle. Biopsy reveals squamous cell carcinoma.

1. What is the comprehensive work-up for a "high" neck cervical lymphadenopathy presentation in CUP?

A. PET CT
B. Indirect and direct laryngoscopy, bronchoscopy, and upper endoscopy
C. Bilateral tonsillectomies
D. All of the above

In CUP with high metastatic cervical adenopathy with squamous cancer presentation, all of the above modalities help in search of the primary and with the management of these patients. Bilateral staging tonsillectomies is often performed since random tonsillar biopsies tend to miss the primary tumor in the deeper tonsillar crypts, and studies have shown that occult tonsillar carcinoma is found in up to 30% of patients undergoing tonsillectomies and is sometimes found in the contralateral tonsil. Panendoscopy includes a direct laryngoscopy, bronchoscopy, and esophagoscopy and is part of the work-up in patients presenting as above. PET–CT is recommended for staging in this patient population. Finding a primary cancer has some implications—the radiation field can be restricted to minimize xerostomia, and it helps with future surveillance as well. As previously discussed, patients presenting with cervical adenopathy and squamous cell histology fall generally into a more favorable subgroup.

Case study 127.4

A 60-year-old female patient, who was a lifetime smoker, was found to have hilar adenopathy on examination with a chest X-ray after a fall on ice. The incidental finding triggered further work-up, and a PET–CT scan revealed no further abnormalities besides the findings above (no parenchymal lung lesions). Bronchoscopy was negative for a primary tumor. Tissue was reported as poorly differentiated adenocarcinoma, and IHC stains included CK7, CK20, CDX-2, TTF, vimentin, and S-100.

1. Which of the following stain pattern would be suggestive of a lung primary in this case?

A. CK7−, CK20+, CDX2+
B. CK7+ and CK20+, S100−
C. CK7+, CK20−, TTF1+
D. S100+, Vimentin+, CK7−

Useful immunohistochemical stains in the work-up for this patient include cytokeratin 7 and 20, as well the thyroid transcription factor-1 (TTF1). TTF1 is a nuclear transcription factor and is frequently found in adenocarcinomas of the lung (66–87%), and it is less consistently expressed in the squamous cell subtype. CK7 is positive in a variety of cancers, including pulmonary and gynecology malignancies, upper gastrointestinal cancers, and pancreaticobiliary cancers, and CK20 is often associated with gastrointestinal adenocarcinomas. CK7+/CK20− and positive staining for TTF1 are highly suggestive of a lung primary. Napsin A is another stain that is used to help with the diagnosis of a lung profile CUP presentation.

Case study 127.5

1. A 30-year-old white man, nonsmoker, presents with a 10 cm mediastinal mass, worsening chest pain, and unintentional weight loss of about 15 lbs. over the last 2 months. Biopsy of the mass is reported as "poorly differentiated carcinoma," and IHC is negative for TT-1 and CK20, but positive for PLAP and OCT4. CT evaluation reveals a midline mediastinal tumor, and otherwise no evidence of disease elsewhere. An ultrasound of the testes is negative. His beta human chorionic gonadotropin is elevated to 110 mIU/ml, and his alpha-fetoprotein levels are normal.

1. What is the most appropriate treatment for him?

A. Taxane-based therapy
B. Cisplatin-based therapy
C. Anthracycline-based therapy
D. Rituximab-based chemotherapy

In patients with CUP, it is important to try to identify those who have chemosensitive tumors and therefore offer the best treatment possible. This patient likely has an extragonadal germ cell tumor with his history, age, and elevated beta human chorionic gonadotropin. Testicular ultrasound is mandatory in all patients in whom extragonadal germ cell tumor is suspected. These patients have a more favorable prognosis with a curative potential. Standard of care for extragonadal germ cell tumors is a cisplatin-based chemotherapy. Taxanes form the backbone for lung primaries, anthracyclines are being used in the treatment of breast malignancies, and rituximab is the main component in regimens used for lymphomas.

2. In this patient, what abnormality would be most likely seen on genetic analysis?

A. Isochromosome of the short arm of chromosome 12 (i12p)
B. Deletion of 3p
C. Deletion of 11p
D. Deletion of 1p

In select patients, cytogenetics can aid in the further work-up of CUP. Isochromosome of 12p is most often seen in germ cell tumors. Deletion of 3p is seen in small-cell carcinomas, deletion 11p in Wilms tumor, while deletion of 1p is seen in neuroblastoma. For patients with a poorly differentiated presentation (with nonspecific markers) and a high suspicion for testicular cancer, the work-up includes testing for i12p.

Case study 127.6

A 65-year-old woman is evaluated for increased abdominal girth over the last 2 months as well as mild abdominal pain. She recently noticed some anorexia, increased fatigue, and weight loss of >10% of her body weight since the symptoms first started. CT of the abdomen and pelvis confirms ascites and diffuse peritoneal implants, but no obvious ovarian mass or any additional abnormalities. Transvaginal ultrasound is normal (no ovarian abnormalities). Her CA-125 is elevated to 1245 U/ml, and CT-guided biopsy of one of the peritoneal implants reveals poorly differentiated adenocarcinoma, favoring papillary serous type.

1. The best treatment approach in this patient would be which of the following?

A. Surgery
B. Chemotherapy
C. Radiation
D. Optimal debulking surgery followed by chemotherapy

Female patients presenting with CUP consistent with isolated carcinomatosis and adenocarcinoma can be normally divided into two broad categories: primary peritoneal serous carcinoma (PPSC) and the non-PPSC group. The non-PPSC group is composed largely of CUP consistent with other cancers, including upper and lower gastrointestinal cancers, pancreaticobiliary cancers, appendiceal, and occasionally mucinous ovarian cancers. Rarely, patients with peritoneal mesothelioma are misdiagnosed as poorly differentiated carcinoma. Given the available treatment choices for metastatic colon cancer, it is important to consider further investigation with immunohistochemical stains (CK20+, CK7, and CDX2+) and, when indicated, directed endoscopies.

In patients with PPSC, taxane- and platinum-based chemotherapy can prolong survival in these patients to a median of 13 months (or longer) with a 25% rate of PFS exceeding 2 years. The approach is therefore the same as for women with ovarian cancers.

Case study 127.7

A 68-year-old female presents with shortness of breath and is found to have isolated left pleural effusion. She has a long-standing history of smoking. Further work-up is consistent with CUP (no other areas of disease) and isolated pleural effusion.

1. Which of the following statements is true in regard to this entity?

A. The cause for the effusion is most likely underlying mesothelioma
B. Pleurodesis is contraindicated in these patients
C. Immunohistochemistry should include TTF-1, CK 7/20, calretinin, breast (ER/PR/GCDFP-15), and ovarian (WT-1, PAX-8) markers
D. Radiation therapy to the chest wall of the side of the effusion is standard of care

Isolated pleural effusions are usually adenocarcinomas. Sometimes it may be difficult to differentiate from mesotheliomas, but epitheloid malignant mesothelioma typically stains for calretinin, CK5/6, and WT1. Symptomatic relief might be achieved by pleurodesis or pleural catheter, especially when the effusion re-accumulates quickly. Radiation, especially to the chest wall, has no role in patients with presumed pulmonary primary, and mainstay of therapy is a taxane–carboplatin or gemcitabine–cisplatin doublet. Symptomatic improvement can be seen in up to 78% chemotherapy, with a median survival of about 12 months (range 3–60).

3. True or false? 18F-fluorodeoxyglucose PET (FDG-PET) is warranted in the work-up of all patients presenting with CUP.

A. True
B. False

PET–CT tends to be overused in the diagnostic work-up of patients presenting with CUP. For most patients, a good-quality intravenous contrast CT scan is the initial diagnostic modality recommended. One exception is patients presenting with cervical adenopathy and squamous cell histology on pathology, and PET–CT is often recommended. Also, PET–CT may be used in patients with solitary metastatic disease since it may influence the use of definitive therapy, including surgery and/or radiation therapy; other settings where PET–CT could be used for a more cost-sensitive approach are in patients with predominant osseous metastatic presentation and on active therapy. In these patients, PET–CT can be used instead of combining CT and MRI to monitor the extent of disease and response to therapy.

4. True or false? Tissue-of-origin (ToO) profiling is an emerging tool in the pathological work-up of CUP patients.

A. True
B. False

ToO profiling is a promising technique using reverse-transcriptase polymerase chain reaction (RT-PCR) or DNA microarray. A recent study tested the reliability of using RT-PCR to determine the tissue of origin in patients. Tumor tissue of CUP patients with adequate biopsies and in whom the primary tumor site was identified later on was molecularly profiled using RT-PCR in a blinded fashion. In 75% of the examined cases, the assay prediction matched the latent primary tumor site. Using indirect validation, several studies (using the mRNA- and micro-RNA-based assays) have shown that molecular-profiling assays perform well in defining the putative primary site in CUP cancers. ToO profiling tests are not indicated in cases where a diagnostic IHC suffices. They are helpful where IHC is nondiagnostic despite adequate tissue. Comparative effectiveness studies comparing ToO to IHC are ongoing and in the era of molecular diagnostics, the development of novel therapies for known cancers will help us leverage those therapies for CUP subsets.

Case study answers

Case study 127.1

Question 1: Answer A

Case study 127.2

Question 1: Answer B

Case study 127.3

Question 1: Answer D

Case study 127.4

Question 1: Answer C

Case study 127.5

Question 1: Answer B
Question 2: Answer A

Case study 127.6

Question 1: Answer D

Case study 127.7

Question 1: Answer C

Multiple choice answers

Question 1: Answer C
Question 2: Answer D
Question 3: Answer B "False"
Question 4: Answer A "True"

Selected reading

Culine S, Kramar A, Saghatchian M, *et al*. Development and validation of a prognostic model to predict the length of survival in patients with carcinomas of an unknown primary site. J Clin Oncol. 2002;20:4679–83.

Oien KA, Dennis JL. Diagnostic work-up of carcinoma of unknown primary: from immunohistochemistry to molecular profiling. Ann Oncol. 2012;23 (Suppl. 10):x271–7.

van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, *et al*. Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in southeast Netherlands, 1984–1992. Eur J Cancer. 2002;38:409–13.

Varadhachary G. Molecular profiling for CUP cancers: are we there yet? Onkologie 2012;35:11–12.

Varadhachary GR. Carcinoma of unknown primary: focused evaluation. J Natl Compr Canc Netw. 2011;9:1406–12.

CHAPTER 128

Geriatric oncology

Nayana Kamath and Supriya Gupta Mohile

University of Rochester James P. Wilmot Cancer Center, Rochester, NY, USA

1. What is geriatric oncology, and why is it important?

By 2030, approximately 20% of the population in the United States will comprise people aged 65 years and older, and the fastest growing subgroup of the population is those aged 75 and older. It is known that cancer is a disease of aging, with approximately 60% of all cancers and 70% of cancer mortality occurring in persons aged 65 years and over. It is also well known that older age is related to differences in cancer biology, patterns of care, and outcomes. Age is an independent predictor of distant metastases in prostate cancer, even after initial treatment. In non-Hodgkin's lymphoma, one of the negative prognostic factors for outcomes is age >65 years. In the realm of leukemia, older patients have more adverse effects from intensive treatment compared to younger patients. There are multiple factors that may be linked to the higher incidence and prevalence of cancer in the elderly population, including a decline in immune system function, longer duration of carcinogenic exposure over lifetime, altered DNA repair mechanisms with increased susceptibility to carcinogens, inherited or acquired oncogene activation or amplification, and tumor suppressor genes defects.

The Cancer Therapy Evaluation Program (CTEP), a Division of Cancer Treatment of the US National Cancer Institute (NCI), sponsors clinical trials of cancer treatment and helps in identifying the best treatment strategies for patients with cancer. Although, in most cases, age restriction is not a valid eligibility criterion for adult NCI trials, studies have shown that only 25–32% of participants in cancer clinical trials are elderly. This gap is especially concerning for those cancers in which a high proportion of patients are elderly. For example, although one-third of all lung cancer patients are aged 75 and older, less than 10% of patients in clinical trials are within this age range. Several reasons have been proposed to explain the paucity of elderly patients enrolled in trials, including a history of prior malignancy, comorbid chronic health, advanced stage of disease, low educational level, and perception among patients, family members, and clinicians that the tolerance to and benefit attained with aggressive treatment by older patients may not be as substantial as that seen by younger patients.

All of these factors and more have resulted in the development of geriatric oncology, a subspecialty in oncology, where clinicians are trained both as oncologists and geriatricians to recognize that aging is a highly individualized process and that age-related changes are important to indentify. Geriatric oncologists advocate the use of a comprehensive geriatric assessment is used to ensure that elderly patients with cancer are provided with the best possible care based on individual functional reserve and life expectancy.

2. What is the comprehensive geriatric assessment? Are there alternatives?

The comprehensive geriatric assessment (CGA) is the gold standard used by geriatricians to assess a patient's physical, mental, and psychosocial well-being (Table 128.1). The combined data from the CGA can be used to stratify patients into risk categories to better predict their tolerance to treatment, disease prognosis, and chemotherapy toxicity. The CGA can also help to identify geriatric syndromes that may complicate cancer care. CGA has been advocated by the National Comprehensive Cancer Network (NCCN) for use with all patients aged 70 and over with health conditions other than cancer. All measures in the geriatric assessment predict morbidity and mortality in community-dwelling older adults and can be used to identify impairments that could negatively impact the outcomes of older cancer patients. Geriatric oncologists use the CGA to guide interventions to improve care. However, one criticism of

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Table 128.1 Components of a comprehensive geriatric assessment (CGA).

Parameter assessed	Elements of the assessment
Function Physical performance: Timed Up and Go, SPPB	Performance status Activities of daily living Independent activities of daily living
Comorbidity	Number of comorbid conditions Severity of comorbid conditions (comorbidity index)
Socioeconomic conditions	Living conditions Presence and adequacy of a caregiver
Cognition	Folstein's minimental status or other tests
Emotional conditions, anxiety	Geriatric Depression Scale (GDS)
Pharmacy	Number of medications Appropriateness of medications Risk of drug interactions
Nutrition	Mini-nutritional assessment (MNA)
Geriatric Syndromes	Dementia Depression Falls Neglect and abuse Spontaneous bone fractures

the CGA is that it can be cumbersome and time-consuming to administer.

The Cancer and Aging Research Group (CARG) chemotoxicity assessment tool uses elements of the CGA to help risk stratify elderly patients. This tool assesses the likelihood of older cancer patients developing grade 3–5 toxicity from standard treatment. Another tool available is the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), which looks at laboratory test values and geriatric assessment parameters besides age, such as functional and nutritional status, comorbidity, cognition, psychological state, and social support to help the oncologist objectively decide whether treatment is beneficial for the older cancer patient. Both these tools are less time consuming and easier to interpret than the CGA, thereby making them accessible to oncologists in the community with limited resources.

3. What factors affect health status in older adults?

Factors that affect health status in older adults include chronic health conditions (comorbidities), disabilities, and geriatric syndromes. Older age is associated with increased comorbidities and decreased organ function, which can lead to an increased risk of adverse events such as hospitalization, loss of independence, and death. In a study of 19,268 patients with newly diagnosed cancer, the duration of survival was compared between patients with no comorbid conditions and patients with mild, moderate, or severe comorbid conditions. In all tumor types, decreased duration of survival was seen in patients with mild, moderate, or severe comorbid conditions, as compared to patients without comorbid conditions.

Disability in the geriatric population is based on the evaluation of ADLs (activities of daily living) and instrumental ADLs (IADLs). ADLs are skills required for basic self-care, such as the ability to bathe, feed, dress, toilet, and transfer one-self as well as maintain continence. These skills are necessary to maintain independence in one's own home, whereas IADLs are the skills necessary to maintain independence in the community. IADLs include the ability to perform housekeeping and laundry, prepare meals and shop for groceries, administer medication, manage finances, access transportation systems, and use the telephone. Dependence on others for ADL and IADL assistance has been shown to be predictive of mortality in geriatric oncology patients, and it has been observed that older patients with cancer have a higher incidence of ADL and IADL deficiencies when compared to age-matched controls.

The term "geriatric syndrome" is used to capture those clinical conditions in older persons that do not fit into discrete disease categories. Geriatric syndromes develop as a consequence of physiologic vulnerability, presence of multiple comorbidities, and effects of therapeutic interventions. Examples of geriatric syndromes include significant depression, dementia, delirium, incontinence, confusion, falls, and skin breakdown. Evidence of geriatric syndromes in a clinical encounter with an older patient should signal to the physician that the patient may be vulnerable to toxicity from cancer-directed therapy or at increased risk for adverse outcomes.

4. What is frailty?

"Frailty" is a term from geriatrics that describes older patients who are vulnerable to stressors and susceptible to adverse outcomes, including falls, disability, hospitalization, and death. A commonly accepted operational definition developed by Fried and colleagues (2012) is a clinical syndrome in which three or more of the following five criteria are present: involuntary weight loss, exhaustion, weakness, slow gait speed, and sedentary lifestyle. If 1–2 criteria are present, then patients are classified as vulnerable.

There are several frailty models that have attempted to provide important prognostic information for the elderly;

Table 128.2 Balducci criteria for frailty.

Frailty criteria	Characteristics
Age	Greater than 85 years
Activities of daily living	Dependence for 1 or more
Comorbidity	≥3 or 1 life-threatening
Geriatric syndromes	One or more of the following: • Delirium • Dementia • Depression • Osteoporosis • Incontinence • Falls • Neglect and abuse • Failure to thrive

however, very few address outcomes specifically for the oncology patient population. One attempt that addresses this concern is the Balducci frailty criteria (Table 128.2).

In addition to the clinical definition, research has also increasingly focused on the identification of reliable biomarkers of frailty. While the pathophysiology of frailty is not completely understood, chronic inflammation has been proposed as an underlying biological mechanism, and thus the use of inflammation biomarkers have been proposed for predicting frailty. In particular, high CRP, low D-dimer, high interleukin-6, low hemoglobin, albumin, and low cholesterol are some of the identified biomarkers associated with functional decline and mortality.

The general consensus is that as people get older, they are less likely to survive due to chronic diseases in combination with the loss of mobility, sensory, and cognitive function. Older people with these deficits are less likely to tolerate minimal stressors, and may be at high risk for side effects from cancer-directed therapies. As the population ages, vulnerability and frailty are important conditions that need to be assessed before decisions are made about cancer care for the elderly.

5. How does aging impact cancer treatment?

Although cancer treatment for older adults can sometimes be complicated and challenging, treatment can be helpful. The goals of cancer treatment in older adults may include curing cancer, prolonging life, and improving quality of life through palliation. In general, age itself is not a contraindication or limitation to chemotherapy, although poor performance status, functional impairment, and comorbid conditions that are frequently present in the elderly population likely influence the ability to tolerate efficacious treatment. Although aging is a heterogeneous process, there are certain common and characteristic age-related physiologic changes that can lead to differences in the pharmacology of cancer therapies in elderly patients as compared to their younger counterparts. These age-related changes can be subtle and difficult to identify. Pharmacokinetic studies of cancer chemotherapy have included only a very small number of older patients, and it is often difficult to apply these data to the clinical care of older populations. Consequently, the data that are utilized for chemotherapy dosing is inferred from clinical trials that did not specifically target older persons.

In older cancer patients, nonadherence to prescribed medications is prevalent and can influence survival. Nonadherence to therapies may result from both clinician and patient factors. The clinician may fail to understand the patient's cognitive, functional, or financial status. The patient may not fully understand the reasons behind certain medications and may not fully grasp the scheduling and dosing of complex treatment regimens. In addition, depression or dementia and the use of multiple other medications may impact adherence.

Physiological comorbid conditions such as renal impairment, heart failure, and the presence of ascites or pleural effusions increase the volume of distribution and require dose adjustment of certain agents. Albumin concentration can affect protein-bound drugs. Albumin concentrations are decreased in older patients due to decreased manufacturing ability of the liver. Therefore, protein-bound drugs are displaced in older patients, leading to higher drug concentrations.

Age-related changes in renal function can affect the elimination of anticancer therapies. These changes include decreased renal blood flow, a decreased number of functioning nephrons, and decreased renal tubular secretion. Serum creatinine is the most common tool that is utilized to evaluate renal function. While serum creatinine tends to accurately reflect the glomerular filtration rate in younger adults, it does not always truly reflect the renal function in older patients. In older patients, serum creatinine can stay in the normal range, masking changes in creatinine clearance due to a lower lean body mass and a lower glomerular infiltration rate. Chemotherapy that is primarily excreted through the kidney must be utilized with extreme caution in older patients with renal dysfunction.

Stem cell and hematopoietic reserve can be compromised in older patients. This lowered reserve can lead to potentially serious adverse chemotherapy effects. The risk of neutropenia from chemotherapy is also significantly higher in older patients, and leads to greater complications, increased hospitalizations, and a higher mortality rates. Due to concerns of potential toxicity due to lower bone marrow reserve, older patients may receive less effective doses of chemotherapy, even in the adjuvant or curative setting. Primary prophylaxis with granulopoietic growth factors has been advocated for older patients receiving chemotherapy. One systemic review of 17 randomized

controlled studies revealed a 46% decrease in the rate of febrile neutropenia and a 40% decrease in death during chemotherapy in patients who received primary prophylaxis.

Other important patient characteristics such as sex, ethnicity, comorbid conditions, polypharmacy, frailty, and stress may overlap with and significantly impact cancer treatment options for the elderly cancer patient.

6. How can information from the CGA be incorporated into oncology clinical care?

The CGA is a useful multidimensional tool that has been used in preventing geriatric syndromes, recognizing cognitive deficits, and identifying potential complications that can affect cancer treatment. In doing so, the CGA is helpful in preventing toxicity due to complications from treatment.

Although some might argue that the CGA is time consuming to administer, once done, it can be used to risk stratify patients into three categories of aging: fit, vulnerable, and frail[2] (Table 128.3). Based on this initial assessment, patients who are healthy should be candidates for full standard-of-care treatment. Patients who are vulnerable should be referred for rehabilitation or should undergo modified treatment. Based on how well one does with rehabilitation, further treatment options can include full standard-of-care versus tailored treatment. Those patients who are identified as frail should be offered treatment options based on life expectancy. For frail elderly patients with a life expectancy >6 months, treatment should address controlling the symptoms caused by the cancer, such as pain, nausea, poor feeding, fatigue, weight loss, and depression, or best supportive care. Frail patients with a low life expectancy are likely at risk of having adverse consequences from treatment, and hence the astute clinician should consider referral to palliative care or hospice.

Table 128.3 Stages of aging using the CGA.

FIT (excellent, good)
- No functional impairment
- No significant comorbidities
- No geriatric syndromes

Vulnerable (good, fair)
- Dependence in an instrumental activity of daily living but not activities of daily living
- Comorbidities but not severe or life threatening
- No geriatric syndromes other than mild memory disorder or mild depression

Frail (poor)
- Dependence in activities of daily living
- Three or more comorbidities or one life-threatening comorbidity
- A clinically significant geriatric syndrome

Selected reading

Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist 2000;5(3):224–37.

Kilari D, Mohile SG. Management of cancer in the older adult. Clin Geriat Med. 2012;28(1):33–49.

Mohile SG, Xian Y, Dale W, *et al*. Association of a cancer diagnosis with vulnerability and frailty in older medicare beneficiaries. J Natl Cancer Inst. 2009;101(17):1206–15.

Muss, HB. Older age: not a barrier to cancer treatment. New Engl J Med. 2001;345:1128–29.

Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. Cancer J Clin. 2010;60(2):120–32.

CHAPTER 129

Nuts and bolts of cancer immunotherapy

Christopher R. Heery and James L. Gulley
National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Case study 129.1

A 52-year-old female was diagnosed with stage II triple negative breast cancer (estrogen receptor (ER), progesterone receptor (PR), and HER2 negative by immunohistochemistry (IHC)) 1 year ago. She had standard adjuvant therapy with dose dense AC→T after breast-conserving surgery and radiation. She presents for a second opinion because a computed tomography (CT) ordered for increasing dyspnea on exertion and cough identified multiple new lesions in her liver and lungs. Her Eastern Cooperative Oncology Group (ECOG) performance status is 1, but she feels noticeably weaker and more fatigued than she did just 2 weeks ago. She would strongly like to consider a cancer vaccine because she read about them in a magazine and they sound promising.

1. What would you recommend?

A. Phase I trial of a vaccine alone
B. Standard chemotherapy
C. Phase II trial combining vaccine with standard chemotherapy
D. Phase II trial of immune checkpoint inhibitor

There is no clearly right answer here. Instead, the answer for your recommendation will rely on the patient's wishes and why she was interested in a vaccine therapy to begin with. If this patient thinks a vaccine alone is going to cure her or help her significantly in the setting of a very aggressive and apparently fast-growing cancer, she should have an informed discussion letting her know that there is evidence that vaccines (when given alone) on average probably take 3–4 months to achieve any antitumor effect, which may explain the lack of improvement in progression-free survival even in the trial with vaccines (and other immunotherapy) that have been positive for overall survival improvement. If the patient's primary goal is to take a therapy that will have minimal or no side effects and may benefit her at some point, but she knows that is very unlikely, a phase I trial of a vaccine may be reasonable. In the setting of her disease as described, given that there are known chemotherapeutic agents with response rates up to 50% (and in some series higher), if she wants to prolong her life, regardless of potential toxicity, an option not including standard chemotherapeutic options is probably less than ideal. In this situation, answers B and C are both reasonable. Given her desire to try a vaccine, and given the fact that there are usually minimal or no overlapping toxicities with chemotherapies, option C may be the best option. In a trial like this, care should be taken to ensure that there is a rational combination with chemotherapeutics that may improve (or at a minimum not inhibit) an immune response. Zitvogel and Kroemer (2010) have spearheaded the charge describing immunogenic cell

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

death (and its likely mechanism) with certain cytotoxic agents. Hodge and his team (2012) have described immunogenic modulation with some of the same agents as well as others.

The use of an immune checkpoint inhibitor would certainly be a reasonable option in her case as radiographic tumor responses have been seen with these agents. However, response rates with these agents have not been as high (to date) as standard chemotherapeutic agents, and these agents do not have the same benign side effect profile as therapeutic cancer vaccines, which was the patient's request. Immune checkpoint inhibitors (anti-CTLA4, anti-PD1, and anti-PD-L1) have known potential to induce autoimmune-mediated toxicity that can be severe in some cases (colitis, diarrhea, endocrinopathies, and rash are most common). Again, an exploration of the patient's rationale for her request would be needed to help her make an informed decision.

Case study 129.2

A 56-year-old woman who previously had a partial nephrectomy for renal cell cancer is found to have an enlarged retroperitoneal lymph node on CT scan performed in the emergency room after a fall at home. She is seen by medical oncology for a recommendation for treatment. She has no other medical issues of which she is aware, and she is completely asymptomatic. On imaging, she has a single retroperitoneal lymph node that is 2.7 cm in maximum dimension. A CT-guided biopsy confirms the presence of metastatic renal cell carcinoma. She would like your input on data she heard on the news about anti-PD-L1 and anti-PD-1 monoclonal antibodies.

1. Which of the following is true about these agents?

A. They bind to a target on a tumor and directly destroy the tumor

B. There is a defined test to help determine the likelihood of benefit

C. These agents indirectly assist in tumor destruction

D. Side effects of these drugs occur often but are clinically insignificant

The accepted mechanism of action of checkpoint inhibitors, which include anti-PD-L1, anti-PD-1, and anti-CTLA4 monoclonal antibodies, is not a direct effect on tumors. Although some antibodies targeting PDL-1 may induce antibody-dependent cellular cytotoxicity (ADCC), this requires other immune cells to become involved to kill the tumor, and thus answer A is incorrect. Indeed, these agents manipulate T-cell-signaling pathways that are part of the normal process to prevent autoimmunity or overstimulation of T-cells. A normal T-cell expresses both CD28 and CTLA4. When an antigen-presenting cell presents an antigen on MHC class I, it also must send a costimulatory signal to the T-cell through CD80 or CD86 (also called B71 and B72). That costimulatory signal is also called "signal 2" and is required for potent T-cell activation. However, upon T-cell activation, T-cells upregulate the regulatory receptor CTLA4 in response. This balance helps to prevent overstimulation of the T-cell, modulates T-cell-mediated lysis, and appears to play a significant role in preventing autoimmune diseases. Similarly, T-cells increase expression of PD-1 after signal 1 and 2 have provided the full "activation" signal. When PD-1 binds with its ligand, PD-L1 (B7-H1) or PD-L2 (B7-DC), a regulatory signal is sent to the T-cell, diminishing its activity. So, the mechanism of action of all of these agents is related to the prevention or reversal of T-cell inhibition by these signaling pathways. Unfortunately, there is not yet a validated test to indicate which patients' tumors will respond to these therapies (answer B). It has been postulated that tumor cells overexpressing the ligands (e.g., PD-L1) may be more likely to respond, but this is not yet confirmed. In theory, blockade of PD-L1 may have less induction of autoimmune toxicity because the binding site is more likely to be on the tumor cells than elsewhere in contrast to CTLA4 or PD-1, both of which are expressed on T-cells, making their response to inhibition potentially less specific for tumor cells. In fact, the clinical studies of anti-CTLA4 (ipilimumab and tremelimumab) have reported significant autoimmune colitis, rash, and endocrine dysfunction. However, the phase I studies of anti-PD-1 and anti-PD-L1 appeared to have an improved toxicity profile, with fewer grade 3 or 4 adverse events. Notably, severe colitis was infrequently noted in the anti-PD-L1 study. As a result, answer D is not correct, these side effects are not common, but when they do occur, they can be severe and life-threatening. Figure 129.1 illustrates the interaction of these potential targets with T-cells, antigen-presenting cells, and tumor cells.

(*Continued*)

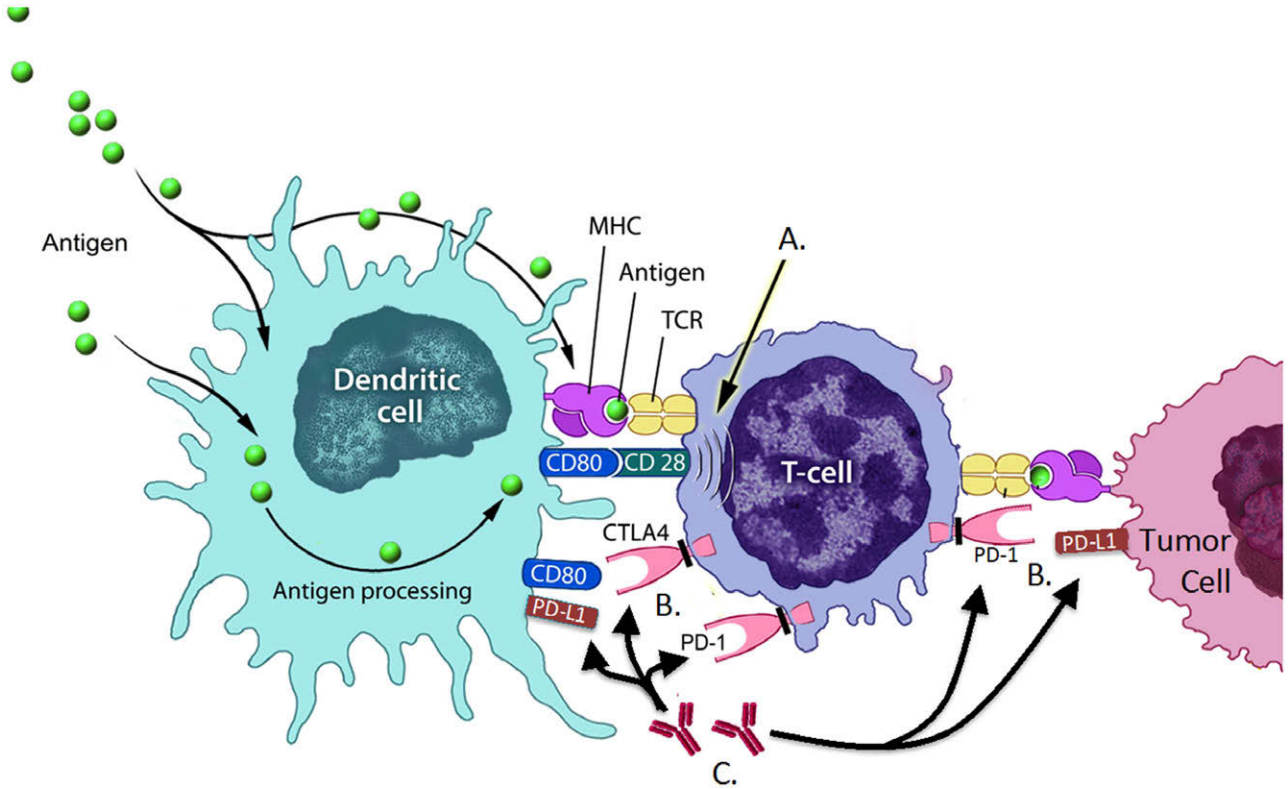


Figure 129.1 (A) T-cells become activated through a two-signal process. Signal 1 occurs when an antigen-presenting cell, in this case a dendritic cell (DC), presents an antigen via MHC class 1, which binds to the T-cell receptor (TCR). Signal 2 is the costimulatory signal, in this example CD80 on the DC binds to CD28 on the T-cell, activating the T-cell against the antigen presented. (B) After activation, the T-cell effector function can be downregulated or suppressed. Upon activation, the T-cell will increase the expression of cytotoxic T-lymphocyte antigen-4 (CTLA4) and programmed cell death receptor 1 (PD-1). When these receptors on the T-cell bind with their respective ligands (CTLA4 → CD80 and PD-1 → PD-L1), the effector function of activated T-cells is suppressed. (C) A therapeutic intervention that may allow T-cells to remain highly activated or become reactivated is inhibition of the regulatory signals provided by CTLA4 → CD80 and PD-1 → PD-L1 interactions. There are currently monoclonal antibodies in development or already approved targeting CDLA4, PD-1, and PD-L1. By binding these receptors and preventing the suppressive signal, T-cells are more capable of tumor lysis resulting in potential clinical benefit (Source: Adapted from Tarassoff CP *et al.* The Oncologist 2006;11(5):451–62. Reproduced with permission of AlphaMed Press).

1. How do cancer cells escape immune surveillance?

In the interaction of host and tumor cells, three essential phases have been proposed: elimination, equilibrium, and escape (Figure 129.2). The bulk of the evidence at this point appears to suggest that the inciting event in tumor formation, a genetic mutation that leads to uncontrolled cell growth, simply may or may not result in an immunogenic signal identifiable by the immune system. A mutated cell may undergo multiple cell divisions before coming to the attention of the immune system. In that time, one mutation may have led to multiple mutations, and a single cell capable of evading immunosurveillance may appear. Over time, even if the immune system is capable of eliminating all but that cell, a tumor can develop from clones of the unrecognized cell. The tumor cells may also go into an equilibrium with the immune system such that tumor cells are being killed at the same rate that daughter cells are being made.

The cells that avoid recognition may employ a number of strategies. Commonly, cells that escape immunosurveillance have decreased or eliminated expression of HLA class I and associated antigen-presenting molecules, which are necessary for T-cell binding and killing. Additionally, tumors may produce signaling proteins (e.g., nitric oxide, TGF-beta, indoleamine 2,3-dioxygenase, prostaglandin-E2, and cyclooxygenase-2, among many others) that inhibit appropriate antigen presentation by dendritic cells and prevent T-cell proliferation. The combination of these elements can limit the potential for the identification of novel tumor antigens within the tumor and allow an already relatively difficult-to-recognize tumor to grow with less immunosurveillance in place.

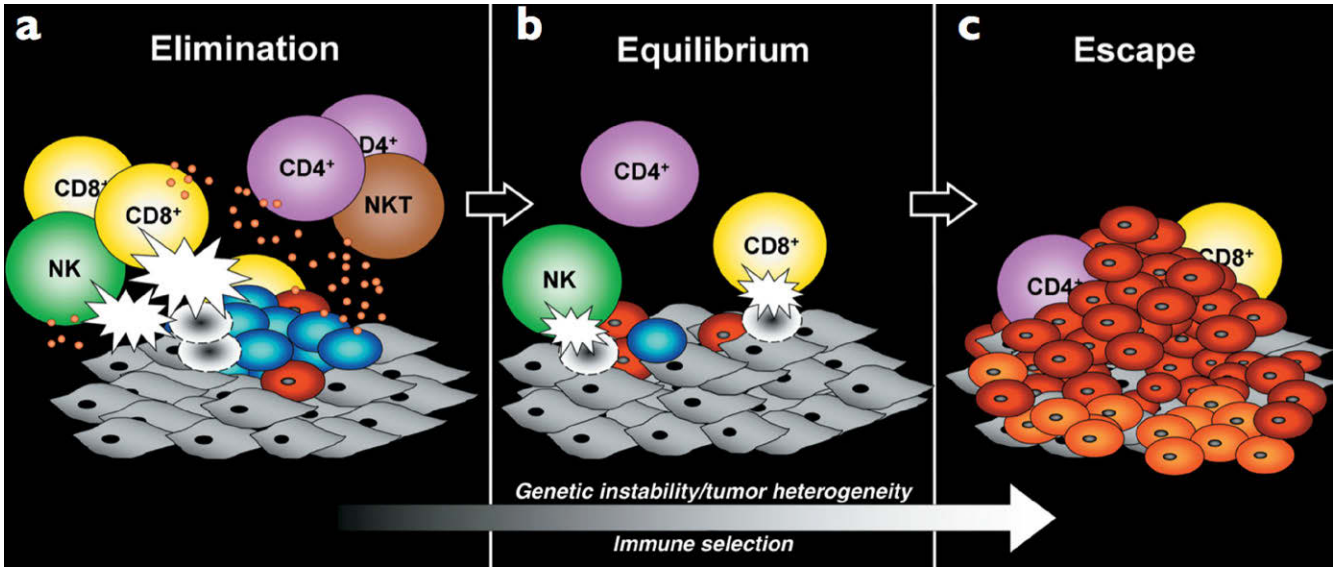


Figure 129.2 (A) Immune cells, including CD4+, CD8+ and natural killer (NK) cells, overwhelm a small number of tumor cells and eliminate cancer completely. (B) Despite immune-mediated killing of cancer cells, the tumor finds equilibrium as new cells are created at a rate equal to the rate of destruction of tumor cells. During this period, the tumor may evolve to suppress immune cells or "hide" from the immune system by downregulating immunogenic targets. (C) As the tumor grows and evades immune detection, the balance shifts and the tumor cells replicate more quickly than the immune system can destroy tumor cells. This may be due to tumor-mediated immune suppression or the evasion of detection of the tumor by the immune cells (Source: from Dunn GP *et al*. Nat Immunol. 2002;3(11):991–8. Reproduced with permission of Nature Publishing Group).

Case study 129.3

A patient with metastatic castration-resistant prostate cancer (mCRPC) presents to clinic inquiring about the use of a therapeutic cancer vaccine for treatment. His prostate-specific antigen (PSA) is doubling about every 5 months. He has bone disease with minimal symptoms. You are aware that sipuleucel-T has demonstrated an overall survival benefit in phase III trials and PSA-TRICOM is in a phase III study after randomized phase II results indicated a clinically and statistically significant improvement in overall survival as well. However, you have seen that these studies found almost no objective or biochemical responses (PSA declines), and you do not know how to determine if a vaccine is benefiting your patient.

1. How would you advise this patient?

A. Ignore vaccine therapies until a biomarker of efficacy is validated
B. Use other agents first, and then use vaccines as a last resort
C. Call a vaccine expert and ask for input
D. Plan to use vaccine followed by a standard therapy

Simply, there is no right answer to this question. It is intended to point out the clear clinical dilemma of medical oncologists in using vaccines or other immunotherapies. While there is now good evidence that therapeutic cancer vaccines can improve median overall survival in a population of patients, it is difficult to tell which individual patients have received a benefit. There is currently no validated biomarker of efficacy for vaccine therapy in mCRPC (as mentioned in answer A) because PSA and radiographic responses are rare. However, answer B, based on accumulating data from many clinical trials and the prevailing opinion of experts in the field, is probably not the best use of vaccine therapies. In fact, there appears to be an inverse correlation with the patient's overall disease burden and likelihood of benefiting from a therapeutic cancer vaccine. Multiple clinical trials groups have described this. If one were to choose answer C and call an expert in the field for input, the most likely suggestion would probably be answer D. As discussed above, the evidence seems to indicate that patients with less overall disease are more likely to benefit. There are multiple therapeutic options capable of inducing a PSA and radiographic response in mCRPC (docetaxel, abiraterone,

(*Continued*)

enzalutamide, and cabazitaxel), which are all now approved for use by the US Food and Drug Administration. While this patient is minimally symptomatic, it may make sense to treat with a vaccine for 3–6 months and induce an immune response, which may, over time, slow the tumor growth rate. One could then treat with these standard therapies, which could directly kill tumor cells, decrease the disease burden, and, by killing tumor cells, induce antigen spreading, a phenomenon described by many preclinical and clinical groups. Antigen spreading is a process through which the immune system becomes activated against other antigens present in tumor cells despite those antigens not being the target of the vaccine with which the patient was treated. Evidence also continues to accumulate, indicating that subsequent therapies may boost the effect of vaccines through antigen spreading, but also by altering the tumor phenotype, making it more amenable to T-cell mediated killing. Finally, it is possible that a reduction of tumor volume may improve the tumor microenvironment for T-cell-mediated killing by decreasing tumor density (allowing T-cell infiltration) and decreasing the cytokine signaling that may inhibit T-cell killing or prevent immune cell infiltration.

2. How do we know that the immune system fails in cancer?

Various hypotheses dating back at least 100 years (e.g., Paul Ehrlich in 1909) have suggested that the innate immune system may play a role in eliminating tumor cells prior to detection in a majority of cases in humans. This idea became more popular in the late 1950s with the work of Macfarlane Burnet and Lewis Thomas, who named the process "cancer immunosurveillance." While one cannot definitively know that this goes on in a human throughout his or her lifetime, a large quantity of data from murine models indicates that, indeed, the immune system can eliminate or slow the growth of tumors by killing tumor cells. To know that the immune system plays a role in tumor surveillance, various groups have systematically removed components of the normal immune system in mouse models prior to exposure to injection of small quantities of tumor. Over time and many experiments, validated by many groups, it has become quite clear that interferon-gamma and/or RAG2 (recombination-activating gene 2) knockout prevents control of inserted tumor and also makes mice more susceptible to spontaneous neoplasms when observed over time. It also appears that tumors that form despite the presence of an intact immune system are less likely to be immunogenic without manipulating the immune system into recognizing them. Additionally, we know, from historical data, that patients who are immunosuppressed due to solid-organ transplant or underlying autoimmune disease have a significantly increased risk of cancer, which appears to diminish if immunosuppression can be removed.

Case study answers

Case study 129.1

Question 1: Answer requires insight into patient motivation

Case study 129.2

Question 1: Answer C

Case study 129.3

Question 1: Best answer is D

Selected reading

Gulley JL. Therapeutic vaccines: the ultimate personalized therapy? Hum Vaccin Immunother. 2013;9(1):219–21.

Hodi FS, O'Day SJ, Mcdermott DF, *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.

Kantoff PW, Higano CS, Shore ND, *et al*. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411–22.

Madan RA, Gulley JL, Fojo T, *et al*. Therapeutic cancer vaccines in prostate cancer: the paradox of improved survival without changes in time to progression. Oncologist 2010; 15(9):969–75.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252–64.

CHAPTER 130

Controversies related to oncology clinical trial development

Elihu H. Estey

University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

1. Is the "3 + 3" design the best means to determine dose for phase II?

In my opinion, the answer is "no." The 3 + 3 design is the most common method used in phase I studies to determine dose for subsequent trials. If none of the first three patients treated at a given dose have dose-limiting toxicity (DLT), the next three receive the next higher dose, while if two or three of the first three have DLT the next three are treated at a lower dose. If DLT occurs in one of the initial three, the next three receive the same dose, and that dose is used subsequently if DLT is seen in one of the six, with the dose considered too high if DLT occurs in 2–4 of these six.

The 3 + 3 design has the advantage of simplicity. However, fundamental to any statistical design are its "operating characteristics" (OCs). OC refers to how a design performs under various clinical scenarios. For example, by declaring that a DLT frequency of 16% (1/6) is "acceptable" but a frequency of 33% (2/6) is not, we may infer that an acceptable DLT rate is 25–30%. Now let us assume that a new drug has a true DLT rate of 50%. Application of the binomial theorem indicates that in this scenario, the probability that two or three of the first three patients will have DLT is 50%. Thus, there is a 50% chance that the next cohort of patients will be treated at an even higher dose. Even if the true DLT rate is 70%, this probability is 21%. This simple example suggests that the 3 + 3 does not have good OC.

A preferable alternative is the "continuous reassessment method" (CRM). The CRM is a Bayesian design. Thus, it begins with a prior probability of DLT at each of several doses such that the higher the dose, the higher the prior probability. As patients are treated, Bayes theorem is used to incorporate the DLT data with the prior probability to derive a posterior (or current) probability of toxicity for each dose. The next cohort of patients is treated at the dose associated with a posterior probability of DLT closest to 25–30%. A feature of the CRM is that a dose found to be "too toxic" can subsequently be found to be acceptable if new patients have no or very little toxicity. This is known as "Bayesian learning." It should be contrasted with the 3 + 3, in which the dose for the next cohort is determined solely by the data from the most recent cohort regardless of what occurred on cohorts prior to the most recent. Because it thus makes use of more information than the 3 + 3, it is intuitive that the CRM will have better OC than the 3 + 3 and this has been demonstrated many times.

Although the CRM is superior to the 3 + 3, both methods suffer from the assumption that toxicity is solely a function of dose. Intuition suggests that this is not the case, as, everything else being equal, a 70-year-old might be expected to have more toxicity at a given dose than a 40-year-old. And it seems paradoxical to recognize the effect of covariates ("prognostic factors" in phase II (efficacy) trials but not in phase I trials). Rogatko *et al*. (2004) have shown that, among patients eligible for phase I trials, performance status, weight loss, tobacco use, alkaline phosphatase level, and other criteria are as important as dose in forecasting toxicity. Since it makes decisions based on only 3–6 patients, the 3 + 3 is particularly susceptible to confounding an effect of dose on DLT with an effect of, for example, patient age. In fact, there may not be one dose for all patients, but different doses may be appropriate in different patients. Publications have appeared allowing the analysis of effects of covariates in phase I studies.

Typically, DLT is defined based on the occurrence of grade 3–4 toxicity. While the criteria for grade 3–4 toxicity are straightforward with symptomatic toxicity, this may not be the case with asymptomatic toxicities such as elevations in liver enzymes or creatinine. Thus, at least in acute myeloid leukemia (AML), the relation between grade 3–4

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

asymptomatic toxicity and death, which presumably an event dose reduction is intended to prevent, is not at all clear. Recognizing that such relations may reflect associations rather than causation, a more empirically based system to replace the somewhat arbitrarily defined criteria for grade 3–4 asymptomatic toxicities seems warranted.

Finally, it is now becoming clear that the maximum tolerated dose (MTD) may be higher than the optimum biologic dose (OBD). This calls into question the presumption of a direct relation between higher dose, increased efficacy, and increased toxicity that underlies many phase I designs. One means to test the hypothesis that the OBD rather than the MTD is the dose of interest for many "targeted" therapies would involve, over many targeted therapies, the randomization of patients between these doses with the aim of seeing which dose produced a higher response rate, was associated with longer survival, and so on.

2. Is the Simon phase II design the best phase II design?

Again, I believe the answer is "no." Just as the 3 + 3 is the standard phase I design, the Simon two-stage is the standard phase II design. Here the investigator specifies a rate of "no interest" (called p_0), often the historical efficacy rate; a rate "of interest" (p_1), typically the anticipated efficacy rate with the new treatment; and acceptable rates of false positivity and false negativity (typically, 10% for each). The design then specifies how many patients would be treated in a first stage and how many of these must respond before subsequent patients are entered into a second stage. The design also notes how many are to be entered into the second stage and how many responses must be seen in all patients for the drug to be called a "success" (i.e., that it has achieved its target efficacy rate, with the specified false-positive rate).

A problem with the design was noted by Thall and Simon (2008). Specifically, it assumes that p_0 is a constant rather than a statistic. That is, it assumes p_0 is based on treatment of an infinite number of patients when in fact it may be based on relatively few patients. The smaller the number of historical control patients, the greater the false-positive and false-negative rates are increased relative to their nominal values and should be adjusted as noted by Thall and Simon (2008).

Much as the 3 + 3, the Simon two-stage ignores patient heterogeneity. We will use a trial of a new agent for relapsed AML as an example. The average historical complete response (CR) rate with standard therapy is about 15%, and so this might be taken as p_0. However, the CR rate depends heavily on the duration of first CR and number of prior therapies the patient has received. Depending on these covariates, the CR rate ranges from 60% (for patients with first CR durations >1 year who are receiving the new drug(s) as initial therapy for relapse) to <1% for patients with first CR duration <6 months who have received several prior therapies for relapse. Given the relatively small number of patients often entered in the first stage of the design, it is quite plausible that the result might be falsely negative if most patients entered in this stage are in the <1% group and falsely positive if many patients entering the first stage are in the 60% group. One possible solution is separate trials in each prognostic subgroup. However, this does permit use of data from one trial to adaptively affect conduct of the others. Rather than ignoring heterogeneity or conducting separate trials Wathan, Thall, and Estey (2008) proposed a Bayesian design that considers subgroup treatment interactions (STIs) and uses the incoming data to assess the extent to which the results from the subgroups can be combined. Consider a Simon two-stage design in which p_0 is 0.21 and p_1 for the new therapy is 0.21 + 0.18 = 0.39. With false-negative and false-positive rates each at 0.10, the design calls for entering 22 patients in a first stage and proceeding to a second stage if more than four CRs are observed; the second stage would enroll an additional 21 patients, and the new therapy accepted as successful if the CR rate was >12/43. We will contrast this design with the STI design parameterized to also enter 22 patients in a first stage with false-negative rate 0.1. The STI assumes there are two subgroups, the first (patients with a long CR) with a historical CR rate of 0.43 and the second (patients with a short CR) with a historical CR rate of 0.11; given the number of patients in the two groups, the overall historical CR rate (p_0) is 0.21, as in the two-stage Simon design. Table 130.1 compares the probability of rejecting the new treatment and the mean number of patients treated using the Simon two-stage design (S2S) and the STI.

In scenario 1, the new therapy is truly an advance in the better, but not the worse, group, while in scenario 2 the opposite applies. Because it does not recognize heterogeneity, the S2S has the same probability of rejecting the new treatment independent of subgroup. In contrast, the STI has better OC, and in particular is much less likely to (mistakenly) reject the new treatment in the better group in

Table 130.1 Scenarios comparing the probability of rejecting new treatment and the mean number of patients treated using the Simon two-stage design (S2S) and the subgroup treatment interaction (STI).

Scenario	Subgroup	True CR rate	Probability of rejecting new treatment (STI, S2S)	Mean number of patients treated (STI, S2S)
1	Better	0.58	0.10, 0.75	21, 10
1	Worse	0.11	0.90, 0.75	19, 25
2	Better	0.43	0.50, 0.26	13, 11
2	Worse	0.31	0.10, 0.26	27, 30

scenario 1 and in the worse group in scenario 2 and more likely to (correctly) reject the new treatment in the worse group in scenario 1 and in the better group in scenario 2. Furthermore, and desirably, a greater proportion of patients treated with the STI than the S2S belong to the better group in scenario 1 and to the worse group in scenario 2. Further simulation studies indicate that this type of adaptation would not be possible if separate trials were done.

Perhaps the biggest weakness of the Simon two-stage design is its single-arm nature. This delays comparison of a new therapy with a standard therapy (or another new therapy) until phase III. Although in principle multivariate analysis could be performed to assess whether, after accounting for covariates, the new therapy is best, such an analysis can only account for known covariates. Randomization is needed to account for unknown covariates. It seems paradoxical that randomization is a fundamental part of phase III trials but not of the phase II trial that determines whether the phase III trial will be undertaken. This has led several authors to propose the use of randomized phase II trials whose intent is to select the best therapy to take into a larger trial. These trials are often criticized as "underpowered." And, indeed, consequent to their small sample sizes relative to phase III trials, their ability to detect differences should they exist ("power") is frequently only 50–60% of the time, contrasted with the 80% common to many large phase III trials. However, this 80% power is only nominal. Consider a case where there are four candidate new therapies to compare versus a standard in a phase III trial. As is often the case, preclinical rationale is insufficient to know which of the four to select. It follows that, in the absence of clinical data, the chance of selecting the best of the four is only 25%. Thus, the phase III trial has a power of 80% only if the process by which the new therapy was selected is ignored. If it is not ignored, the power is $25\% \times 80\% = 20\%$, and it is the latter figure that the 50–60% power of the selection design competes against. Simply put, the worse false-negative may result from not investigating a new therapy at all, and it is this possibility that has spurred interest in randomized phase II selection designs, which are now routinely used in AML trials of the National Cancer Research Institute (Medical Research Council) in the United Kingdom.

3. Does the standard phase III design serve us well?

I believe the answer is often no and will use AML to explain. The typical phase III trial in AML enrolls about 400 patients into a standard and an investigational arm. This often requires several years to accomplish, not counting the time needed for follow-up of the last patients enrolled. During these years, other therapies are not investigated, which may be problematic if there are several new therapies of interest. Phase III trials often enroll so many patients because they aim to detect relatively small differences between standard and investigational regimens with 80–90% power (corresponding to a false-negative rate of 10–20%) and $P = 0.05$ (corresponding to a false-positive rate of 5%). The first question is whether the differences we aim to detect are truly meaningful clinically. For example, assume an otherwise healthy 68-year-old with newly diagnosed AML would live an additional 15 years (180 months) if he or she did not have AML. Standard treatment results in a median survival of 12 months, and thus the patient loses $168/180 = 93\%$ of anticipated life expectancy. A new treatment prolongs survival to 18 months, thus resulting in a loss of $162/180 = 90\%$ of life expectancy. Many patients might consider this improvement, which is quite similar to those often targeted, medically insignificant. A second question is whether a false-negative rate of 20% and false-positive rate of 5% are acceptable for all diseases. Certainly in diseases where good treatment exists, the consequences of a false positive are much greater than in a disease such as AML or many solid tumors where standard treatment is routinely unsuccessful. Hence, I think revision of phase III trials for diseases such as AML to aim for larger differences, with $P = 0.10$, would be more consistent with clinical reality and would permit investigation of a larger number of treatments.

4. Are we too fixated on $P = 0.05$?

Yes, I think we are. A *P*-value is defined as the probability that under the hypothesis of no difference ("null hypothesis), a result as extreme (or more extreme) than that observed would occur. For example, when flipping coins, the null hypothesis is that heads and tails will each occur with a probability of 50%. Under the binomial theorem, the probability of five heads and one tail in six tosses is 0.09 and the probability of six heads is 0.015; thus, the *P*-value associated with five heads and one tail is $0.09 + 0.02 = 0.11$. Although it seems that there is little real difference between a 94% probability that the null hypothesis is incorrect ($P = 0.06$) and a 95% probability ($P = 0.05$), the acceptance of the latter but not the former as a statistically significant result is widespread. Furthermore, there appears to be a tendency to confuse statistically and medically significant results. A result can be statistically significant only because many patients have been treated, not because the differences are clinically meaningful. Another problem is that the *P*-value depends not only on the data but also on the way an experiment was designed. As a simple example, it is intuitive that if a relation is found between a covariate and probability of response only after 10 other covariates have been examined, the *P*-value should be higher than if no other covariates have been examined. Yet this type of information is very seldom provided, complicating interpretation of *P*-values. Another problem with *P*-values

is that they provide incomplete information. Questions such as, given the data, what is the probability that a new therapy is 10% (or 20%, 30%, etc.) better than an older therapy are not addressed. Rather, these types of questions are often the province of Bayesian posterior probabilities. These ask, given the data, what the probability of a hypothesis is, whereas *P*-values ask, given a hypothesis, what the probability of the data is.

5. What are the advantages of designs that simultaneously monitor more than one outcome?

Much of this presentation has focused on means by which standard phase I, II, and III trial designs ignore clinical reality given their tendencies to ignore patient heterogeneity, delay comparison of new therapies, aim for medically insignificant improvements, and use the same 5% false-positive and 20% false-negative rates in all diseases regardless of how successful a standard therapy is for that disease. Another way in which standard designs ignore clinical reality is by their focus on only one outcome, for example "toxicity" in phase I. Yet it is very likely that patients enter phase I trials not to have "no toxicity" but to have a response. "Response" is conventionally ignored in phase I probably because it seems likely that responses only occur as dose is increased. However, it seems plausible that truly effective drugs will produce responses even at low doses. Indeed, it would be interesting to examine response rates in phase I with drugs that proved effective in phase II. With this in mind, phase I–II designs have been published that monitor response and toxicity, stopping if it becomes likely that no dose is associated with a probability of response <30% (see above) or probability of response appropriate to the disease in question (e.g., 12% in AML salvage). Table 130.2 depicts four doses (D1–D4) with varying probabilities of response (θR) and toxicity (θT) for each of three dose–outcome cases. In the first dose, levels 3 and 4 are acceptable because each is associated with acceptable rates of response (>12%) and toxicity (<30%). In the second scenario, only dose level 4 is acceptable, while in the third scenario no doses are acceptable because while each is associated with acceptable toxicity, none is associated with acceptable response. Table 130.3 compares the ability of the 3 + 3 and the phase I–II designs to correctly select the correct dose level (levels 3 and 4 in case 1, level 4 in case 2, and no level in case 3). Because it ignores response and focuses only on toxicity, the 3 + 3 incorrectly selects one of the four doses in 99% of the case 4 simulations. While the phase I–II design treats more patients, in fact fewer patients would be treated than in the conventional setting where a phase I would be followed by a phase II.

Multiple outcomes of interest are as common in oncology as in medicine in general. Another example is CR and survival. CR has long been thought to be a surrogate for survival in AML. However, recent examples suggest that higher CR rates may not translate into longer survival, but that cure is unlikely absent CR. Hence, it appears reasonable to formally monitor survival and CR during a trial of a new drug. Specifically the goal of the trial would be to improve survival without decreasing the CR rate. Early termination would occur should it appear likely that survival would not be improved or that CR rate would be decreased. This type trial becomes more practical as survival time becomes less (e.g., 3–4 months) and if patients do not present for treatment before previous patients have been evaluated. Another example formally and adaptively monitors CR rate, toxicity, and the proportion of eligible patients who are treated on a given trial, with early termination occurring should it appear likely that response will be too low, toxicity too high, or feasibility too low.

In sum, I think it is appropriate to ask whether current phase I, phase II, and phase III designs, while having the virtue of simplicity and familiarity, truly reflect the complexity of medical practice and of clinical trials.

Table 130.2 Dose–outcome scenarios.

D1		D2		D3		D4	
θ(R)	θ(T)	θ(R)	θ(T)	θ(R)	θ(T)	θ(R)	θ(T)
.02	.10	.05	.15	.15	.25	.20	.30
.01	.05	.05	.10	.10	.15	.20	.25
.01	.05	.02	.10	.05	.15	.02	.25

Table 130.3 Operating characteristics: PI-II versus 3 + 3.

Case	Correct Doses	Prob P12	Correct 3 + 3	Select P12	# Pts 3 + 3
1	3,4	.89	.35	44	14
2	4	.83	.12	43	14
3	None	.86	.01	29	14

Selected reading

Estey EH and Thall PF. New designs for phase II clinical trials. Blood 2003;102(2):442–8.

Garrett-Mayer E. The continual reassessment method for dose-finding studies: a tutorial. Clin Trials 2006;3(1):57–71.

Hills RK and Burnett AK. Applicability of a "pick a winner" trial design to acute myeloid leukemia. Blood 118(9):2389–94.

Rogatko A, Babb JS, Wang H, *et al*. Patient characteristics compete with dose as predictors of acute treatment toxicity in early phase clinical trials. Clin Cancer Res. 2004;10(14):4645–51.

Thall PF, Nguyen HQ, Estey EH. Patient-specific dose finding based on bivariate outcomes and covariates. Biometrics 2008;64(4):1126–36.

CHAPTER 131

PET scan in oncology

Shaunagh McDermott and Michael A. Blake
Massachusetts General Hospital, Boston, MA, USA

1. My patient's PET–CT had to be rescheduled because his blood glucose was too high. Is it really necessary to reschedule?

Fluoro-deoxyglucose (FDG) is an analog of glucose that is taken up by metabolically active cells using facilitated transport similar to that used by glucose. The rate of uptake of FDG by the cells is proportional to their metabolic activity. Similar to glucose, it undergoes phosphorylation to form FDG–6-phosphate; however, unlike glucose, it does not undergo further metabolism, thereby becoming trapped in metabolically active cells. Good control of blood glucose is required because the uptake of FDG into cells is competitively inhibited by glucose, as they use a common transport mechanism for facilitated transport into both normal and tumor cells.

Furthermore, the administration of insulin for glucose control in diabetes can exaggerate physiologic uptake in muscles (Figure 131.1). Patients are also instructed to avoid any strenuous activity prior to the examination and to lie still following injection of the radioisotope to avoid physiologic muscle uptake of FDG. Exaggerated physiologic muscular FDG uptake limits the amount of FDG available for uptake in the tumor and therefore reduces the sensitivity of the exam.

Other agents interfering with FDG uptake to be aware of include granulocyte colony-stimulating factor, which causes increased marrow and splenic FDG uptake, and metformin, which causes increased colonic FDG uptake.

2. Should a diagnostic computed tomography (CT) be performed as part of the positron emission tomography (PET)–CT, or would the low-dose attenuation correction CT suffice?

We routinely perform a diagnostic CT with both oral and intravenous contrast as part of our PET–CT protocol. The advantages of administrating intravenous contrast includes (A) increased conspicuity and characterization of lesions, which is of particular importance in lesions in which FDG does not accumulate (Figure 131.2); (B) providing additional information, which can help differentiate benign from malignant lesions that have nonspecific FDG uptake; (C) providing lesions' vascular relationships important for preoperative planning; and (D) helping to precisely localize lesions that have increased FDG uptake that would not be clearly seen on unenhanced CT because of the absence of contour abnormality or similar attenuation to the surrounding structures. These advantages are particularly helpful in the liver, but some investigators propose that following the initial staging, a lower radiation dose of non-contrast-enhanced CT may be sufficient to follow patients with treated lymphoma who have a low clinical suspicion for recurrence.

The addition of oral contrast can aid in the evaluation of FDG uptake in the bowel. Physiologic bowel uptake is known to be highly variable and range from diffuse low-level uptake to heterogeneous and multifocal uptake. The use of oral contrast can aid in the evaluation of gastrointestinal FDG uptake because distending these segments can allow more confident exclusion or diagnosis of luminal or mural disease. Either negative oral contrast or low-density barium sulphate (LDB) is suitable as LDB does not induce increased FDG bowel activity.

3. How is response determined on PET–CT?

There are two basic approaches for assessing the metabolic changes of treatment: qualitative or quantitative. Most PET–CT scans in clinical practice are typically interpreted using qualitative methods in which the intensity of ^{18}F-FDG uptake in potential tumor foci are compared to blood pool or tracer uptake in nearby normal structures.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

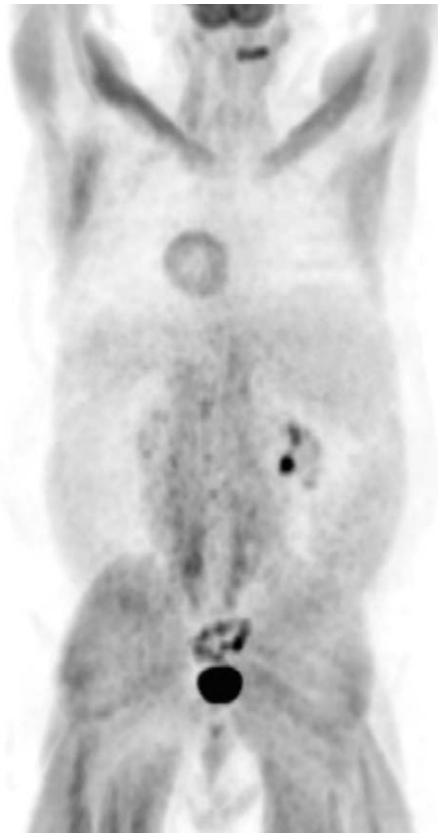


Figure 131.1 A 52-year-old man with poorly controlled diabetes and a history of lymphoma. PET–CT shows extensive muscular uptake, which limits the exam due to less available FDG for potential tumor uptake. No abnormal uptake.

The potential to detect small changes in tumor glucose metabolism quantitatively is appealing, especially in clinical trials. The standard uptake value (SUV), defined as ^{18}F-FDG retention normalized to injected dose and patient body weight, is an established index for quantifying glucose metabolic activity in tissues. The determination of SUV is dependent on identical patient preparation and on adequate scan quality that is similar between the baseline and follow-up studies. Ideally, the scans should be performed on the same scanner with comparable injected doses of ^{18}F-FDG and with comparable uptake times before scanning. Although some studies have demonstrated that SUV measurements are highly reproducible, other studies have found a higher variance of SUV measurements. A meta-analysis found that SUV_{mean} had better repeatability performance than SUV_{max}, and that both measures showed poor repeatability for lesions with low ^{18}F-FDG uptake. Attempts at greater standardization are ongoing and are being supported by various societies involved in PET scanning, but it is important to be aware of the current potential pitfalls of SUV measurements.

4. A 68-year-old man 8 months after Whipple procedure for ampullary cancer has developed an FDG-avid soft tissue mass within the postoperative bed. Could this be anything other than recurrence?

FDG uptake can also occur as a result of granulomatous disease, postsurgical changes, abscess, or inflammation (Figure 131.3). An ongoing bowel leak may simulate recurrent disease. Acute radiation changes can also lead to increased FDG uptake in its field. Several cytotoxic chemotherapy agents, such as 5FU plus leucovorin, can cause enteritis that will show FDG uptake. The CT component of the PET–CT study can often help identify hypermetabolic nonneoplastic conditions, thereby reducing false-positive interpretations. Some benign tumors can also demonstrate intense FDG uptake (Figure 131.4), and their features can sometimes be recognized by CT.

5. A lesion seen on CT is not FDG-avid. Does this mean it is benign?

Some cancers inherently demonstrate relatively low FDG uptake, including renal cell carcinoma, low-grade hepatocellular carcinoma, carcinoid tumor, marginal zone lymphoma, and low-grade sarcoma. Some of these tumors are less conspicuous in part because of the background FDG uptake in the organ that they arise in, for example, urothelial lesions because of FDG excretion (Figure 131.2) and hepatic lesions because of normal liver FDG uptake. In addition, necrotic and mucinous tumors demonstrate poor accumulation of FDG and can give false-negative results (Figure 131.5).

Also, false-negative uptake can result from tumors that are too small to be observed. Typically, the threshold for lesion detection with PET–CT is approximately 6 mm.

6. Are there criteria for treatment response that take into account metabolic activity?

Accurate monitoring of patient response to cancer therapy is vital for both the provision of effective treatment and the development of novel therapies. Most of the available criteria for assessing treatment response, such as the World Health Organization (WHO) criteria and the Response Evaluation Criteria in Solid Tumors (RECIST and RECIST 1.1) criteria, depend only on changes in size of the primary tumor and metastases. A new criteria, PET Response Criteria in Solid Tumors (PERCIST 1.0), based on PET metabolic criteria has been proposed. PERCIST recommends computing the standardized uptake value at lean body mass (SUL) peak value, which is defined as the largest possible mean value of a 1 cm^3 spherical VOI (volume of interest) positioned within a tumor. A complete metabolic response (CMR) is defined as visual disappearance of all metabolically active tumors, and a drop in SUL peak to that

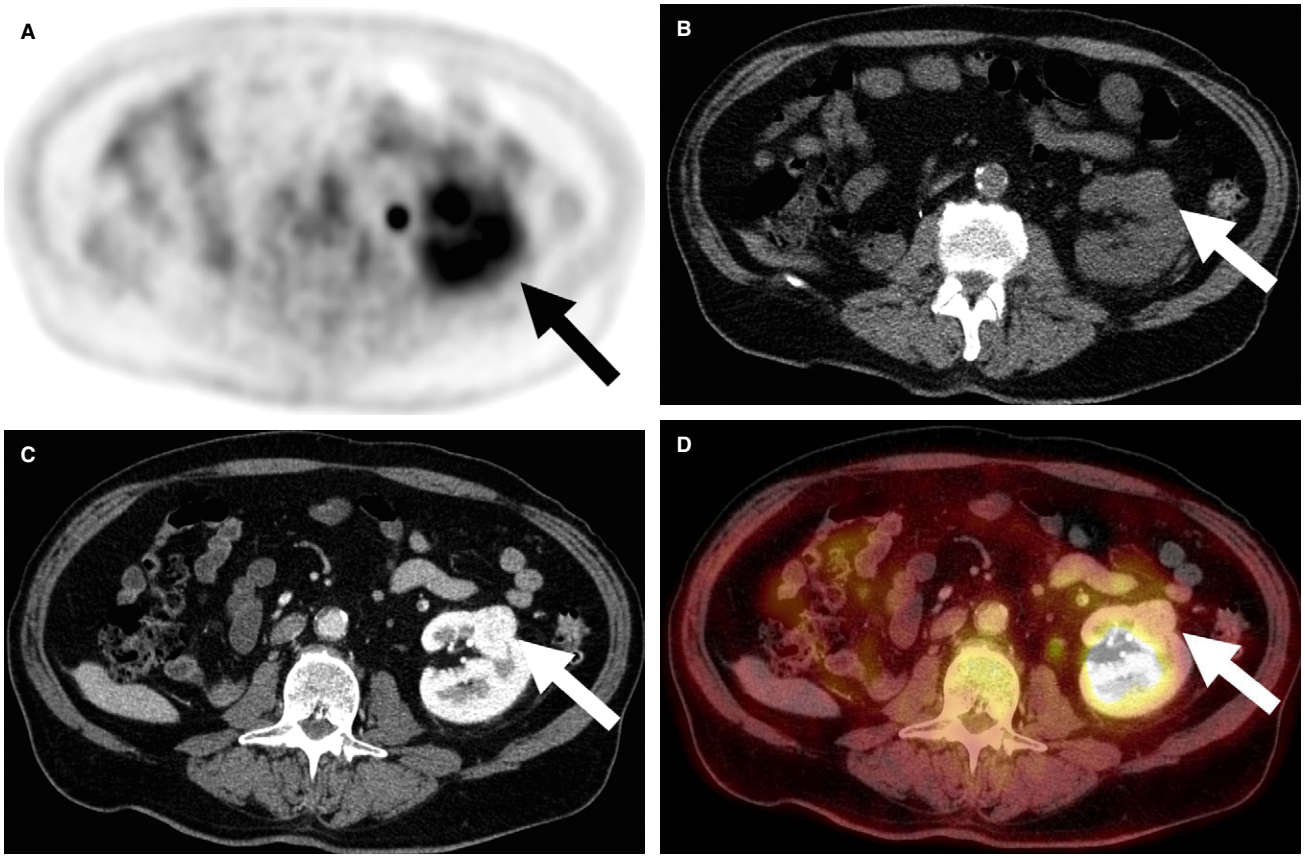


Figure 131.2 A 70-year-old with a history of renal cell carcinoma treated with right nephrectomy. (A) PET demonstrates normal FDG excretion in the left kidney (arrow). (B) Low-dose CT demonstrates a hyperdense lesion in the left kidney (arrow), which is incompletely characterized. (C) Contrast-enhanced CT demonstrates enhancement of the left renal mass (arrow). (D) PET–CT confirms that the left renal mass does not demonstrate FDG avidity. Biopsy was positive for renal cell carcinoma. (Color plate 131.1)

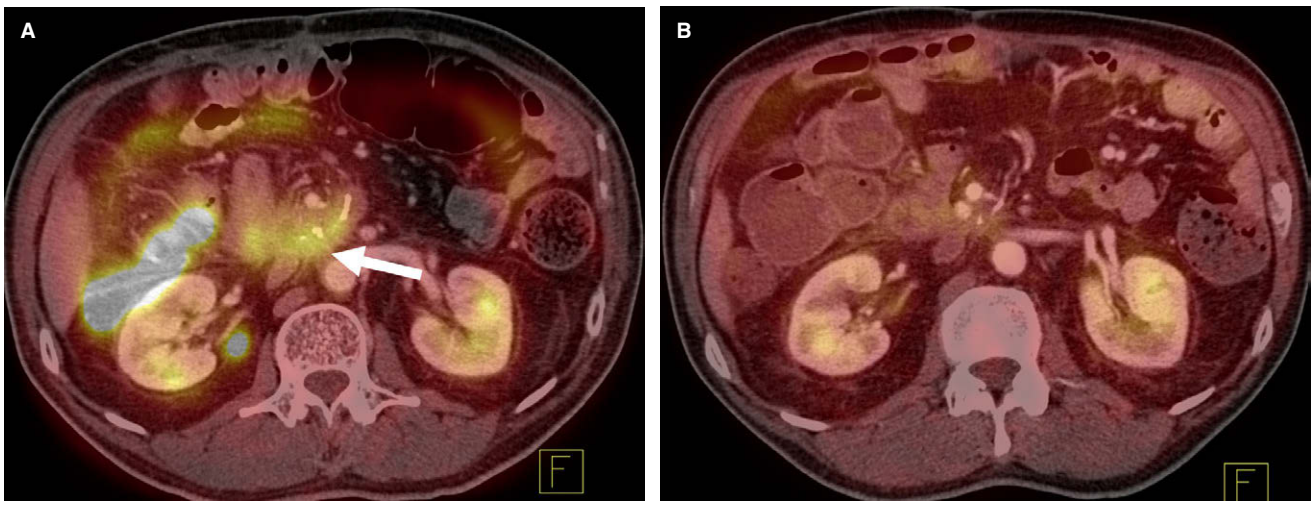


Figure 131.3 A 65-year-old man eight months post Whipple procedure for pancreatic cancer. (A) PET–CT demonstrates a mass at the resection margin with avid FDG uptake (arrow). Biopsy of this region was positive for actinomycosis. (B) After treatment with IV penicillin and vancomycin, the mass and FDG avidity resolved. (Color plate 131.2)

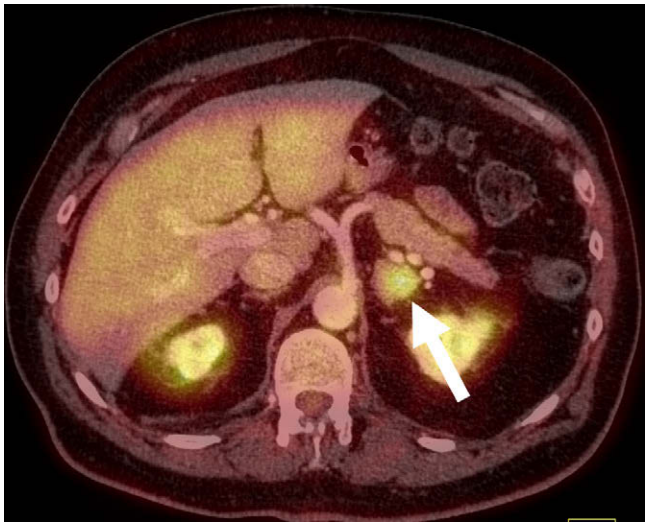


Figure 131.4 A 45-year-old woman with history of GIST. PET–CT found an FDG-avid left adrenal nodule (arrow). This nodule was stable over 5 years and was consistent with a benign FDG-avid adenoma. (Color plate 131.3)

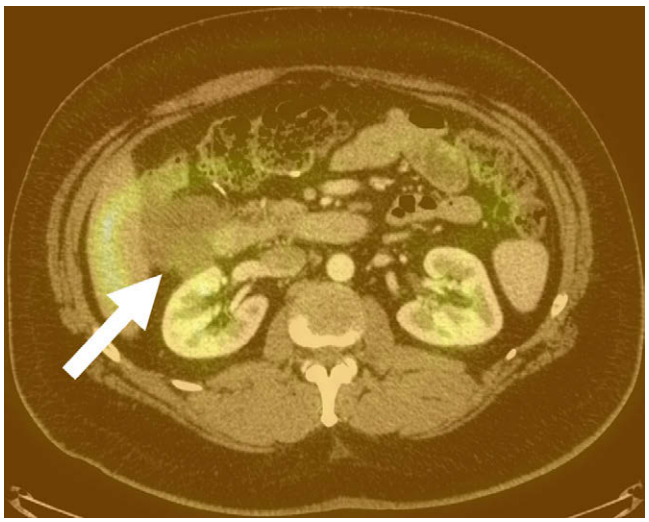


Figure 131.5 A 52-year-old man post right colectomy for colonic adenocarcinoma. Follow-up PET–CT demonstrated a mass in the right upper quadrant (arrow) adjacent to the anastomosis, which did not demonstrate FDG uptake. Biopsy found atypical signet ring cells in a background of abundant mucoid acellular material, consistent with origin from an FDG-negative adenocarcinoma. (Color plate 131.4)

of background. A partial metabolic response (PMR) is defined as at least a 30% and 0.8 unit decrease in SUL peak between the most intense pretherapy lesion and the most intense posttherapy lesion. Progressive metabolic disease (PMD) involves at least a 30% increase in SUL peak or the appearance of new lesions. Stable metabolic disease (SMD) is the classification if the criteria for CMR, PMR, or PMD are not met.

7. What is the role of PET–CT in monitoring response to cytostatic chemotherapeutic agents?

Some chemotherapeutic agents, such as sunitinib and imatinib, are cytostatic in nature and halt the tumor growth but do not cause cell death. Therefore, monitoring response to treatment with these agents using conventional imaging modalities such as CT or MRI would not be ideal as the basis for assessing response by these modalities is reduction in size of the tumor.

Studies have shown that in patients with gastrointestinal tumors (GIST) treated with imatinib therapy, 18F-FDG PET may be used to detect both short-term and long-term tumor responses that may not be apparent with CT, can predict outcome, and can detect both primary and secondary resistance to imatinib. Studies have also shown that in patients with melanoma treated with BRAF inhibitors, FDG PET–CT can detect early response and may help identify patients with a shorter time to progression (Figure 131.6). Similar findings have been seen in patients with non-small-cell lung cancer treated with EGFR tyrosine kinase inhibitor and MEK inhibitors (Figure 131.7).

These studies and others exemplify the role of FDG PET–CT for guiding the selection of novel investigation drugs, choosing dose in early-phase clinical development, and predicting nonresponding patients early in treatment.

8. Does PET–CT have a role to play in predicting response to treatment?

One of the possible applications of PET–CT is to individualize therapy by early identification of patients with nonresponding tumors. Identifying these nonresponders can prevent adverse events, such as tumor progression during treatment and the side effects and cost of an ineffective treatment, and allows for early appropriate modification of the treatment protocol.

For example, studies have found that in patients with esophageal carcinoma, changes in tumor metabolic activity after 14 days of preoperative therapy are significantly correlated with tumor response and patient survival (Figure 131.8). A follow-up study generated the hypothesis that early termination of chemotherapy based on PET does not negatively affect clinical outcome in metabolic nonresponders with esophageal cancer. In addition to these patients and those with GISTs, as above, promising results for FDG predicting response to treatment have also been found in studies of certain patients with lymphoma, melanoma, and other tumors.

9. Does PET–CT have a role in guiding and follow-up of interventional procedures?

Unenhanced CT is often used to guide percutaneous biopsy. However, some lesions detected with PET may have little

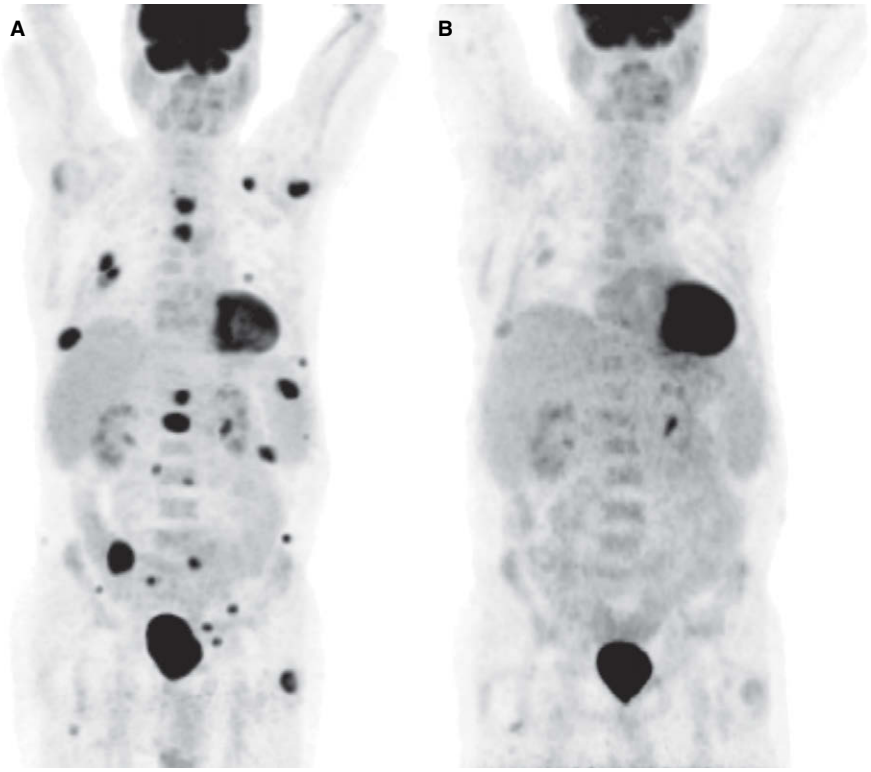


Figure 131.6 A 70-year-old man with newly diagnosed melanoma on his back. (A) Initial staging PET–CT found multiple bony and soft tissue metastases. BRAFV600E mutation was found on biopsy. (B) Follow up PET–CT after 2 months treatment with a BRAF inhibitor found a dramatic decrease in FDG uptake, although the morphological findings were unchanged on CT (not shown).

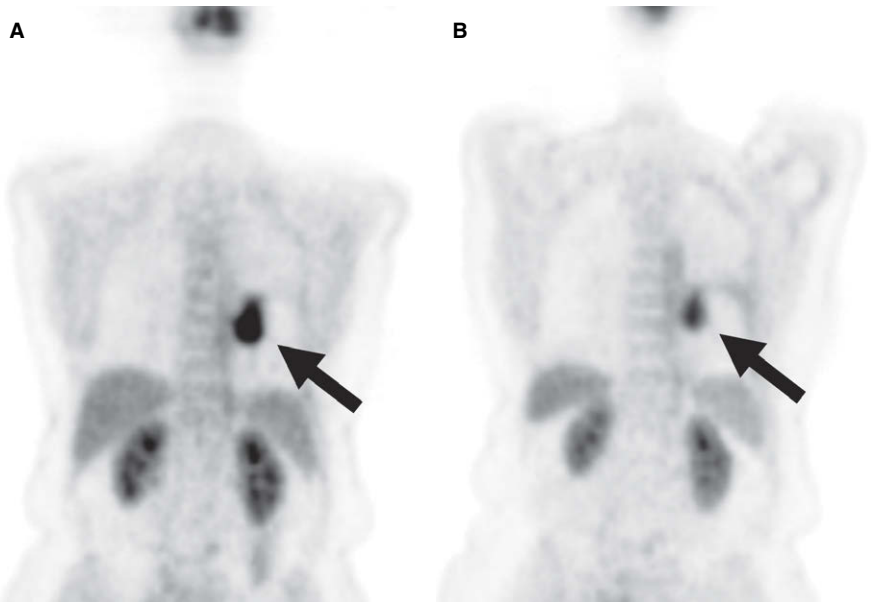


Figure 131.7 A 61-year-old woman with metastatic non-small-cell lung cancer. Snapshot testing revealed EGFR mutation. She was commenced on EGFR inhibitor, but follow-up imaging showed progression. Rebiopsy demonstrated secondary EGFR mutation. PET–CT before (A) and 3 weeks after (B) commencing a MEK inhibitor demonstrated decreased FDG avidity of a left lower lung mass (arrow).

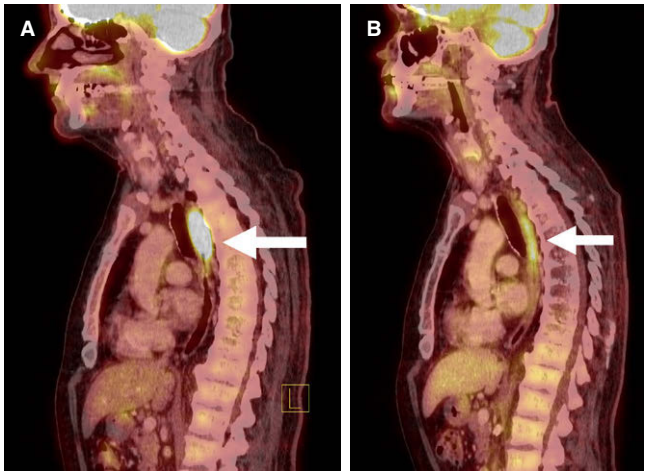


Figure 131.8 A 67-year-old man with squamous cell cancer of the upper esophagus. FDG PET–CT before (A) and one month post (B) neoadjuvant chemoradiation shows a decrease in FDG avidity of the tumor (arrow). At resection, there was no residual viable carcinoma. (Color plate 131.5)

or no correlative CT findings, or may only contain metabolically active tumor cells in only a part of the mass. PET–CT-directed and PET–CT-guided biopsy have been shown to be feasible and may be helpful when performing biopsies in the above scenarios. PET–CT may also help both choose the most suitable body site to sample and also target the most metabolically active site of tumor, which may increase the diagnostic yield. A recent study found that over one-half of morphologically benign lesions and one-third of subcentimeter lymph nodes that were FDG-avid were found to be malignant at biopsy, suggesting that benign morphologic appearances alone should not preclude further work-up of a PET-positive lesion.

PET–CT also has a role in the follow-up of interventional procedures. Radiofrequency ablation (RFA) is being increasingly used in clinical practice because of its minimally invasive nature. Differentiation between postablation changes and residual disease is important to verify the adequacy of the procedure. Studies have shown that early PET, within 1–2 days after RFA of liver metastases, can predict the completeness of the procedure and can detect residual disease. Studies looking at long-term follow-up post RFA have found that PET–CT is superior to either PET or CT alone and equivalent to MRI in detecting local tumor progression.

10. Who should interpret a PET–CT scan?

Before PET–CT, PET alone had already become a widely accepted imaging test for the assessment of many malignancies. With the clinical introduction of PET–CT, different philosophical and practical concepts emerged regarding the interpretation of the combined study and the use of the CT data. PET–CT readers should be able to recognize characteristic or important abnormalities on CT images, as well as normal variants and disease- and treatment-specific patterns of tracer uptake. There is both an art and a science to interpreting PET images, and in our experience, the best interpreters are sensibly practical and usually possess a combination of clinical acumen, broad medical knowledge, and discerning judgment. A study on radiology practices at major US cancer centers found that nuclear medicine physicians dictate more than half (57%) of the PET–CT studies at those institutions surveyed. They also found that when abdominal imagers dictate the CT portion of a PET–CT study, most review the PET images (85%) and many confer with a nuclear medicine staff member all or some of the time before approving their reports (32% and 36%, respectively). At our institution, PET–CT readout sessions are attended jointly by chest and abdominal radiologists and nuclear medicine physicians.

Selected reading

Cronin CG, Prakash P, Blake MA. Oral and IV contrast agents for the CT portion of PET–CT. AJR Am J Roentgenol. [Review]. 2010 Jul;195(1):W5–13.

McDermott S, Skehan SJ. Whole body imaging in the abdominal cancer patient: pitfalls of PET-CT. Abdom Imaging. [Review]. 2010 Feb;35(1):55–69.

Nguyen MT, Gervais DA, Blake MA, *et al*. Image-guided biopsy of FDG-avid extrapulmonary lesions: does lesion location and morphology affect the positive predictive value for malignancy? AJR Am J Roentgenol. 2013;201(2):433–8.

Purandare NC, Rangarajan V, Shah SA, *et al*. Therapeutic response to radiofrequency ablation of neoplastic lesions: FDG PET–CT findings. Radiographics. 2011 Jan–Feb;31(1):201–13.

Wahl RL, Jacene H, Kasamon Y, *et al*. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009 May;50 (Suppl. 1):122S–50S.

CHAPTER 132

Hematopoietic growth factors

LeAnn B. Norris, Jametta Magwood, and Charles L. Bennett
Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA

Case study 132.1

RJ is a 55-year-old postmenopausal woman who was diagnosed with breast cancer 5 years ago. Mammography revealed a 2 × 1.5 cm mass in the right breast with microcalcifications. Core biopsies of the right breast confirmed an invasive ductal carcinoma, nuclear grade 3, estrogen and progesterone receptor negative (ER−/PR−) and HER-2neu negative. Her past medical history includes no comorbid illnesses. RJ underwent a mastectomy with sentinel lymph node biopsy. She was diagnosed with stage IIB (T2N0M0) hormone-receptor-negative, HER2-negative breast cancer, or "triple-negative" disease. After mastectomy, she received four cycles of dose-dense adjuvant doxorubicin and cyclophosphamide with granulocyte colony-stimulating factor (G-CSF) support followed by four cycles of paclitaxel. She was out of work for 4 months during treatment but did not experience any episodes of febrile neutropenia or dose delays. Two months ago, she began experiencing pain in her hip. A bone scan was performed that indicated a suspicious area of uptake in her lumbar spine, which was confirmed by X-rays. Computed tomography (CT) scan revealed multiple liver lesions, and a biopsy confirmed recurrent breast cancer (ER−/PR). She was initiated on paclitaxel every 3 weeks and has since progressed through treatment. An oncologist is now recommending a new chemotherapy regimen with a breast cancer chemotherapy regimen that has an estimated rate of febrile neutropenia of less than 20%.

• Is filgrastim (G-CSF) or peg-filgrastim (peg-G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) (the three colony-stimulating factors (CSFs) that are approved by the US Food and Drug Administration (FDA)) required following the first cycle of this chemotherapy?

For women receiving dos-dense adjuvant breast cancer chemotherapy, guidelines from the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Center, and European Organization for the Research and Treatment of Cancer recommend G-CSF support for primary prophylaxis for this patient. ASCO guidelines from 1996, 1997, and 2000 recommended that CSFs should be given in a prophylactic setting if the risk for febrile neutropenia is greater than 40%. In 2006, updated guidelines from ASCO lowered the pivot point for CSF use in conjunction with chemotherapy regimens that have rates of chemotherapy-induced febrile neutropenia of 20% or greater. This was based on a randomized clinical trial that randomized patients with breast cancer to receive pegfilgrastim or no G-CSF after docetaxel 100 mg/2 every 3 weeks for four cycles. The incidence of febrile neutropenia (1% vs. 17%) and hospitalization for febrile neutropenia (1% vs. 14%) was reduced by >90% with pegfilgrastim ($P < 0.001$).

• The patient does develop febrile neutropenia following the first cycle of chemotherapy. She is admitted to the hospital, and broad-spectrum antibiotics are initiated. Should she receive G-CSF, peg-G-CSF, or GM-CSF in addition to the antibiotics?

A data synthesis of 13 trials that compared CSFs plus antibiotics versus antibiotics alone for treatment of established febrile neutropenia indicates that CSFs reduced hospital stays and neutropenia, and had a marginally significant

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

improvement in reducing infection-related mortality (OR: 0.51; 95% CI: 0.26–1.00). However, the potentially beneficial effect was reduced when one low-quality trial that included patients with acute myeloid leukemia was excluded in the sensitivity analysis; also, the study found that administration of CSFs did not improve overall mortality. In practice, a CSF is rarely administered with antibiotics among cancer patients with chemotherapy-induced febrile neutropenia and is generally not recommended.

• **The patient is successfully treated for febrile neutropenia and is discharged from the hospital after three days. Her white blood cell count is now 3000 cells/mm3, and she is due for cycle 2, day 1 of the same regimen. Should she receive the same dosages that were administered in cycle 1 with support by a CSF (termed secondary prophylaxis)?**
Secondary prophylaxis has not been extensively studied in randomized controlled trials. However, one meta-analysis reports that the effects are comparable to those seen in primary prophylaxis in terms of reducing rates of febrile neutropenia. Most clinicians in treating this patient with palliative chemotherapy would reduce the chemotherapy dosages in the second cycle, rather than maintain the dosages and add a CSF.

• **If the patient were being treated with dose-dense chemotherapy for advanced breast cancer with the intent of cure (rather than a palliative regimen), would an up-front administration of a CSF have been indicated? The estimated rate of febrile neutropenia with this regimen is greater than 20%.**
The most recent ASCO Update on CSFs (2006) states that primary prophylaxis with a CSF is recommended for prevention of febrile neutropenia in patients who have a high risk of developing this complication after chemotherapy, and equally effective treatment programs that do not require myeloid colony-stimulating factors are not available. While high risk is operationally defined as a risk greater than 20%, additional considerations supporting the use at lower expected rates of febrile neutropenia include older age, medical history or comorbid medical illnesses, or particular characteristics of the cancer.

1. Are there differences in the FDA labeled indications among the various FDA-approved CSFs in the setting of febrile neutropenia prophylaxis?

G-CSF and peg-G-CSF received FDA approval for primary prophylaxis against febrile neutropenia following chemotherapy in 1991 and 2002, respectively. Both G-CSF and peg-G-CSF are indicated for incidence reduction of febrile neutropenia and associated infection. G-CSF- and peg-G-CSF-labeled indications in the setting of febrile neutropenia prophylaxis do not differ. GM-CSF received FDA approval in 1996 for prevention of fungal infections and primary prophylaxis against febrile neutropenia following induction chemotherapy among older persons with acute myeloid leukemia. GM-CSF can also be concomitantly used with chemotherapy and reduces neutrophil recovery time as well as incidence of infections GM-CSF label indications differ from those of G-CSF and peg-G-CSF.

2. Do existing ASCO guidelines differentiate among the various CSFs?

The 2006 ASCO guideline indicates that no guideline recommendation can be made regarding the equivalency of the G-CSF and GM-CSF.

3. If a CSF is to be used, what are the appropriate dosing and scheduling recommendations?

Filgrastim is administered at 5 mcg/kg, and sargramostim is administered at 250 mg/m^2/day daily via subcutaneous injection and continued until the nadir white blood cell count recovers or returns to near-normal levels. The duration of therapy is contingent on myelosuppressive potential of the chemotherapy agents involved. Premature discontinuation of CSF therapy should be avoided. Pegylated filgrastim is administered as a onetime dose of 6 mg subcutaneously. Either agent when administered should be administered 24–72 hours after the completion of chemotherapy. The overwhelming majority of CSF use in the United States is with G-CSF or peg-G-CSF.

4. What are the most common adverse effects associated with CSF use?

Injection site discomfort, including some constitutional symptoms such as fever, malaise, and flu-like symptoms, is common. The main CSF-related toxicity, mild to moderate bone pain, develops in 10% to 30% of filgrastim- and pegfilgrastim-treated patients. Nonnarcotic analgesics usually control this toxicity. GM-CSF is associated with higher rates of fever following its administration.

5. Are there any rare side effects associated with CSFs?

Rare cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and splenic rupture have been reported in cancer patients as well as healthy donors of peripheral blood stem cells who received G-CSF, GM-CSF, or peg-G-CSF. While G-CSF may be independently correlated with low overall absolute AML and MDS risks in the setting of breast cancer chemotherapy, the benefits outweigh the small absolute risks of developing AML or MDS.

6. The clinician and patient strongly support trying to stay on schedule with the dose-dense chemotherapy regimen for breast cancer. Does G-CSF or pegylated G-CSF have any utility here?

G-CSF or pegylated G-CSF is frequently used to facilitate the administration of chemotherapy in full doses or to maintain schedule. The rationale for full doses relies on the assumption that the dose intensity should not be compromised in settings where giving a full dose of chemotherapy may be more efficacious. In the metastatic disease setting, the importance of maintaining chemotherapy dose intensity is less clear, although maintaining schedule is also important.

Selected reading

Cooper KL, Madan J, Whyte S, *et al*. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer. 2011;11:404.

Dubois RW, Pinto LA, Bernal M, *et al*. Benefits of GM-CSF versus placebo or G-CSF in reducing chemotherapy-induced complications: a systematic review of the literature. Supp Cancer Ther. 2004;2:34–41.

National Comprehensive Cancer Network (NCCN). Myeloid growth factors v1.20012. Available from: http://www.nccn.org.

Tigue CC, McKoy JM, Evens AM, *et al*. Granulocyte-colony stimulating factor administration to healthy individuals and persons with chronic neutropenia or cancer: an overview of safety considerations from the Research on Adverse Drug Events and Reports project. Bone Marrow Transpl. 2007; 40:185–92.

US Food and Drug Administration Drug databases. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

CHAPTER 133

Anticoagulation issues in oncology

Steven M. Corsello[1,3] and Jean Marie Connors[2,3]

[1]Dana-Farber Cancer Institute, Boston, MA, USA
[2]Brigham and Women's Hospital, Boston, MA, USA
[3]Harvard Medical School, Boston, MA, USA

Case study 133.1

A 54-year-old male presents with a worsening chronic cough. Chest imaging and subsequent needle biopsy reveal the presence of metastatic lung adenocarcinoma. The patient has no prior history of venous thromboembolism (VTE), remains active, and has a normal Body Mass Index (BMI) and complete blood count (CBC). Systemic chemotherapy with a bevacizumab-containing regimen is planned.

1. Is pharmacologic VTE prophylaxis indicated for this patient? If so, what is the preferred agent?

A. Yes, therapeutic low-molecular-weight heparin (LMWH)
B. Yes, therapeutic warfarin
C. Yes, prophylactic LMWH
D. No; prophylaxis is not indicated

The use of VTE prophylaxis in ambulatory cancer patients receiving chemotherapy has demonstrated efficacy in the past, and has recently been studied in large, industry-sponsored trials using LMWH. While these studies have found decreased event rates in patients receiving prophylaxis compared with placebo, overall event rates are low. Risk assessment scores have been developed to identify those patients at increased risk who might derive greater benefit from prophylaxis.

The risk for a VTE event varies among patients. Data from a prospective observational study involving approximately 2700 cancer patients were used to derive a risk model for VTE (shown in Table 133.1).

The study authors found that the total risk score correlated with VTE risk in a separate validation cohort. The incidence of VTE was 0.3% in low-risk patients (0 points), 2% in intermediate-risk patients (1–2 points), and 6.7% in high-risk patients (≥3 points) over a median of 2.5 months.

Table 133.1 Khorana Risk Assessment Score.

Patient characteristic	OR (95% CI)	Risk score
Stomach or pancreas site	4.3 (1.2–15.6)	2 points
Lung, lymphoma, GYN, bladder, or testicular site	1.5 (0.9–2.7)	1 point
Platelet count ≥350,000 per μl	1.8 (1.1–3.2)	1 point
Hemoglobin <10 g/dL	2.4 (1.4–4.2)	1 point
WBC count >11,000 per μl	2.2 (1.2–4)	1 point
BMI ≥35 kg/mg^2	2.5 (1.3–4.7)	1 point

BMI, Body Mass Index; CI, confidence interval; GYN, gynecological; OR, overall response; VTE, venous thromboembolism; WBC, white blood cell. Source: Connors JM, Venous Thromboembolism Prophylaxis in Ambulatory Cancer Patients. New Engl J Med. At Press. Copyright 2014 Massachusetts Medical Society. Reproduced with permission of the Massachusetts Medical Society.

The baseline risk of VTE in a given patient with cancer can be estimated using this straightforward metric.

This Khorana risk-scoring model was applied to the patient population in the SAVE-ONCO trial, the largest VTE prophylaxis study in this setting to date. Approximately 3200 ambulatory patients receiving chemotherapy for locally advanced or metastatic cancer were randomized to receive semuloparin 20 mg daily versus placebo. The overall incidence of VTE in the semuloparin group was 1.2%, versus 3.4% in the placebo group (HR: 0.36; $P < 0.001$). In the subset analyses reported at ASH 2011, patients with a Khorana risk

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

score of >3 receiving prophylaxis had a VTE rate of 1.5% compared to 5.4% for the placebo group (HR: 0.27; 95% CI: 0.09–0.82). Overall bleeding rates were comparable between the semuloparin arm and placebo; however, bleeding rate increased with corresponding increase in Khorana risk score. The overall VTE event rate in the general ambulatory cancer patient population is low, and no survival benefit has been demonstrated. In summary, while the relative risk reduction with prophylactic anticoagulation is significant, the absolute risk difference is small.

One trial was recently reported that employed apixaban, a new oral anticoagulant, for VTE prophylaxis. This trial demonstrated that apixaban has a good safety profile compared with placebo, with increased risk of bleeding as dose increases, but was not powered to demonstrate efficacy. Insufficient data currently exist to recommend the use of any new oral anticoagulant for VTE prophylaxis in oncology patients, especially since the utility of prophylactic anticoagulation in this setting has not been demonstrated.

Current ACCP guidelines suggest against the use of prophylaxis except in those patients with additional risk factors. We reserve empiric prophylaxis for ambulatory patients treated with highly thrombogenic myeloma regimens, history of prior unprovoked or life-threatening VTE, or strong inherited thrombophilias (such as homozygous factor V Leiden). The patient in this case has no past history of thrombosis and no other VTE risks. His Khorana risk score is 1, with a VTE incidence rate of 2%. The contribution of bevacizumab to thrombotic risk is not clear, given conflicting reports. There are no data to support the routine use of prophylactic anticoagulation with bevacizumab-containing regimens. Additional studies are needed to better prospectively identify ambulatory cancer patients at high risk for VTE who may benefit from such prophylactic anticoagulation.

The efficacy and safety of prophylactic anticoagulation in the hospitalized cancer patient and in patients undergoing oncology surgery, who have a higher risk of post-op VTE than non-oncology patients, have been clearly demonstrated. We have not covered these indications in this chapter. As in all situations where anticoagulation treatment is considered, the risks and benefits need to be carefully evaluated and understood for each individual patient.

After two cycles of chemotherapy, restaging computed tomography (CT) scan is performed. Incidental pulmonary embolus is found in a right lower lobe segmental artery. Although the patient is fatigued and has an infrequent non-productive cough, his heart rate is 85 beats per minute, his blood pressure is 128/72, and room air oxygen saturation is 96%. Brain natriuretic peptide is within normal limits, and there is no evidence of right heart strain on physical exam. CT also suggests a response to therapy, and plans are to continue with the current treatment regimen.

2. Which of the following agents would be preferred for initial treatment?

A. Warfarin
B. Intravenous (IV) unfractionated heparin (UFH)
C. Dalteparin
D. Dabigatran
E. Rivaroxaban

This patient presents with an apparently asymptomatic pulmonary embolism (PE). In a retrospective study, however, 75% of cancer patients who were diagnosed with unexpected PE did in fact have symptoms, including fatigue and dyspnea, that had been previously attributed to the cancer or its treatment. Clinicians need to have a high index of suspicion for VTE in the evaluation of new symptoms in the cancer patient. Treatment of incidental VTE is warranted. A study comparing recurrent VTE, bleeding, and mortality rates in oncology patients with incidentally detected versus symptomatic PE found no difference in outcome for either group, suggesting that the incidental PE group had just as high a risk of adverse events associated with VTE as symptomatic patients. Regardless of symptoms, the presence of thrombus serves as an indicator for true hypercoagulable state. In our experience, when patients with asymptomatic VTE are observed and re-imaged, there is a high rate of extension or development of new thrombus in other locations.

Initial treatment of acute VTE requires the use of rapid-acting agents to prevent clot propagation. Use of warfarin alone is associated with an unacceptably high rate of thrombus extension and is not appropriate initial therapy in this patient or any patient with acute VTE. Intravenous UFH, LMWH, fondaparinux, and, recently, rivaroxaban have all been demonstrated to have good efficacy and safety in the initial treatment of VTE in the general population. LMWH has many pharmacokinetic advantages over UFH, including fixed weight-based dosing with no need for monitoring. There would be no reason to hospitalize this ambulatory patient for treatment with UFH. Although the current standard of care of PE in many institutions is to admit patients for treatment and observation, we have found that many reliable patients who have an unexpected finding of PE can be treated in the outpatient setting. Clinical judgment incorporating an assessment of clot burden, degree of symptoms, oxygen saturation, and hemodynamic function can be used to determine the need for hospitalization. A recent meta-analysis of 13 studies with a total of 2458 patients supports outpatient treatment in low-risk patients. Despite the use of different risk stratification schemes, the risk of recurrent VTE, fatal PE, and major bleeding was low.

(*Continued*)

Based on the results of multiple trials, LMWH is the standard of care for initial treatment of cancer-associated VTE in ambulatory patients. The largest study of acute VTE treatment in oncology patients to date is the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial. Approximately 700 patients who were actively receiving chemotherapy were randomized to treatment with dalteparin 200 units/kg/day for one month followed by a decrease in dose to 150 units/kg/day for 5 months, or initial dalteparin for 5–7 days followed by warfarin for 6 months. The probability of recurrent VTE was 9% for those treated with dalteparin alone versus 17% for warfarin ($P = 0.002$). There was no difference in risk of bleeding.

As a result of these findings, LMWH has been widely recommended as the preferred treatment for acute VTE in the cancer patient, without transition to warfarin. Guidelines from American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and American College of Chest Physicians (ACCP) endorse the use of LMWH as monotherapy for 3–6 months in this population. While oncology patients have sometimes failed therapeutic warfarin, warfarin management itself in this population is difficult due to drug–drug interactions, hepatotoxicity from chemotherapy, and absorption issues due to the significant gastrointestinal impact of chemotherapy. It should be noted that the CLOT trial had a warfarin time in therapeutic range (TTR) of only 46%, reflecting the management difficulty in this population. Most of the recurrent events occurred during the first month of anticoagulation treatment, when optimal warfarin dose is being defined. Almost half of the recurrent events in the warfarin arm occurred when the international normalized ratio (INR) was <2.0, which may account for some of the differences seen between the treatment arms. For certain patients, however, transitioning to warfarin after initial therapy with LMWH may be appropriate or unavoidable. The cost of LMWH can be prohibitive for many patients, and the once- or twice-daily subcutaneous injections can be difficult to tolerate. In addition, LMWH should be used with caution in the setting of renal insufficiency.

Dabigatran, which directly inhibits thrombin, and rivaroxaban and apixaban, which target factor Xa, are oral anticoagulants that have been developed as alternatives to warfarin and are available for prescribed use. While most trials so far show equivalent efficacy and possibly improved safety compared with warfarin, these drugs have only been studied in highly selected patient populations. Experience and data for use outside these populations is limited or nonexistent. Dabigatran and apixaban are approved for stroke prophylaxis in patients with nonvalvular atrial fibrillation, but not for treatment of acute VTE. Rivaroxaban is now also approved by the US Food and Drug Administration (FDA) for the treatment of DVT and PE. Dabigatran labeling was recently changed to list use in patients with mechanical valves as an absolute contraindication, based on the early termination of the RE-ALIGN trial due to increased events with dabigatran compared to warfarin. This unexpected result demonstrates that caution is warranted when prescribing new anticoagulants for patients with high-risk thrombotic indications that have not been specifically validated. In addition to having a high risk for thrombosis, cancer patients are also commonly prescribed medications (including certain antibiotics, antifungals, antivirals, and seizure medications) that affect plasma concentrations of these oral anticoagulants. These interactions occur via p-glycoprotein transport in the case of dabigatran, or both p-glycoprotein and CYP3A4 for rivaroxaban and apixaban.

Rivaroxaban, or use of the other new oral anticoagulants, would not be considered first-line therapy for a cancer patient on cytotoxic chemotherapy.

3. After 6 months of treatment, this patient is hospitalized with acute kidney injury related to volume depletion and ibuprofen use. Recent restaging scans showed partial recanalization of subsegmental pulmonary emboli. Metastatic disease remains present but stable. Chemotherapy is currently on hold for a number of months. Initial labs show a creatinine clearance of 20 ml/min and a partial thromboplastin time (PTT) of 80 seconds. Anti-Xa level is 3.8 units per mL (drawn 4 hours after his last injection). How should the patient's anticoagulation be managed?

A. Decrease enoxaparin to once daily and monitor anti-Xa level

B. Discontinue LMWH and transition to warfarin

C. Change to rivaroxaban

D. A or B

Indefinite anticoagulation is indicated given the prior pulmonary embolus and chronic hypercoagulable state in the setting of metastatic malignancy. Discontinuing anticoagulation at this point has been shown to result in high recurrence rates. This patient may have a short-term increased risk of VTE given concurrent hospitalization.

LMWH is almost exclusively cleared by the kidneys. The elevated anti-Xa level in this patient reflects accumulation due to decreased renal function. There are two approaches that can be employed. One is to continue with LMWH at a decreased dose, with close monitoring and dose adjustment based on anti-Xa levels. The current creatinine clearance is borderline for this approach. Alternatively, one could transition to warfarin.

While LMWH is preferred for initial treatment of VTE in cancer patients, its superiority for long-term treatment after 6 months has not been evaluated. Given this patient's impaired renal function and lack of ongoing chemotherapy,

warfarin is a valid option. Transitioning directly to warfarin can be accomplished without the need to continue a parenteral agent until therapeutic INR is reached, since the current role of anticoagulation is secondary prevention of a new VTE event, not prevention of clot propagation. If the patient remains hospitalized, which increases his thrombotic risk, IV UFH bridge can be initiated when the anti-Xa level declines to below the therapeutic range.

4. The patient recovers but is readmitted 2 months later to the intensive care unit with persistent hemoptysis. INR on warfarin is 2.1. Anticoagulation is stopped and reversed. Lower-extremity Doppler ultrasound shows no evidence of DVT. Is an inferior vena cava (IVC) filter indicated for secondary prophylaxis of pulmonary embolism?

A. Yes
B. No

Unfortunately, this challenging scenario is commonly encountered in clinical practice. The patient has now developed a contraindication to anticoagulation but remains at risk of recurrent VTE. Improvements in IVC filter technology (such as the development of retrievable filters) make them more attractive, but data regarding efficacy are lacking. Only one randomized controlled trial of IVC filter use has been performed in any patient population, and patients in this study were also given full-intensity anticoagulation. Although there was a lower incidence of PE during the first 12 days following filter placement (1.1% vs. 4.8%), there was a twofold increase in the rate of lower-extremity DVT in patients with filters at 2 years. After 8 years, the filter group still demonstrated increased DVT rates and decreased PE rates, but no difference in mortality.

Studies of IVC filters in cancer patients are limited to retrospective case-control studies. Their use does not obviate the need for anticoagulation as the filter itself does not address the underlying hypercoagulable state. Overall, there are often increased complications, including increased rates of lower extremity DVT, with no demonstrated improvement in survival in oncology patients.

In this patient, who has no lower extremity DVT, we would strongly advise against the use of an IVC filter as there is no evidence to support clinical benefit. We reserve the use of IVC filters for those with acute DVT of the lower extremity in a large proximal thigh vein who have an absolute contraindication to anticoagulation, such as large untreated brain metastases or primary central nervous system (CNS) tumor, or for those with severely limited cardiac or pulmonary function in whom a new PE would truly be life-threatening. Other situations include perioperative retrievable filter placement in those patients with similar absolute contraindications to anticoagulation. Patients need to be continually reassessed for their ability to tolerate anticoagulation. Anticoagulation should be started as soon as practical to prevent development of lower-extremity DVT or filter thrombosis. When anticoagulation is restarted, the IVC filter should also be removed. Retrieval of IVC filters has often been overlooked, with studies demonstrating at best an 8.5% to 18% retrieval rate. As the use of IVC filters has not been shown to improve survival and is in fact often associated with increased morbidity, the life expectancy of the cancer patient must also be considered prior to filter placement. For those with advanced-stage disease and short life expectancy, IVC filter placement may be an unnecessary intervention with a higher risk of harm than benefit.

Case study 133.2

A 42-year-old woman is diagnosed with squamous cell carcinoma of the head and neck. Treatment is planned with combined radiation and chemotherapy with high-dose cisplatin. A port-a-cath is placed in the right internal jugular vein for venous access due to small peripheral veins. She presents one week later with right arm swelling. There is no evidence of compartment syndrome. Ultrasound demonstrates an occlusive right axillary vein thrombus.

1. Which of the following is the most appropriate next step in management?

A. Start enoxaparin 1 mg/kg BID
B. Remove port-a-cath immediately
C. Start enoxaparin 1 mg/kg BID; remove port-a-cath in one week
D. Start therapeutic warfarin

Catheter-associated thrombosis is a known complication of central venous access devices. One prospective trial of approximately 440 oncology patients showed that 4.3% of patients with central lines developed catheter-associated thrombosis. Upon diagnosis of DVT, the first step is to re-evaluate the indication for the line. In this case, the patient requires access for necessary chemotherapy. She has no known contraindication to anticoagulation. There is no clear evidence that early catheter removal in the absence of severe symptoms affects outcome. In one study of 74 patients with catheter-associated thrombosis, investigators were able to treat with anticoagulation and leave the line in place with low risk of line failure or of recurrence or extension of upper-extremity DVT.

Thus, in this case, we would favor initiation of anticoagulation with therapeutic LMWH and would keep the line in

(*Continued*)

place. If symptoms fail to improve within 1–2 weeks, then line removal should be considered. NCCN guidelines recommend anticoagulation for as long as the catheter is in place, with a minimum total of 3 months of therapy. Over time, patients with chronic central access catheters that are not routinely being used are at risk for superior vena cava syndrome due to thrombus or stenosis.

The question of routine central access catheter prophylaxis has been addressed in a number of studies, often with low-dose anticoagulation such as fixed low-dose warfarin or UFH. Two meta-analyses have found conflicting results. Many individual studies were small, and different agents were used—including UFH, LMWH, and fixed low-dose warfarin. A randomized, placebo-controlled trial of dose-adjusted warfarin with target INR 1.5–2.0 in 174 patients found no evidence of efficacy.

At present, routine central access catheter thromboprophylaxis is not recommended for all patients. We reserve its use for patients with a past history of significant thrombosis or strong inherited thrombophilia. Intensity (prophylaxis versus full-intensity) is determined after assessment of the patient's baseline VTE and bleeding risks.

2. The patient begins therapeutic enoxaparin 1 mg/kg twice daily (BID), and her arm swelling improves. However, after 2 weeks she refuses injections due to abdominal skin bruising and pain. What recommendation should be made?

A. Change to once-daily fondaparinux
B. Change to rivaroxaban
C. Change to warfarin
D. Discontinue anticoagulation

Subcutaneous hemorrhage and pain at injection sites are sometimes encountered in patients on LMWH. Patients should be taught proper injection technique, encouraged to use ice packs on the site after injection, and advised not to wipe the site with alcohol after the injection in order to minimize bruising. Other sites beside the abdomen can be used for injection, including the upper thigh, buttocks, and triceps areas. Patients can be instructed to insert just the tip of the needle into the skin, past the beveled edge but not to the hub of the syringe, to minimize trauma with injections.

Often, the above instructions combined with reassurance and counseling on the benefits of parenteral anticoagulation are sufficient for many patients to continue with LMWH. If these measures are unsuccessful, a change in therapy may be required. Changing to a once-daily parenteral formulation is the next step. In our experience, fondaparinux is associated with less burning upon injection. The FDA-approved once-daily administration of fondaparinux or dalteparin can often be better tolerated than the twice-daily dosing of enoxaparin. While the use of enoxaparin 1.5 mg/kg daily is widely used in other settings, it has not been evaluated in the oncology population.

Rivaroxaban should not be selected due to the potential for medication interactions and lack of data in this patient population. Warfarin would not be the first choice given possible drug interactions with cisplatin and expected variations in nutritional status and the potential need for enteral support on this highly emetogenic chemotherapy regimen. Anticoagulation is required while the catheter remains in place.

3. The port-a-cath was removed after completing chemotherapy. Restaging scans at 6 months show no evidence of disease. An upper-extremity ultrasound shows continued right subclavian vein occlusion with collateral flow. Symptoms have resolved, and arm swelling is no longer present. D-dimer is <500. The patient expresses a preference to stop anticoagulation if possible. What recommendation should be made?

A. Stop anticoagulation
B. Continue anticoagulation indefinitely

The patient appears to have developed chronic organized thrombus in the right subclavian vein despite 6 months of anticoagulation. The line has been removed, and planned cancer treatment is complete. The decision regarding cessation of anticoagulation should be made based on individual considerations of risk versus benefit, while incorporating patient preferences. In this case, the indication for extended anticoagulation is not definite. The provoking factors of cancer, chemotherapy, and central access catheter use are no longer present, and the patient has received adequate duration of anticoagulation therapy for the initial clot. There is no evidence of postthrombotic syndrome, which might indicate a need for continued anticoagulation to prevent recurrent thrombus in the same arm. Stopping anticoagulation can be safely considered provided the patient is educated to contact a provider immediately for any new symptoms.

D-dimer measurement is not specifically validated for cancer patients with provoked VTE. Thus, treatment decisions should not be made based on the d-dimer value alone until prospectively validated in an oncology-specific population.

Case study 133.3

A 63-year-old woman with a history of metastatic pancreatic adenocarcinoma is found to have new occlusive right portal vein thrombosis on restaging scans at 6 weeks. Right upper quadrant ultrasound confirms the presence of thrombus with markedly decreased Doppler flow in the right portal vein. There is no evidence of cavernous transformation. She is currently on cycle 4 of weekly gemcitabine, and the tumor burden is stable. Recent mild transaminitis and right upper quadrant discomfort were previously attributed to chemotherapy. Platelet count is 90,000 per μl, and prothrombin time (PT) and PTT values are normal.

1. What step should be taken next?

A. Start aspirin 325 mg daily
B. Start clopidogrel 75 mg daily
C. Start dalteparin 200 units/kg daily
D. No treatment is required for an incidental portal vein clot

Patients with cirrhosis or underlying malignancy are at increased risk of portal vein thrombosis (PVT). The risk is further increased in the presence of inherited thrombophilias and myeloproliferative disorders (including JAK2 mutations). Complete portal vein occlusion reduces the liver blood flow by up to two-thirds and is associated with hepatocyte apoptosis in animal models. Anticoagulation is indicated for the treatment of acute PVT in order to prevent clot extension and facilitate recanalization. In cancer patients, we view the development of any thrombosis as demonstration of a hypercoagulable state. With persistent malignancy and ongoing chemotherapy, this patient is at increased risk for extension of thrombus. Anticoagulation in this patient should prevent progression to complete thrombosis of the right portal vein and extension to the main portal vein and other splanchnic vessels.

The role of anticoagulation for management of chronic PVT is more controversial, particularly in patients with increased bleeding risk due to cirrhosis and esophageal varices; this is the patient population from which most of the data are derived. There is still controversy about the role of anticoagulation in this setting. We do not recommend anticoagulation for the cancer patient with clearly old thrombus and good collateral circulation.

Patients with a platelet count of 90,000 per μl can be safely anticoagulated with LMWH unless there are other major contraindications to anticoagulation. Generally accepted practice endorsed by ASCO, NCCN, and ACCP is to hold anticoagulation for platelet counts lower than 50,000 per μl; however, individual patient assessments have allowed us to continue anticoagulation with platelet counts down to 30,000 per μl. The severity and age of thrombus determine the importance of anticoagulation. In patients with severe persistent thrombocytopenia and new acute clot such as main pulmonary artery PE, platelet transfusion support may be necessary to allow anticoagulation treatment.

2. The patient is started on therapeutic LMWH. Six weeks later, she develops right lower extremity swelling and pain. Lower extremity Doppler ultrasound reveals occlusive right femoral vein thrombosis. Neurologic exam remains normal. What step should be taken next?

A. Change to warfarin
B. Add antiplatelet agent
C. Increase LMWH dose by 25%
D. Place IVC filter
E. Choices C or D

Oncology patients remain at increased risk of recurrent VTE, even while receiving effective anticoagulation. In the CLOT trial, this risk was 9% for the group treated with dalteparin over 6 months. There is no single optimal approach to management of recurrent VTE while on therapy. Patient compliance and effectiveness of medication administration can be assessed with a random anti-Xa level. It is also reasonable to check the anti-Xa level 4 hours after injection of LMWH to document achievement of the therapeutic target, particularly in obese patients for whom dose of anticoagulant may be capped and for whom optimal dosing strategies have not been defined.

Assuming the anti-Xa level is therapeutic, there are two strategies available. Dose escalation of LMWH has been evaluated in a small series. One retrospective cohort study examined the outcomes of 70 oncology patients with recurrent, symptomatic VTE. The majority of patients had metastatic disease. The dose of LMWH was increased by 20–25% for those already on therapeutic dosing. During a 3-month follow-up period, 8.6% of patients had a second, recurrent VTE, while 4.3% had bleeding complications. Larger trials are needed to fully evaluate the efficacy and safety of this approach. Dose escalation may not be appropriate for patients with known CNS metastases, significant thrombocytopenia (platelet count below 50,000 per μl), or other significant bleeding risk factors.

IVC filter placement is also an option for this patient given the proximal DVT. However, the risk of recurrent DVT is as high as 35% over 8 years following IVC filter placement (see Case study 133.1, Question 4). The filter itself may serve as a nidus for further thrombus formation in the setting of a hypercoagulable state. For this patient, we would favor dose escalation of LMWH as the initial approach.

Case study answers

Case study 133.1

Question 1: Answer D
Question 2: Answer C
Question 3: Answer D
Question 4: Answer B

Case study 133.2

Question 1: Answer A
Question 2: Answer A
Question 3: Answer A

Case study 133.3

Question 1: Answer C
Question 2: Answer E

Selected readings

Blom JW, Doggen CJM, Osanto S, *et al*. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293:715–22.

Carrier M, Le Gal G, Cho R, *et al*. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost. 2009;7:760–65.

den Exter PL, Hooijer J, Dekkers OM, *et al*. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. J Clin Oncol. 2011;29:2405–9.

Kovacs MJ, Kahn SR, Rodger M, *et al*. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (the Catheter Study). J Thromb Haemost. 2007;5:1650–3.

Lee AYY, Levine MN, Baker RI, *et al*. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146–53.

CHAPTER 134

Symptom management and palliative care

Rony Dev and Eduardo D. Bruera
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case study 134.1

A 53-year-old woman with metastatic colon cancer involving the liver, abdominal pleura and lymph nodes, thoracic spine, and brain. Palliative care consultation was placed for symptoms of vertigo and nausea with projectile vomiting.

Initial treatment included a right-sided hemicolectomy for an obstructing adenocarcinoma of the cecum. She has since received multiple regimens of systemic chemotherapy including phase 1 treatment, as well as undergone craniotomy, stereotactic radiosurgery for brain metastases, and radiation therapy to the thoracic spine. Currently, she is not a candidate for any further chemotherapy and was recently informed of a poor prognosis of 4–6 weeks to live.

The patient is now admitted with a 2–3 day history of nausea, vomiting, vertigo and headache. She attributes her nausea to the administration of opioids and has a history of acathesia with metoclopramide. For nausea, she finds ondansetron to be ineffective and prefers to take lorazepam 0.25–0.5 mg as needed.

Her Edmonton Symptom Assessment Scale is: Pain 5, fatigue 6, nausea 7, depression 0, anxiety 0, drowsiness 2, appetite 2, feeling of wellbeing 1, shortness of breath 0, sleep 0.

Her symptoms are significant for left-sided, constant, frontal headache which is worse in the morning hours and non-radiating intermittent chronic mid to low back pain. Headache has persisted for the past 3 days, rates the intensity as a 5/10. She achieves some pain relief with acetaminophen. In addition, she reports vertigo with any type of movement or with standing. Otherwise, the remainder of the review of systems is negative.

Vital Signs include afebrile temperature, pulse 56, respiration rate 17, BP 121/90, O_2 saturation was 94% on room air. Physical examination is notable for a chronically ill-appearing woman who is somewhat anxious and talks openly about her concerns. Laboratory values are within normal limits.

1. Which of the following factors may be contributing to the patient's nausea?

A. Gastroparesis
B. Increased intracranial pressure
C. Anxiety
D. Vestibular dysfunction
E. All of the above

Nausea with or without symptoms of vomiting is not uncommon in patients with advanced cancer. A stepwise, thoughtful approach is needed for the workup of nausea including a detailed history and physical examination. Once an underlying mechanism is identified, therapy can be tailored to each unique clinical scenario. However, as in the above case, multiple factors may play a role requiring more than one intervention in order to block multiple pathways resulting in emesis.

The first step in the evaluation of nausea includes a thorough history characterizing the symptom with attention for clues to the underlying etiology. Early satiety may indicate gastroparesis, nausea and vomiting in the morning hours with symptoms of head discomfort suggest increased intracranial pressure, nausea relieved by infrequent, large emesis may indicate a bowel obstruction, and a temporal pattern of

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

nausea associated with emotional reaction suggests underlying anxiety. Cancer which has metastasized to the liver, peritoneum, or brain is often associated with nausea.

A complete review of medications is also critical. Research indicates common factors resulting in nausea and vomiting include medications (i.e. opioids, chemotherapy, antibiotics) and constipation. Other factors associated with nausea in cancer patients include infections, metabolic abnormalities, gastroparesis secondary to autonomic dysfunction, radiation especially to the abdomen and pelvis, and bowel obstruction.

Physical examination may provide additional clues regarding the underlying etiology for the nausea and vomiting. Loss of heart rate variability or orthostatic hypotension suggests autonomic dysfunction, evidence of mucositis or thrush may result in oropharyngeal or esophageal irritation, abdominal distention or masses provide evidence of abdominal cancer or malignant ascites, and rectal examination may reveal impaction suggesting constipation.

Nausea and vomiting are the result of stimulation of the following pathways:

- chemoreceptor trigger zone
- cortex with input from the senses
- peripheral pathways via mechanoreceptors in the gastrointestinal tract, vagus and splanchnic nerves, glossopharyngeal nerves, and sympathetic ganglia
- vestibular system.

In cancer patients, common causes of nausea include opioid use, chemotherapy, autonomic dysfunction, and bowel obstruction. Opioid treatment results in nausea and vomiting in 40% of patients by stimulation of the chemoreceptor trigger zone, gastroparesis, constipation, and alterations in vestibular function. In advanced cancer patients with chronic nausea, autonomic dysfunction may result in gastroparesis and constipation. Autonomic failure affects the majority of patients with advanced cancer and is associated with decreased survival.

Autonomic dysfunction in cancer patients has a multifactorial etiology including cachexia, medications including chemotherapy, direct tumor invasion of nerves or paraneoplastic syndrome, and co-morbidities such as diabetes or heart failure.

Measures to prevent constipation and avoid medications which may exacerbate autonomic dysfunction should be implemented.

2. To control the patient's intractable nausea with vomiting, which medication would you initiate?

A. Metoclopramide
B. Dexamethasone
C. Haloperidol
D. Diphenhydramine
E. Ondansetron

Two approaches to the management of nausea and vomiting have been proposed. One approach involves treatment based on underlying mechanism and found to be effective in up to 90% of patients with advanced disease. Others have proposed initiation of an empirical anti-emetic regimen, usually a D2 antagonist, irrespective of the underlying etiology. No head-to-head comparison of the two strategies has been studied to date.

In clinical practice, patients with advanced cancer often have symptoms of nausea and vomiting due to multiple underlying factors. All potential reversible etiologies must be assessed and treated while simultaneously administering an antiemetic to control symptoms. A D2 antagonist such as metoclopramide or haloperidol would be a sensible empiric treatment for nausea.

In the case presentation, the patient has a history of acathesia to metoclopramide. Her history of head discomfort and early morning nausea with MRI revealing progression of brain metastasis would argue to initiate steroids as first line therapy. With the above change in treatment, patient has less projectile vomiting but continues to be symptomatic despite a trial of several anti-emetic medications.

In the next 48 hours, the patient develops increase confusion with periods of agitation at night resulting in distress to the patient, family, and nursing staff. Family at bedside observes that agitation has a temporal relationship with the administration of lorazepam which causes brief sedation followed by agitation and confusion. Memorial delirium assessment scale was conducted by palliative care fellow at beside and found to be 10/30.

3. Which of the following treatments is the first line therapy to control agitation secondary to underlying delirium?

A. Repeat dose of lorazepam
B. Haloperidol
C. Chlorpromazine
D. Diphenhydramine
E. Physical restraints

Delirium is common symptoms at the end of life and results in distress not only for patients but also for their family and healthcare providers. Delirium is characterized by a disturbance in consciousness with an inability to focus, shifts in attention, perceptual disturbances which fluctuating over time. The majority of patients have a good recollection of their experience while delirious resulting in distress. Appropriate interventions are needed to treat underlying precipitation factors including infections, dehydration, electrolyte abnormalities such as hypercalcemia and hyponatremia, organ failure, medications such as opioids and benzodiazepines, intracranial disease, as well as a number of other factors and must be initiated rapidly. In cancer patients, delirium is frequently underdiagnosed

resulting in undertreatment. Several clinical tools to assess for delirium exist, but only the Memorial Delirium Assessment Scale (MDAS) and the brief observational Nursing Delirium Screening Scale (NuDESC) are both diagnostic and able to quantify the severity of delirium, allowing patients to be monitored over time.

Limited research exists examining pharmacological treatment of delirium. In hospitalized patients with AIDS, Breitbart *et al*. performed a seminal double-blind, randomized comparison trial of haloperidol, chlorpromazine, and lorazepam. Both haloperidol and chlorpromazine were effective; however, chlorpromazine was associated with a significant decline in cognitive function. The arm receiving lorazepam was stopped early secondary to side effects including excessive sedation, worsening mentation and disinhibition, and ataxia. The combination of haloperidol with lorazepam have been proposed for the treatment of agitated, delirious patients in order to minimize extrapyramidal side effects but more studies are needed. In addition, atypical antipsychotic medications secondary to decreased risk of extrapyramidal adverse effects are being evaluated in the treatment of delirium; however, high quality randomized controlled trials are lacking.

The same day, the patient's primary oncologist visits the patient who is agitated and distressed. He recommends transfer to an inpatient Palliative Care Unit and consideration for palliative sedation.

4. Which of the following conditions is palliative sedation clearly indicated?

A. Chronic nausea
B. Anxiety and depression
C. Terminal delirium with agitation
D. Transient respite care
E. Existential pain

Patient is transferred to the acute Palliative Care Unit and reversible causes of delirium were worked-up and treated by an interdisciplinary team. Patient remained agitated despite administration of haloperidol (>10 mg/day) and a trial of chlorpromazine was initiated and found to be ineffective in controlling symptoms. No reversible etiology was noted and the patient was diagnosed with terminal delirium. Discussions with the patient's family caregivers about palliative sedation to control symptoms at the end of life were deliberated and agreed upon.

5. Which of the following medications titrated to control symptoms would be appropriate for palliative sedation?

A. Intermittent lorazepam as needed for agitation
B. Continuous midazolam titrated to control symptoms
C. Continuous morphine drip titrated to control symptoms
D. Scheduled haloperidol every 4 hours
E. Scheduled haloperidol every 4 hours with intermittent lorazepam as needed for agitation

Palliative sedation is a treatment of last resort for refractory symptoms in patients with cancer. Symptoms are refractory when they are inadequately controlled despite aggressive treatment which does not compromise consciousness. An interdisciplinary team with specialists in pain and symptom management should ideally be involved in assessment and treatment of symptoms prior to categorizing them as refractory.

A potential for misunderstanding exists regarding palliative sedation which may result in distress for a patient's family and healthcare providers as well as loss of reputability of the physicians involved and institutions resulting in potential litigation. The European Association of Palliative Care has outlined four "problem practices":

i. Abuse of palliative sedation with the goal of hastening death.
ii. Injudicious use of palliative sedation when healthcare providers inadequately assess or treat symptoms, resort to sedation out of frustration or burnout, or use of palliative sedation upon request of a distressed family member.
iii. Injudicious withholding of palliative sedation when avoidance of difficult discussions or concerns about hastening death result in providing ineffective treatments.
iv. Substandard implementation of palliative sedation including inadequate consultations with all parties involved regarding indications for sedation, goals of care, outcomes and risks; inadequate monitoring of symptoms while providing sedation; escalation of sedatives when not required; use of inappropriate medications (e.g. opioids); or inadequate emotional and spiritual support is provided for a patient's family.

Indications for palliative sedation varies widely between groups and settings and consensus is often lacking. Emergency situations where palliative sedation for patients with advanced cancer is clearly indicated include intractable convulsions, massive hemorrhage, asphyxiation, terminal dyspnea or delirium refractory to medical therapy. At our institution, the most common indications were delirium (82%), dyspnea (6%), and other symptoms (6%) including bleeding and seizures. In terminal patients, indications with no clear consensus for palliative sedation include refractory depression, anxiety, or existential distress.

No evidence exists for a first line treatment for palliative sedation, but benzodiazepines are the most commonly used sedative. Of the benzodiazepines, midazolam is the

most frequently used and is typically administered parentally. Because of its short half-life, midazolam is easily titrated to control symptoms and possesses anxiolytic and anticonvulsant properties which make it desirable for palliative sedation. Barbituates, such as phenobarbital and propofol, are also occasionally used for palliative sedation. Opioids such as morphine are not useful agents for palliative sedation since they provide sedation only at toxic doses, and their use is associated with side-effects including worsening delirium, myoclonus, and respiratory sedation. However, if patients are on chronic opioid therapy for the management of pain, they should be continued.

Case study 134.2

A 49-year-old man with a recent diagnosis of unknown primary with metastatic disease involving his abdominal lymph nodes and an abdominal mass adjacent to the left kidney. He was referred for symptoms of abdominal pain, anxiety, and insomnia. He has a history of chronic neck and back pain, status post lumbar laminectomy (3x) and describes the pain as intermittent, sharp, and worse with activity. His pain is associated with numbness and weakness in his lower extremities. Hydrocodone with acetaminophen (10/325 mg) was prescribed for pain, which he takes up to 12 tablets a day as well as alprazolam, 4 mg every 8 hours as needed, for uncontrolled anxiety.

Comorbidities include history of obesity, hypertension, high cholesterol, coronary artery disease with history of myocardial infarction requiring the placement of cardiac stents on clopidogrel. Type 2 diabetes for 10 years which is controlled without medication after recent history of weight loss.

Review of systems is positive for on and off headaches; chronic dry cough, wheezing, shortness of breath and stiffness in joints. Occasional he has difficulty with swallowing, fatigue, decreased appetite. Otherwise the review of systems is unremarkable.

His Edmonton Symptom Assessment Scale is: Pain 9, fatigue 8, nausea 4, depression 5, anxiety 10, drowsiness 1, appetite 5, feeling of wellbeing 5, shortness of breath 5, sleep 1.

Social history is significant for 66 pack-year history of smoking which he continues to engage in. Positive CAGE questionnaire 2/4. No history of intravenous drug use. He previously worked in the construction industry and is divorced. He has two teenaged daughters, and his goal in life is to live to see them graduate.

Laboratory work-up was unremarkable with the exception of elevated glucose elevated at 126. Vital signs are stable and physical examination was unremarkable.

For pain, the patient has been previously prescribed morphine, which caused itching, rash, hives and difficulty breathing. He is reluctant to use any strong opioids at this time. He feels that hydrocodone is controlling his pain and was instructed to continue hydrocodone but not exceed 8 tablets per day. For symptoms of underlying anxiety with severe adjustment disorder, expressive supportive counseling was provided. He was counseled on need to wean off alprazolam which he was reluctant to do, but he did agree to decrease alprazolam to 1 mg twice daily as needed for anxiety.

1. Which of the following is not a risk factor for chemical coping?

A. Active tobacco use
B. Positive CAGE questionnaire
C. History of being divorced
D. Using more hydrocodone pills than what was prescribed

2. Which of the following is evidence for aberrant behavior indicative of possible opioid abuse or misuse?

A. Acquiring opioids from multiple healthcare providers
B. Use of opioids exceeding what was prescribed resulting in request for early refills
C. Missing scheduled appointment
D. Non-compliance with other recommendations
E. History of "lost" or "stolen" prescription
F. All of the above

Patients with cancer may experience a host of symptoms of a physical or emotional nature. Pain is often rated the most distressing of symptoms and can be due to the underlying tumor or metastasis, surgery, radiation, or chemotherapy. Cancer pain is highly variable and subjective experience and is often undertreated. Patients who are addicted to opioids can be challenging to treat and strategies to reduce the risk of opioids misuse and abuse must be implemented. When treating cancer patients with chronic pain, physicians need to be able to distinguish tolerance, chemical coping, pseudoaddiction, and addiction.

Pseudoaddiction is characterized by drug-seeking behavior occurring in the context of unrelieved pain which disappears when pain is treated effectively. Addiction is characterized by behaviors of one or more of the following: impaired control over drug us, compulsive use, craving, and persistent use despite harm. Tolerance is the development of decreased analgesic effect of a given dose of opioid over time, or when a larger dose is required to produce the same

analgesic effect. Chemical coping is defined as the aberrant use of addictive substance such as opioids medications to help cope with life stressors.

Chemical coping and addiction in patients with advanced cancer is associated with a history of alcohol or tobacco abuse. The CAGE (cut down, annoy, guilt, eye opener) questionnaire is a brief screening tool to detect a history of alcohol abuse. Since aberrant drug behavior is associated with a history alcohol abuse, the CAGE questionnaire is a useful screening tool in patients with advanced cancer. The identification of a positive history should not prevent the prescriptions of opioids for cancer pain but should identify patients that need closer monitoring of opioid use and target them for more intensive counseling to assist with coping with the burden of cancer.

Aberrant behavior that may indicate the risk of abuse or diversion of opioids include the following:

- hoarding of medications during periods of decreased symptom burden
- acquiring medications from multiple healthcare providers
- aggressive demands for increase of addictive medications, despite a good functional status
- patient increasing dosage of medication without contacting healthcare professional
- missing appointments and returning as a walk-in, unscheduled
- non-compliance with other aspects of the treatment plan
- insistence on a specific opioid regimen or specific route of administration.

On follow-up visit, the patient's oncologist recommends that acetaminophen not be used on a continuous basis. Work-up of his back pain revealed underlying metastasis to his 7th thoracic vertebrae.

3. Which opioid would you recommend to treat his chronic back pain?

A. Morphine
B. Codeine
C. Oxycodone
D. Fentanyl

True allergy to morphine results in hives or difficulty breathing. Often, nausea and itching as a result of morphine administration is confused with an allergic reaction. The patient appears to have a true allergy to morphine. Morphine as well as codeine, hydrocodone, hydromorphone, ocycodone, and oxymorphone belong in the same class of phenanthrenes and it is advisable to try an opioid in another class such as fentanyl (phenylpiperidines) or methadone (phenylheptylamines).

With regards to his cancer, the patient has been non-compliant with testing and follow-up with his oncologist. Patient has followed up intermittently with the palliative medicine team, often visiting unscheduled. His fentanyl dose has been increased to 125 mcg every 72 hours and he was using hydromorphone 4 mg for breakthrough pain. The patient's friend called the clinic regarding poorly controlled pain and confusion. He was recently seen at a local emergency room and informed that he may have brain metastasis and instructed to follow-up with his oncologist. He returns with symptoms of confusion, MDAS 12/30 and admitted to the hospital for further workup. MRI reveals no evidence of brain metastasis. Workup revealed no sources for infection, no electrolyte abnormalities, or reversible etiologies which would result in confusion. Patient rated both his chronic back pain and now has new diffuse abdominal pain, a 10/10.

4. The switching of one opioid to another opioid using a equianalgesic table is known as opioid rotation. Which of the following are indications to rotate opioids?

A. Neurotoxicity from opioids like hallucinations, myoclonus, and confusion
B. Uncontrolled pain despite opioid titration and addition of adjuvants
C. Financial burden of the cost of an opioid
D. Opioid related nausea despite adequate medical management
E. All of the above

5. Which opioid would be the best to control his pain?

A. Increase fentanyl patch to 150 mcg every 72 hours with hydromorphone 4 mg as needed for breakthrough pain
B. Change to methadone 10 mg every 12 hours with oxycodone 5 mg every 4 hours as needed for breakthrough pain
C. Change opioids to oxycodone extended release 20 mg every 12 hours with oxycodone 5 mg every 4 hours as needed for breakthrough pain
D. Change to morphine extended release 100 mg every 12 hours with morphine 15 mg every 4 hours as needed for breakthrough pain

Opioid rotation is recommended for the development of adverse effects including opioid induced neurotoxicity like confusion, myoclonus, and hallucinations as well as uncontrolled pain despite the adjustment of dose. Other practical concerns that might result in opioid rotation include minimizing the number of pills or cost of the medication, better compliance (e.g. rotation to a transdermal delivery system in a patient unable to tolerate an oral regimen, and in cases of organ failure (e.g. rotation to methadone in the setting of renal failure).

The reason why opioid rotation is successful is unclear. Incomplete cross-tolerance to the analgesic effects of opioids being greater than the cross-tolerance to adverse effects may

(*Continued*)

play a role. Opioid rotation to methadone is difficult secondary to the lack of reliable equianalgesic conversion ratios, large inter-individual variability in pharmacokinetics, and pharmacological interactions of methadone with other drugs. Rotation to methadone is best performed by specialist in palliative care or pain management and requires strict monitoring.

The patient presents with delirium most likely secondary to opioid escalation resulting in neurotoxicity. Opioid rotation would be indicated, and methadone would be a reasonable second line strong-opioid under close supervision. Compared to other strong opioids, methadone has a number of potential advantages including no known active metabolites and no significant elimination by the kidneys. In addition, methadone is a relatively potent N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA as well as other excitatory amino acids have been implicated in the development of neuropathic pain and opioid tolerance. The use of methadone as a first line strong-opioid for the treatment of cancer pain is unclear and more research is needed.

After rotating his opioids, the patients' delirium improved. Additional history from family included that the patient had made frequent visits to emergency rooms with complaints of pain and had received opioid prescriptions from multiple providers.

6. Managing a cancer patient with history of opiate abuse would involve which of the following treatment plan?

A. Assessing medical and psychiatric stability of the patient
B. Determining the motivational factors for his behavior
C. Encouraging an open and honest communication
D. Arranging for weekly follow-ups and dispensing only one week supply of medications
E. Encouraging compliance with follow-up, remaining engaged and not abandoning the patient
F. All of the above

Patients with advanced cancer have the same risk factors and potential for abuse of prescription opioids as non-cancer patients. It is imperative that healthcare professional in a firm but non-judgmental manner continue to provide care for the patient. Assessing and treating all underlying medical, physical, psychological, and spiritual/existential factors are critical in order to provide adequate palliation. Open and honest communication with the patient and close supervision with weekly follow-ups may be needed.

With close supervision, patient's clinical burden is managed and no other aberrant behaviors are observed in the next 3 months. The patient is offered chemotherapy but declines and he was informed by his oncologist that he has less than 6 months to live. To assist with pain control, he decides to pursue palliative radiation to a metastatic lesion at T7. The patient dies prior to completion of radiation therapy.

7. Regarding the estimation of prognosis for advanced cancer patients, physicians tend to?

A. Overestimate by 6–10 fold
B. Overestimate by 2–5 fold
C. Be accurate most of the time
D. Underestimate by 2–5 fold
E. Underestimate by 6–10 fold

Decisions regarding the pursuit of aggressive testing and treatment, discharge planning, and enrollment in hospice care depend on an accurate prognosis for patients with advanced cancer. Physicians often over-estimate survival which can result in unnecessary testing and therapy or enrollment late, often only a few days, in hospice care.

Communication accurate prognostic information is challenging for clinicians who often overestimate life expectancy. A recent study suggests that when physicians who convey an optimistic view of chemotherapy are perceived to be better communicators. In the same study, more than two-thirds of patients had expectations of chemotherapy providing a cure. Patients often have unrealistic expectations for treatment secondary to poor communication by healthcare professionals, inability to understand the information provided by their physicians (e.g. the use of the term such as "response" or "tumor shrinkage" may be misinterpreted as a cure), or patients are in denial and having difficulty coping with death. Patients may often need time to process and repeat information to improve their understanding. Patients unable to cope with their advanced cancer may proceed to deny information provided. Healthcare professionals need to be cognizant of a patient's coping mechanism and empathetically assist them through the emotional transition from curative to comfort care.

In recent years, the use of hospices and hospital-based palliative care services have increased. A recent study shows that despite increased enrollment of terminally ill patients in hospice care and deaths at home, hospitalizations in an ICU prior to death and transitions to comfort care only in the last 3 days of life or less have increased. Integration of palliative care services earlier in the disease trajectory may improve end-of-life care. In one study, early palliative care consultation for patients with metastatic non-small cell lung cancer was shown to improve morbidity and mortality. More research is needed to improve end-of-life care and transitions from curative treatment to comfort care.

Case study 134.3

A 63-year-old man with a diagnosis of non-small-cell lung cancer. He was initially treated with 4 cycles of neo-adjuvant chemotherapy including carboplatin and paclitaxel. He had a significant clinical response and underwent a left sided pneumonectomy. Despite treatment, he developed recurrence of his cancer in his kidney and subsequently received docetaxel plus amplimexon with continued progression of his underlying disease. He presents to an outpatient palliative care clinic with complaints of decreased appetite, weight loss as well as severe fatigue. Despite his symptom burden, he continues to work. Patient also describes syncopal episodes after getting up from a seated position. His past medical history is significant for renal vein thrombosis. Medications include megestrol acetate, prescribed for anorexia by his oncologist and lovenox.

His Edmonton Symptom Assessment Scale is: Pain 0, fatigue 9, nausea 0, depression 0, anxiety 0, drowsiness 3, shortness of breath 2, appetite 2, sleep 2, feeling of well-being 7.

Physical examination is unremarkable with stable vital signs. Weight 81.2 kg, height 193 cm, BMI = 21.8, laboratory values are significant for a hemoglobin of 10.8.

1. Which of the following are known complications of megesterol acetate?

A. Edema
B. Adrenal insufficiency
C. Thromboembolism
D. Hypogonadism in male patients
E. All of the above

Megestrol acetate is an appetite stimulant with predominantly progestational and anti-gonadotropic effects. Side-effects of megestrol include edema, adrenal insufficiency, thromboembolism, and hypogonadism in male patients. Systematic reviews have concluded that megestrol has a beneficial effect on appetite and overall weight; however, no effect was reported on lean body mass and overall quality of life. To reduce the risk of side effects, it has recommended to start at the lowest effective dose and titrate to a maximum of 800 mg/day.

For symptoms of anorexia, the patient has noticed a significant improvement since initiating megestrol. In view of his symptom improvement, he was suggested to consider decreasing his dose to 400 mg and to continue lowest effective dose. In addition, a testosterone, morning cortisol, and thyroid panel were ordered.

For his fatigue, he was recommended to resume exercising as tolerated twice a week and offered a trial of methylphenidate which he declined in favor of a non-pharmacological approach.

At the 1 month follow-up visit his labs were: thyroid stimulating hormone 1.67, cortisol 1.9, total testosterone 31, and albumin of 3.4. His symptom burden was unchanged.

He was discontinued on megestrol and supplemented with steroids, dexamethasone 4 mg in the morning, with instructions to taper. The following month, he rated fatigue a 1/10 and was compliant with recommendations to exercise and his appetite remained good while he was on steroids.

2. Which of the following is the best assessment of weight in cancer patients with cachexia?

A. Body Mass Index (BMI)
B. Dual-energy X-ray absorptiometry (DEXA)
C. Bioelectrical impedance analysis (BIA)
D. Computed tomography

Body mass index is easily calculated with a patient weight and height. In general, BMI <20 has been used as a marker for nutritional deficiency and cachexia. However, the accuracy of BMI has been shown to be limited and does not factor a patient's age, gender, or proportion of bone, lean body mass, and fat content. Chronically ill patients despite having a normal BMI may have decreased fat-free mass and increased fat mass.

DEXA scans are highly accurate measure of weight and can differentiate body composition but are mainly used in the research setting. Computed tomography and magnetic resonance imaging may also be useful, but due to the high cost, their use in clinical practice is limited. BIA is a low cost assessment of weight and can distinguish fat-free mass and fat mass. But in patients with cancer, BIA underestimates fat-free mass compare to DEXA and edema may affect the accuracy of the recordings.

The patient continues to lose weight and is distressed about his weight loss. He is counseled in the clinic by a nutritionist and requests another pharmacological intervention to treat his weight loss.

3. Which of the following pharmacological interventions has shown promising results in the treatment of cancer cachexia?

A. Dronabinol
B. L-carnitine (4 g/day) and celecoxib
C. L-carnitine (4 g/day), celecoxib, and megestrol acetate
D. Cyproheptadine

Alterations in body image as a result of cachexia often results in distress for both cancer patients and their family.

(*Continued*)

Cachexia is an ominous sign of impending death and psycho-social support for patients and family is critical. With regards to cachexia, the social benefits of eating at the dinner table and the pleasure of tasting food should be emphasized over the exact amount of total caloric intake. Often, patients and family have to be counseled that decreasing appetite and oral intake resulting in cachexia is not an uncommon symptom but a part of the natural process that occurs with advancing illness.

There are several treatments undergoing research for the treatment of cancer cachexia.

Initial pilot studies of dronabinol, a cannabinoid, showed promise for the treatment of anorexia; however, a double-blind, placebo controlled study failed to show a beneficial effect. Cyproheptadine, a histamine antagonist with anti-serotonergic properties, in a small pilot study reported a small improvement in appetite but no significant effect on weight.

Interventions that appear to be promising for the treatment of cancer cachexia include L-carnitine and NSAIDs. L-carnitine is a quaternary ammonium compound required for the transport of fatty acids to the mitochondria where they are utilized to generate metabolic energy. In cancer patients, decreased caloric intake and diminished endogenous synthesis results in low levels of L-carnitine. A recent well-designed placebo controlled clinical trial reported that L-carnitine supplementation increased body mass index and quality of life in patients with pancreatic cancer. NSAIDs such as celecoxib have been shown to increase weight in cancer patients either as a single agent or in combination with megestrol acetate.

Other interventions that may be promising in the treatment of cancer cachexia is omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, which are found in fish oil and known to reduce inflammation. Initial studies have been inconclusive, however, recent studies have been more encouraging. The recent positive results have been attributed to efforts to improve compliance with fish oil supplementation and provide interventions earlier in the disease trajectory.

Since the underlying mechanism of anorexia-cachexia syndrome is complex, researchers have argued that a single therapeutic agent would be ineffective in reversing weight loss and that a better approach would be to incorporate multi-modal therapy targeting simultaneously multiple underlying physiological processes which result in weight loss. One study, examined the combination of L-carnitine (4 g/day) and celecoxib (300 mg/day) with or without megestrol acetate and found identical responses.

Up to 4 different agents for the treatment of cancer cachexia have been studied and more research is needed to delineate the right combination of medications which provide benefit without side-effects. For this patient, a combination of L-carnitine and celecoxib may be reasonable to initiate.

Case study 134.4

A 56-year-old woman with metastatic non-small lung cancer, has been referred by her oncologist for the management of fatigue. She has complications of a malignant pleural effusion which has required a thoracentesis. Recently, she has received chemotherapy with carboplatin, pemetrexed, and bevacizumab, which was followed by maintenance pemetrexed and bevacizumab. She is maintaining her weight and her Zubrod performance status is 1. The patient has mild pain at the site of pleurodesis which is described as aching, intermittent, but she does not require pain medications.

Past medical history is notable for thyroid follicular cancer treated with total thyroidectomy followed by iodine treatment. She is married with two teenaged children. Social history is otherwise unremarkable.

Her Edmonton Symptom Assessment Scale is: Pain 2, fatigue 8, nausea 6, depression 8, anxiety 3, drowsiness 8, shortness of breath 3, appetite 8, feeling of well-being 8, sleep 3.

Review of systems significant for the following: The patient requires frequent napping which does not relieve symptoms of fatigue. She also had a history of fleeting thoughts of hurting herself but denies having a plan in place. She denies symptoms of anhedonia, feelings of hopelessness, worthlessness or guilt. In the past, the patient has been prescribed bupropion and mirtazapine for symptoms of clinical depression which she discontinued because she "didn't like the way the medications made her feel." She occasionally takes lorazepam to assist with falling asleep which she recently has been taking on a nightly basis.

Other medications include rosuvastatin, dexamethasone with chemotherapy, furosemide as needed for lower extremity edema, thyroid supplementation, and two blood pressure medication, losartan and amlodipine.

Laboratory values are notable for hemoglobin of 10.9 g/dL, otherwise complete blood count and electrolyte panel are normal. PET/CT scan revealed stable residual nodule in left upper lobe consistent with treated malignancy.

Vital signs: Temperature 36.5, pulse 94, respiratory rate 18, blood pressure 109/59, O_2 saturation 95%, weight 76.8 kg. Physical examination is otherwise normal with the exception of dry oral mucosa and flat affect.

1. Which of the following is true regarding the role of lorazepam for the treatment of sleep disturbances in patients with advanced cancer?

A. When used for a short term it reduces the time of sleep onset and improves sleep efficacy
B. Prolonged use may result in fragmented sleep, tolerance and/or dependence
C. May cause day time delirium, sedation and fatigue in older adults
D. May exacerbate respiratory suppression when they are used in combination with opioids
E. All of the above

Benzodiazepines are used because of their sedative properties to reduce the time to sleep onset and to improve sleep efficiency. Unfortunately, tolerance to these medications occurs rapidly and their prolonged use can cause sleep disturbances, such as fragmented sleep and dependence on medication for sleep onset. In addition, several side effects have been observed with benzodiazepines, such as daytime sedation, delirium, and fatigue. Benzodiazepine dose has also been associated with increased falls particularly in adults with cancer.

2. With regards to the patients cancer related fatigue, which of the following would not help improve her symptoms?

A. Trial of methylphenidate
B. Weaning lorazepam and discontinue diuretic if not clearly indicated
C. Dexamethasone
D. Modafinil
E. Antidepressants

Pharmacological treatments for fatigue are limited and a paucity of randomized controlled trials exists for patients with advanced cancer. Glucocorticoids, including dexamethasone (8 mg/day for 14 days), has been shown to improve fatigue in patients with advanced cancer. Long-term use of glucocorticoids are limited by side effects including increased infections, insomnia, elevation of blood glucose, myalgia, mood swings, edema, poor wound healing, and gastritis. Cancer patients at the last stages of life may derive the most benefit from glucocorticoids.

Psychostimulants including methylphenidate (5 mg at breakfast and lunch time titrated to a maximum of 40 mg/day) and modafinil (200 mg in the morning) have been shown to be helpful in the management of fatigue in cancer patients; however, the data from randomized controlled trials are mixed. Caution should be applied in cancer patients with heart disease and cognitive dysfunction.

In this patients case lorazapam was weaned off and furosemide was discontinued. She presented with no clear signs of major depression; however, she was closely monitored over the next 3 months. For symptoms of fatigue, a trial of methylphenidate was initiated and titrated to 10 mg in the morning and mid-day. Her symptoms of fatigue and her mood have improved.

Case study answers

Case study 134.1

Question 1: Answer E
Question 2: Answer B
Question 3: Answer B
Question 4: Answer C
Question 5: Answer C

Case study 134.2

Question 1: Answer C
Question 2: Answer F
Question 3: Answer D
Question 4: Answer E
Question 5: Answer B
Question 6: Answer F
Question 7: Answer B

Case study 134.3

Question 1: Answer E
Question 2: Answer B
Question 3: Answer B

Case study 134.4

Question 1: Answer E
Question 2: Answer E

Selected reading

Breitbart W, Alici Y. Agitation and delirium at the end of life: "We couldn't manage him." JAMA. 2008;300(24):2898–910.

Dev R, Parsons HA, Palla S, *et al*. Undocumented alcoholism and its correlation with tobacco and illegal drug use in advanced cancer patients. Cancer. 2011;117(19):4551–6.

Fearon K, Strasser F, Anker SD, *et al*. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489–95.

Weeks JC, Catalano PJ, Cronin A, *et al*. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367:1616–25.

Wood GJ, Shega JW, Lynch B, *et al*. Management of intractable nausea and vomiting in patients at the end of life "I was feeling nauseous all of the time … nothing was working". JAMA. 2007;298(10):1196–207.

CHAPTER 135

Metabolic and nutritional issues in oncology

Julia Fechtner,[1] Carolyn Lammersfeld,[2] Carol Ireton-Jones,[2] Pankaj Vashi[1]

[1]Midwestern Regional Medical Center, Cancer Treatment Centers of America, Zion, IL, USA
[2]Cancer Treatment Centers of America, Dallas, TX, USA

Introduction

Nutritional management of the patient with cancer is multifactorial. Individuals may have been well nourished prior to diagnosis or may be debilitated from weight loss or surgical procedures and other therapies. In addition, prognosis and available therapies play a role in the overall plan for nutrition care. Assessment of nutrition status forms the basis for the nutrition plan and allows the determination of type and route of administration of nutrients.

Multiple choice question

Nutritional evaluation tools in oncology patients

1. True or false? Serum albumin is a good indicator of nutritional status in oncology patients.

A. True
B. False

Using serum albumin alone to make an assessment of nutritional status or risk in people with cancer is not recommended. In oncology patients who receive large amounts of fluid with chemotherapy or after surgery, a low serum albumin can be secondary to a dilution effect rather than malnutrition. Similarly, a dehydrated patient may present with a normal serum albumin that will drop with hydration.

Several tools exist to assess nutritional status; however, few have been validated in the oncology population. The Subjective Global Assessment (SGA) was originally validated for use in gastrointestinal (GI) surgical patients, but it has been used in the oncology population with good sensitivity and specificity. It has been shown to have more sensitivity and specificity than serum albumin. The SGA takes into account weight loss history, oral intake, GI symptoms, functional capacity, and stress of disease. A potential drawback is that it requires a nutrition-related physical examination. The Scored Patient-Generated Subjective Global Assessment (PG-SGA) is an adaptation of the SGA developed by Ottery to be more specific to the oncology population. This tool is completed by the patient and scored by a clinician. It includes nutrition impact symptoms and a triage component.

Case study 135.1

A 54-year-old male with a 30-year history of chewing tobacco developed an ulcer on the tongue, causing difficulty with speech and swallowing. The ulcer was eventually biopsied, and squamous cell cancer of the tongue was diagnosed (Figure 135.1). The patient had a 20-lb. weight loss prior to diagnosis and is scheduled for chemoradiation therapy (CRT).

1. What is the best nutritional intervention for this patient?

A. Naso-gastric (NG) feeding
B. Nutrition counseling and supplementation
C. Percutaneous endoscopic gastrostomy (PEG) tube placement before starting CRT
D. Megesterol acetate as an appetite stimulant
E. B and C

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

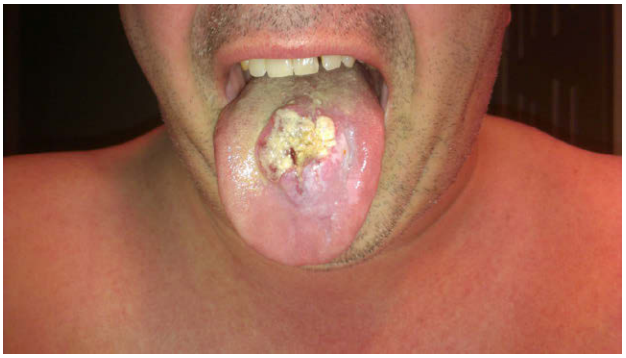


Figure 135.1 Large infiltrative tumor of the tongue with severe dysphagia (Source: Pankaj Vashi, Cancer Treatment Centers of America. Reproduced with permission of Pankaj Vashi).

Although nutritional counseling and PEG tube should be considered for this particular patient due to dysphagia and weight loss, the role of enteral feeding (nasogastric or PEG) in asymptomatic patients is controversial due to a lack of good randomized trials. Nutritionally compromised patients with head and neck squamous cell cancer (HNSCC) have a higher incidence of infection, increased complications, and poor treatment response. Currently, most HNSCC patients receiving radiation therapy (RT) or CRT are offered nutrition counseling and nutritional supplements plus enteral tube feeding if significant weight loss is present prior to treatment. Randomized studies have shown the benefit of continued nutrition counseling and oral supplementation and should be offered to all of the patients. Poor patient tolerance to NG tube feeding has made it a less desirable option in most of the developed countries. Radiotherapy treatment toxicities that compromise nutritional status include painful mucositis, dysgeusia (altered taste), xerostomia (dry mouth), odynophagia, thickened secretions, and anorexia. Many of these symptoms can last for months after the radiation therapy is completed. Thus, addressing these symptoms with topical regimens that include local saliva substitutes for dry mouth, and zinc-containing products to improve taste sensation, is crucial in improving oral intake, nutritional status, and quality of life.

The decision for timing of PEG tube placement should be made at diagnosis given the risks and benefits of this procedure. It is important to facilitate risk assessment, appropriate placement, effective patient counseling, and monitoring for major and minor complications. Nutritional outcomes need to be measured and evaluated. These include the effects of enteral feeding on nutritional status, gastrostomy complications, and overall survival. Patient-related factors that can dictate the need for enteral feeding prior to radiation therapy in HNSCC include dysphagia, weight loss of more than 10% within the previous 6 months, and poor performance status.

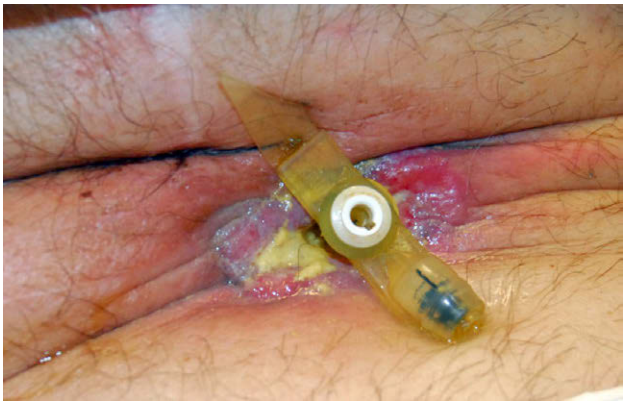


Figure 135.2 Malignant seeding at the percutaneous endoscopic gastrostomy (PEG) site—a rare complication of endoscopically placed G tubes (Source: Pankaj Vashi, Cancer Treatment Centers of America. Reproduced with permission of Pankaj Vashi).

2. PEG and radiologically inserted gastrostomy are safe procedures and should be considered for all the patients receiving radiation therapy for head and neck cancers?

A. Yes
B. No

Gastrostomy tube insertion can be achieved with PEG, RIG (radiologically inserted gastrostomy), or surgical gastrostomy. PEG remains a preferred procedure for most of the patients with HNSCC who have dysphagia and weight loss. Surgical gastrostomy is only considered for patients who have failed PEG or RIG. Complications related to PEG or RIG can be divided into postprocedure mortality, either minor or major complications. Wollman *et al*. (1995) reported a procedure-related fatality rate 0.3% for RIG and 0.53% for PEG, which has been also reported in other meta-analysis. Other major complications include bowel perforation, GI hemorrhage, intra-abdominal abscess, peritonitis, aspiration, and sepsis. Minor complications include dislodged tube, tube malfunction, peristomal leak, peristomal infection, postprocedure ileus, subcutaneous emphysema, and recently reported cases of mucosal herniation-induced occlusion. Meta-analysis of 2379 patients has shown no statistical differences in major and minor complications with PEG or RIG procedures.

In HNSCC, the success of either procedure depends on the experience of the performing physician and the status of the lumen of the upper GI tract to allow either an endoscope or a nasogastric tube to be introduced into the stomach. Malignant seeding at the PEG tube insertion site is a rare but recently recognized complication of the PEG procedure (Figure 135.2). A recent review of 44 cases has shown that this complication is most common with pharyngoesophageal cancers. In potentially curable HNSCC, this rare

(*Continued*)

complication should be discussed with the patients, especially with pharyngo-esophageal cancer, and other options including RIG or surgical gastrostomy tube placement should be considered.

• **What are the nutritional needs, and what tube-feeding formula is appropriate for this patient?**

Energy intake should be 1.2 to 1.5 times the predicted resting energy expenditure, or about 30–35 kcal/kg/day. Protein intake can be from 1.5 to 2 grams/kg/day. To counteract cachexia, the lipid intake may need to exceed 30% of total calories. A standard tube feeding (enteral) formula would be appropriate for this patient.

Commercially available tube feedings can be categorized into the following groups:

Standard: 1–1.2 kcal/ml with 50–55% carbohydrates, 30–35% fats, and 15–18% of proteins. These may or may not contain fiber, and most are isotonic.

Calorically dense: 1.5–2 kcal/ml with approximately the same percentage of carbohydrate, fat, and protein.

Specialized: This includes peptide-based and chemically defined or elemental formulas for patients with malabsorption or GI intolerance. These contain easily digested forms of carbohydrate, protein, and fat, and most are fiber-free.

Disease specific formulations: These are also available; however, the current American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines support the use of these products in specific cases and not for general use. Immunomodulating formulations (usually 1 kcal/ml), enriched with arginine, glutamine, omega-3 fatty acids, and nucleotides and antioxidants, are recommended for patients with major elective surgery, trauma, burns, and head and neck cancer, and for critically ill patients on mechanical ventilation.

• **When should you use bolus versus continuous feeding?**

Bolus feedings are administered 3 to 4 times a day over about 15 to 30 minutes and should be considered for all patients with PEG tubes. The volume of each bolus feeding will depend on the patient's caloric needs. Gastric residual should be checked initially prior to each feeding to evaluate tolerance while an inpatient. High fat and osmolarity containing tube feedings may be poorly tolerated by some patients due to their impact on gastric emptying. In patients who are able to take some oral intake during the day, it may be beneficial to consider continuous feeding, which is accomplished with an enteral infusion pump during the night. In patients with gastroparesis and previous abdominal surgeries, bolus feeding may not be tolerated. In these patients, continuous feeding should be considered. Jejunal feeding is another alternative for these patients. This can be achieved by converting a PEG tube to a PEJ (percutaneous endoscopic jejunostomy) tube or with the help of a surgical jejunostomy placement.

Case study 135.2

A 44-year-old female with metastatic recurrent ovarian cancer presents with persistent nausea and vomiting. She has had previous cytoreductive surgeries. Evaluation with CT scan revealed extensive carcinomatosis with bowel obstruction. Patient is not a surgical candidate. She has lost 40 lbs. of weight in the last 6 months, and her BMI now is 18. The patient is a likely candidate for an experimental chemotherapy.

1. What is the next option?

A. Place a nasogastric (NG) tube for suction
B. Start intravenous (IV) fluids, and consider hospice care
C. Evaluate for a venting PEG tube
D. Start chemotherapy, and give antinausea medication

Bowel obstruction in advanced stages of ovarian and gastrointestinal cancer can occur in up to 50% of patients. Many of these patients are not a candidate for surgical intervention. Palliation for severe debilitating symptoms of nausea and vomiting should be the primary goal for these individuals. An NG tube for decompression may be considered for short-term use. Unfortunately, besides being very uncomfortable, if left in place for more than a week, it can cause sinusitis, erosion of nasal cartilage, aspiration, abscess formation, esophageal erosion, pharyngitis, and social isolation. PEG tube placement in advanced inoperable metastatic ovarian and GI cancers is technically feasible and safe in the palliative setting. This allows patients to have better quality of life and to be managed in an outpatient setting.

2. What are the major metabolic complications with a venting PEG tube?

A. Metabolic alkalosis
B. Hypochloremia
C. Hypokalemia
D. Prerenal azotemia
E. All of the above

Managing dehydration and metabolic–electrolyte abnormalities can be challenging in patients with a venting PEG tube. A large volume of fluid losses from the stomach can cause loss of hydrochloric (HCl) acid and produce an increase of bicarbonate in the plasma to compensate for the lost chloride and sodium. The result is a hypokalemic

hypochloremic metabolic alkalosis. Alkalosis shifts the intracellular potassium to the extracellular compartment, and the serum positive potassium is increased factitiously. With continued gastric losses, the renal excretion of potassium increases in order to preserve sodium. The adrenocortical response to hypovolemia intensifies the exchange of potassium for sodium at the distal tubule, with subsequent aggravation of the hypokalemia. The daily IV potassium needs for these patients can sometimes exceed 100 mEq. Alkalosis can be corrected by an increase in chlorides in the PN or IV fluids. Frequent blood chemistry should be checked until the patient is stabilized. Daily IV fluid needs can range from 2 to 5 L depending upon the gastric losses.

3. Should PN be considered for this patient?

A. Yes
B. No

The use of PN in patients with incurable malignancies with bowel obstruction is controversial. A systemic review of the literature has shown that for those whose weight loss and malnutrition are consequences of tumor-mediated cachexia, as demonstrated by anorexia and elevated C- reactive protein level, parenteral nutrition (PN) is unlikely to improve the outcome. This analysis did not include bowel obstruction patients with a venting PEG tube.

Recent studies in selected group of patients with advanced cancer and bowel obstruction with a venting PEG tube have shown that PN not only improves their quality of life but also may prolong survival. Transition to hospice care should be considered in these patients when the quality of life starts deteriorating and no other therapeutic options are available.

4. Major challenges with home PN (HPN) include which of the following?

A. Central line sepsis
B. Metabolic abnormalities
C. Deep vein thrombosis
D. Emotional stress
E. All of the above

The most common diagnosis for HPN today in the United States is cancer, accounting for over 40% of patients. Major complications related to HPN include catheter sepsis, catheter occlusion, central venous thrombosis, liver failure, metabolic bone disease, and fluid–electrolyte disturbances. The risks and benefits of HPN should always be evaluated before starting any patient on this very expensive and dangerous therapy.

Case study 135.3

A well-nourished, 55-year-old female with a history of vulvar melanoma status post wide local excision of vulvar lesion is receiving chemotherapy with radiation to the pelvis. The patient has a history of well-controlled irritable bowel syndrome (IBS), reports regular bowel movements 1–2 times daily, and is taking many vitamins and herbal supplements. After five fractions of radiation, the patient presents to the radiation oncologist with a 6-lb. weight loss and multiple episodes (4–6) of diarrhea.

1. What is the appropriate nutrition intervention for her radiation-induced diarrhea? (Choose all that apply.)

A. Daily IV fluid administration
B. Imodium (loperamide): 2 capsules for initial dose, then 1 capsule following each unformed stool, for a maximum of 8 capsules per day
C. Registered dietitian consult for diet and supplement management
D. PN

Prior to using any antidiarrheal medications, it is very important to rule out infectious causes of diarrhea, especially *Clostridium difficile*–induced diarrhea. Intestinal transit inhibitors such as loperamide (Imodium®), diphenoxylate (Lomotil®), and opiates are commonly used to control radiation-induced diarrhea. These act to slow down intestinal motility by decreasing the amount of acetylcholine released by nerve endings in the gut that control motility. It has been shown that radiation-induced diarrhea typically occurs after 4–5 days of pelvic radiation, and initiation of Imodium is recommended. If no improvement after 3–4 days of Imodium therapy, the addition of Lomotil may be needed.

A consult with a RD is essential to provide appropriate medical nutrition therapy to help manage and control the patient's radiation-induced diarrhea. The damage and inflammation caused by radiation can affect the enzymes in the intestine, particularly lactase, which is the enzyme needed for lactose digestion. Patients will often experience lactose malabsorption during radiation and for weeks post radiation until the intestinal mucosa is healed. Diet education to remove lactose from the diet and regarding the importance of appropriate fiber intake and its effects on bowel motility are important to help control diarrhea. Insoluble fibers tend to accelerate the movement of food through the digestive tract, whereas soluble fibers tend to

(*Continued*)

slow movement through the tract. A low-fiber, low-fat, low-lactose diet has been shown to decrease the frequency and severity of diarrhea as well as decrease the need for antidiarrheal agents.

The patient has now received 14/30 fractions to pelvis and presents to the emergency room (ER) with cramping, increased abdominal pain, and uncontrolled diarrhea (14–16 episodes per day). Stool specimen was positive for *Clostridium difficile*. The ER physician holds loperamide and prescribes metronidazole.

2. What additional nutrition therapy is indicated for the patient?

A. Probiotic therapy
B. Potassium replacement
C. Parenteral nutrition
D. Enteral nutrition

Probiotics are live microorganisms consisting of nonpathogenic yeast and bacteria that are believed to restore the microbial balance of the GI tract altered by antibiotic therapy and infection with *C. difficile*. Probiotics can protect against colonization, pathogen adhesion, and invasion of the gastrointestinal mucosa. Probiotics can be consumed in capsule form and are also available in various food sources, like yogurt. The goal of probiotic therapy is to help repopulate the gut flora, decrease antibiotic-induced diarrhea, and prevent the recurrence of *C. difficile* infection. Multiple strains of probiotics exist, so it is important to recommend the appropriate strain. Saccharomyces boulardii, a yeast, given with antibiotics has been shown to be useful in treatment and avoidance of recurrence of *C. difficile*. Research suggests that preventative probiotic therapy has the potential to decrease the incidence and severity of radiation-induced diarrhea by protecting the GI tract from radiation injury. Due to increased lactose intolerance during radiation therapy, yogurt may not be tolerated, and therefore an oral capsule probiotic may be indicated.

Case study 135.4

A 46-year-old well-nourished male with relapsed T-cell lymphoblastic lymphoma is admitted for chemotherapy and allogeneic hematopoietic stem cell transplant (allo-HSCT). On Day +2, the patient has mild nausea, mucositis, and mild diarrhea (2–3 episodes per day). The physician orders intravenous fluids (IVFs) and a registered dietitian (RD) consult.

1. What is the most appropriate nutrition intervention at this time? (Choose all that apply.)

A. Enteral nutrition
B. Parenteral nutrition
C. Diet modification
D. Oral nutritional supplements

The goal of nutrition therapy is to maintain or improve nutritional status, prevent or minimize nutrient deficiencies, protect the functioning of the GI tract, and optimize oral intakes. An RD will assess the patients' medical history, anthropometrics, clinical symptoms, labs, and food preferences to provide diet recommendations to maximize patients' oral intakes to help meet nutritional requirements and prevent weight loss and muscle atrophy. Considering the patient's treatment and symptoms, a soft, low-lactose, low-acid, low-bacteria (neutropenic) diet and initiation of high-calorie, high-protein oral nutrition supplements would be appropriate.

Neutropenic diets (NDs) were originally introduced more than 30 years ago for use after HSCT to prevent infection from organisms and bacteria colonizing in the GI tract. While definitive evidence to support benefit of ND is lacking, present practice suggests implementing a diet that restricts high-risk foods, such as sushi, raw eggs, and undercooked meats, and promotes safe food handling and preparation until immunosuppressive therapy has been discontinued.

The patient is now day +5 with grade IV mucositis. The patient is unable to open his mouth well, has multiple open ulcers and visible swelling of the tongue, and is experiencing large-volume diarrhea (8–9 episodes daily). Oral intake has been inadequate for 6 days, and there are no signs of engraftment at this time.

2. What is the appropriate nutrition therapy for this patient?

A. Enteral nutrition
B. PN
C. Continued IV fluid administration
D. Liquid diet with a high-calorie, high-protein nutrition supplements

Enteral nutrition is the preferred route of nutrition when patients have a functional GI tract, although due to the severity of mucositis and diarrhea and the highly catabolic state that this patient is experiencing, initiation of PN is recommended. Oral mucositis usually presents 5–10 days post initiation of chemotherapy and may continue for up to 6 weeks. Damage and inflammation post high-dose chemotherapy are often present throughout the entire GI tract, resulting in mucositis and diarrhea. Resolution of mucositis post HSCT often resolves with recovery of white blood cell count and when ANC >500 cells/μL. Considering that this

patient is only at Day +5 with grade 4 mucositis without signs of engraftment, it is likely that the mucositis will persist for many days. A.S.P.E.N. guidelines recommend initiation of PN in a well-nourished patient with a nonfunctioning GI tract after 7–10 days of inadequate oral intakes. PN has been associated with improved long-term disease-free survival when compared to only IV fluid support in allogeneic patients receiving myeloablative-conditioning regimens. Other indications for PN use in HCT patients may include the development of severe intestinal GVHD, high-volume infectious diarrhea, or failure to receive adequate enteral nutrition.

Case study 135.5

A 56-year-old male with a malignant bowel obstruction status post intestinal resection and chemo and radiation therapy is admitted to the hospital. This patient has lost a significant amount of weight (18lbs. in 2 months, 15% of usual body weight) and is unable to consume adequate calories due to nausea and vomiting. Nasogastric tube feeding is attempted; however, the patient was unable to tolerate feeding. Patient started on PN in the hospital. Patient is tolerating the PN well but continues to receive antinausea medications and is unable to eat. He is drinking only small amounts of fluids. Patient is scheduled for another round of chemotherapy in 4–6 weeks but is now ready to go home.

1. Is the patient a candidate for HPN?

A. Yes
B. No

PN support can be not only lifesaving but also life supporting in the face of treatments or a disease process that prohibits enteral or oral feeding. Discharge planning should include the nutrition therapy that will be received at home. Both enteral and parenteral nutrition can be successfully administered at home as long as careful consideration is given to the caregiver support, complexity of the nutrition therapy, home environment, patient's medical stability, and reimbursement for HPN.

2. What are the outcomes associated with HPN?

A. Weight gain
B. Improved functional status
C. Ability to return to work or normal activities
D. All of the above

While home PN can be an onerous task at first, it has been shown to be successful in improving weight and tolerance to anticancer therapies and should not be overlooked. A recent study by showed that cancer patients receiving HPN improved their body weight, but, perhaps even more importantly, patient scores related to symptoms and quality of life also improved significantly while on home PN. A study in pancreatic cancer patients demonstrated that home PN improved nutritional status and therefore the ability to tolerate tumor therapy without interruption. Additionally, quality of life improved even in late-stage pancreatic cancer patients. In patients with advanced cancers associated with a GI obstruction, home PN has shown to increase survival by providing nutrition support that could not be consumed orally or enterally.

Multiple choice answer

Question 1: Answer B

Case study answers

Case study 135.1

Question 1: Answer E
Question 2: Answer B

Case study 135.2

Question 1: Answer C
Question 2: Answer E
Question 3: Answer A
Question 4: Answer E

Case study 135.3

Question 1: Answer B and C
Question 2: Answer A

Case study 135.4

Question 1: Answer C and D
Question 2: Answer B

Case study 135.5

Question 1: Answer A
Question 2: Answer D

Selected reading

August D, Huhmann MB. A.S.P.E.N. Clinical Guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. J Parenter Enteral Nutr. 2009; 33(5):472–500.

DiBaise JK, Scolapio JS. Home parenteral and enteral nutrition. Gastroenterol Clin North Am. 2007 Mar; 36(1):123–44.

McClave SA, Martindale RG, Vanek VW, *et al*. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) J Parenter Enteral Nutr. 2009 May–Jun; 33(3):277–316.

Murray SM, Pindoria S. Nutrition support for bone marrow transplant patients. Cochrane Database Syst Rev. 2008; 8(4): CD002920.

Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. Crit Rev Oncol Hematol. 2000 Jun; 34(3):137–68. Review. PubMed PMID: 10838261.

CHAPTER 136

Bone-related issues in oncology

S. Mujtaba Rizvi[1], Helen Collins[2], and Alan Lipton[1]

[1]Pennsylvania State University, Hershey, PA, USA
[2]Amgen Inc., Thousand Oaks, CA, USA

Introduction

Skeletal integrity is frequently compromised throughout the course of cancer and its treatment. With improvements in effective therapies and recurrence-free survival, patients are living longer and, therefore, a greater emphasis is being placed on overall health and quality of life. Increased rates of bone loss are seen in certain cancer treatment settings. Chemotherapy-related ovarian failure, use of aromatase inhibitors (AIs), androgen deprivation therapy (ADT), and steroid use are common risk factors for cancer treatment–induced bone loss. Treatment goals may include relieving pain, improving mobility, and preventing complications associated with bone loss. Cancer also frequently metastasizes to the bone. The exact incidence is not known, but it is estimated that more than half of the people who die of cancer have bone involvement. Cancers of the breast, prostate, kidney, bladder, and lungs metastasize to bone most commonly, and pain, debility, and decreased motility are often observed as a result. Bone metastases can cause serious, irreversible complications called skeletal-related events (SREs), which include pathological fractures, radiotherapy or surgery to the bone, and spinal cord compression. Hypercalcemia is a potentially reversible complication that may occur in some patients.

1. How does bone remodeling occur under normal circumstances?

The skeletal environment comprises a dynamic interplay between bone resorption and deposition through the actions of osteoclasts and osteoblasts, respectively. Osteoclasts play an important role in bone resorption by removing bone mineral and matrix. These cells are derived from the monocyte–macrophage lineage. RANK ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) are essential for their activation and functional integrity. Systemic factors, such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3, upregulate RANKL and hence play a regulatory role as well. Osteoblasts are mesenchymal cells that are involved in bone deposition. Although less well understood, they are thought to rely on Runt-related transcription factor 2 (Runx-2) and Wnt signaling pathways for differentiation and activation.

2. How do bone metastases occur?

Case study 136.1

A 60-year-old woman presents to the emergency department with severe lower back pain. She reports no history of trauma or heavy lifting. She has bilateral lower extremity weakness and reports acute onset of urinary incontinence. A computed tomography (CT) of the spine shows a compression fracture at L2–L4, with multiple blastic-appearing lesions in the thoracic and lumbar vertebrae. There is a palpable, 2 cm mass in the lower left quadrant of her left breast and palpable adenopathy in the ipsilateral axilla.

The skeleton is the most common site of metastasis in patients with metastatic disease, with an estimated prevalence of 1.5 million patients globally. Breast, prostate, and lung cancers most commonly metastasize to the bone. The preferential localization and growth of tumor cells in the bone are caused by the interplay between tumor cells

Acknowledgment: Lori Gorton, PhD, of Amgen Inc. provided editing, formatting, and graphic support for the preparation of this book chapter.

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

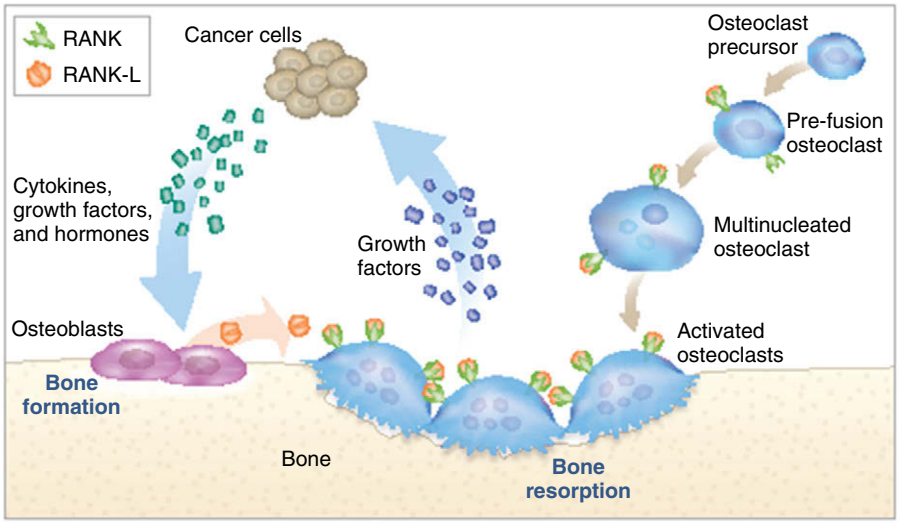


Figure 136.1 Cancer cells that metastasize to bone secrete cytokines, growth factors, and hormones that upregulate RANK ligand (RANKL). RANKL binds to its receptor RANK on the surface of osteoclasts and osteoclast precursors, stimulating osteoclast-mediated bone resorption. Calcium and growth factors are released from the resorbed bone, which in turn promote cancer cell growth and create a "vicious cycle."

and the bone microenvironment, a concept referred to as the "seed and soil hypothesis." Infiltrating tumor cells secrete regulatory and growth factors such as parathyroid hormone-related protein (PTHrP), interleukin-6 (IL6), and tumor necrosis factor (TNF), which in turn upregulate RANKL from newly synthesized osteoblasts. RANKL binds to its receptor RANK on the surface of osteoclasts, thereby increasing osteolysis, which leads to the release of growth factors that can promote tumor cell growth (Figure 136.1), ultimately leading to what has been termed "the vicious cycle."

The consequences of bone metastases can be devastating, as described in this patient case. Although only 5% of women with breast cancer in the United States present with stage IV disease, approximately 25% of patients who are diagnosed with earlier-stage disease will develop metastatic disease in their lifetime. The most common site of metastases for breast cancer is bone, which can lead to pain, spinal cord compression, or fracture. The term "skeletal-related event" (SRE) is often used to describe complications of bone metastases. SREs are usually defined as a fracture, prophylactic surgery to prevent or treat a fracture, radiation to the bone to prevent a fracture or treat pain, and/or spinal cord compression. Sometimes, hypercalcemia of malignancy, secondary to bone metastases, is also included in this definition.

Spinal cord compression is a neurosurgical emergency. Of the patients with metastatic disease to the bone, 40% develop vertebral metastases and an estimated 10–20% of these patients will develop spinal cord compression. Pain usually starts several weeks before the onset of neurological deficits, and therefore new vertebral pain in a patient with known bone metastases should be evaluated promptly; particularly if the pain is worse at night or is triggered by activities that increase intradural pressure (e.g., sneezing or defecation). Although this patient presented to the emergency room, and it appears most likely that her cord compression is due to L2–L4 compression fracture, it is important that such a patient undergo a sagittal screening magnetic resonance imaging (MRI) of the complete spine. The source of her spinal cord compression could be due to epidural disease elsewhere, such as in the lower thoracic spine. This patient's potential to recover neurological function will be based upon the speed with which the pressure of the bone metastases on her spinal cord can be surgically relieved. Unfortunately, even in a patient with known metastatic cancer, delays in diagnosing spinal cord compression often occur. These are likely due to delays in evaluation, as "pain and weakness" may be mistakenly attributed to the expected sequelae of progressive disease and chemotherapy and due to a lack of awareness that spinal cord compression represents a neurosurgical emergency. It is important that patients be educated about the symptoms of this potential risk and that triage staff understand the importance of this bone complication.

3. How are metastatic bone lesions characterized?

Bone lesions can be characterized as osteolytic or osteoblastic based on how they appear radiographically. Osteolytic lesions are characterized by bone destruction and osteoblastic lesions by abnormal bone deposition. In certain tumor types, metastatic bone disease can be predominantly osteolytic or osteoblastic; for example, osteolytic metastases are most commonly seen in breast, lung, renal, and thyroid cancers, and in multiple myeloma, whereas prostate cancer leads to the formation of osteoblastic foci in bone. Some lesions can have both osteoblastic and osteolytic features. For example, although the lesions in the breast cancer case described above were considered to be osteoblastic, this patient likely had a mix of both osteoblastic and osteolytic lesions.

4. What is cancer-treatment induced bone loss, and which patients are at risk?

Case study 136.2

A 56-year-old, postmenopausal, Caucasian woman undergoing adjuvant treatment for breast cancer with an AI presents for a routine follow-up visit. She is underweight for her height and appears pale. She mentions reading about osteoporosis in a magazine recently and asks if she is at risk and needs to be treated.

Therapy for cancer can compromise skeletal integrity. Hypogonadism induced by hormonal and nonhormonal therapies leads to increased bone resorption and turnover. Patients undergoing treatment with AIs (in the breast cancer setting), ADT (in the prostate cancer setting), corticosteroids, and chemotherapeutics that lead to gonadal failure are at an increased risk of developing osteoporosis. Surgical removal of the gonads in hormone-sensitive malignancies also adversely affects bone density. Even without receiving cancer treatment, postmenopausal women are at an increased risk of developing fractures secondary to osteoporosis. The estimated lifetime risk of developing osteoporosis is 50% for women over 50 years of age and 25% for men in the same age group.

The rate of bone loss secondary to cancer treatment be can as high as 10 times that of age-related bone loss. Bone mineral density (BMD) decreases by 0.5–1% per year in men starting at midlife. In men treated with ADT for prostate cancer, it can be as high as 4–5% per year. Women typically experience bone loss at a rate of 2% per year in the perimenopausal period, which then declines. In postmenopausal women, AI therapy can accelerate the rate of bone loss in osteopenic patients, as suggested by data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, which compared adjuvant anastrozole to tamoxifen in women with early-stage breast cancer. Women with breast cancer receiving AI therapy who have the highest risk of an osteoporotic fracture are those with low preexisting BMD.

Unfortunately, as osteoporosis is asymptomatic, it is often not detected until a bone fracture occurs. However, only 3–32% of high-risk patients undergo bone density screening. The American Society of Clinical Oncology (ASCO) recommends bone density screening for women at high risk for osteoporosis. These risks include women older than 65 years of age and women 60–64 years with a family history of fracture, body weight less than 70 kg, and prior nontraumatic fracture, among others. Risk factors also include premenopausal women with treatment-induced ovarian suppression secondary and postmenopausal women receiving AI therapy. Another set of guidelines, which have broader application to all patients, including men receiving ADT for prostate cancer, are those of the National Osteoporosis Foundation, which uses the World Health Organization Fracture Risk Assessment Tool (FRAX) to assess fracture risk.

5. How are bone metastases treated in patients with castration-resistant prostate cancer?

Case study 136.3

An 80-year-old man with castration-resistant prostate cancer was recently diagnosed with a metastatic lesion in the left proximal femur after he complained of pain in his left hip. He has been having problem bearing weight and wants advice on his treatment options.

Metastatic disease of the bone in prostate cancer is a significant cause of morbidity and increased mortality, and it decreases a patient's quality of life. Predominantly, bone lesions secondary to prostate cancer are osteoblastic. Treatment is largely palliative. External-beam radiation is used for palliation of pain if there are a limited number of areas involved. Bone-targeted radio-isotopes may be used in patients with multiple metastatic foci in bones or when conventional external-beam radiation therapy has failed. Demonstration of isotope uptake at the site of pain prior to initiation of treatment is a prerequisite for bone-targeted radio-isotope therapy. Radium-223 was shown to increase overall survival and decrease SREs in the phase III ALSYMPCA trial. This alpha particle–emitting isotope may have a better toxicity profile than beta-emitting isotopes used in the past. For radium-223, new drug applications are currently under review by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Surgery is generally reserved for patients with fractures or evidence of spinal cord compression. However, bone metastases in specific weight-bearing locations such as the femur may be considered for prophylactic surgery because of the significant morbidity associated with fractures. Location, size, severity of pain, type of lesions (lytic, blastic, or mixed), and shape of the bone metastases have been used to develop scoring systems that estimate the risk of fracture over the next 6 months. Although these scoring systems were developed prior to the availability of antiresorptive agents, patients with bone metastases in a weight-bearing bone should undergo a plane X-ray or CT scan with bone windows to evaluate potential fracture risk.

Although metastatic sites in prostate cancer are primarily osteoblastic, there is a significant osteolytic component as well. Metastases primarily involve the axial skeleton, and bone destruction is thought to play an important role in the etiology of pain. Therapy for prostate cancer also

leads to bone loss, as described above. Antiresorptives, bisphosphonates (e.g., pamidronate and zoledronic acid (ZA)), and denosumab, therefore, play a role in decreasing bone loss and preventing SREs.

The mechanism of action for bisphosphonates is not fully understood. One mechanism that has been postulated is through apoptosis of osteoclasts. ZA is approved in the United States for treatment of bone metastasis secondary to castration-resistant prostate cancer and has been shown to decrease the incidence of SREs in this population. Bone-targeted agents are recommended for the treatment of osteoporosis if the 10-year probability of fracturing the hip greater than or equal to $\geq$3% or of having any osteoporosis-related fracture is greater than or equal to 20% in the setting of long-term treatment with ADT.

Denosumab is a bone-targeted agent that possesses a mechanism of action that is distinct from bisphosphonates. Denosumab is a fully human monoclonal antibody that inhibits osteoclasts by binding to RANKL. RANKL is a critical regulator of osteoclast-mediated bone resorption. It is approved for the prevention of SREs in patients with metastatic disease from solid tumors and to increase bone mass in men at high risk for fracture receiving ADT for nonmetastatic prostate cancer. Denosumab has been shown to delay the time to first and multiple SREs compared with ZA in men with prostate cancer and bone metastases. In the pivotal SRE study, overall survival and time to disease progression were similar between groups, as was the incidence of osteonecrosis of the jaw (denosumab 2%, ZA 1%; $P = 0.09$). Denosumab has further been shown to delay the time to bone metastases, including symptomatic and multiple metastases, in men with nonmetastatic castration-resistant prostate cancer. Recent guidelines from the European Society for Medical Oncology (ESMO) include denosumab as a treatment option to delay the development of bone metastasis in this setting.

Hypocalcemia can occur with denosumab use, and it is contraindicated in patients with clinically significant hypersensitivity to any components of the drug. Denosumab requires no dose adjustments with renal dysfunction and is administered by subcutaneous injection. Appropriate vitamin D and calcium supplementation is recommended.

6. How is bone metastasis treated in patients with breast cancer?

Case study 136.4

A 50-year-old woman undergoing evaluation for breast cancer was diagnosed with a metastatic area in her left proximal femur. She presents to her oncologist's office to discuss treatment options.

Breast cancer is the most common cancer among women worldwide and the leading cause of cancer-related deaths. Bone is the most common site of metastasis in women with breast cancer. Younger age, tumor size, and estrogen receptor–positive status are among the predisposing risk factors for bone metastasis. The median survival for breast cancer with metastatic bone disease is 2 years. However, there is variability within tumor subtypes. For example, in patients with hormone-receptor positive breast cancer who have bone as their only site of metastases, the reported median survival is more than 5 years. Treatment approaches for metastatic breast cancer integrate systemic chemotherapy, local disease control with radiation treatment modalities, osteoclast inhibition, and pain control.

Both denosumab and ZA delay the development of SREs, but neither has shown a survival benefit in their overall clinical study populations. Moreover, neither is indicated for use in the nonmetastatic setting. Currently, there are two parenteral bisphosphonates, ZA and pamidronate, which are both approved in the United States for the treatment of patients with bone metastasis secondary to solid tumors. In patients with bone metastases from breast cancer or multiple myeloma, ZA was noninferior to pamidronate in delaying the time to first SRE (hazard ratio (HR): 0.92; 95% confidence interval (CI): 0.77–1.09; $P = 0.32$). In patients with breast cancer and bone metastases, when compared with ZA, denosumab was superior in prolonging the time to first SRE (HR: 0.82; 95% CI: 0.7–0.95; $P = 0.01$).

The oral bisphosphonate ibandronate is approved for patients with breast cancer and bone metastases outside the United States, and clodronate is also available as an anti-bone-resorptive agent outside the United States.

7. How are bone metastases treated in patients with multiple myeloma?

Case study 136.5

A 60-year-old African American woman presented to the emergency department with severe right arm pain. X-ray showed a lytic lesion of the right proximal humerus. Laboratory work-up was significant for anemia, hypercalcemia, acute renal failure, and increased total protein. An oncology consultation and evaluation led to a diagnosis of multiple myeloma.

In a patient presenting with a metastatic bone lesion, palliation of symptoms should be the first priority. Maintaining adequate pain control with analgesics and an evaluation by an orthopedic surgeon and/or radiation oncologist should follow. Even for patients who undergo surgical repair of a malignancy-related fracture, postoperative radiation is

usually recommended. The choice of treatment for hypercalcemia of malignancy should take into account the albumin-corrected level of hypercalcemia and the presence or absence of symptoms. In general, patients with severe hypercalcemia (corrected serum calcium >14 mg/dL) or those who experience symptoms will require intervention, which can include hydration, glucocorticoids, calcitonin, bisphosphonates, gallium nitrate, or even dialysis. As this patient has both hypercalcemia and renal insufficiency, careful monitoring of fluid status and the potential use of a diuretic may be necessary to avoid fluid overload. Furthermore, as bisphosphonates may cause worsening renal toxicity, appropriate dose modifications for existing renal dysfunction may be necessary.

In patients with a confirmed diagnosis of multiple myeloma with bone involvement, intravenous (IV) bisphosphonates are favored over oral agents. In a phase III clinical trial of patients with multiple myeloma or bone metastasis secondary to breast cancer, ZA was found to be noninferior to pamidronate in reducing the percentage of patients with an SRE and the time to the first SRE. Currently, both agents are approved for patients with multiple myeloma. Bisphosphonates have also been shown to reduce pain in patients with multiple myeloma.

Denosumab is not licensed for use to prevent SREs in patients with multiple myeloma. A phase III randomized controlled trial comparing denosumab to ZA in patients with metastatic bone disease secondary to solid tumors (excluding breast and prostate) or multiple myeloma demonstrated non-inferiority between agents in delaying the time to first on study SRE. However, in an unplanned analysis, the small cohort of patients in the multiple myeloma subset had a shorter overall survival compared with ZA. The survival findings in the multiple myeloma subset were deemed inconclusive. A phase III clinical trial is currently being conducted to evaluate the effects of denosumab in patients with multiple myeloma.

Selected reading

Aboulafia AJ, Levine AM, Schmidt D, *et al*. Surgical therapy of bone metastases. Semin Oncol. 2007;34(3):206–14.

Guise TA. Bone loss and fracture risk associated with cancer therapy. Oncologist 2006;11(10):1121–31.

Lopez-Olivo MA, Shah NA, Pratt G, *et al*. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. Supp Care Cancer 2012;20(11):2985–98.

Peddi P, Lopez-Olivo MA, Pratt GF, *et al*. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treat Rev. 2013;39(1):97–104.

Sartor O, DiBiase SJ. Bone metastases in advanced prostate cancer: clinical manifestations and diagnosis. In: Ross ME, editor. UpToDate. Waltham, MA: UpToDate; 2012.

CHAPTER 137

Integrative medicine in oncology

Weidong Lu and David S. Rosenthal

Harvard Medical School *and* Dana-Farber Cancer Institute, Boston, MA, USA

Multiple choice and discussion questions

1. What is integrative oncology, and when should cancer patients be referred for integrative oncology consultations?

The term "integrative medicine" (IM) or integrative oncology is used to more accurately describe how complementary therapies are being used today in oncology practice. The old terminology, "complementary and alternative medicine" (CAM) is controversial since the words "complementary" and "alternative" have completely different meanings and should not be connected by an "and" but by an "or." Complementary therapies as defined by the National Center for Complementary and Alternative Medicine are those therapies used to complement or to be used *alongside* conventional methods of therapy, whereas alternative methods refer to those therapies that are used *instead* of known conventional therapies and have not been shown to be effective. CAM is tremendously popular helping people deal with wellness and health concerns. In the United States, an estimated $36 to $47 billion is spent annually by the public on CAM methods of therapy, and in a National Health Interview Survey in 2007, 37% of adults used at least one form of CAM. CAM practices have become very popular in individuals with a chronic disease such as hematologic malignancies and cancer.

The major categories of integrative medicine include mind–body approaches, body-based manipulative therapies, acupuncture, and natural products. Mind–body approaches include prayer, meditation, mindfulness meditation, guided imagery, music therapy, creative arts therapy, self hypnosis, yoga, tai chi, and qigong. Body-based manipulative therapies include chiropractic and massage therapy. Natural products include dietary supplements, for example antioxidants as well as herbs and botanicals.

The major reason why patients use integrative therapies or remedies not prescribed by their hematologist or oncologist is in an effort to improve their treatment outcome to manage their symptoms and to be a participant in their own care. Patients therefore should be referred for an integrative oncology consultation to assist the primary oncologist in:

1. Advising the physician and patient about the use of various supplements and antioxidants, healthy nutrition, and practicing physical activity

2. Making appropriate recommendations about nonpharmacologic approaches in managing the patient's symptoms from the cancer and its treatment

3. Addressing the fact that the majority of cancer patients experience anxiety, stress, and/or depression during the course of their disease.

2. What interventional therapies are available to the oncology team in managing these patients?

Mind–body therapies are generally not in the portfolio of an oncologist's recommendations while managing their cancer patients, yet mind–body therapies are frequently studied interventions in patients with chronic diseases such as cancer. The most common reasons why patients use these therapies are to manage their pain, fatigue, anxiety, and stress. Chronic stress has been shown to decrease immune function, perhaps through the mechanism of decreasing natural killer cells and impairing the effectiveness of DNA repair. In the 1970s, Dr Herbert

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

Benson studied Tibetan monks as they meditated and experienced the "relaxation response." The mind–body techniques available to cancer patients include meditation, mindfulness meditation, guided imagery, and hypnosis. In addition, music therapy and physical activities such as yoga, tai chi, and qigong also are related mind–body programs.

Randomized clinical trials (RCTs) have demonstrated that relaxation training and guided imagery significantly reduce nausea and anxiety. When compared to medication, relaxation therapy showed similar decreases in anxiety and depression, although medication might have been slightly faster in its effect. Other randomized trials have shown decreases in tension, depression, anger, and fatigue during relaxation training and/or imagery. In children, hypnosis has been found to be especially effective. In an RCT comparing hypnosis or nonhypnotic distraction such as the relaxation techniques versus joining a placebo attention control group, the children in the hypnosis group reported significant reduction in anticipatory and chemotherapy-induced nausea and vomiting.

Mind–body therapies have also been used to alleviate pain. In an RCT examining the effects of the relaxation response therapy (RRT) versus reiki therapy in men being treated with external-beam radiotherapy for prostate cancer, RRT improved emotional well-being and eased anxiety, while reiki therapy had a positive effect on anxiety. Expressive arts therapy and music therapy as well as repetitive exercise, yoga, tai chi, qigong, and Pilates also may reduce stress and anxiety.

Music therapy is considered a mind–body intervention, and it uses a variety of active and passive music experiences. Randomized trials have shown statistically significant improvements in mood and physical discomfort. Music therapy has also been shown to be an effective adjunct to antiemetic therapy. Yoga has been studied to determine whether there is a related reduction in symptoms of depression and anxiety. In a 12-week yoga intervention in healthy subjects, it was demonstrated that there was greater improvement in mood and anxiety than a metabolically matched walking exercise.

In summary, mind–body therapies can reduce anxiety, temper adverse effects of chemotherapy and radiation treatments, relieve pain, and possibly stimulate immune responses. By reducing stress and anxiety, these therapies can help patients deal with a wide range of relationship issues and decision making as they move through the diagnostic and therapeutic phases of their malignancy. Mind–body approaches have very minimal risk and potentially significant benefits. Most importantly, they are often self-taught and therefore low cost. Mind–body practices should be considered as an adjunct to usual care regardless of whether patients are beginning or recovering from chemotherapy.

3. True or false? Over-the-counter antioxidants can lessen the toxicity and boost the effects of chemotherapy and radiation therapy.

A. True
B. False
C. Debated

The answers are still debated, and below are the pros and cons of the use of antioxidants.

Antioxidants (such as beta-carotene; lycopene; vitamins C, E, and A; and other substances, such as coenzyme Q10 and quercetin) are among the most common classes of supplements used by patients with cancer; with use directed for cytotoxic effects, for synergy with conventional therapy, or to lessen the toxicity of conventional therapy. An estimate of use by cancer patients varies considerably, with rates ranging from 13% to 87% depending on the survey and the type of cancer studied.

Antioxidants are substances that counteract free radicals and prevent them from causing tissue and organ damage. Evidence supporting the potential role of antioxidants in preventing and treating disease include preclinical studies, which have correlated oxidative stress and an antioxidant-depleted diet with the development of diseases, including cancer. Much of the controversy surrounding antioxidants and cancer therapy has arisen because radiation therapy and certain classes of chemotherapy agents exert some of their anticancer effects through the generation of reactive oxygen species, or free radicals. The anthracyclines (e.g., doxorubicin), platinum-containing complexes (e.g., cisplatin and carboplatin), and alkylating agents (e.g., cyclophosphamide and ifosfamide) are good examples. The theoretical concern is that antioxidants might interfere with or counteract the activities of these anticancer agents. However, to date, preclinical experiments and clinical studies have not definitively shown an impact on treatment outcome. An observational cohort study from the Fred Hutchinson Cancer Research Center in Seattle evaluating the prevalence of supplement use in persons before receiving hematopoietic stem cell transplant and the association of select supplements with outcomes found that pretransplant intake of vitamin C ($\geq$500 mg/day) or vitamin E ($\geq$400 International Units/day) was associated with increased risk of relapse or mortality.

Specific examples include the interactions of antioxidant supplements with the proteosome inhibitor, bortezomib. Vitamin C inhibited the in vitro multiple myeloma cell cytotoxicity of bortezomib. Green tree polyphenols and dietary supplements such as quercetin bind and inhibit the activity of bortezomib on malignant B-cell and multiple myeloma cells in vitro. In summary, these studies suggest that antioxidant supplements should be avoided in patients receiving certain chemotherapeutic classes of drugs and radiation therapy.

Specific recommendations for clinical practice at the current time include the following:

- Patients should be advised to avoid dietary antioxidant supplements above the basic nutritional requirements during radiation therapy and alongside certain chemotherapeutic classes that are associated with high oxidative stresses.
- Use of antioxidant supplements while receiving chemotherapy associated with low oxidative stress (e.g., purine and pyrimidine analogs, antimetabolites, monoclonal antibodies, vinca alkaloids, taxanes, and corticosteroids) is less likely to be associated with interactions. Caution should be taken with other agents (e.g., antiangiogenic agents and tyrosine kinase inhibitors) for which there is insufficient information.

Case study 137.1

Your 45-year-old female patient wants take to supplements and herbs alongside her conventional therapy.

- **What do you tell her?**

Most conventional medical and radiation oncologists recommend that their cancer patients avoid all supplements, especially during active radiation or chemotherapy. Much of this recommendation is based on the concern that evidence to support the use of any of these agents is lacking. There are significant concerns about supplement use; for example, (i) the potential for supplement–drug interactions via a pharmacokinetic pathway, (ii) the oxidant–antioxidant issue, and (iii) the impact of the supplement on clotting, which is a particular problem for patients with thrombocytopenia or on or off anticoagulants, as many of the supplements are "anti-inflammatory."

Chemotherapy–supplement or chemotherapy–herb interactions are not uncommon and could lead to a clinically important interaction, causing either an increase or decrease in the effects of either component. As 35% of currently prescribed oncology drugs are metabolized by the CYP3A4 isoform of the hepatic cytochrome p450 enzyme system, use of supplements that either induce or inhibit the pathway can be problematic. In treatment of hematologic toxicities, cyclophosphamide, the epipodophyllotixins, and vinca alkaloids are all dependent on CYP3A4 for their metabolism. For example, the botanical supplement St. John's wort used for the treatment of mild depression is a strong inducer of many CYP isoforms. In a classic pharmacokinetic interaction study, 10 healthy volunteers were administered a single 400 mg oral dose of imatinib before and after 2 weeks of treatment with St. John's wort 300 mg three times daily. The investigators found that the pharmacokinetics of imatinib were significantly altered by St. John's wort, with reductions of 32% in the median area under the concentration–time curve ($P = 0.0001$), 29% in maximum observed concentration ($P = 0.005$), and 21% in half-life ($P = 0.0001$). The conclusion was that coadministration of St. John's wort might compromise the clinical efficacy of imatinib. It is generally recommended that cancer patients receiving any intervention avoid taking St. John's wort.

Patients with hematologic malignancies are often at increased risk for bleeding problems. Thrombocytopenia of unclear etiology in cancer patients has often been attributed to botanical supplements that they are taking, particularly traditional Chinese medicine herbs. Some herbs and botanicals contain derivatives of dicoumeral.

There are some over-the-counter substances that can be of help with managing patients. Epidemiologic data suggest an inverse relationship between the intake of marine omega-3 fatty acids and the development of a number of hematologic malignancies and a good risk–benefit profile. Some animal studies suggest longer remissions and/or survival when subjects were fed an omega-3 fatty acid diet.

Increasing evidence suggests that vitamin D_3 deficiency may be related to the risk of a number of solid tumors—particularly breast, colon, prostate, and pancreas. An ongoing RCT is currently looking at a 2×2 factorial design of omega-3 fatty acids and/or vitamin D_3 supplementation in older adults to assess cancer risk reduction among other endpoints. In the meantime, it may be appropriate in view of the widespread incidence of vitamin D insufficiency, especially in older adults, to measure 25-hydroxy-vitamin D levels in patients with malignancies and supplement with a fat-soluble vitamin D_3 preparation to bring the levels into sufficient or optimal range.

There are conflicting data on whether green tea should be recommended. Green tea (*Camellia sinensis*) is an increasingly consumed beverage that is used for beneficial health effects and is an inhibitor of CYP3A4 metabolism as well as a potent source of vitamin K. Thus, green tea may interact with prescribed anticancer drugs or anticoagulant therapies. However, green tea polyphenols have been shown to have antiproliferative activity against a wide variety of cell lines such as chronic lymphocytic leukemia. Epigallocathechin-3-gallate (EGCG) is the specific green tea polyphenol that is an antioxidant with chemopreventive and chemotherapeutic actions. One trial demonstrated that the polyphenon E preparation utilized was well tolerated in the 33 participants and that the majority of participants had decreased total lymphocyte counts and/or lymphadenopathy. Of note, when taken on an empty stomach, green tea catechins (GTC) prepa-

rations have been associated with a risk of hepatotoxicity. The question as to whether health benefits against hematologic malignancies can be achieved by simply drinking an as-yet-unknown quantity of the beverage or if higher dose preparations such as GTC or EGCG are required is not known, and safety may be an issue with high doses of green tea extract.

There is controversy regarding the use of green tea with patients with multiple myeloma on bortezomib, because of its potential to negate the treatment effects of bortezomib. It has been reported that various green tea constituents, in particular EGCG and other related polyphenols, effectively prevented tumor cell death induced by bortezomib in vitro and in vivo. The doses of EGCG used in vitro and in the animal model are levels that could not be achieved from the drinking of green tea, however. Nonetheless, the authors concluded that because green tea polyphenols in their experiments had the potential to negate the therapeutic efficacy of bortezomib, consumption of green tea products may be contraindicated during cancer therapy with the proteasome inhibitor. Subsequently, other investigators investigating EGCG in plasma concentrations commensurate with dietary or supplemental intake showed no antagonism of bortezomib antitumor activity, suggesting that patients do not need to avoid normal dietary consumption of green tea or EGCG supplements. As this was also a study in mice, perhaps erring on the side of caution and allowing drinking green tea but discouraging GTE and EGCG supplements in bortezomib-treated patients is most prudent at this time.

Case study 137.2

A 48-year-old white male has a history of T2b, N2b, M0, squamous cell carcinoma of left tonsil, human papillomavirus virus (HPV) positive, status post-chemoradiation therapy completed 24 months ago followed by a neck dissection 19 months ago, with a current status of no evidence of disease. The patient is presenting with persistent left neck pain at 6 out of 10 on the pain scale and dry mouth. The patient refuses to take nonsteroidal anti-inflammatory drugs (NSAIDs) for the neck pain due to his ongoing acid reflux condition.

1. If acupuncture is recommended to the patient, which following is true?

A. The patient would notice immediately relief in his pain after one acupuncture session

B. Because of his history of head and neck cancer, acupuncture is contraindicated

C. Acupuncture is appropriate for this patient because acupuncture has a long history of clinical use

D. Acupuncture is appropriate for his patient because evidence from RCTs suggests its benefits

Before referring cancer patients to acupuncture, it is imperative to be aware of two acupuncture-related factors: one is the risk a cancer patient faces at time of the referral, and the second is the setting where acupuncture treatment will be delivered. The treating oncologist should review the overall oncologic status of the patient regarding the timing of acupuncture, whether the patient is at a high-risk phase of chemotherapy or radiation, with a severely impaired hematologic profile, or the patient is at a low-risk phase such as postsurgery or postchemotherapy with a normal hematologic profile. It is strongly preferred that a cancer patient at a high-risk phase should be treated by an in-house acupuncture team, where medical data such as lab and imaging reports are accessible by the team and a rapid communication could take place between the treating oncologist and the acupuncturist. A community-based acupuncture practice would be appropriate for patients who are off active anticancer treatment and have no evidence of disease, when potential risks of complications are low. Two RCTs suggest that it is reasonable to use acupuncture for posttreatment chronic neck pain and radiotherapy-induced xerostomia in head and neck cancer patients, especially for patients who are not willing to take pain medication due to complications, side effects, or personal preference.

The National Comprehensive Cancer Network (NCCN) guideline for adult cancer pain recommends the use of acupuncture, as an integrative intervention, in conjunction with pharmacologic intervention as needed.

- **What are specific patient criteria for acupuncture? How often should the patient go, and how many acupuncture sessions does a patient need, before an improvement would be noticed?**

Based upon Pfister and Simocock's study, the following patient eligibility criteria are generally recommended for patients who request acupuncture for neck pain:

1. Head and neck cancer patients treated with neck dissection or/and radiotherapy

2. Postradiation or surgery approximately between 18 and 39 months

3. No evidence of disease

4. Persistent neck pain between 7–4 out of 10 on a pain scale and/or dry mouth

5. Intolerance to pain medication.

Clinically meaningful results are expected after 5–6 weekly sessions of acupuncture, with a reduction of approximately 2 points on a pain scale. A continuous benefit is expected if acupuncture treatment is extended beyond 6 weeks.

3. What kind of acupuncture protocol is most appropriate in oncology?

Historically, acupuncture is a highly heterogonous profession. There are virtually no standard acupuncture needling protocols for the majority of conditions. Each practitioner designs a treatment protocol for each individual patient mainly based upon his or her own clinical experience. The current majority of acupuncture-training programs do not provide training in oncology acupuncture, the emerging subspecialty that specifically manages the symptoms of cancer patients. Therefore, the referral physician should also be aware of the appropriate qualification of the practitioner to whom he or she is referring.

We recommend two acupuncture protocols. The first one is the acupuncture protocol used in the above-mentioned trial. The second is the one we have been using at the Dana-Farber Cancer Institute.

First, the patient is in a recumbent position on the right side with the left neck and shoulder well exposed for treatment. Second, painful areas are identified by palpating the left neck and around the scar tissue. After routine skin preparation with alcohol, stainless-steel acupuncture needles, size 36/32 gauge and 1 inch and 1/2 inch in length, are inserted into so-called Ashi points, the tender sites, and other regular acupuncture points as follows: TW 16, TW 17, GB 20, SI 17, SI 16, ST 6, ST 5, and LI 16. Special attention should be given to the area around the incision scarring line. The depth of needle insertions is usually 5 to 10 mm and should be tailored based upon the patient's sensitivity to needling. The general needling approach is to start from the peripheral realm of the painful region, then gradually move into the center area at each session. As the pain level reduces, the size of the tender region also diminishes. The firmness of the scarring region becomes softer.

Once needles are placed, they are manipulated with light twists or flicking, in order to elicit the specific needling sensation called *Deqi*. An electroacupuncture stimulator will be used to connect needles at GB 20 and one of the Ashi points to enhance the *Deqi*. The frequency is set at 2 Hz initially. The orally reported intensity level is initially around 3–4 out of 10, in which the patient should clearly feel the tapping sensation without discomfort. The electroacupuncture-generated tapping sensation will gradually diminish within 10–15 min. An infrared heat lamp is then placed above the neck of the patient at a distance of 60 cm. The patient then rests in the treatment room with a call button in hand for about 30 min. At the end of the session, the patient usually feels relaxed or falls asleep. The needles are finally removed with cotton balls pressing on the needling sites to prevent potential bleeding. The session will be repeated once a week for 6–8 weeks. Once reported pain level reduces to 1–2 out of 10, the interval of following session could be extended to once every 2 weeks.

Case study 137.3

A 66-year-old woman was seen regarding ongoing management of her metastatic breast cancer. The patient was first diagnosed with T1, N1b, estrogen receptor (ER)-positive right breast cancer in 1985; and she was treated with axillary lymph node dissection (ALND), CMFVP chemotherapy (containing cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone), and irradiation therapy. In 1991, she underwent mastectomy and nine cycles of AC chemotherapy (cyclophosphamide and doxorubicin) due to tumor recurrence, followed by eight years of tamoxifen. In 2003, she was found to have a metastatic breast cancer in the left axilla without an evident primary in her left breast. The node was resected, and she was put on anastrozole (Arimidex®). In 2006, she developed a subcutaneous nodule in the left axilla, along with liver metastases and asymptomatic bone metastases. She then had several more surgeries in her left axilla and was switched to fulvestrant and later capecitabine (Xeloda®). In 2012, the patient underwent a left breast skin punch biopsy for a lesion that was read as invasive ductal carcinoma, poorly differentiated. No skin ulceration is present. No definite lymphovascular invasion is present. Her recent positron emission tomography–computed tomography (PET–CT) showed equivocal increase in fluorodeoxiglucose (FDG) avidity in her left axilla and mediastinum and unchanged avidity in her bones. She is started on gemcitabine chemotherapy. In the past 2 months, the patient has complained of an increased persistent pain in her left chest. Her pain level is around 6–7 out of 10. The patient asks you whether it is okay to seek acupuncture for her persistent chest pain at the student clinic of a local acupuncture school or by a local practitioner.

1. Which of the following answers would you choose?

A. Okay! Because acupuncture is a safe procedure, it is fine for the patient to get acupuncture treatment there

B. No! Acupuncture won't help you at all. Do not waste your time and money

C. Well, your medical condition is complicated. Maybe you should seek an oncology acupuncture specialist as part of your pain management team

D. Sorry, I do not know anything about acupuncture. I cannot give you any suggestions

When referring a cancer patient for acupuncture, the setting where acupuncture treatment is delivered is extremely important for safety reasons. We generally categorize cancer patients into two categories, high risk and low risk, regarding their suitability for receiving acupuncture.

The following patients are considered to be in the higher-risk category for receiving acupuncture: (i) patients who are currently undergoing chemotherapy or radiation therapy, (ii) patients who are in advanced stage of the disease with major comorbidities, (iii) patients who have severely impaired hematological profiles, (iv) patients with pain and bone metastases, (v) patients who have brain metastases with central nervous system symptoms, and (vi) patients who are on contact precautions for methicillin-resistant *Staphylococcus aureus* (MRSA) or other bacteria and viruses (like *Salmonella* and *Clostridium difficile*). In addition, we have developed a guideline used to determine patient eligibility for acupuncture at the Dana-Farber Cancer Institute.

At this time, acupuncture treatment is *not* recommended to cancer patients with the following conditions:

1. Absolute neutrophil count (ANC) less than 500/ml
2. Platelet count less than 25,000/ml
3. Altered mental state
4. Clinically significant cardiac arrhythmias
5. Other unstable medical conditions (case-by-case consideration).

High-risk patients are not appropriate to be referred out to community acupuncturists because, first, community acupuncturists usually do not have special training in treating cancer patients with advanced stage of disease; and, second, community acupuncturists usually do not have access to the patient's medical information, such as lab reports and imaging studies. "Ashi point needling" is a common needling technique in acupuncture when treating pain condition, in which acupuncture needles are directly inserted into the tender area. However, when pain is caused by bone metastases, insert needles into the sites of bone metastases may exacerbate the patient's condition. Therefore, identifying locations of bone metastases from imaging reports prior to inserting needles becomes a critical step in managing cancer pain with acupuncture.

Nevertheless, the community acupuncture settings may treat the following cancer patients within the low-risk category: (i) patients who have completed chemotherapy or radiation therapy, (ii) patients who have normal hematologic profiles, (iii) patients who have early-stage disease without major comorbidities, (iv) patients with pain but no bone metatheses, and (v) patients with no brain metastases.

Based upon the above-mentioned guidelines, the female patient who clearly is in the high-risk category should not be referred to community acupuncture for treatment. Instead, the patient should be encouraged to seek an oncology acupuncturist who has a hospital-based practice where quickly accessing up-to-the-minute changes of the patient's medical information is possible and the safety of the patient can be ensured.

Case study 137.4

A 63-year-old female with a diagnosis of metastatic pancreatic cancer to the liver is currently receiving cycle six of FOLFIRINOX chemotherapy (a combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin) with pegfilgrastim (Neulasta®). The patient complains of severe and persistent nausea and fatigue during the first week of chemotherapy. She rated her nausea level at 8 out of 10, and her fatigue level at 8 out of 10 (0 being the best and 10 being the worst). She has lost 5 kg since the start of chemotherapy. In managing her nausea and fatigue, she has been given ondansetron (Zofran®), prochlorperazine (Compazine®), and aprepitant (Emend®) at each cycle, but the results were limited.

• Is it appropriate to recommend acupuncture for her chemotherapy-induced nausea and vomiting?

The patient has tried antiemetic medications with a limited benefit. Acupuncture is one nonpharmaceutical option that can provide relief in chemotherapy-induced nausea and vomiting (CINV). CINV is one of the most frequently encountered symptoms in cancer treatment. Up to 80% of cancer patients who are undergoing chemotherapy suffer from CINV, which severely impairs their quality of life. Although antiemetic drugs such as serotonin (5-HT_3) receptor antagonists, neurokinin 1 (NK_1) receptor antagonists, and corticosteroids are the mainstay for managing CINV, many patients are still not able to tolerate CINV well during the treatment. In addition to these antiemetic medications, acupuncture has been suggested for CINV with considerable evidence supporting its use. As early as 1997, NIH Acupuncture Consensus concluded that acupuncture was effective for CINV. Several systematic reviews later also reached similar conclusions. The NCCN guidelines on antiemesis have recently recommended acupuncture for anticipatory emesis prevention and/or treatment.

5. Does acupuncture have any role in alleviating cancer-associated fatigue?

Acupuncture also has been suggested for symptoms of cancer fatigue. In a RCT published in *Journal of Clinical Oncology*, breast cancer patients (N = 246) experiencing persistent fatigue at 1 month and up to 5 years after completing chemotherapy were randomly assigned to usual care versus acupuncture plus usual care (1:3 ratio). Participants received acupuncture once a week for 6 weeks. The Multidimensional Fatigue Inventory (MFI), the Hospital Anxiety and Depression Scale, and the Functional Assessment of Cancer Therapy—General Quality of Life Scale were used to assess the outcomes. At 6 weeks, the mean General Fatigue score was −3.11 (95% CI: −3.97 to −2.25; $P < 0.001$) between those who were on acupuncture and who were not. Other improvements in anxiety, depression, and quality of life in the acupuncture group were observed. The authors concluded that acupuncture is an effective intervention for managing the symptom of cancer-related fatigue and improving quality of life. NCCN guidelines on cancer-related fatigue have also recommended acupuncture as part of nonpharmaceutical intervention for patients on active treatment.

Case study answers

Case study 137.2

Question 1: Answer D

Case study 137.3

Question 1: Answer C

Multiple choice answers

Question 3: Answer C

Selected reading

Garcia MK, McQuade J, Haddad R, *et al*. Systematic review of acupuncture in cancer care: a synthesis of the evidence. J Clin Oncol, 2013;31(7):952–60.

Golden EB, Lam PV, Kardosh A, *et al*. Green tea polyphenols block the cancer effects of bortezomib and other boronic acid based proteasome inhibitors. Blood 2009;113:5927–37.

Joske DJL, Rao A, Kristjanson L. Critical review of complementary therapies in haemato-oncology. Int Med J. 2006;36:579.

Liu FT, Agrawal SG, Movasaghi Z, *et al*. Dietary flavonoids inhibit the anticancer effects of the proteasome inhibitor bortezomib. Blood 2008;112:3835–46.

National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: cancer-related fatigue, version 1. 2012. Available from: http://www.nccn.org

CHAPTER 138

Naturopathic medicine in oncology

Christina M. Shannon[1], Tracey Thomas[1], and Shauna Birdsall[2]

[1]Cancer Treatment Centers of America, Zion, IL, USA
[2]Cancer Treatment Centers of America, Goodyear, AZ, USA

Integrative oncology is the use of conventional medicine along with evidence-based complementary therapies. Conversely, the use of the term "CAM," which stands for complementary and alternative medicine, is often used to represent a wide variety of therapies, both proven and unproven. CAM may represent alternative therapies that patients choose instead of, as well as, those combined with conventional care. In an oncology setting, naturopathic medicine is used as part of an integrative approach to oncology. The medical training of a naturopathic doctor allows them to play an important role in integrative oncology as their training includes extensive education in nutrition, the proper use of nutraceuticals, botanical medicine, mind–body techniques, and physical medicine.

The importance of an integrative approach is represented in studies showing that patients are using these therapies, often without any medical guidance. According to a survey in 2002 by the National Center for Complementary and Alternative Medicine, 80% of patients with cancer have used an alternative or complementary modality. The most commonly reported therapies were spiritual healing and prayer, herbal medicines, and chiropractic care. Patients report using CAM therapies to improve physiologic and psychosocial well being, because they value the closer relationships possible with CAM practitioners and because they want more control and greater responsibility for self care. Despite their widespread use, most patients did not tell their healthcare provider they were using CAM therapies, and according to a systematic review from 2011, this lack of disclosure was often due to the practitioner's lack of inquiry or the patients anticipating the provider's disapproval.

These studies highlight the importance of an integrative approach to oncology and the role for specialists in integrative medicine. In this chapter, the focus will be on the role of naturopathic medicine in oncology care through the exploration of case examples with an emphasis on botanical medicine.

Case study 138.1

A 52-year-old woman with metastatic breast cancer has been working with her oncologist for one year. She is currently receiving ixabepilone. She is also on gabapentin to control neuropathy and lorazepam for nausea. She finally reveals to her medical oncologist that she has been taking green tea, turmeric, protocel, and alkaline water for 3 months as recommended by her sister who researched them online. She explains that she feels much better since taking them and has more energy. The medical oncologist advises the patient to stop all supplements as he is concerned about interactions. The patient feels very strongly about continuing.

1. What is the role, if any, for naturopathic medicine in oncology?

A. There is no role for natural therapies in mainstream oncology care
B. There is a limited role for therapies like yoga and mind–body medicine, but the data are lacking for most other natural therapies
C. Integrative medicine, combining conventional medicine with complementary therapies for which there is evidence of safety and effectiveness, provides a role for naturopathic medicine in oncology

(*Continued*)

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

There are many misconceptions about the use of naturopathic medicine in oncology care. The most common misunderstanding is how naturopathic doctors approach the management of oncology patients. Naturopathic doctors evaluate oncology patients using criteria very similar to those used by medical oncologists. The management of the patient relies heavily on their diagnosis, performance status, and oncology treatment plan, as well as on other medical comorbidities. Naturopathic doctors also focus on the patient's current use of natural therapies and evaluate those therapies based on safety, level of evidence, appropriateness, potential for drug interactions, and dosing. Naturopathic doctors spend time educating patients and their caregivers on the safe and appropriate use of evidence-based natural therapies. Prior to providing recommendations, naturopathic doctors critically think through the oncology treatment plan, anticipating short- and long-term side effects, in order to recommend specific interventions with data supporting their use. The recommendations for naturopathic side effect management are made within the context of predicting known or even theoretical herb–drug–nutrient interactions, so that any naturopathic intervention is carefully evaluated to ensure both safety and lack of impact on treatment effectiveness. In addition, naturopathic doctors function as a resource to patients and their caregivers in answering questions and teaching them to think critically about complementary and alternative therapies in their cancer care. In the case of this breast cancer patient, the naturopathic doctor involved with the care of the patient would advise against protocel, as there are no data for its use and the risk for adverse effects or interactions is unknown, and would also educate the patient on basic human physiology and acid–base balance in regard to her attempt to "make her body more alkaline" with alkaline water. In regards to the green tea and turmeric, the naturopathic doctor would evaluate the patient's medications and oncology treatment plan, and advise as to whether these supplements are appropriate to take, what the risk might be for interactions, and, if indicated, at what doses they should be taken.

To address the green tea consumption in this case, you would first need to determine if there are herb–drug interactions and then determine whether green tea is indicated in advanced-stage breast cancer.

There are several studies worthy of discussion that looked at green tea and its pharmacokinetics. Ixabepilone, whose primary route of metabolism is oxidation via the hepatic cytochrome P450 (CYP) isoenzyme CYP3A4, may have negative interactions with green tea. In 2009, an in vitro study showed that various brands of green tea inhibited 3A4 from 5.6% to 89.9%. This variability could be due to variations in growing conditions, harvesting, extraction methods, or whether the tea was decaffeinated or caffeinated. Second, there is an in vivo study with mice showing increased teratogenesis when green tea was combined with cyclophosphamide by increasing CYP2B and inhibiting CYP3A4.

However, an in vivo human study in 2006 of 42 healthy volunteers who were given a decaffeinated green tea supplement with 800 mg epigallocatechin gallate (EGCG) for 4 weeks prior to a series of probe drugs were found to have only a small reduction in CYP3A4 activity, resulting in a 20% increase in the area under the plasma buspirone concentration. This study of 42 healthy volunteers is not adequate enough to ensure that the inhibition seen would not interfere with the metabolism of ixabepilone, especially given the in vitro study showing large variations in inhibition with different green tea supplements.

Just as important, however, is the second consideration of whether the addition of green tea would provide benefit in advanced-stage breast cancer, and the data to date does not support its use in this clinical setting. Two studies that were conducted in Japan looked at the correlation of green tea intake with disease recurrence. Both studies indicated benefit in decreased recurrence for those diagnosed with stage I and II breast cancer but no benefit with later-stage disease. These larger studies on green tea and breast cancer have looked at recurrence rates and green tea consumption and have not looked at the use of green tea with late-stage breast cancer. However, given the lack of benefit in recurrence rates for stage III and IV disease, you would anticipate limited benefit, if any, in the case being discussed here. Therefore, in this patient, there is potential for harm with the consumption of green tea supplements and no evidence to indicate benefit.

Based on the above studies combined with the in vitro and in vivo data, there may be a role for green tea in preventing the recurrence of early-stage breast cancer. Research on green tea indicates many areas for potential benefit. The most researched compound in green tea is epigallocatechin-3-gallate (EGCG), and it has been shown to be a powerful antioxidant and to inhibit a number of tumor cell proliferation and survival pathways, including inhibition of metaloproteonases, various protein kinases, and tumor proteasomal activity. It has also been shown to regulate DNA replication and transformation.

Another important application of the use of green tea may be with the treatment of chronic lymphocytic leukemia (CLL). A phase I trial of daily oral polyphenon E with a standardized dose of EGCG was given to patients with asymptomatic RAI stage 0–II lymphocytic leukemia. The results were that one patient experienced a US National Cancer Institute Working Group (NCI WG) partial remission, 33% of patients had a $\geq$20% reduction in absolute lymphocyte count (ALC), and 92% of patients with palpable adenopathy experienced at least a 50% reduction in the sum of the products of all nodal areas during treatment. This is a small study of 33 patients; however, the results are very promising, and a follow-up phase II study showed similar

results. When an oral dose of 2000 mg was administered two times daily to patients with CLL, 69% met the criteria for a biologic response with either a sustained decline ≥20% in the ALC, and/or a reduction ≤30% in the sum of the products of all lymph node areas at some point during the 6 months of active treatment.

2. Is there any role for curcumin in her treatment plan?

A. There is no role for curcumin in the treatment of breast cancer

B. There is interesting in vitro and in vivo research on the role of curcumin in the treatment of cancer, and more research is needed to define its specific role in the treatment of breast cancer

C. Curcumin has only been shown to be effective in prevention of colorectal cancer

Curcumin, from the spice turmeric, is another botanical that has been researched for its potential role in oncology. In vitro and in vivo studies have shown curcumin to modify the expression and activity of many proteins. Proteins affected include inflammatory cytokines and enzymes, transcription factors, and gene products linked with cell survival, proliferation, invasion, and angiogenesis. Curcumin is continuing to be researched due to findings that show that it may have a role in chemoprevention and treatment of several cancer cell types.

In vitro studies of curcumin have indicated that the botanical could have an important role in the treatment of breast cancer. Studies have shown modulation of Wnt/beta-catenin signaling x, downregulation of NF-κB, cyclin D and MMP-1 transcription, and inhibition of the transforming growth factor beta (TGFβ)–Smad and TGFβ–Erk signaling pathway in breast cancer cells. In addition, curcumin was shown to decrease the HER2 oncoprotein, and in a xenograft model the combination of Taxol and curcumin had an antitumor effect comparable with that of Taxol and Herceptin.

When looking at herb–drug interactions, the data on curcumin is mixed. There have been various in vitro and in vivo studies looking at curcumin's effect on pharmacokinetics that have shown either no effect or hepatic inhibition of various CYP450 isoenzymes. Three in vivo rat investigations resulted in enhanced oral bioavailability of the drugs given, and therefore the combination of curcumin and oral chemotherapies or endocrine treatments for breast cancer may have clinically important implications, but further studies are needed. There was a human study in healthy volunteers in 2012 that showed no clinically significant interactions with short-term use (2 days) of a curuminoid–piperine mixture on CYP3A, CYP2C9, or the acetaminophen conjugation enzymes, but this was a very small study with short-term use.

One study of women with breast cancer receiving intravenous chemotherapy of a similarly metabolized agent to ixabepilone included a phase I dose escalation study of docetaxel and curcumin in 14 women with advanced or metastatic breast cancer. The curcumin was given for 7 consecutive days starting on day 4 of the cycle and continuing for six cycles. A curcumin dose of 500 mg to 8000 mg per day was used. The safety profile of the combination was consistent to that of monotherapy alone. Further study is needed to look at the potential for increased response rate with the combination therapy. Other areas to consider with further evaluation of curcumin combined with chemotherapy for breast cancer would be improved antiangiogenic actions and the potential to downregulate P-glycoprotein to decrease drug resistance.

Therefore, further studies are needed to look at the efficacy and safety of using a combination of curcumin with conventional agents to enhance the benefits to women diagnosed with breast cancer and being treated with either chemotherapy or endocrine treatments.

Other promising areas of the application of curcumin in oncology are with multiple myeloma and colon cancer.

There is both compelling in vitro and in vivo data indicating an important role of curcumin in the prevention and treatment of colon cancer. In vitro, curcumin was shown to inhibit the proliferation of human CRC cell lines, potentiate capecitabine-induced apoptosis, inhibit nuclear factor kappa B (NF-kB) activation, and suppress NF-kB-regulated gene products. In nude mice, the combination of curcumin and capecitabine was found to be more effective than either agent alone in reducing tumor volume.

In a phase II clinical trial of curcumin for the prevention of colorectal neoplasia, curcumin showed a 40% reduction in aberrant crypt foci with 4 g per day of oral curcumin for 30 days. Another very small study, but significant given the clinical implications that come with a diagnosis of the autosomal-dominant disorder of familial adenomatous polyposis, showed a 60.4% reduction in number and a 50.9% reduction in size of adenomas with 480 mg of curcumin and 20 mg of quercetin orally 3 times a day after a mean of 6 months of treatment. Finally, a study in China of patients with colorectal cancer showed upregulation of p53 and improved general health with the use of curcumin.

Curcumin may also have an important role in slowing the disease process of multiple myeloma. Given that monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are considered premyeloma conditions, interventions that can slow the process with minimal side effects are important. Two small RCTs, using 4 g of curcumin daily, showed promise with significant improvements in clinical parameters.

(*Continued*)

3. This patient with metastatic breast cancer tells you she wants to start a supplement to "support her immune system." What do you tell her?

A. If she is on a regimen that requires growth factors, you will order Neulasta
B. The immune system plays a role in surveillance prior to the development of cancer, but may not play a role in cancer treatment, albeit for a few cancer types
C. There is some data, although quite limited, on immune stimulating botanicals used in conjunction with conventional cancer treatment that may provide some benefit

Immune function and cancer is a challenging topic, and the implications vary by cancer type. Patients are often focused on "wanting to do something to support immune function," and healthcare providers field questions as to how they can best accomplish this task. There are standard recommendations for prevention of infection, but patients are often drawn to supplements claiming to support or stimulate the immune system. A reasonable approach may be to offer patients options based on data of supplements that at least show some promise in this regard, and are at low risk for interactions or adverse effects. One such supplement is *Coriolus versicolor*, also known as *yun zhi*, a medicinal mushroom with a long history of use in Japan. Evidence indicates that it may function as a biological response modifier and may confer benefits ranging from recovery from immunosuppression induced by humoral factors such as TGFβ or as a result of surgery and chemotherapy, activation of antitumor immune responses including maturation of dendritic cells, correction of Th1–Th2 imbalance, and enhancement of the antitumor effect of chemotherapy by induction of apoptosis and inhibition of metastasis through direct actions on tumor cells. There is also a potential increased survival advantage for patients taking *Coriolus* with standard conventional cancer treatment versus conventional treatment alone. According to a recent meta-analysis, in patients randomized to *yun zhi*, there was a 9% absolute reduction in 5-year mortality. In patients with breast cancer, gastric cancer, or colorectal cancer treated with chemotherapy, the effects of the combination of *yun zhi* preparation on the overall 5-year survival rate was more evident than with other cancer types. *Coriolus* may be a reasonable option for this breast cancer patient to take to support immune function and may confer other benefits as well.

Case study 138.2

A 50-year-old male patient with a stage IV adenocarcinoma of the colon is now on FOLFIRI. He started experiencing depressive symptoms and started St. John's wort. He wants to know your opinion about taking it.

1. What do you tell the patient?

A. Do not take any form of dietary supplements or herbal medicine while on chemotherapy
B. St. John's wort is not a good option, as the risk of drug interactions is too high
C. It doesn't matter what you take as supplements do not have any effect

In general, the challenge with St. John's wort is that it may interfere with up to 50% of all medications. The issue in this particular case is that St. John's wort has been shown in an unblinded, randomized crossover study to decrease the plasma levels of the active metabolite of irinotecan, SN-38, by 42% due to induction of CYP3A4. The more global challenge is that the combined use of botanical therapies and chemotherapy may increase or decrease the effects of chemotherapy, leading potentially to greater toxicity or treatment failure. Most known drug–herb interactions are pharmacokinetic in nature and are due to changes in metabolic routes related to altered expression or functionality of cytochrome P450 (CYP) isoenzymes, but interactions can also take place via P-glycoprotein and glucuronosyltransferases (UGTs). Induction and inhibition of these enzymes and transporters are considered important mechanisms for herb–drug interactions. Pharmacodynamic interactions can also take place, although they are not as common. Further complicating the issue, individual botanicals, unlike synthetic drugs, are a mixture of structurally diverse compounds and are subject to growing conditions and harvesting and extraction methods; therefore, active constituents can vary widely from batch to batch of the same herb, which can affect both bioavailability as well as interaction potential. A good understanding of the mechanisms of herb–drug interactions is essential for clinical risk assessment and is vital to minimize risk, as well as to ensure that taking herbal medicines is as safe as possible.

Case study 138.3

A 52-year-old female with a locally advanced gastric adenocarcinoma is status post gastrectomy and is currently receiving weekly chemotherapy with carboplatin, paclitaxel, and concurrent radiation. She reports severe nausea and decreased dietary intake. She is compliant with her antinausea medication. She asks her naturopathic doctor, "Are there any botanicals that I can take to decrease nausea?"

1. Which of the following botanicals would be helpful to decrease chemotherapy-induced nausea?

A. Curcumin
B. Milk thistle
C. Ginger
D. All of the above

Seventy percent of patients receiving chemotherapy report compliance with their antiemetic medication, and they continue to experience symptoms of nausea. Ginger root (*Zingiber officinale*) is well known for its ability to decrease nausea associated with pregnancy and motion sickness. Evidence demonstrating its efficacy for chemotherapy-induced nausea and vomiting has been mixed. A phase II trial reported that ginger provides no additional benefit for reduction of the prevalence or severity of acute or delayed chemotherapy-induced nausea and vomiting. However, a recent multicenter clinical trial conducted over 6 years with 576 cancer patients reported that ginger supplementation at a daily dose of 0.5–1.0 g significantly reduced the severity of acute nausea in adult cancer patients receiving chemotherapy. Additionally, another study demonstrated that combining ginger with a high-protein meal not only reduced the delayed nausea of chemotherapy but also decreased the patient's use of antiemetic medications. Ginger has anti-inflammatory and antispasmodic activity, and these actions may be a possible explanation for its ability to decrease nausea. Research shows that antiemetic medications, 5-HT receptor antagonists, are more effective with emesis than decreasing nausea. Thus, ginger may be considered a safe and effective complement to antiemetic therapy through its antinausea properties.

As the cases discussed in this chapter indicate, there is an important role for integrative oncology. The role of naturopathic medicine in integrative oncology is to help patients navigate the conflicting information on natural therapies and use these therapies safely and effectively. Naturopathic doctors work with patients to avoid herb–drug–nutrient interactions, manage side effects, improve quality of life, potentially improve response to treatment, prevent recurrence, and empower patients through education and options.

Case study answers

Case study 138.1

Question 1: Answer C
Question 2: Answer B
Question 3: Answer C

Case study 138.2

Question 1: Answer B

Case study 138.3

Question 1: Answer C

Selected reading

Carroll RE, Benya RV, Turgeon DK, *et al*. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res (Phila). 2011 Mar;4(3):354–64.

Golombick T, Daimond TH, Manoharan A, *et al*. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. Am J Hematol. 2012 May;87(5):455–60.

Shanafelt TD, Call TG, Zent CS, *et al*. Phase I trial of daily oral polyphenon E in patients with asymptomatic Rai stage 0 to II chronic lymphocytic leukemia. J Clin Oncol. 2009 Aug 10;27(23):3808–14.

CHAPTER 139

Anesthesiology consultation for localized cancer pain

Abed Rahman[1], Magdalena Anitescu[2], and Raed Rahman[1]

[1]Cancer Treatment Centers of America, Zion, IL, USA
[2]University of Chicago Medical Center, Chicago, IL, USA

Case study 139.1

A 54-year-old male with advanced pancreatic cancer reports severe epigastric pain radiating to his middle back, worsening over the last 2 months. His pain score is 9/10, and he describes it as aching and throbbing, with sharp intermittent episodes. He has tried oxycontin and oxycodone with minimal analgesia, and has noticed severe mental sluggishness. He was rotated to morphine immediate release and extended release with intolerable mental sedation and poor analgesic control. He feels his quality of life is poor and is being referred to a psychiatrist for anxiety and depression. He dislikes opioids and their side effects.

1. Which of the following pain management options is appropriate for this patient?

A. Rotating to another opioid; hydromorphone short and long acting
B. Start acetaminophen 500 mg every 8 hours for analgesia
C. Start amitryptyline 25 mg every evening for depression
D. Evaluate the patient for a celiac plexus block
E. Hold off on further pain management changes until the psychiatric evaluation is complete

Epigastric pain is common in patients with pancreatic cancer. If the adverse effects of opioids are intolerable or escalating doses are ineffective for analgesia, a celiac plexus block can be beneficial. Pancreatic cancer can cause severe pain in up to 70% of patients and can be difficult to treat. A celiac plexus block can be effective technique for reducing the pain severity for up to 1 year if a destructive neurolytic agent (95% alcohol or 6% phenol) is used. The celiac plexus innervates the distal esophagus, stomach, duodenum, liver, and pancreas. Rotating to hydromorphone and escalating doses will take days to weeks, and this patient is not interested in further opioids. The most common side effect is temporary pain or soreness at the injection site. Uncommon risks involve bleeding, infection, spinal block, epidural block, collapsed lung, and injection into blood vessels and surrounding organs. Patients should not have this block if they are allergic to any of the medications being injected, if the patient is on blood-thinning medications, if the patient has an active infection, or if the patient has poorly controlled diabetes or heart disease (Figures 139.1 and 139.2).

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

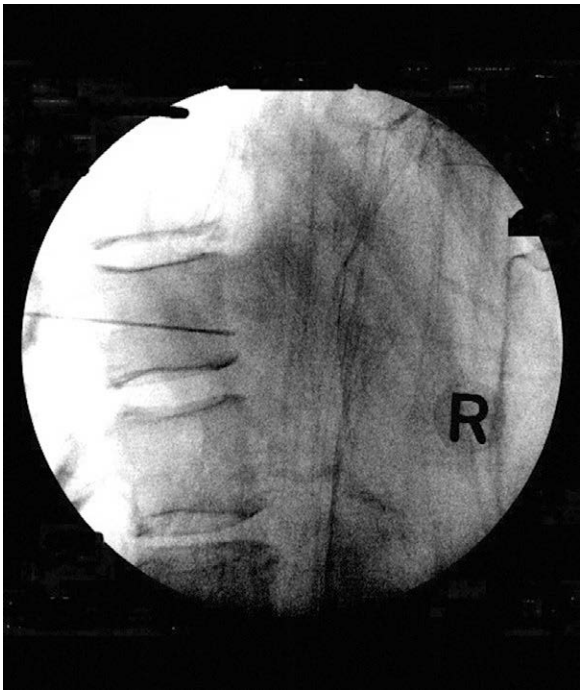


Figure 139.1 Celiac plexus block needle tip anterior to the L1 vertebral body prior to contrast being injected.

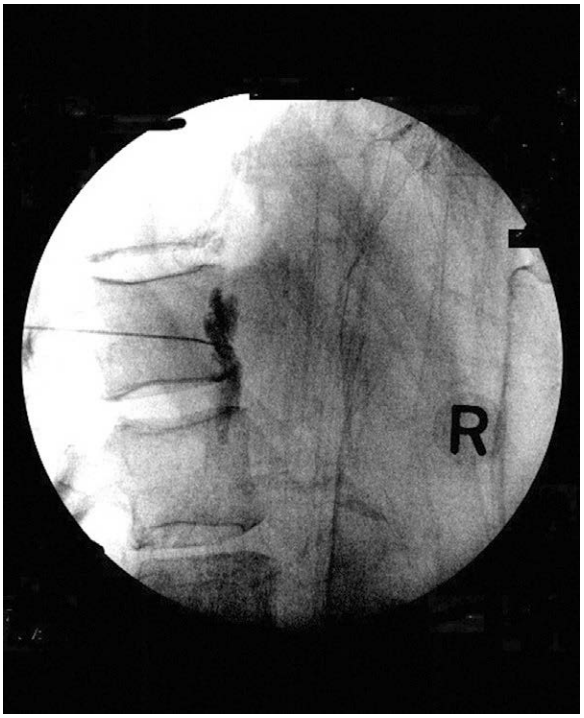


Figure 139.2 Celiac plexus block needle tip anterior to the L1 vertebral body after contrast was injected.

Case study 139.2

A 34-year-old female with colon carcinoma complains of moderate to severe abdominal pain, worsening over the last week. Her pain is located at her right upper quadrant with radiation to her right thoracic spine area. She is currently on methadone 10 mg every 12 hours and morphine immediate release 30 mg every 2 hours for pain control. An updated CT abdomen and pelvis study shows new metastatic lesions to her liver, with encroachment on the liver capsule.

1. Which of the following pain management options is indicated?

A. Rotate her morphine to codeine for improved analgesia
B. Start acetaminophen 1000 mg orally every 4 hours
C. Consult a palliative medicine specialist for hospice admission
D. Start Lyrica 150 mg orally four times daily
E. Start ibuprofen 800 mg orally every 8 hours

Starting an anti-inflammatory, non-opioid medication for liver capsular pain is appropriate. The type of pain described is primarily inflammatory in its nature and can be effectively controlled with a nonsteroidal anti-inflammatory drug (NSAID). NSAIDs produce analgesia by inhibiting the enzyme cyclogenase, COX, and they reduce the production of peripheral and central prostaglandins. The two main isoforms are COX1 and COX2, which are involved in physiologic function and inflammation. Opioid rotation from a strong opioid (morphine) to a mild opioid (codeine) will not help with liver capsular pain. Acetaminophen is an analgesic for mild pain and has limited (if any) anti-inflammatory properties. The patient is having nociceptive visceral pain for a few days, and is not at the end of her life and thus requiring admission to a hospice program. The pain is not neuropathic; therefore, Lyrica would not be effective.

Case study 139.3

A 45-year-old male with locally advanced sarcoma to his right leg had an amputation of his right leg below the knee 2 months ago. He complains of sharp, burning, constant sensations to his right toes. He thought this was normal after surgery and would get better, but now he is refusing rehabilitation therapy due to the pains. He is married with children and is unable to work through the pains as a postal carrier, although he wants to get back to work as soon as possible.

1. How would you classify this patient's pain?

A. Stump pain
B. Phantom limb pain
C. Central pain
D. Malingering
E. Postsurgical pain

Chronic pain following limb amputation may involve stump pain, phantom pain, or both. Phantom limb pain can result from loss of limb due to cancer, trauma, vascular disease, or infection. More than 50% of patients report phantom limb pain syndrome. Of those, up to 10% experience severe and debilitating pain, primarily neuropathic, often as burning, tingling, and numbness distal to the site to the amputation. Stump pain may be due to a neuroma formation several months after the amputation, and is pain at the site of the actual amputation. Central pain results from damage to the central nervous system and reorganization of the transmitting pathways. Malingering is exaggerating an illness for secondary gain. Postsurgical pain is acute and is present in the immediate postoperative period.

Case study 139.4

A 55-year-old female with a history of breast carcinoma started complaining of severe pelvic pain over the last 3 months. She had imaging of her abdomen and pelvis that showed new metastatic lesions to her cervix. She is undergoing chemotherapy and radiation therapy, with a minimal decrease in her pain severity. She has never taken opioids and refuses to take them. She is not able to tolerate lying on the radiology suite table for further radiation treatments. Her radiation oncologist refers her to the pain management service for assistance.

1. Which of the following pain management options is appropriate for this patient?

A. Evaluate the patient for a celiac plexus block
B. Evaluate her for a lidocaine infusion trial
C. Start duloxetine 30 mg twice daily
D. Start fentora 100 mcg every 6 hours, as needed, for severe pain
E. Evaluate the patient for a superior hypogastric plexus block

Superior hypogastric plexus blocks may be used for visceral pelvic pain that is refractory to medical management (Figures 139.3 and 139.4). The superior hypogastric plexus lies in the retroperitoneum and extends from the anterior aspect of L5 to the superior portion of the sacrum. Female pelvic pain can be adequately treated with this block. The superior hypogastric pelvic nerves innervate the lower abdomen and pelvic organs. A celiac plexus block would be useful in malignancies arising from upper abdominal viscera such as the esophagus, stomach, and liver. A lidocaine infusion and duloxetine are primarily for neuropathic pain conditions, and they have fewer efficacies in visceral nociceptive pain syndromes. This patient is opiate naïve and should not be started out on fentora, and her fear of taking opioids for analgesia should be further investigated. The most common side effect is temporary pain or soreness at the injection site. Uncommon risks involve bleeding, infection, spinal block, epidural block, collapsed lung, and injection into blood vessels and surrounding organs. Patients should not have this block if they are allergic to any of the medications being injected, if the patient is on blood-thinning medications, if the patient has an active infection, or if the patient has poorly controlled diabetes or heart disease.

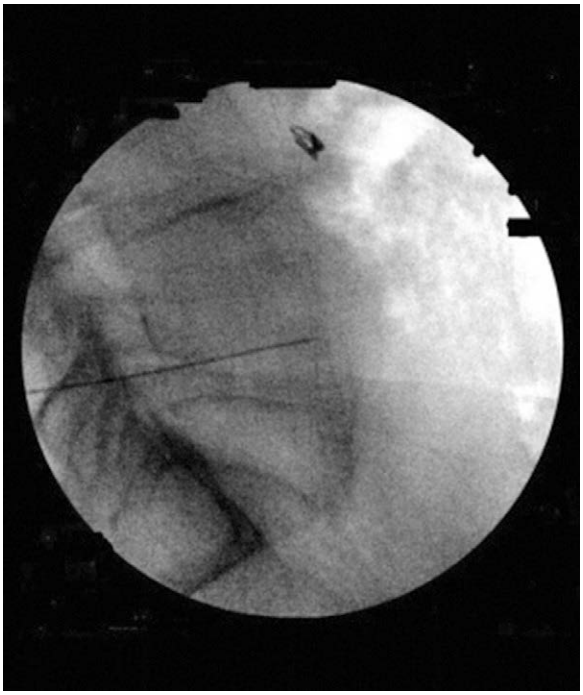


Figure 139.3 Superior hypogastric plexus block needle tip anterior to the L5 vertebral body prior to contrast being injected.

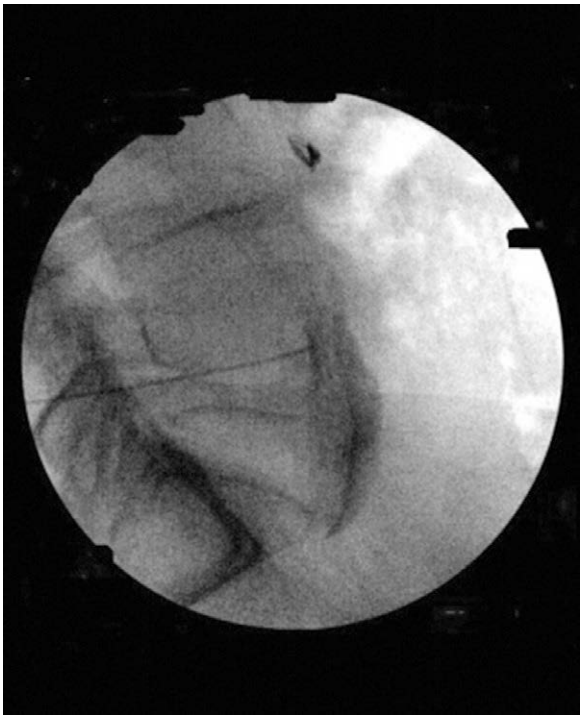


Figure 139.4 Superior hypogastric plexus block needle tip anterior to the L5 vertebral body after contrast was injected.

Case study 139.5

A 44-year-old man with rectal carcinoma undergoes a left bowel resection and is started on a morphine PCA with continuous, demand, and clinician doses for postoperative pain on the surgical-medical floor. The following morning, he is found asleep, arousable to deep physical stimuli with a respiratory rate of 6 breaths per minute. His oxygen saturation on room air is 95%, his heart rate is 88, and his blood pressure is 128/74. The patient's family is satisfied with his level of pain control, but is concerned that he has a difficult time waking up after sleeping for the last 20 hours.

1. Which of the following steps is appropriate?

A. Prepare for an emergent intubation, and notify the intensive care unit

B. Continue to monitor the patient, and inform the family that this is adequate analgesia

C. Administer diluted naloxone intravenously until his respiratory rate and level of consciousness improve

D. Administer multiple doses of naloxone intravenously, 1.0 mg, to reverse his sedation

E. Discontinue his morphine PCA, and wait for him to wake up

Naloxone is indicated when a patient is difficult to arouse, has shallow respirations, or has a respiratory rate of less than 8 breaths per minute. If the patient awakens to verbal stimuli or light physical stimuli, the patient is sleeping and has well-controlled postoperative pain. Intubation is not the first option in a hemodynamically stable patient who is arousable and appears sedated. Simply monitoring this patient with no changes in his care plan can lead to further respiratory depression and respiratory arrest. Administering a full dose of naloxone, 0.4 mg or more, can result in complete reversal of sedation symptoms, severe pain, and possible pulmonary edema from sympathetic overflow and dislodgement of the opioids from the receptors. Discontinuing all opioids is not appropriate after an extensive operation and will result in uncontrolled postsurgical pain.

Case study 139.6

A 35-year-old female with advanced liver carcinoma with metastasis to her right thigh has poorly controlled abdominal and right leg pains. She reports her right upper abdominal pain as squeezing and aching, and her right thigh pain as shooting and numb-like. Her pain score ranges from 5/10 to 10/10. She has been taking ibuprofen 800 mg every 6 hours for analgesia. In the ER, she is found to have thrombocytopenia and an elevated international normalized ratio.

1. Which of the following medications is appropriate for her pain control?

A. Stop the ibuprofen and start methadone
B. Continue her ibuprofen
C. Add acetaminophen
D. Add dexamethasone
E. Stop ibuprofen and start aspirin

Methadone is a mu opioid receptor agonist and an NMDA receptor antagonist. This patient has nociceptive and neuropathic pain and would benefit from an opioid with mixed pain mechanisms of action such as methadone, which can prove its value in multiple pain syndromes. NSAIDs and aspirin products should be avoided in patients with elevated bleeding risks. Acetaminophen is safe in low doses, 2 g per day, but is usually avoided in patients with liver failure. Steroids may worsen the risk of bleeding in this patient and should be avoided.

Case study 139.7

A 56-year-old female, admitted with metastatic renal carcinoma and abdominal pain, is on long-acting morphine 240 mg every 12 hours, and 60 mg of immediate-release morphine every 4 hours for pain. Over the weekend, her hospitalist increases her long-acting morphine, due to worsening pain, to 300 mg every 8 hours. On Monday morning, as you are rounding with the pain team, the day shift nurse informs you that the patient's pain was poorly controlled last night and she started having twitching of her extremities this morning. The patient is awake during the twitches and considers them annoying.

1. Which of the following is likely causing the patient's complaints?

A. General seizure disorder
B. Panic attack
C. Opioid addiction
D. Major depression
E. Myoclonic jerking

Patients on high-dose opioid therapy begin to have myoclonic jerking from opioid metabolite accumulation. This patient had a recent increase in her opioid dosing. Myoclonus is an uncontrollable spasm of muscle groups in either upper or lower extremities. It is a common dose-related effect of opioids that can be associated with mental clouding and somnolence. A patient experiencing a grand mal seizure should have loss of consciousness. Panic attacks, major depression, and opioid addiction are not suggested by this history.

Case study 139.8

A 49-year-old woman with endometrial cancer with metastasis to her bones was admitted for poor pain control. She takes oxycodone controlled-release 80 mg orally (po) every 12 hours and oxycodone immediate release 10 mg po every 4 hours as needed for breakthrough, for her chronic, severe, low-back pains. On the floor, she complains of 10/10 sharp, aching pain in the spine and hips bilaterally. On admission, she was given escalating doses of morphine to lower her pain from 10/10 to 9/10. On the second day of admission, she has her morphine doses doubled, but the pain is only lowered to 8/10. On hospital day number 3, she has her morphine doses doubled again to improve her pain control. By the late afternoon, she complains of severe back pain at 20/10, and states her pain is worse than ever before. She states her pain is all over her body. At the bedside, the physical exam reveals a thin, anxious patient constantly moaning and screaming out. Cardiac exam is significant only for tachycardia; her lung fields are clear; her abdominal exam is benign; she is able to move all her extremities.

1. Which of the following treatments is best for her?

A. Call a psychiatry consult
B. Increase her morphine
C. Add toradol
D. Rotate to another opioid, hydromorphone
E. Continue to observe the patient

This patient is experiencing opioid-induced hyperalgesia (OIH). OIH is a state of nociceptive sensitization that is caused by exposure to opioids. This state is characterized by a paradoxical response where the patient receiving opioids for analgesia may actually become more sensitive to painful stimuli. Opioid rotation to another opioid may reduce or eliminate the opioid neurotoxic side effects. Option A is incorrect. Calling a psychiatry consult for her anxiety may be useful later, on but she is obviously in pain and an increase in her medication only makes her pain worse. She needs her analgesia effectively managed. Option B is incorrect, because morphine is the cause of her opioid-induced hyperalgesia. Option C is incorrect, because toradol may help with the somatic pain, but it will not decrease the effect of the central pain crisis from her OIH.

Case study 139.9

A 30-year-old female with locally advancing and infiltrating ductal carcinoma breast cancer started having bilateral feet pains after starting chemotherapy 2 months ago. She has gone to a chiropractor and has had spinal manipulation with no pain relief. She has seen a massage therapist, which felt good for her back and legs temporarily, but did not relieve the pain. She is contemplating stopping her chemotherapy due to her severe feet dysesthesias.

1. This pain may be due to which of the following adverse effects of cancer therapies?

A. Neuropathic pain
B. Nociceptive pain
C. Psychosomatic pain
D. Tolerance
E. Hypoalgesia

Cancer therapies can include anticancer and cancer symptom medications. Surgery, radiation, and chemotherapy can alter tissue and cause pain. Neuropathic pain is pain that occurs following injury to nerves in the somatosensory nervous system. These nerves are not functioning normally. Thus, neuropathic pain results from damage to or pathology within the nervous system; it can be central or peripheral. Chemotherapy for breast cancer frequently causes peripheral neuropathic pain. Option B is incorrect due to nociceptive pain being pain arising from damage to nonneural tissue, and being a normal function of the somatosensory nervous system. Option C is incorrect; psychosomatic pain is pain due to mental, emotional, or behavioral factors. Option D is incorrect. Tolerance to opioid analgesics is a diminished analgesic effect that occurs after chronic exposure to a drug, necessitating larger doses to maintain the same analgesic effect. Option E is incorrect. Hypoalgesia is a diminished pain in response to a normally painful stimulus.

Case study 139.10

A 54-year-old woman with metastatic liver carcinoma recently received a pain pump in the hospital. The patient had suffered for months with severe abdominal pains, and was poorly responding to escalating doses of opioids and nonopioids. The patient was frequently admitted to the hospital for pain control.

1. Which of the following options is a potential complication of intrathecal opioid analgesia?

A. Frequent dose changes
B. Increased constipation
C. Frequent pump refills
D. Increased break through pain medication usage
E. Granuloma formation

Formation of inflammatory masses at the intrathecal catheter tip is rare, and it can complicate intrathecal opioid administration. Intrathecal opioid therapy is an effective way to provide large doses of opioid analgesics directly to the central nervous system. In this way, much smaller doses of opioid analgesics are required, and it does not need to pass through the blood–brain barrier. Due to the small doses required for analgesia, pumps are refilled an average of every 3–6 months. Side effects are less than with oral or parenteral medications, and fewer breakthrough doses are required. Some complications of intrathecal therapy can occur, such as infection, catheter migration, dislodgement, granuloma formation, and lower-extremity numbness.

Case study 139.11

A 60-year-old woman with lung carcinoma with metastasis to her kidneys has had increasing low back pain for the past 3 months. She had an intrathecal pain pump placed 1 year ago for worsening malignant pain. Her pump solution has morphine at 15 mg/ml. Over the past 3 months, her intrathecal infusion is increased from 4 mg/day to 8 mg/day with no improvement in pain control and a slight decrease in bilateral lower extremities, more on the right. A contrast dye study revealed the system to be functioning normally. The tip of the intrathecal catheter is visualized at the level of T9.

1. What is the next step in management of this patient's pain?

A. Increase in her morphine concentration solution to 20 mg/ml
B. Order an MRI of the thoracic spine
C. Increase her infusion rate to 12 mg/day
D. Referral to a psychiatrist
E. Evaluate for OIH

A complication of intrathecal opiate infusion involves the formation of granuloma at the tip of the catheter. Granuloma formation is related to the amount, concentration, and duration of intrathecal opioids. If the granuloma is not stopped from accumulating, it can result in spinal cord or nerve root compression. Formation of inflammatory masses at intrathecal catheter tips can complicate intrathecal opioid administration. To decrease the risk for intrathecal granuloma formation, the concentration of morphine in the intrathecal pumps should be kept to the lowest possible dose; therefore, increasing the concentration would not be the answer in this situation. Increasing the infusion to 12 mg/day will only treat the symptoms but will not provide an answer for why this patient has increased back pain. Both D and E are possible answers but are not the first options given the patient's new-onset neurological symptoms and ineffective pain control.

Case study 139.12

A 55-year-old male is undergoing a diagnostic celiac plexus block for gastric carcinoma causing severe abdominal pain. During the procedure, 0.25% bupivicaine with epinephrine is used as the diagnostic test solution. The patient begins to complain of a sour taste in his mouth and ringing in his ears. Shortly thereafter, he stops speaking and is unresponsive to verbal and tactile stimuli.

1. What is the most appropriate medication to administer at this moment?

A. A lipid emulsion bolus
B. Ammonia smelling salts
C. Morphine bolus
D. Rocoronium bolus
E. Lidocaine bolus

This patient is having local anesthetic systemic toxicity (LAST) from intravascular injection of bupivicaine. Intravenous lipid emulsion is an effective treatment for LAST. The lipid emulsion provides an expanded intravascular lipid phase that can drive the offending drug from target tissues into the newly formed lipid reservoir. Lipid emulsion therapy is gaining acceptance in emergency rooms and other critical care areas as treatment for local anesthetic toxicity. Ammonia smelling salts will not reverse the effects of the bupivicaine toxicity. Rocoronium is a muscle relaxant, morphine an opioid analgesic, and lidocaine a local anesthetic, and they are not treatment options for local anesthetic toxicity.

Case study 139.13

A 62-year-old woman with metastatic gall bladder carcinoma is taking sustained-release morphine every 12 hours with a total daily dose of 300 mg, with good pain control. She has been having severe nausea and vomiting over the last few days, is refractory to anti-emetics, and has to be converted to intravenous morphine.

1. What is the correct dose of intravenous morphine equivalent to the current dose of sustained-release morphine for this patient?

A. 75 mg daily IV morphine
B. 100 mg daily IV morphine
C. 150 mg daily IV morphine
D. 200 mg daily IV morphine
E. 300 mg daily IV morphine

The conversion of oral to parenteral morphine is 3:1. For example, 30 mg of oral morphine is equal to 10 mg of IV morphine. 300 mg of daily oral morphine consumption is equal to 100 mg of IV morphine over a 24-hour daily period. But keep in mind to decrease the 100 mg of IV morphine to 25–50% for incomplete cross-tolerance. The final morphine intravenous daily dose range is between 50 and 75 mg. Incomplete cross-tolerance relates to tolerance to a currently administered opiate that does not extend completely to other opioids. This will tend to lower the required dose of the second opioid. This incomplete cross-tolerance exists between all of the opioids, and the estimated difference between any two opiates could vary widely. There are inherent dangers of using an equal-analgesic table and the importance of viewing the tabulated data as approximations. Many experts recommend, depending on age and prior side effects, reducing the dose of the new opiate by 25–50% to account for this incomplete cross-tolerance. This new regimen can then be re-titrated to patient response. Repeated comprehensive assessments of the patient's pain are necessary in order to successfully control the pain while minimizing side effects.

Case study answers

Case study 139.1

Question 1: Answer D

Case study 139.2

Question 1: Answer E

Case study 139.3

Question 1: Answer B

Case study 139.4

Question 1: Answer E

Case study 139.5

Question 1: Answer C

Case study 139.6

Question 1: Answer A

Case study 139.7

Question 1: Answer E

Case study 139.8

Question 1: Answer D

Case study 139.9

Question 1: Answer A

Case study 139.10

Question 1: Answer E

Case study 139.11

Question 1: Answer B

Case study 139.12

Question 1: Answer A

Case study 139.13

Question 1: Answer A

Selected reading

Arcidiaconon, PG, Giliola C, Carrara S, *et al*. Celiac plexus block for pancreatic cancer in adults. Cochrane Database of Systems Review. 2011;(3):CD007519.

Eisenberg E, Berkey CS, Carr DB, *et al*. Efficacy and safety of nonsteroidal anti-inflammatory drugs for cancer pain: a meta-analysis. J Clin Oncol. 1994;12:2756.

Halbert J, Crotty M, Cameron ID. Evidence for the optimal pain management of acute and chronic phantom pain: a systemic review. Clin J Pain. 2002;18:84.

Lema, MJ. Invasive procedures for cancer pain. Pain: Clin Updates. 1998;6:1.

World Health Organization. Cancer pain relief, 2nd ed. Geneva: World Health Organization; 1996.

CHAPTER 140

Musculoskeletal care in oncology

James E. Rosenberg[1] and Charles A. McDonald[2]

[1]Cancer Treatment Centers of America, Goodyear, AZ, USA
[2]Cancer Treatment Centers of America, Zion, IL, USA

1. When and why should an oncology patient be evaluated by a chiropractic physician?

Chiropractic was founded in 1895 and has evolved into a profession that now has more than 60,000 licensed chiropractors in the United States and thousands more worldwide. If there is one word that describes both the public's and other healthcare providers' understanding of chiropractic, it would have to be "confusion." All 50 states license chiropractors, but each state has its own set of laws. Our purpose in this chapter is to address the most commonly accepted aspects of the science, art, and philosophy regarding chiropractic efficacy.

Our approach to answer the questions in this chapter will be where chiropractic is being incorporated into a plan of care that is integrated and where the chiropractor is treating the musculoskeletal and biomechanical deficiencies that commonly occur in all patients but especially in the oncology patient.

So, what is a chiropractic adjustment and how could it benefit an oncology patient? We are going to focus on key benefits that come from treatment to the musculoskeletal system, paying extra attention to the spine. Since its beginning, chiropractors have been saying that besides pain or joint relief, the adjustment can have a direct effect on the nervous system by relieving pressure on a nerve. Not only have we been saying it, but also we have been experiencing or witnessing these benefits personally and professionally with our patients. We have been right all along that the adjustment was affecting the nervous system, but wrong about how it was actually happening. Relieving direct pressure off of a spinal nerve is old school thinking and inaccurate. The current understanding is that joint complex dysfunction creates neuropathologic effects that have been termed "dysafferentation." Nociceptors and mechanoreceptors are the two main types of sensory nerve receptors involved. Potential outcomes of nociceptive input to the spinal cord include pain, autonomic symptoms, vasoconstriction, and muscle spasms. There are other mechanisms involved, but our point is that chiropractic does have a beneficial effect on the nervous system. We like to call it a "quieting of the nervous system" so the body can focus on more important things. Certainly this is a complicated topic and not the primary purpose of this discussion. However, we do want to point out that there is ongoing and mounting evidence that explains the clinical results we see from chiropractic treatment to our patients.

The results of a study in 2005 of patients with moderate to severe musculoskeletal pain ranked chiropractic the highest in pain relief over nerve blocks, narcotics, muscle relaxants, massage, acupuncture, and OTC pain medications.

Oncology patients typically tell us that after a chiropractic adjustment they feel better, have more energy, have a general sense of well-being, sleep better, and can't wait to have another treatment.

If whole person care is the goal, then we feel there is enough potential benefit for any patient diagnosed and being treated for cancer to at least be evaluated by a chiropractor physician to see if chiropractic treatment is indicated. These benefits will improve the patient's quality of life, which should be one of the goals of any treatment plan.

2. What role does the chiropractor play in treatment of an oncology patient?

Oncology patients, at all stages of the disease, are very likely to suffer from neuromusculoskeletal pain and dysfunction. The discovery of the cancer and the subsequent

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

anxiety in itself will cause joint swelling and muscle spasm moderated through the body's natural stress reaction mechanisms. This increases pain and dysfunction.

Musculoskeletal deconditioning is common and accelerated through decreased activity from pain, anxiety, and chemotherapy side effects including pain, nausea, lack of appetite, and decreased energy. Fibrotic changes to normal muscle tissue from radiation therapy also commonly result in musculoskeletal dysfunction.

In another study, David Chapman-Smith (based in Canada) cited low-back pain as the leading cause of disability worldwide, with 80% of the population at some point suffering from severe, debilitating low-back pain. If we add all of the above factors to the oncology patient, then there is increased probability of musculoskeletal pain, which becomes a limiting factor in the patient's ability to travel, ambulate, or tolerate further therapy.

Lack of exercise has been shown, in a recent article published in a physical therapy journal, to increase estrogen levels, which obviously is a factor in numerous cancers.

Chiropractic is, by definition and law, both nonsurgical and without prescription drugs. We are, however, very effective at reducing pain and restoring the patient's physical status. To do so without risking undesirable interaction between pain medications and other medications that the patient needs is to the advantage of the patient and the medical doctor alike. It has been our experience that adding conservative treatments and therapies to the arsenal, which have very little risk when performed by skilled practitioners, is invaluable.

Beyond pain relief and restoration of mobility, numerous studies have shown spinal manipulation to have other general health benefits. Several published studies have documented the benefits of spinal manipulation for hypertension, asthma, and antibody production. Although we are not suggesting that patients should view these as replacements for traditional medical treatment for these conditions, the fact that spinal treatment has created benefit to visceral function is certainly a desirable side effect.

Schneider and Gilford (2001) stated that "the chiropractor provides noninvasive and non-pharmacologic options for decreasing pain and improving function. Chiropractic care can enhance a cancer patient's quality of life at any stage in the disease process by decreasing pain and improving function."

Physical therapy, occupational therapy, massage, acupuncture, light stretching or yoga, and chiropractic are all therapies that could be of tremendous benefit. These benefits include improved quality of life, management of treatment side effects, improved conditioning, an increased likelihood of the ability to stay on a cancer treatment schedule, and even improved self-confidence and hope.

3. What are the common side effects of chemotherapy, radiation therapy, and even surgery in the oncology population that could possibly be helped by chiropractic?

One of the main concerns for all oncologists is the management of the side effects of the various cancer drugs and treatments. There is constant attention to the risk–reward aspect and quality-of-life issues. Let's explore some of the common things we see.

Nausea, fatigue, peripheral neuropathy, headaches, and joint pain are common side effects of chemotherapy drugs. There are many other side effects, like hair loss, appetite issues, depression, xerostomia, and cognitive dysfunction. We are going to focus on the symptoms that our experiences have shown can be more directly affected by a mechanical intervention like chiropractic.

Radiation treatment can result in many of the same side effects listed in the previous paragraph. Radiation can also cause muscle tissue fibrosis, which can then cause pain, muscle weakness, decreased range of motion, joint dysfunction, and even pronounced gait problems. Patients that have any radiation burns or skin issues will be reluctant to move that body part.

Postsurgical patients come with their own unique common challenges. The more obvious issue is immobility during recovery, which, depending on the surgery, could be for a long time. In many cases, there are necessary follow-up surgeries that further delay the restoration of normal body movement and function. Many cancer surgeries result in removal of some muscle tissue or even bone.

It is also important to note that some patients undergoing chemotherapy will have to sit or at least stay in relatively inactive positions for hours during infusion. These postures can also cause tension and tightness, resulting in functional abnormalities.

Many of these situations will result in the patient needing ambulation assistance from a cane, a walker, or even a wheelchair, all of which create more stress to the musculoskeletal system.

We would like to share two examples:

A breast cancer patient who was scheduled to begin her radiation treatments on a Monday morning developed left neck and shoulder pain the day before and couldn't raise her arm at all. Chiropractic evaluation and treatment were successful in regaining her ability to put her arms over her head and stay on schedule.

Another example is a head and neck cancer patient who could not open his mouth more than one finger's width after eight of 32 radiation treatments. A chiropractic adjustment was performed to the cervical spine and the temporomandibular joints. This achieved immediate results, and the patient could now open to three fingers' width, allowing him to continue to eat normally.

As we have discussed, chiropractic intervention before, during, and after all of these circumstances is critical for an

improved outcome and improved quality of life (QOL) for the patient.

Schneider and Gilford (2001) concluded in their study that the chiropractor can assist in the treatment of the complications of prolonged bed rest, chronic pain related to radiation fibrosis, chemotherapy-related neuropathies, and gait or functional abnormalities, thereby decreasing the patient's reliance on pain medication.

4. What are the common challenges or special issues that the treating chiropractor needs to consider in a patient with cancer?

It is just as important to know what we can't do as what we can for a patient with cancer. Knowing the type and primary location of a patient's cancer is just the tip of the iceberg. The chiropractor must know if there any metastases, paying special attention to whether there are any bone metastases. We must also know of any soft tissue masses as well as lymph node involvement. Has the patient received radiation therapy that has possibly changed the density and overall health of bone tissue in the treatment field? Do they have a low platelet count? As a treating chiropractor, these considerations apply regardless of technique. We have years of experience in treating the cancer population, and it is irresponsible to not know everything pertinent about the patient on our treatment table.

Positron emission tomography (PET), magnetic resonance imaging, computed tomography, plain film, and bone scans are some of the likely tests that have been performed on the patient. We also suggest getting their latest bloodwork and paying attention to the platelet count. We do not treat if it is below 50,000, to avoid bruising. We do not treat an extremity with a thrombosis. We do not treat if there is cord compression from a space-occupying lesion. It is also our recommendation to avoid manual adjusting within five spinal segments of any primary bone lesion or unstable bone metastases. Ribs are quite common for metastases, so pressure on the thoracic or lumbar spine must be delicate and performed with a high level of skill. If a mechanical instrument technique is utilized, we have been able to treat within two segments.

Collaboration with all other providers, including physical therapy, occupational therapy, and speech therapy, will avoid duplicating treatment and overstressing the patient's body. Understanding the potential side effects of the patient's medications can be important in planning the patient's chiropractic care. Numerous medications cause bone, muscle, and joint pain and cause neuropathy, which would affect the patient's gait.

Thorough collection of all historical data on our patient has served to promote patient confidence in the chiropractor and improved outcomes.

5. A 50-year-old female with metastatic breast cancer to L5 and the sacrum, who has bone density loss in the thoracic spine from radiation therapy, presents to you complaining of pain in the upper left back and the lower right back. Are there any chiropractic adjustment options?

After a thorough consultation, records review, and examination, we concluded that the patient had biomechanical faults that could be helped with chiropractic. It was unclear whether the patient's pain was from the biomechanical faults or the bone disease. It was decided to initiate chiropractic care, making sure not to compromise bone disease. If treatment is clinically indicated and can be performed safely, then proceed. If their pain is from the bone metastases, then improving joint function is still valuable.

This is an actual patient who we treated with the manual diversified technique to the cervical spine. A neuromechanical adjusting instrument was used to the thoracic subluxations. In the lumbar and pelvic areas, the instrument was used to the paraspinal muscles as well as the gluteal musculature. Her response to treatment was quite favorable. The adjustment always helped her feel and function better. Manual care to the lumbar spine, including a side-lying technique, was contraindicated due to the lumbar and sacral metastases as well as the osteoporotic thoracic spine.

Chiropractic care is an effective treatment option for many oncology patients. Chiropractic treats the patient and not their cancer. The goal is always to improve quality of life, reduce pain, and improve the patient's ability to perform the activities of daily living.

Selected readings

Archives of Physical Medicine and Rehabilitation. 2005. http://www.archives-pmr.org/home/ (accessed February 7, 2014).

Seaman D. Nociception, Mechanoreception and proprioception . . . what's the difference and what do they have to do with subluxation? Dynamic Chiroprac. 1994;12:24.

Schneider J, Gilford S. The chiropractor's role in pain management for oncology patients. J Manip Physiol Ther. 2001;24(1):52–7.

CHAPTER 141

Cancer survivorship and psychosocial issues in oncology

Jabeen Abutalib[1], Shahid Raza[2], and Laura Sunn[1]

[1]Cancer Treatment Centers of America, Zion, IL, USA
[2]Clinical Research Specialist, Hollywood, FL, USA

Case study 141.1

1. You are seeing a newly diagnosed 45-year-old male with stage III colorectal cancer. He comes along with his sister, who is very much involved in his care. Both of them have a positive outlook on the treatment recommended by your team. His sister says, "My brother is a cancer survivor. Am I correct, Doc?" How do you respond?

A. No, not now, but he will be a cancer survivor once he is disease free for minimum of 5 years
B. Yes, you are absolutely correct
C. No, he will be a cancer survivor only if the scans and colonoscopy are negative following therapy
D. I am pretty sure your brother will be a cancer survivor since he doesn't have stage IV disease

The term "cancer survivor" was coined by a physician and a cancer survivor, Dr. Fitzhugh Mullan, in 1985; the definition encapsulates any person who has been diagnosed with cancer from the time of their diagnosis and until the reminder of life. There are at least three distinct phases associated with cancer survival: *acute survival*, the period after diagnosis, when energies are focused on surviving treatment itself; the *period after completion of treatment*, when the survivor's energies are focused on dealing with the physical and psychological consequences of treatment; and *permanent survival*, the period when recurrence seems increasingly unlikely, although the survivor is in a continuous struggle in dealing with the long-term effects of treatment. The patient described here is in the "acute survival" phase and is a "cancer survivor."

2. True or false? Cancer survivors represent a growing population who are homogeneous in their need for medical care, psychosocial support, and practical assistance, with well-established agendas for their research, and coordinated practices are observed between the physicians taking care of them.

A. True
B. False

Definitively, cancer survivors represent a growing population, but they represent a heterogeneous group with regard to their need for medical care, psychosocial support, and practical assistance. The number of cancer survivors will continue to increase due to the aging and growth of the population, improvements in survival rates, and effective cancer screening. To highlight the challenges and opportunities to serve these survivors, de Moor and colleagues obtained the incidence and survival data from 1975 to 2007 from the Surveillance, Epidemiology, and End Results (SEER) program and population projections from the US Census Bureau. Additionally, their report projected cancer prevalence for 2012 and beyond using the Prevalence Incidence Approach Model, assuming constant future incidence and survival trends but dynamic projections of the US population. They concluded that an estimated 13.7 million Americans with a history of cancer were alive on January 1, 2012, and by January 1, 2022, that number will increase to nearly 18 million. Sixty-four percent of this population has survived 5 years or more, 40% have survived 10 years or

Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.

more, and 15% have survived 20 years or more after diagnosis. Over the next decade, the number of people who have lived 5 years or more after cancer diagnosis is projected to increase approximately 37% to 11.9 million. A coordinated agenda for research and practice is needed to address cancer survivors' long-term medical, psychosocial, and practical needs across the survivorship trajectory.

3. The "cancer survivor" described in Question 1 is now in the "permanent survival" phase following successful therapy. Which of the following statements about the care of patients in this particular phase of survivorship are correct?

A. This phase of the cancer journey has long been ignored by medical teams
B. The majority of patients suffer long-term effects in the physical, emotional, and practical domains, which are often unattended by medical teams
C. The US Institute of Medicine's (IOM) committee attempted but failed to provide the goals for increasing patients' and providers' awareness
D. Basic communications between the medical oncologist and the primary care provider (PCP) may have substantial value for the patient and their families, especially during shared and transferring care

The IOM's 2006 report "From Cancer Patient to Cancer Survivor: Lost in Transition" came about because of a recognition that the recovery or permanent-survival phase of the cancer journey had long been ignored. The IOM committee has made a number of recommendations that have largely achieved the goal of increasing patients' and providers' awareness of the many issues that can affect cancer survivors. However, with the exception of a few centers of excellence, most providers have found it difficult to substantively change the way they care for cancer survivors. Salz and colleagues (2012) reported that although the idea of survivorship care plans is looked on favorably among National Cancer Institute (NCI)–designated comprehensive cancer centers, there are concerns about its feasibility. As a result, only 43% of them deliver care plans to their breast or colorectal cancer survivors, and none provide all of the components recommended by the IOM. Finally, it is absolutely correct that basic communication between the medical oncologist and the PCP can go a long way toward easing patient and family concerns.

4. Why it is difficult to operationalize an ideal survivorship care program? (Check all that apply.)

A. Survivorship care is an unfunded mandate for oncologists
B. The evidence base for survivorship care remains weak with few exceptions
C. Manpower shortages in clinics
D. Time limitations in already busy clinics
E. Lack of awareness about cancer survivorship experience (post-treatment)

The perfect models for delivery of survivorship care to the millions of survivors of cancer worldwide are still works in progress, and they will probably require additional evolution and refinement, as well as an information technology infrastructure to make them feel seamless. Raising awareness about the posttreatment cancer survivorship experience has surely been achieved, with national and private organizations throughout the world acknowledging the expanding number of survivors whose needs must be addressed (Table 141.1). According to Earle and Ganz (2012), it is generally recognized that physicians incorporate something new into their practice only if at least one of three conditions is met: (i) it has clearly been shown to be better for their patients, (ii) physicians are specifically remunerated for it, or (iii) it is more efficient for physicians in their practice. Survivorship care as envisioned by the IOM report does not readily meet any of these criteria at the present time due to many (choices A through D) of the reasons.

(*Continued*)

Table 141.1 National Cancer Survivorship Resource Center (Source: Adapted from Siegel R et al. CA Cancer J Clin. 2012;62(4):220–41. Reproduced with permission of John Wiley & Sons).

The National Cancer Survivorship Resource Center (The Survivorship Center) is a collaboration between the American Cancer Society and the George Washington Cancer Institute, funded by the Centers for Disease Control and Prevention. Its goal is to shape the future of posttreatment cancer survivorship care and to improve the quality of life of cancer survivors. The Survivorship Center staff and more than 100 volunteer survivorship experts nationwide developed the tools listed here for cancer survivors, caregivers, healthcare professionals (HCPs), and policy and advocacy efforts.
Tools for cancer survivors and caregivers
Life after Cancer Treatment Guide. A quick, easy-to-read information guide to help cancer survivors and their caregivers understand the various aspects of the survivorship journey. The guide also includes trusted resources for survivorship information and encourages communication with HCPs. The guide is available online at http://www.cancer.org/survivorshipguide. *Survivorship Information Resource Inventory*. An inventory of information resources to assist posttreatment survivors. It is available online at http://www.cancer.org/survivorshipresourceinventory.
Tools for HCPs
Prescription for Cancer Information. A tool to help HCPs talk to survivors about resources available in their office or clinic, in the community, online, and over the telephone. This tool is available online at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-033258.pdf. *Moving beyond Patient Satisfaction: Tips to Measure Program Impact Guide*. A brief guide detailing indicators and outcome measures that can be used to monitor the success of survivorship programs; available online at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-033811.pdf.
Tools for advocates and policy makers
The Survivorship Center recognizes the importance of policies that support quality survivorship care. To educate policy makers on these issues, a white paper was created describing the priority areas for improving survivorship care. This paper is available online at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-031411.pdf. To find out more about the Survivorship Center's activities, visit http://www.cancer.org/survivorshipcenter.

Case study 141.2

A 39-year-old man with esophageal adenocarcinoma is suffering from insomnia. He had significant side effects to benzodiazepines and eszopiclone, which you had prescribed him as his primary oncologist 3 weeks ago. He has responded well to his treatment, but it has resulted in "grogginess," mental "cloudiness," and very late arising in the morning. He has been employed as a teacher for 14 years and now faces disciplinary action because of tardiness.

1. Which of the following strategy do you propose?

A. Writing a letter to his boss, requesting to support him
B. Cognitive-behavioral therapies and consultation with a psychiatrist
C. Continuation of current medications and assisting him with FMLA (family medical leave of absence)
D. Lawsuit against the school system for not supporting him

Pharmacologic agents are the most commonly used interventions for insomnia; the evidence for cognitive-behavioral therapy (CBT) has been neglected despite reassuring outcomes. It would be easy to simply try another sleep aid in the form of sedative or hypnotic medication due to mere convenience and busy oncology practices. At our center, we engage psychosocial support and services early during the course of therapy to avoid many otherwise "unforeseeable" shortcomings. The patient described is active and requires being fully awake, with all his faculties, to continue his employment. Treatment that includes both psychological and behavioral methods (Table 141.2) can achieve his goal of working. CBT is well established for the treatment of primary insomnia in the general population and also has positive results in studies with cancer patients.

Table 141.2 Psychosocial interventions for insomnia.

Intervention	Goal of intervention	Procedural summary
Cognitive-behavioral therapies (CBT)		
1. Sleep hygiene therapy	Improve sleep onset, continuity, and efficiency.	Educate about regularity of schedule, avoid stimulants and exercise near bedtime, and have a dark and quiet environment.
2. Cognitive therapy	Identify limiting factors, false beliefs, and false expectations.	Identify distortions, challenge misconceptions, and reframe.
3. Stimulus control therapy	Establish a sleep–wake schedule, and associate the bed with sleep.	Use the bed or bedroom for sleep only, no TV, and no napping during the day.
Biofeedback therapy (heart rate variability)	Balance parasympathetic and symptomatic nervous system.	Train with a monitor to increase coherent state prior to sleep.
Relaxation therapy	Reduce stress and tension.	Progress muscle relaxation and guided imagery.
Hypnosis	Suggest and reinforce success.	Induce trance and level of suggestivity.

Case study 141.3

A 49-year-old caregiver is newly diagnosed with hypertension and has intermittent insomnia after supporting her eldest daughter through 5 years of treatment for breast carcinoma. She is stressed by the departure of her youngest son moving away for college. She has been finding herself more worried and anxious, and experiences guilt about her tendency to feels "burdened" by all the duties of a caregiver.

1. You counsel her to see a psychiatrist for all of the following interventions EXCEPT:

A. Psycho-educational intervention: short, time limited (less than 7 hours total)

B. Psycho-educational intervention: longer, extended (greater than 7 hours total)

C. Skills training to develop caregiver coping, communication, and problem solving

D. Therapeutic counseling to strengthen patient–caregiver relationships, manage conflict, and deal with loss

Five meta-analyses of caregivers of cancer patients identified longer interventions, "relationship-focused interventions," and skills training to have a positive effect on the health outcomes of cancer caregivers. Additional resources and support organizations that provide "caregiver champions" help establish rapport, collaboration, and synergy to improve the outcome of both the patient and caregiver.

Case study 141.4

A 21-year-old unmarried mother has relapsed Hodgkin's lymphoma. She is forced to move back in locally with her least-preferred divorced parent to facilitate transportation and childcare while she receives treatment. She is training to become a cosmetologist and initially refuses the recommended salvage therapy because of the possibility of hair loss. She chooses her top two institutions for possible high-dose therapy and hematopoietic cell transplantation based on their technology-based interventions and availability of spa services. She is deeply concerned about the ancillary support of massage therapy and candy selection in the gift shop compared to outcome statistics.

1. What do you recommend?

A. Social service consult to address the family dynamics

B. Regular drug screen during every phase of survivorship

C. Fertility counseling

D. Psychiatric consultation prior to initiation of salvage regimen

E. All of the above

Young adults with cancer struggle more with all of the usual developmental milestones of identity formation, intimacy, and independence from their parents. Goal-planning

(*Continued*)

behaviors, organization, and impulse control are not fully functioning before 25 years of age. These "deficits" when compared to those of older adults make communication, adherence, and compliance more problematic with providers and anyone in authority. Other psychosocial challenges include the "experimentation" phase of drug and alcohol consumption, the existential issues of a life-and-death diagnosis, and a yearning for peer support. The recommendations for clinical care to promote young adults' ability to cope with cancer include patient participation in diagnostic conferences and subsequent decision making, finding age-relevant resources for information regarding treatment and late effects, emotional support with professionals who have expertise with this age group, and practical support to maintain employment or schoolwork. Social work consultation will facilitate the actual nature of intervention needed to support treatment. The psychiatrist will assess school performance, determine often concomitant underlying mental health disease, and begin the psycho-education process helping the patient prepare for isolation. Evidence suggests that fertility-related issues concern some patients to the extent that it may influence therapeutic decisions for them. Discussion about fertility should be extensively discussed prior to (and sometimes even after) administration of any gonadotoxic therapy in age-appropriate groups of patients.

Case study 141.5

A 54-year-old widowed Japanese woman with metastasized ovarian cancer has been losing energy, feeling hopeless, losing interest in hobbies, reporting insomnia and anorexia, and wishing to "just go home and die." Now, 14 days post-operative (HIPEC) surgery, the small bowel has not "awakened". She cannot embrace never eating again. She has a positive relationship with a mind–body therapist but refuses psychiatric consultation by saying, "You think I'm crazy?"

1. How do you, as her primary oncologist, respond?

A. State, "No, the current circumstances have made you crazy," and proceed with psychiatric consultation without further discussion
B. State, "No, you are not crazy," and cancel the idea about ordering a psychiatric consultation
C. State, "I will provide you with my rationale for ordering psychiatric consultation," and start a dialog prior to ordering a psychiatric consultation
D. State, "Fine, let's proceed with hospice"

The next crucial step is talking directly to the patient about the process of psychiatric consultation. By joining the patient's resistance to psychiatric intervention in a manner that conveys confidence and successful outcomes, the patient can feel heard and respected. The obvious fear is that she is perceived to be "crazy." Explanations that normalize human emotions validate the patient's experience in survivorship. More helpful hints include inviting the psychiatrist to visit in the presence of the mind–body therapist; expanding communication with the patient to include psycho-education about the relationship between depression and decreased immune functioning as a motivation; increasing cooperation with further psychiatric treatment by using direct, honest communication about follow-up plans and quality of life in survivorship; sitting down at bedside instead of standing to demonstrate interest and persistence; offering to introduce the psychiatrist and/or discuss the specific credentials of the consultant; considering sharing past "success stories" after psychiatric interventions with other cancer patients; discussing with peers and colleagues their individual scripts used to "break bad news"; preparing patients for aversive procedures; and taking into account cultural influences (e.g., in Japan, family members are traditionally first informed of medical facts before the patient; here, they may need to be included after permission is sought from the patient). Always be human and convey compassion, always supply hope, clarify the complexities of the differential diagnoses in layperson's terms. Given the oncologist's personal communication style and preferences, any or all of the described techniques are supported by research that demonstrates improved communication after implementing conscious decisions that increase awareness of the interplay between provider and patient.

2. In cancer patients, are sexual health–related issues considered important and routinely discussed during oncology visits?

A. Yes
B. No

Virtually all cancer survivors encounter sexual problems; however, few physicians broach this subject. Physicians receive little, if any, training about how to address sexual concerns, plus they are generally uncomfortable addressing sexual problems. Additionally, barriers to communication are lack of time and lack of preparation to discuss sexuality with cancer survivors. Similarly, cancer survivors are hesitant to discuss sexual concerns mainly due to the perceived notion of "nothing could be done" and/or avoidance in making their healthcare provider uncomfortable. Importantly, a survivorship care plan should include sexual health teaching providing information and resources pertaining to specific sexual health issues (Table 141.1).

Case study answers

Case study 141.1

Question 1: Answer B
Question 2: Answer B
Question 3: Answer C
Question 4: Answer "All except E"

Case study 141.2

Question 1: Answer B

Case study 141.3

Question 1: Answer A

Case study 141.4

Question 1: Answer E

Case study 141.5

Question 1: Answer C
Question 2: Answer B

Selected readings

Earle CC, Ganz PA. Cancer survivorship care: don't let the perfect be the enemy of the good. J Clin Oncol. 2012; 2012:3764–8.

Ganz PA, Earle CC, Goodwin PJ. Journal of Clinical Oncology update on progress in cancer survivorship care and research. J Clin Oncol. 2012;2012:3655–6.

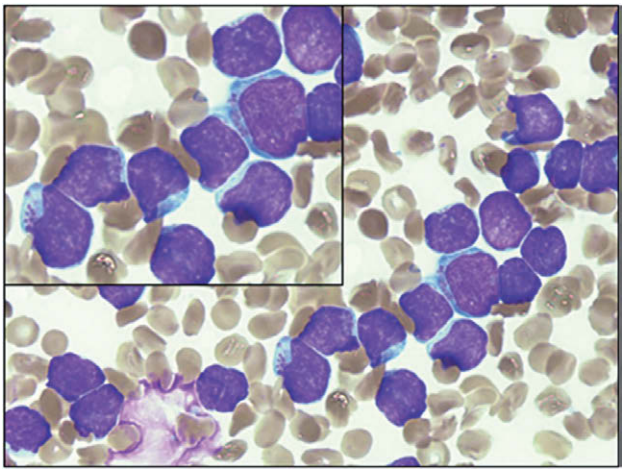
Hewitt M, Greenfield S, Stovall E, editors. From cancer patient to cancer survivor: lost in transition. Washington, DC: National Academies Press; 2006.

National Comprehensive Cancer Network (NCCN). www.NCCN.org, www.nccn.org/professionals/physician_gls/pdf/survivorship

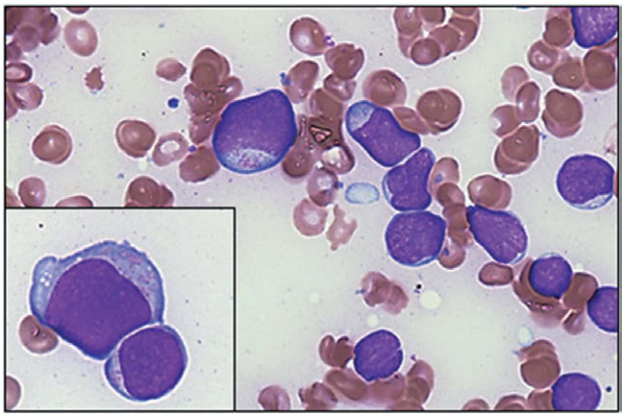
Siegel R, DeSantis C, Virgo K, *et al*. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220–41. PMID:22700443.

Index

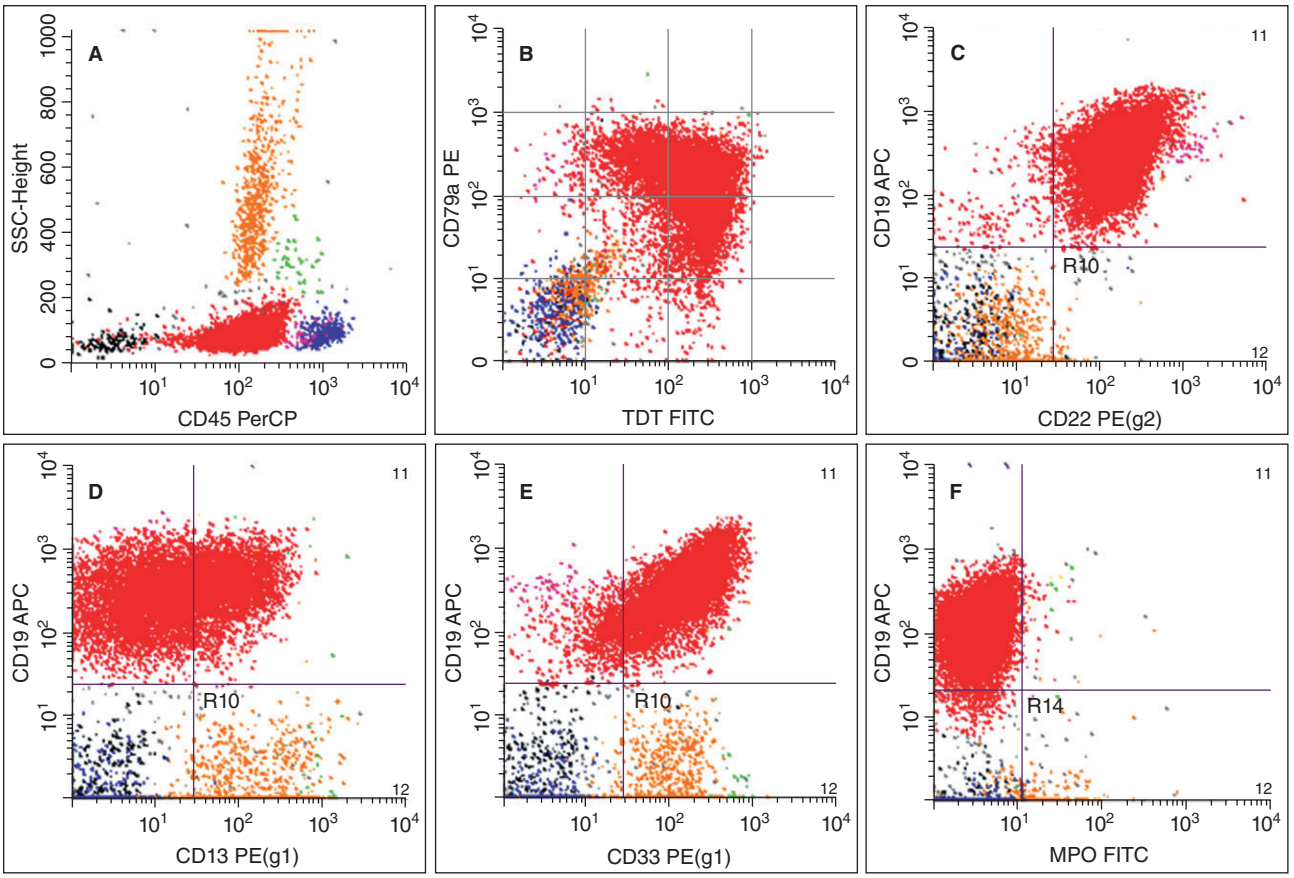
Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.



Color plate 1.1 Peripheral blood smear. A monomorphous population of abnormal cells predominates in the peripheral blood. The insert shows azurophilic granules in the cytoplasm of several of these cells. Wright-Giemsa, 50×; insert, 63×.

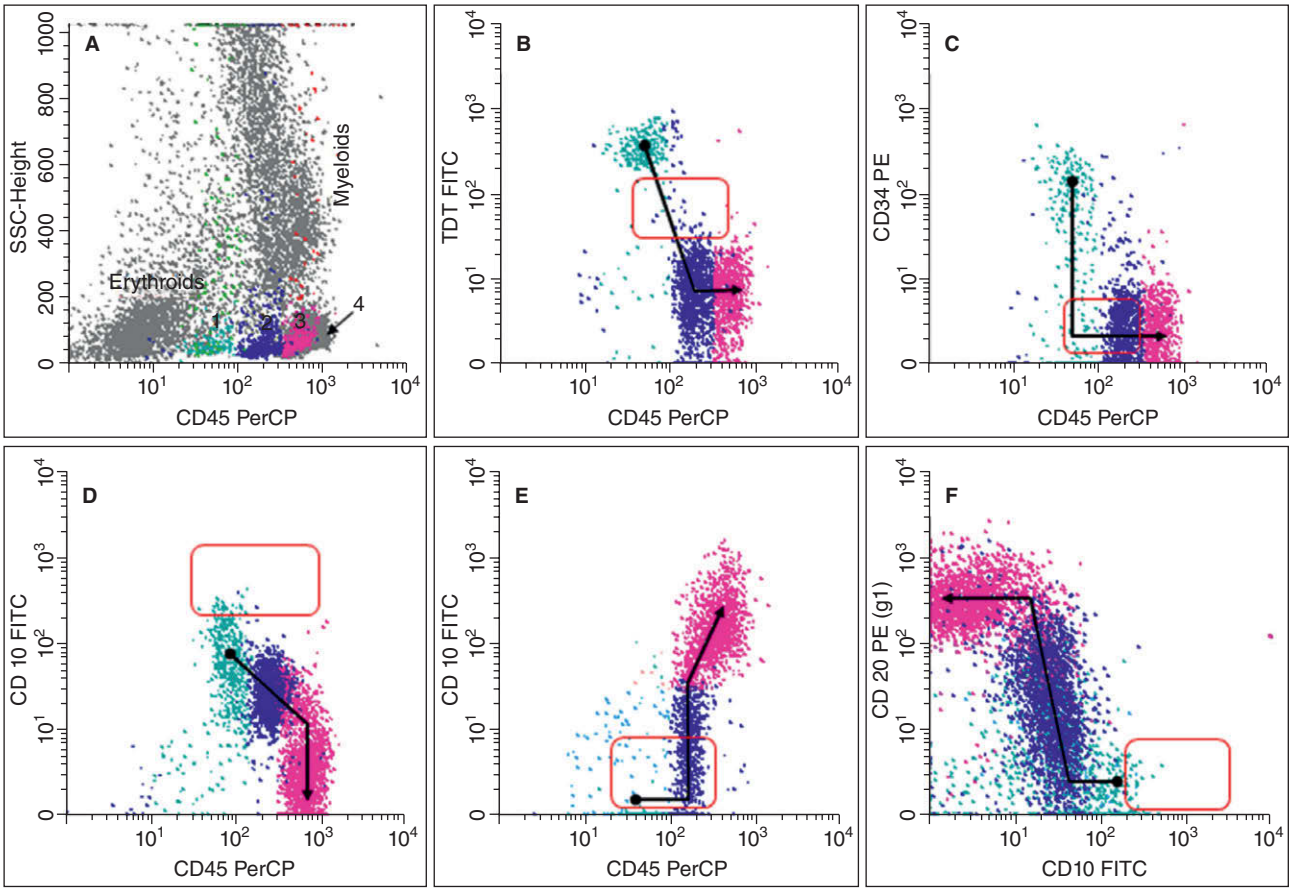


Color plate 1.2 Bone marrow core biopsy touch preparation. Touch imprints of the bone marrow core biopsy substituted for a suboptimal bone marrow aspirate specimen. The marrow is involved with the same abnormal cells present in the peripheral blood. The insert shows two cells containing azurophilic cytoplasmic granules. Wright-Giemsa, 63×; insert, 100×.

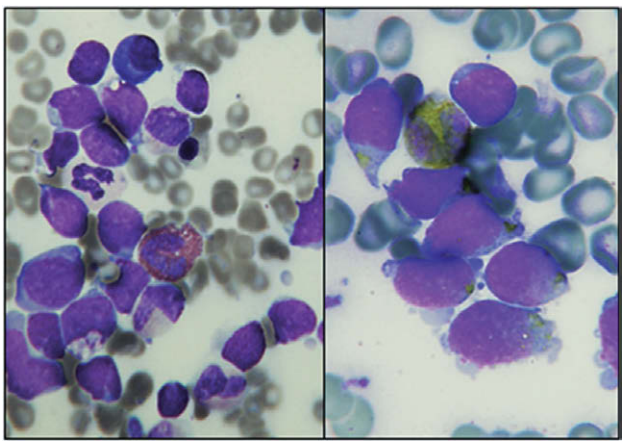


Color plate 1.3 Flow cytometry immunophenotype study of the peripheral blood. The red dots in frames A–F represent the abnormal cells shown in Color plate 1.1. The blue, green, and orange dots represent mature lymphoid, monocytic, and granulocytic elements, respectively. Frame A shows the abnormal cells occupying the region of the histogram normally occupied by blasts and immature cells. Frame B shows these same cells co-expressing B-cell-associated cytoplasmic CD79a and blast-associated TDT (terminal deoxynucleotidyl transferase). The cells located in the lower left quadrant of frames C, D, E, and F are negative for the markers indicated on the x- and y-axes. SSC, side light scatter (a measure of internal cell complexity or granularity); MPO, myeloperoxidase. PerCP, FITC, PE, and APC are fluorochromes conjugated to antibodies used to identify cell antigens.

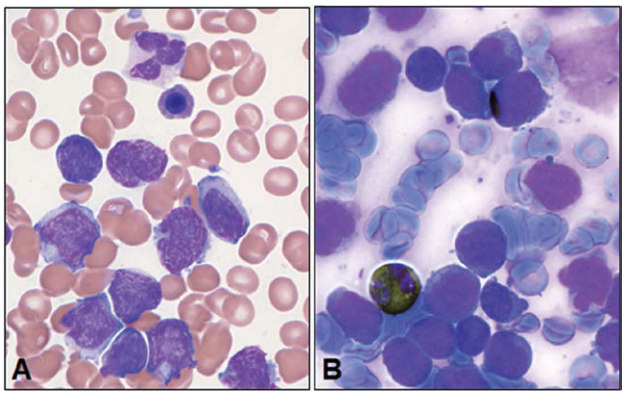
Cancer Consult: Expertise for Clinical Practice, First Edition. Edited by Syed A. Abutalib and Maurie Markman.



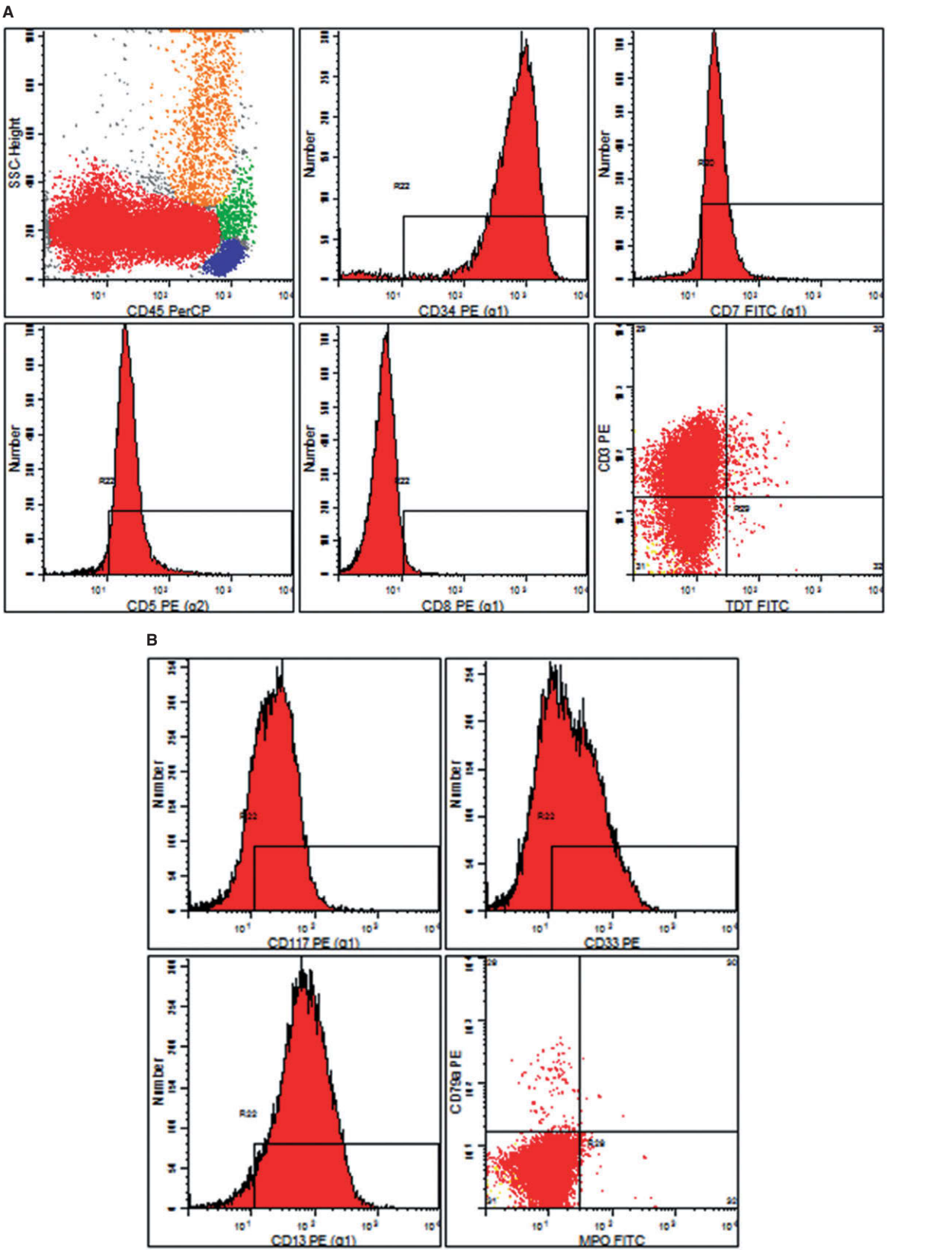
Color plate 1.4 Flow cytometry immunophenotype study of the bone marrow aspirate at 18 months post induction chemotherapy. The pink, dark blue, and light blue dots represent CD19-positive B-cells. Frame A shows the relative positions of these three cell populations; they are labeled 1, 2, and 3, relative to their intensity of CD45 expression. Mature T-lymphocytes are located in the area labeled "4." Frames B, C, D, and E show the marker expression of TDT (terminal deoxynucleotidyl transferase), CD34, CD10, and CD20 based on their CD45 expression. Frame C is different in that it shows the intensities of CD10 versus CD20 for the three B-cell populations. The arrows indicate the direction of increasing B-cell maturation. A review of frame A of Figure 1.3 shows where the leukemic blast would be expected to be in a two-parameter histogram of CD45 versus side light scatter (SSC). The open red rectangles are where the patient's leukemic blasts would be located based on studies prior to the start of therapy.



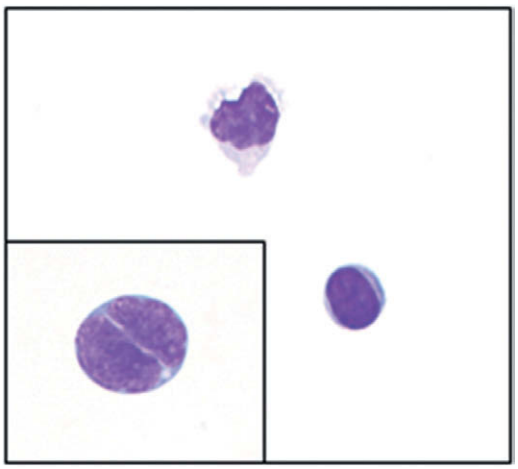
Color plate 1.5 Images of stained bone marrow aspirate smears are shown in two frames. The left frame is a Wright-Giemsa-stained smear showing that the majority of marrow cells are a mix of small and large blasts. The right frame is a cytochemical stain for myeloperoxidase (MPO) using o'toluidine as the detecting agent. A yellow color reaction product indicates the presence of MPO. Note the presence of MPO in a metamyelocyte and weak, focal MPO positivity in several of the blasts. By differential count, >20% of blasts are weakly positive for MPO. Left frame, 40×. Right frame, 100×.



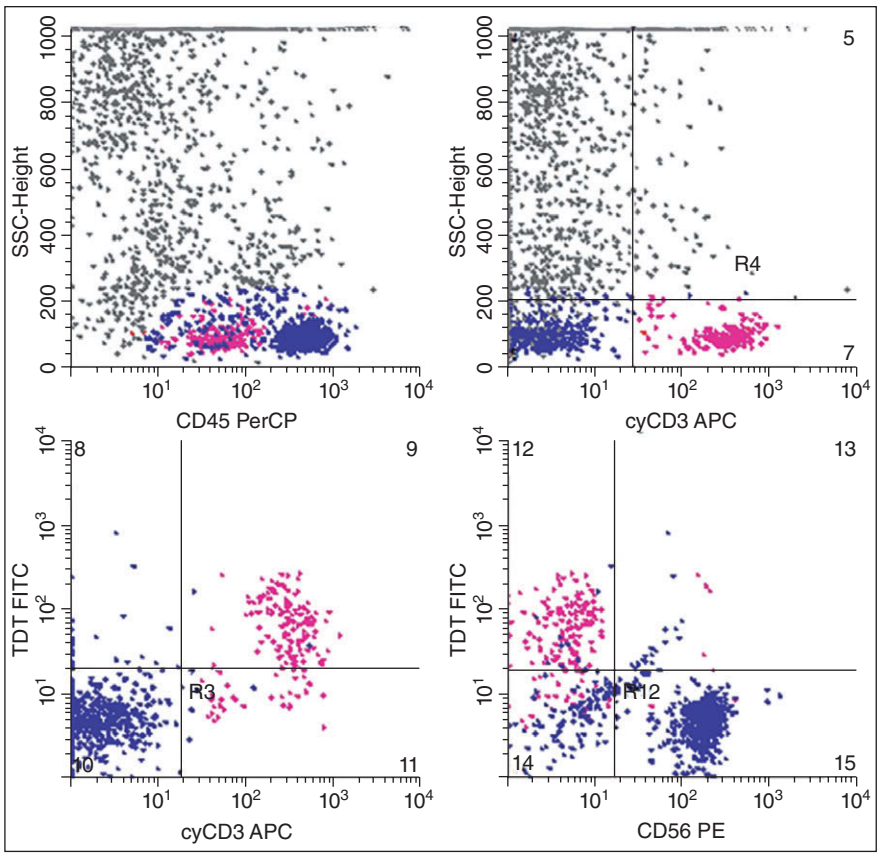
Color plate 1.6 Cells of a bone marrow aspirate are shown in the left and right frames. The left frames show blasts, a neutrophil, and a late-stage erythroblast. Blasts resembling those in the peripheral blood comprise the majority of cells in the bone marrow. These blasts have monocytoid-like nuclear features but contain no cytoplasmic granules or Auer rods. The right frame is a cytochemical stain for myeloperoxidase (MPO) using o'toluidine. A single-band neutrophil is positive for MPO as indicated by its yellow reaction product.



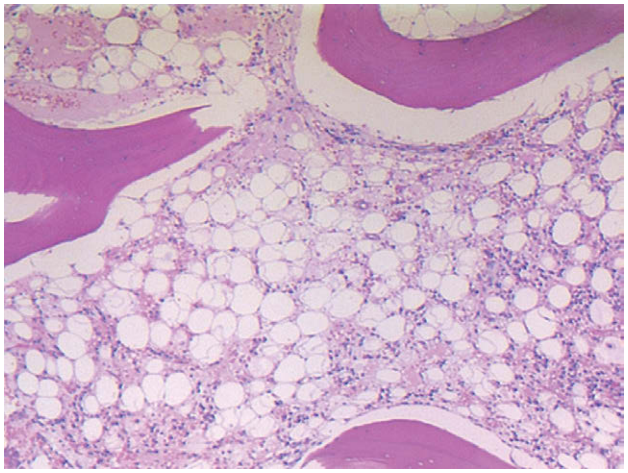
Color plate 1.7 (A) Flow cytometry immunophenotype study of the peripheral blood. Marker expressions of the neoplastic blasts in the peripheral blood are shown in six representative histograms. The red, blue, green, and orange dots represent blasts, mature lymphocytes, monocytes, and granulocytes, respectively. The left upper frame of an SCC (side light scatter) versus CD45 histogram shows no to weak expression of CD45 by the blasts. The cells within the open black rectangles represent blasts that are positive for CD34, CD7, CD5, or CD8. For example, almost all blasts express CD34 but not CD8. As indicated by the lower right histogram, the blasts express weak cytoplasmic CD3 but not terminal deoxynucleotidyl transferase. (B) Flow cytometry immunophenotype study of the peripheral blood. The four frames show additional studies of CD117, CD33, CD13, myeloperoxidase (MPO), and CD79a expression by the leukemic blasts. Refer to Figure 1.8A for interpretation of positive or negative expression of these five markers.



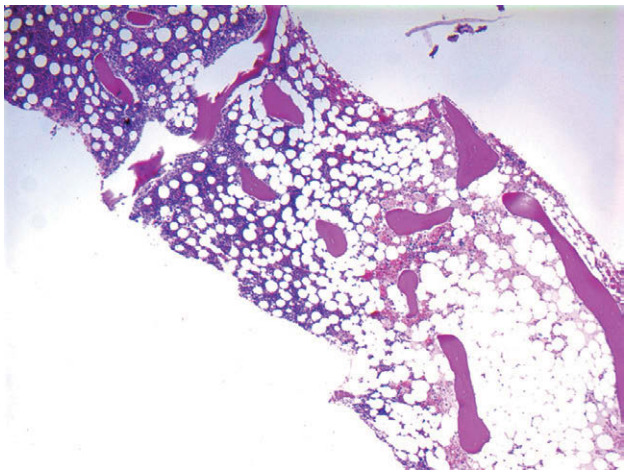
Color plate 1.8 Images of a cerebrospinal fluid (CSF) cytospin preparation. No RBCs are present, indicating a clear "lumbar puncture" not contaminated with peripheral blood. The larger frame (40×) shows a small normal lymphocyte and monocyte. The inserted frame (100×) shows a blast form with a deeply indented nucleus and scant cytoplasm. Wright-Giemsa stain.



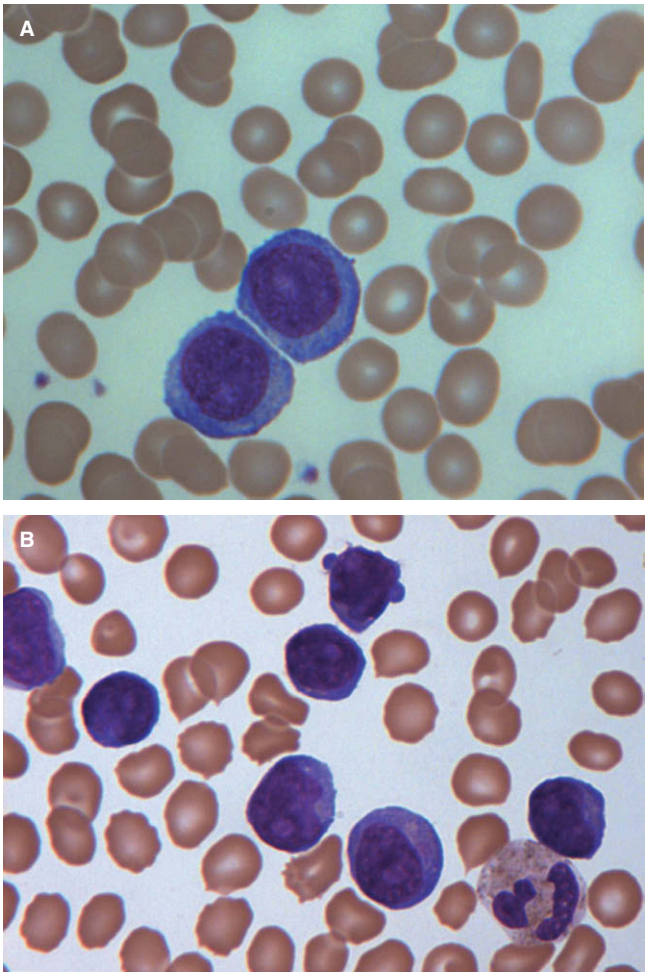
Color plate 1.9 Flow cytometry immunophenotype study of cerebrospinal fluid (CSF). The upper left frame is a study of CD45 (common leukocyte antigen) intensity versus side light scatter (SSC). The blue dots are mature lymphoid elements. The red dots are cells with weak or dim CD45 expression as is typical of blasts. The gray dots are dead cells and cellular debris. The other histograms represent studies of cytoplasmic CD3 (cyCD3 APC), terminal deoxynucleotidyl transferase (TDT FITC), and CD56 (CD56 PE), the latter being a marker of cytotoxic T-cells and NK-cells. The cells represented by the red dots co-express cytoplasmic CD3 and nuclear TDT (shown in the lower left histogram). Normal cerebrospinal fluid does not contain cells that co-express CD3 and TDT.



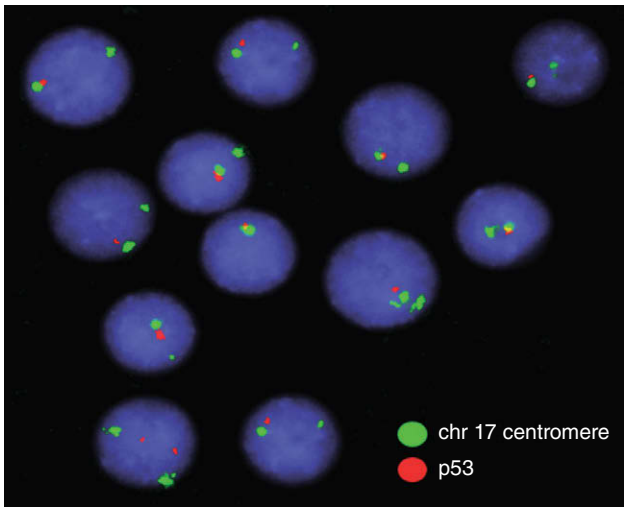
Color plate 14.1 Serous atrophy. This bone marrow biopsy shows serous atrophy characterized by marrow hypoplasia, fat atrophy, and deposition of extracellular gelatinous material. The findings are similar to what is seen in acquired immunodeficiency syndrome.



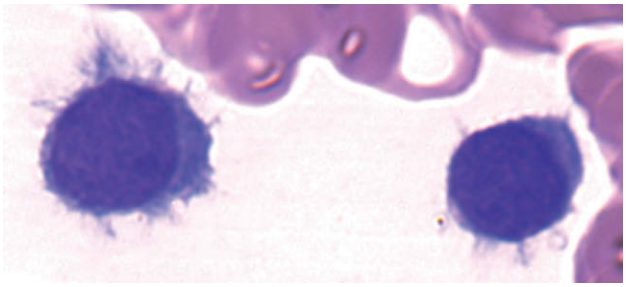
Color plate 14.2 Variable cellularity. This bone marrow biopsy is subcortical and shows variable cellularity ranging from less than 5% cellularity (directly subcortical) to 40% cellularity.



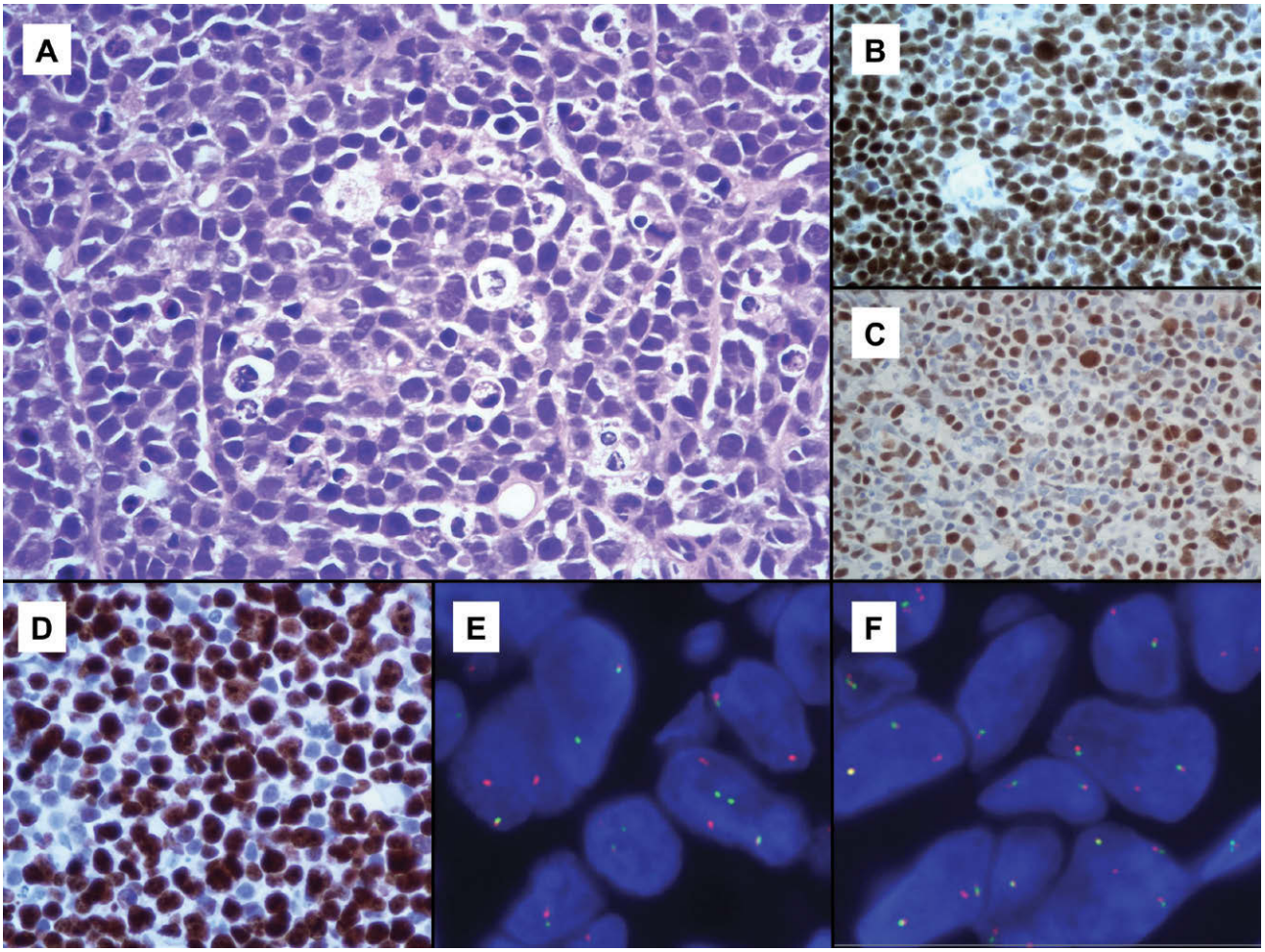
Color plate 33.1 Peripheral blood morphology of prolymphocytic leukemia (PLL). (A) B-cell PLL (B-PLL), showing monomorphic prolymphocytes (PL) with condensed chromatin, prominent nucleolus, and scanty basophilic cytoplasm. (B) T-cell PLL (T-PLL) showing medium-sized lymphoid cells with a regular nuclear outline, single nucleolus, and intense basophilic cytoplasm. An occasional cell shows a cytoplasmic protrusion.



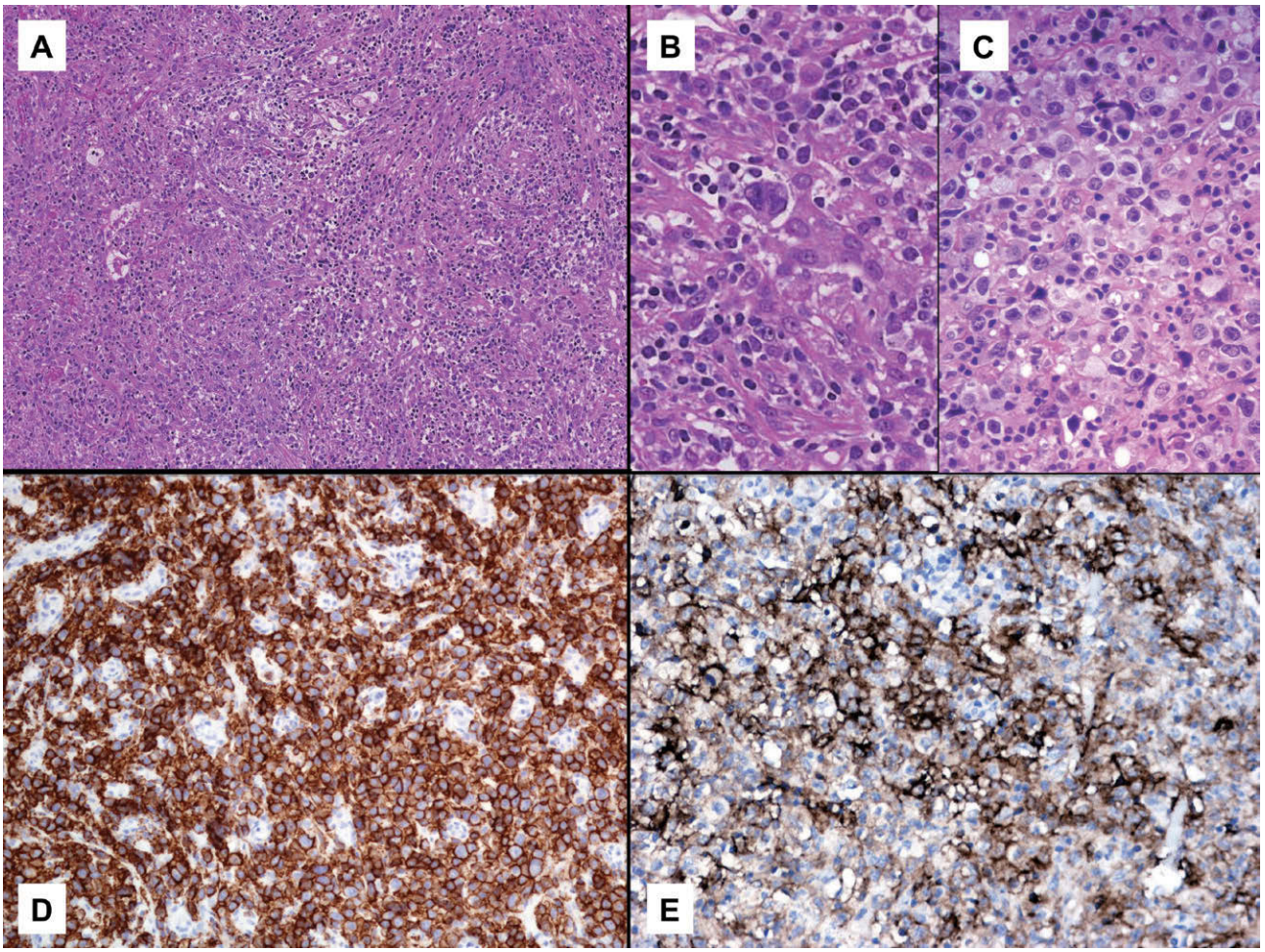
Color plate 33.2 Fluorescent in situ hybridization (FISH) in B-cell prolymphocytic leukemia (B-PLL) showing del17p: the green dot shows the centromere for chromosome 17, and the red dot is the probe for *TP53* (Source: John Swansbury, Royal Marsden Hospital, Surrey. Reproduced with permission of John Swansbury).



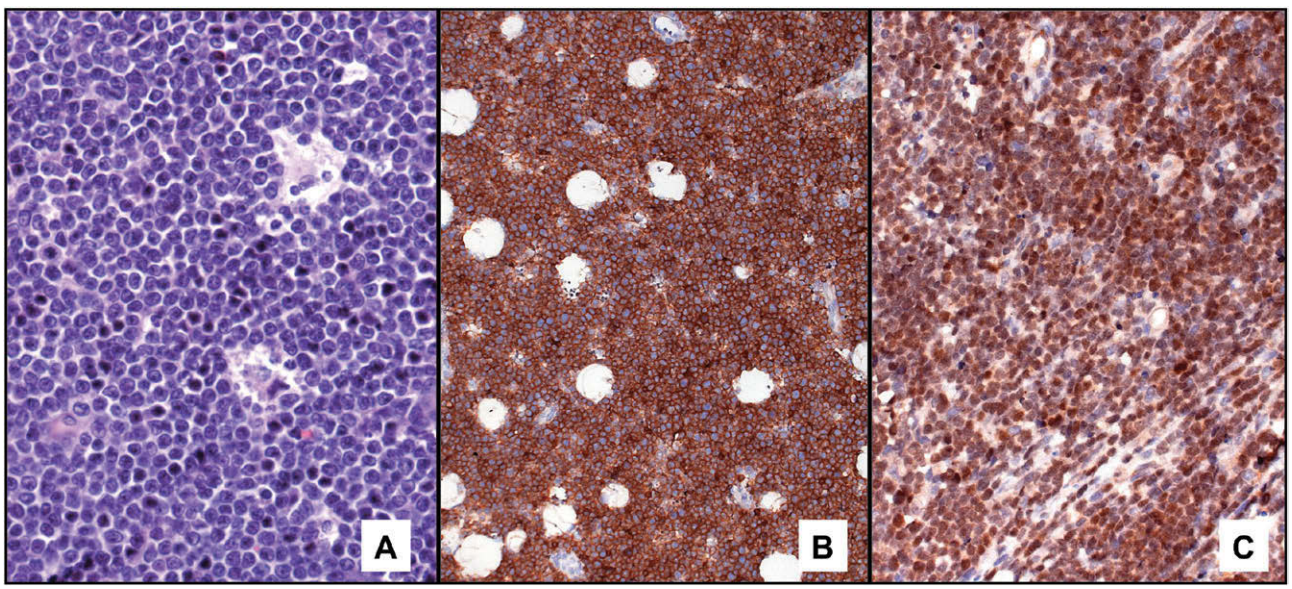
Color plate 34.1 Hairy cells with classic circumferential, hairlike cytoplasmic projections.



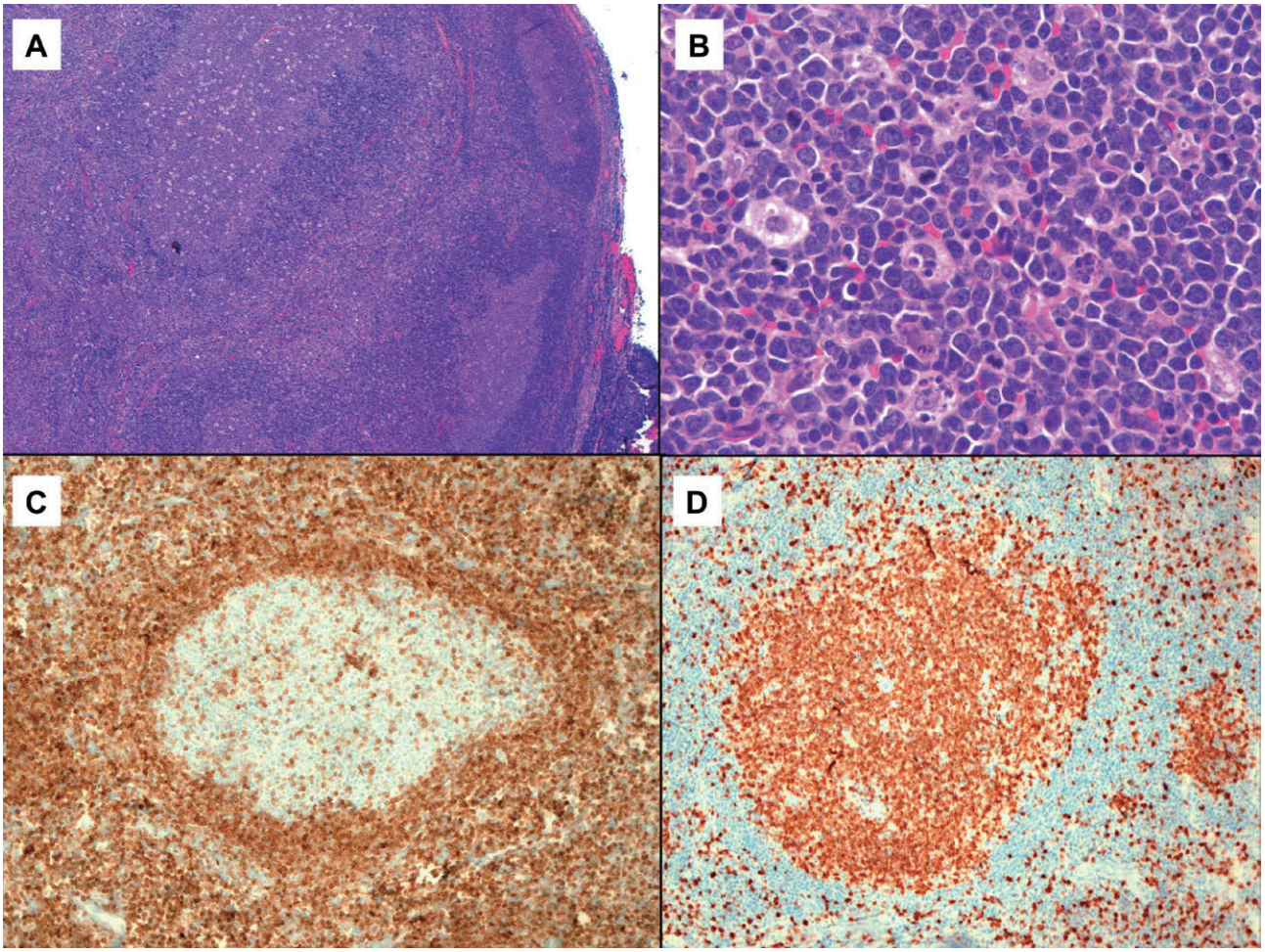
Color plate 38.1 B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. Diffuse proliferation of medium- to large-sized cells with few associated small lymphocytes with starry sky macrophages, numerous mitoses, and prominent apoptosis (A). The lymphoma cells are PAX5+ (B), and most express c-MYC protein (C). The Ki67 proliferation index is estimated to be >90% (D). Fluorescent in situ hybridization (FISH) with break-apart probes for *BCL2* (E) and *MYC* (F) show numerous split signals indicative of rearrangement of both genes.



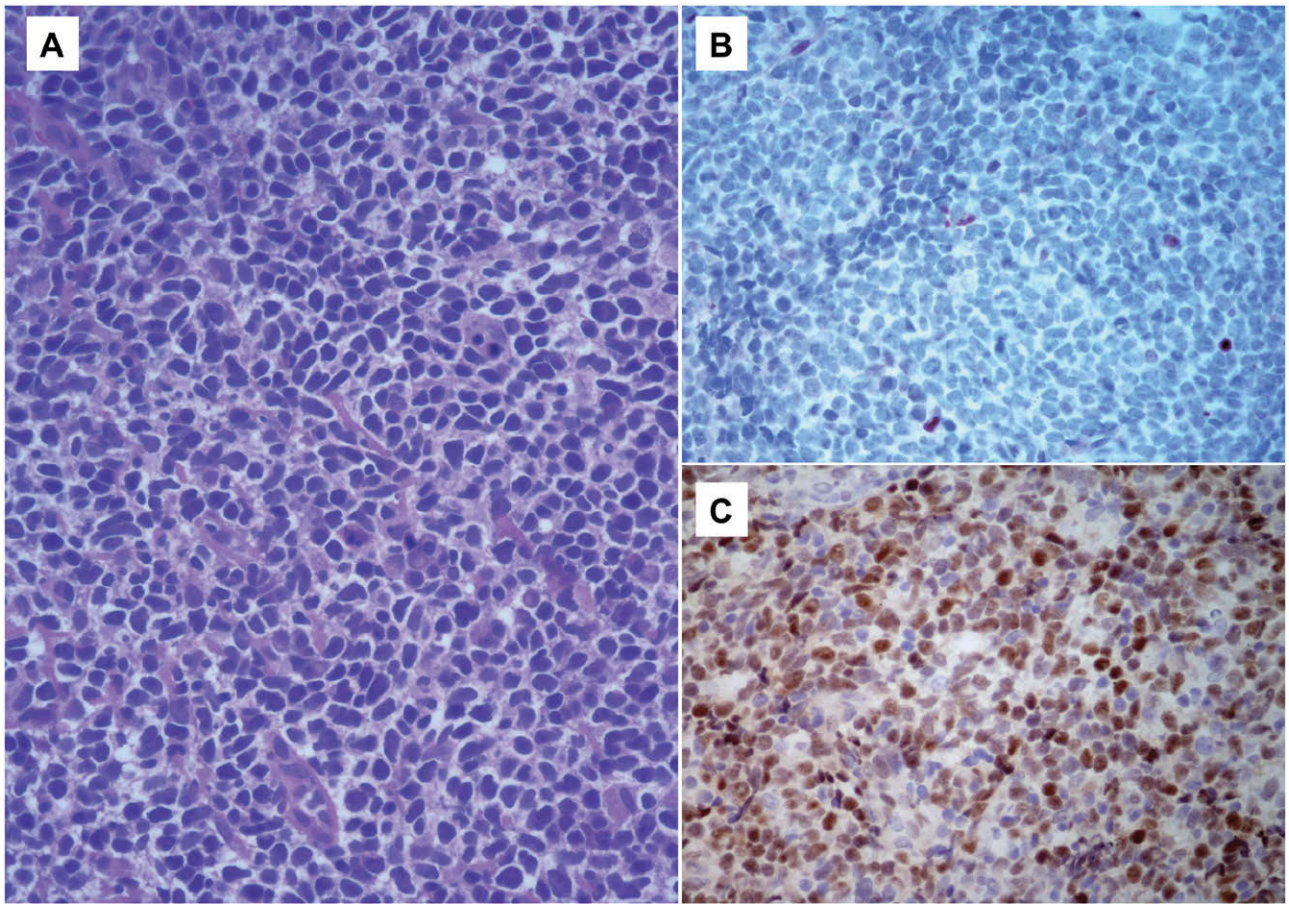
Color plate 38.2 Primary mediastinal large B-cell lymphoma. Diffuse sheets of medium to large cells with abundant eosinophilic or pale cytoplasm admixed with cells with Reed-Sternberg-like appearance in a background of "compartmentalizing" sclerosis (A–C). The lymphoma cells are positive for CD20 (D) and show strong membrane staining for CD23 (E).



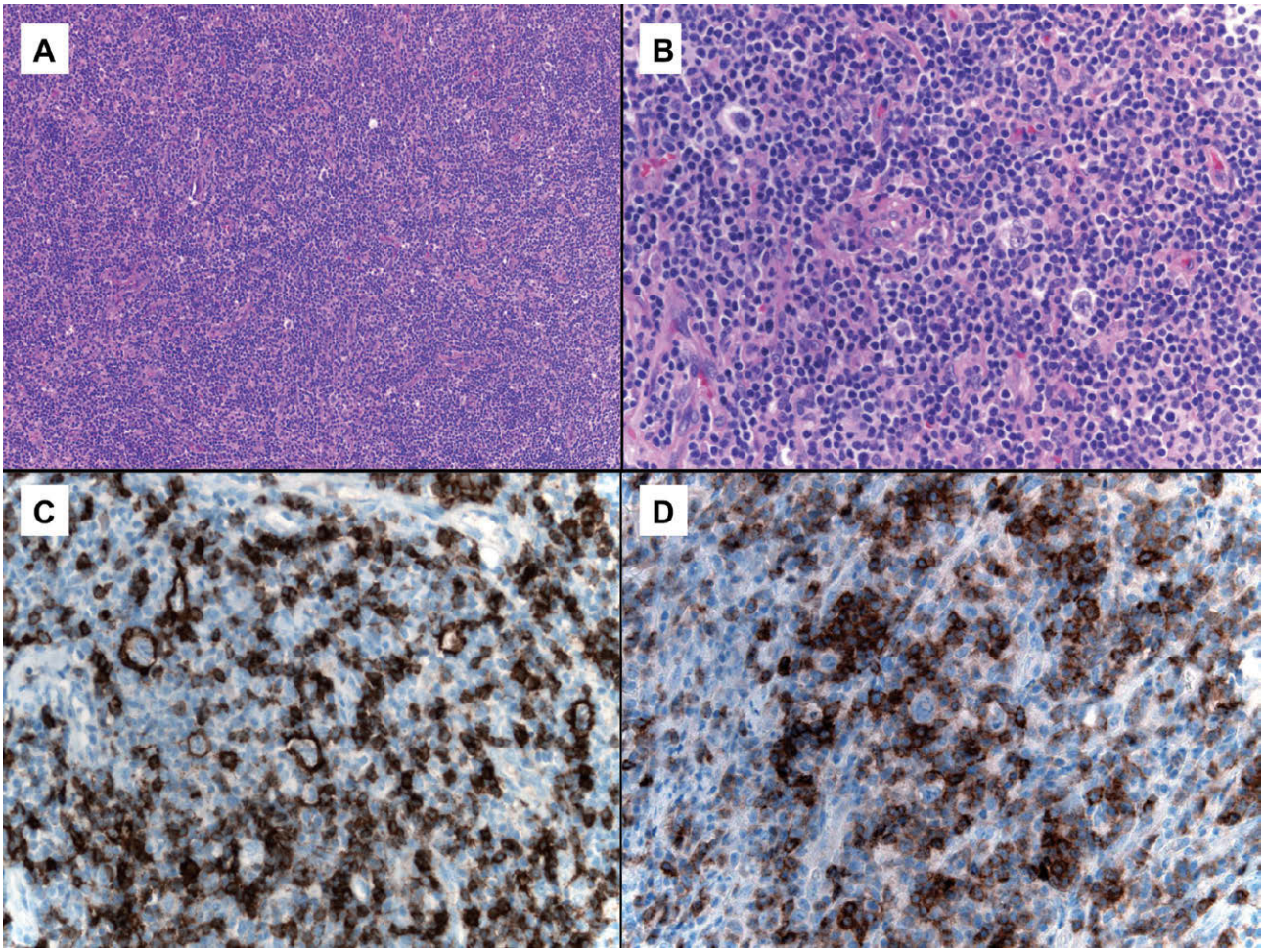
Color plate 38.3 T lymphoblastic leukemia/lymphoma. Diffuse proliferation of medium-sized lymphoid blasts with macrophages imparting a starry-sky pattern (A). The lymphocytes are strongly and diffusely positive for CD5 (B) and TdT (C).



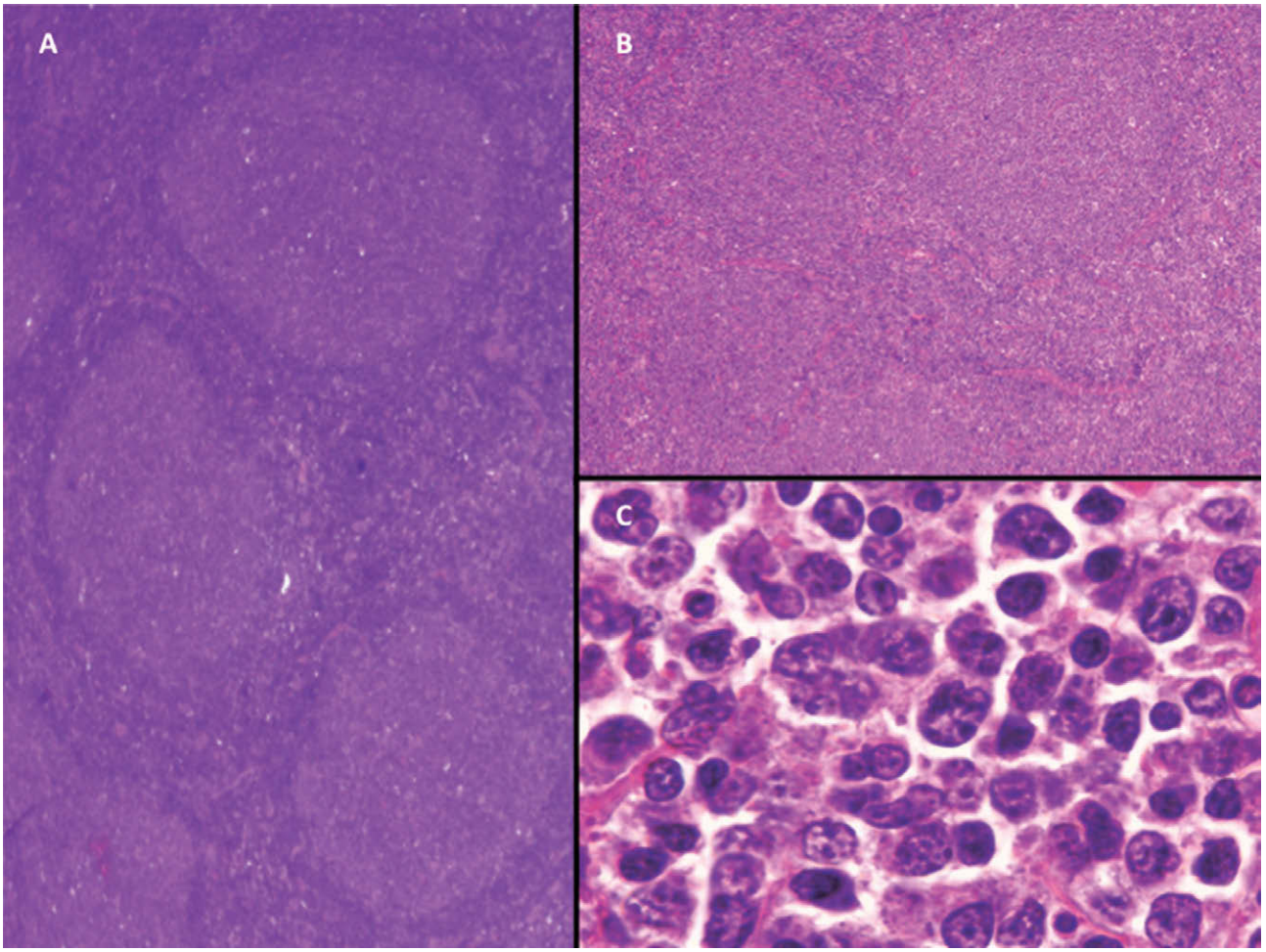
Color plate 38.4 Pediatric follicular lymphoma. The lymph node comprises large, expansile, coalescent follicles (A) composed of medium-sized centroblasts and displaying a "starry-sky" pattern (B). The follicular B-cells are negative for BCL2 (C) and show a high Ki67 proliferation index (D).



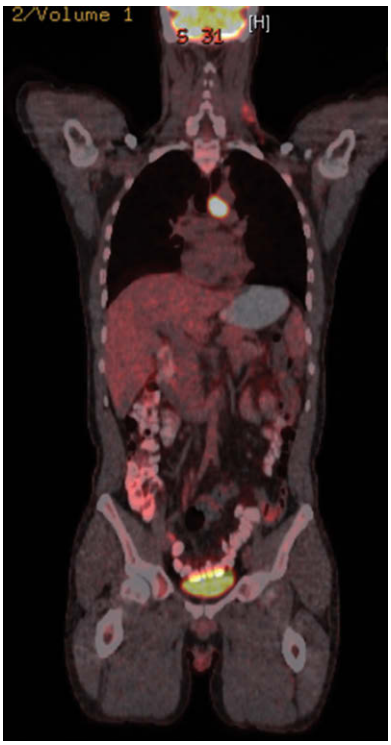
Color plate 38.5 Cyclin D1 mantle cell lymphoma. Diffuse proliferation of small to medium-sized lymphoid cells with centrocytic-like morphology (A), which were positive for CD20 and PAX5 (not shown), negative for cyclin D1 (B), and positive for SOX11 (C).



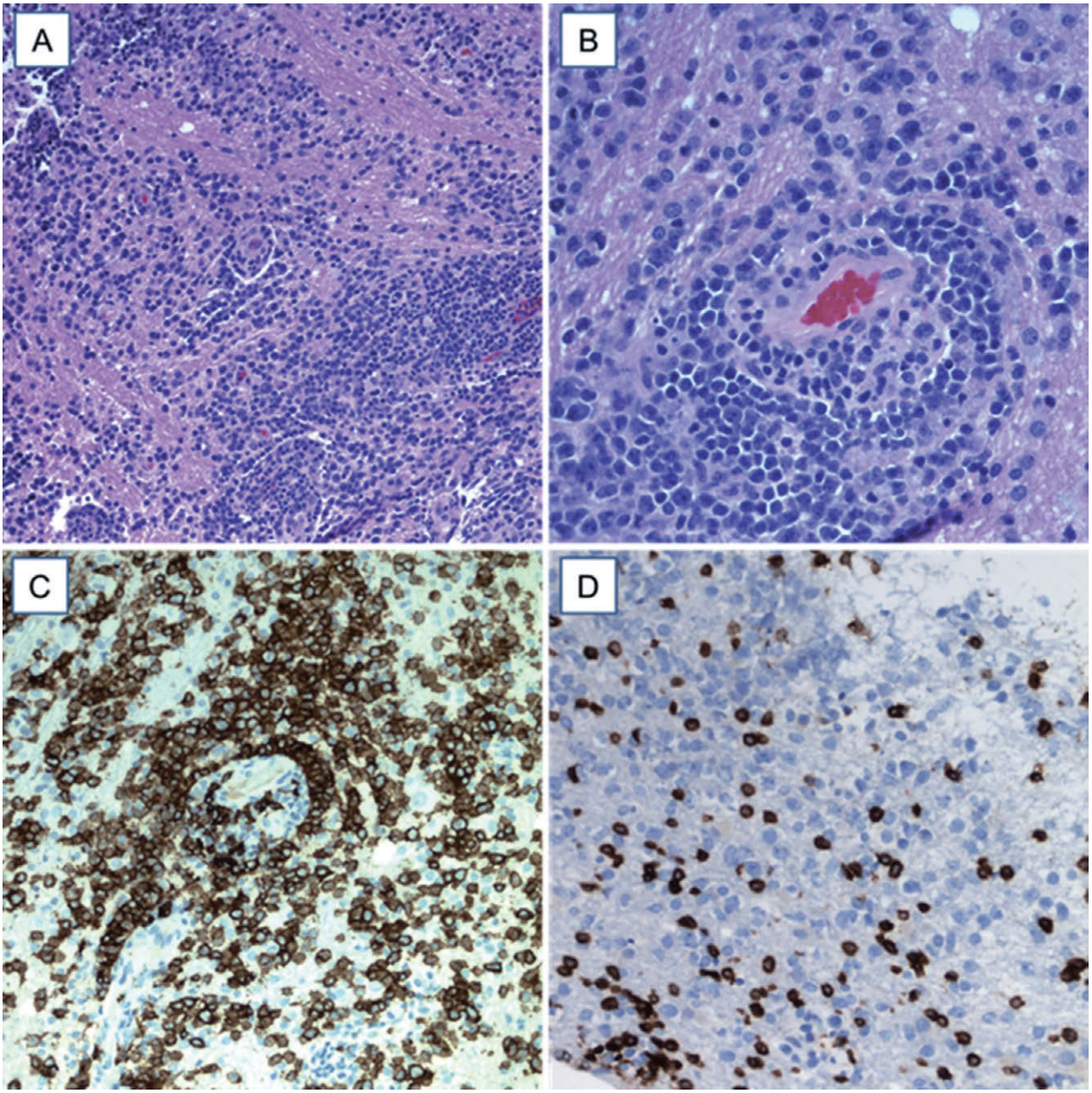
Color plate 38.6 Nodular lymphocyte predominant Hodgkin lymphoma, diffuse pattern. At low magnification, there is a diffuse pattern with a predominance of lymphocytes (A). Diffuse lymphoid infiltrate comprising mostly small lymphocytes with scattered large lymphoid cells with lobated nuclei and moderately abundant cytoplasm (B). CD20 stains the large lymphoid cells and a subset of the small reactive lymphoid cells (C) Numerous PD1+ cells form rosettes around the large CD20+ lymphoid cells (D).



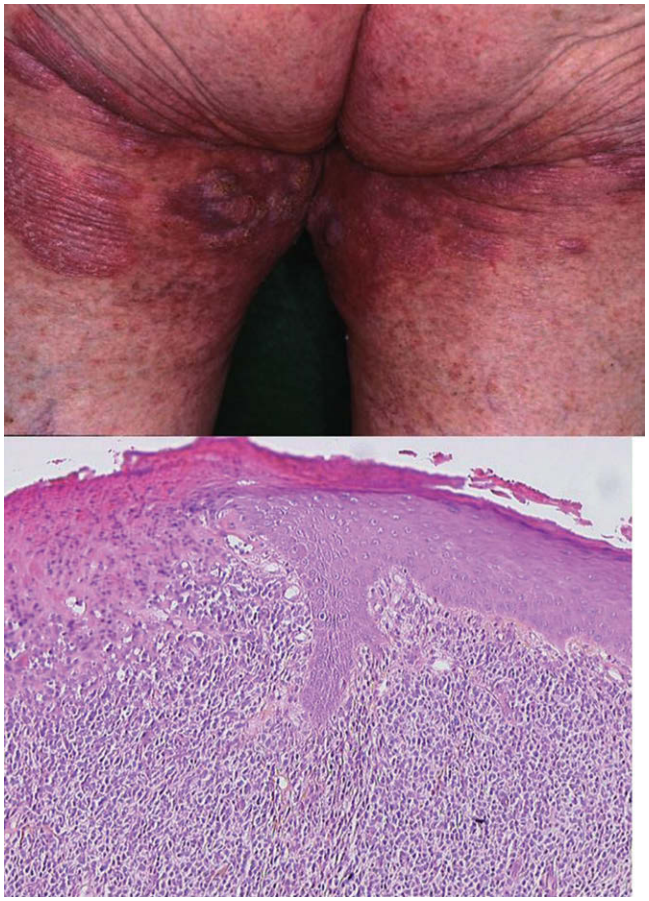
Color plate 46.1 (A) Follicular lymphoma at diagnosis of an untreated patient. (B) At transformation: top area with follicles but diffuse architecture in the lower area composed of sheets of large cells. (C) High-power field of the diffuse area of (B). Large cells, prominent nucleoli, and irregular shape are noted.



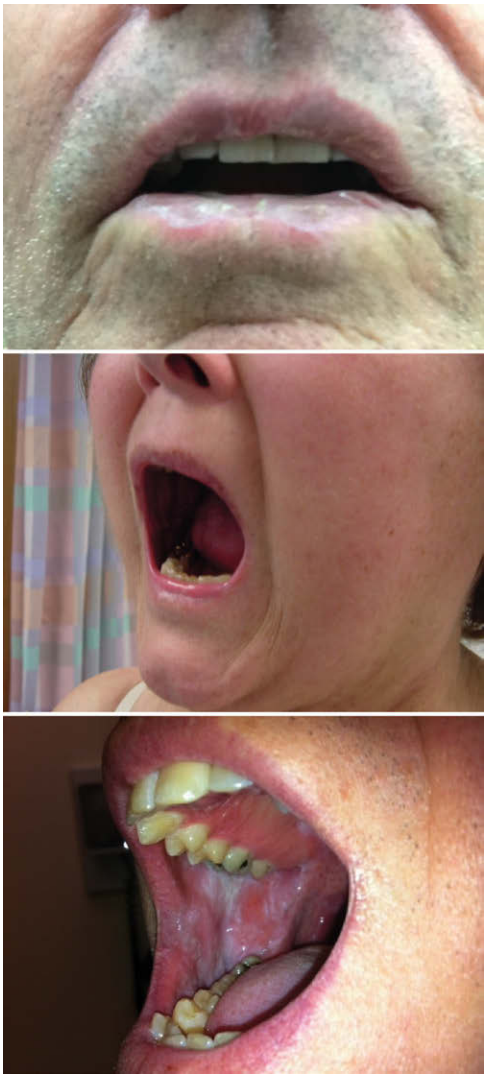
Color plate 46.2 Positron emission tomography–computed tomography (PET–CT) of a newly diagnosed patient with follicular lymphoma (FL). Aorto-pulmonary node had a standardized uptake value of 21.2 compared to 5.4 for a left inferior cervical node. The pathology of the aorto-pulmonary node showed FL, grade 3a.



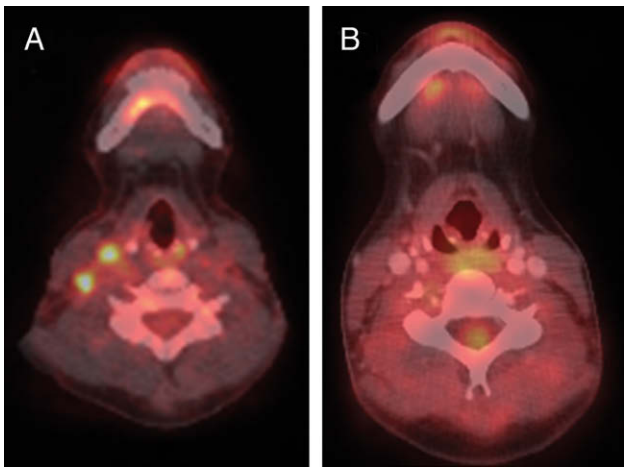
Color plate 48.1 (A) Hematoxylin and eosin stain shows a mononuclear cerebral parenchymal cell infiltrate. (B) At higher-power magnification, the angiocentric arrangement of tumor cells is highlighted. (C) Immunohistochemistry using an anti-CD20 antibody identifies the large atypical cells within the infiltrate as B-cells. (D) A CD3-stain shows a reactive T-cellular infiltrate.



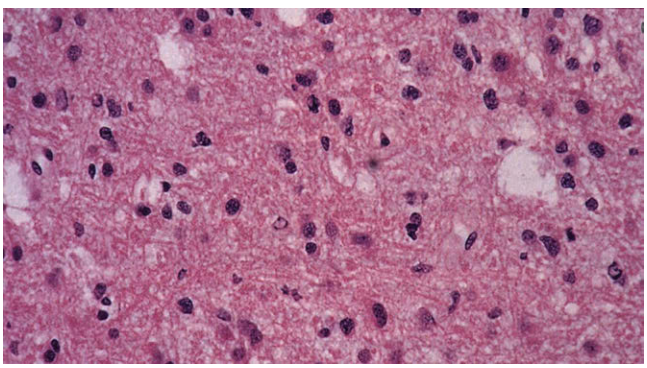
Color plate 50.1 Transformed mycosis fungoides (clinical and pathology pictures).



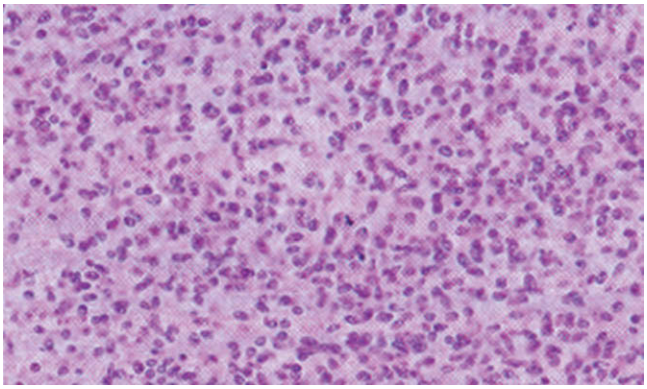
Color plate 69.1 Diagnostic oral manifestations of chronic graft-versus-host disease (cGVHD). Top: Lichenoid cGVHD of the lips. Middle: Restricted mouth opening due to sclerotic cGVHD. Bottom: Lichenoid changes to buccal mucosa consistent with cGVHD.



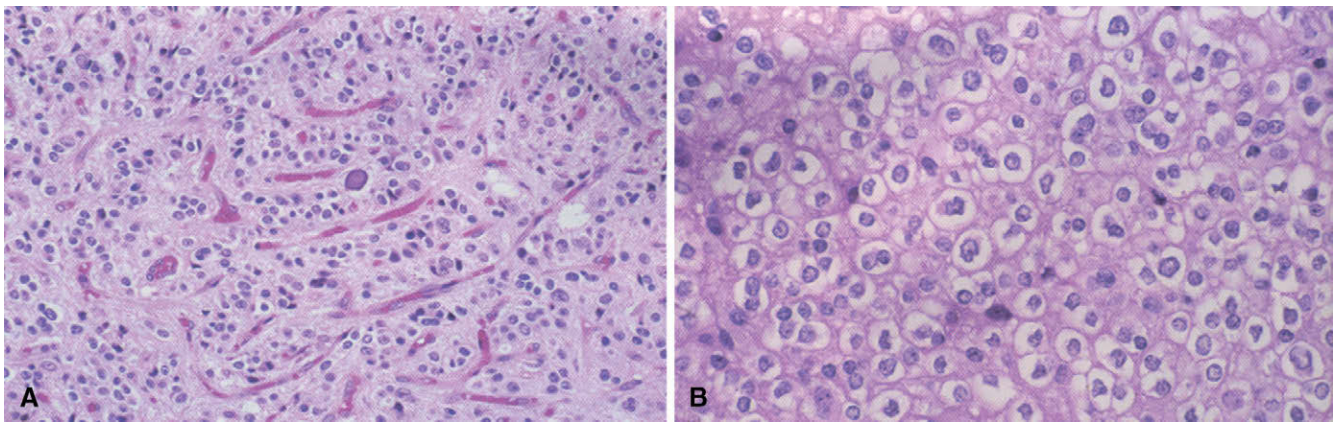
Color plate 63.1 Positron emission tomography–computed tomography (PET–CT) of the neck showing hypermetabolic lymph nodes in the right neck (panel A), which resolved after chemotherapy (panel B).



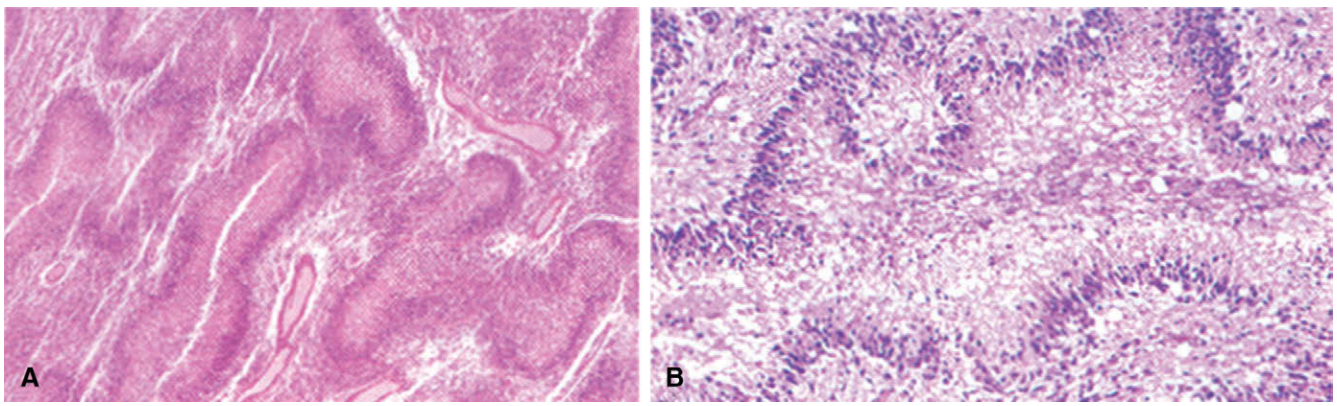
Color plate 70.1 Histologic features of grade II astrocytoma, including increased astrocytic cellularity ("hypercellularity").



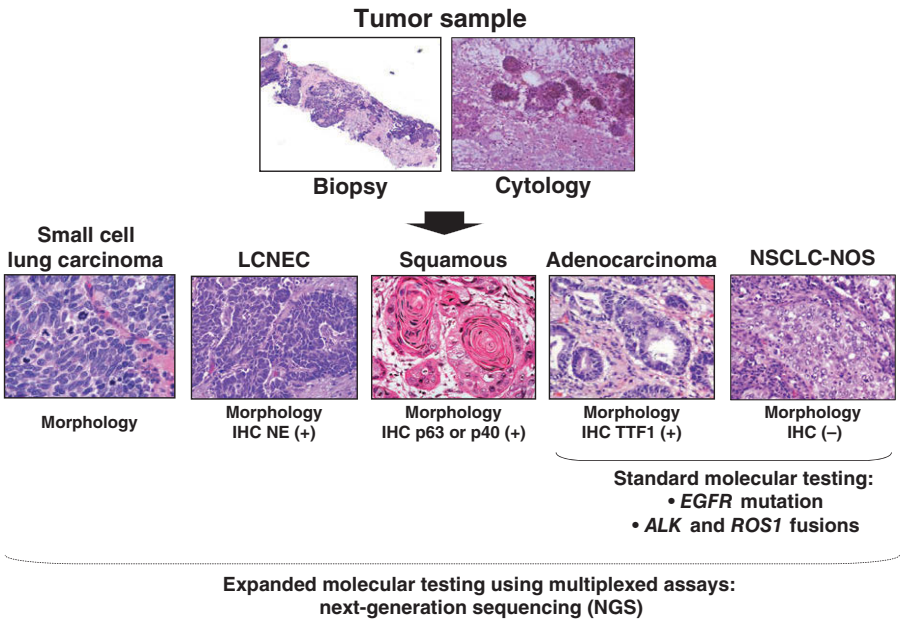
Color plate 70.2 Histologic features of grade III anaplastic astrocytoma, including hypercellularity, atypical nuclei, and mitoses (not shown).



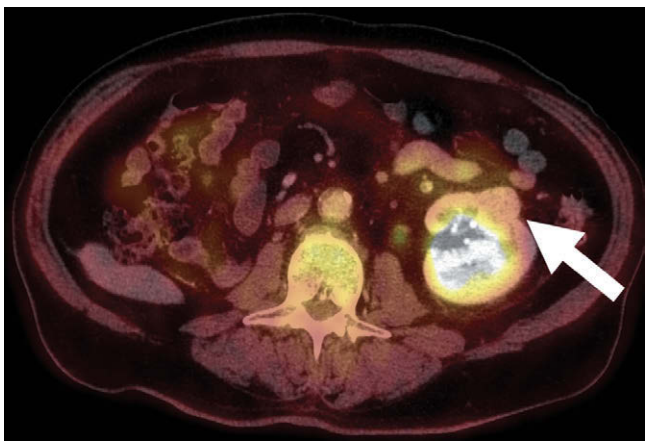
Color plate 70.3 Histologic appearance of oligodendroglioma, with a dense network of branching capillaries ("chicken-wire vessels") (left) and clear cytoplasm with well-defined plasma membrane ("fried egg" artifact) (right).



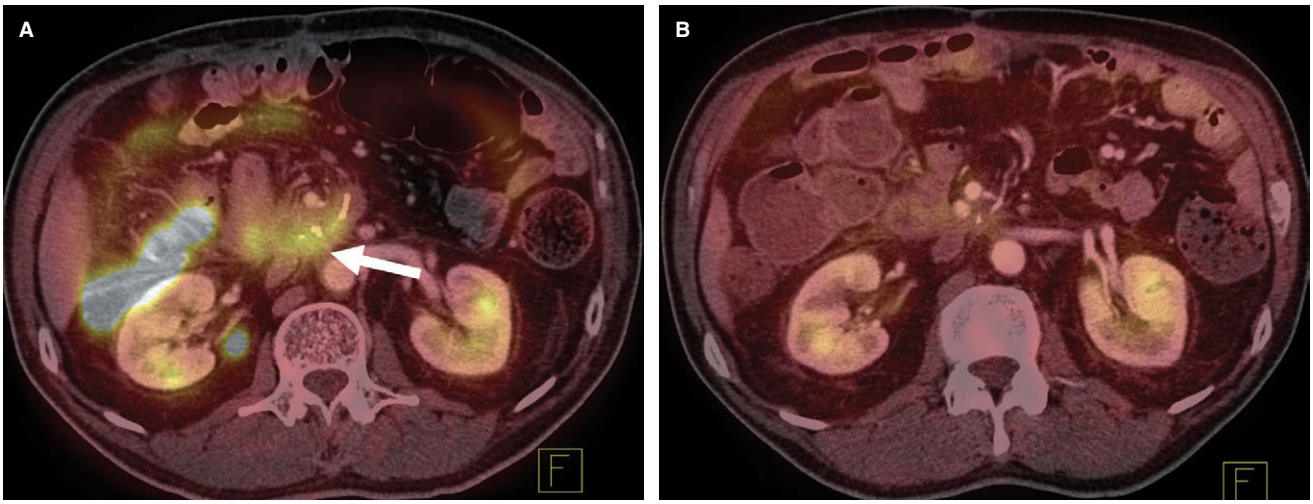
Color plate 70.4 Histologic features of grade IV glioblastoma, including pseudopalisading necroses and endovascular proliferation (not shown).



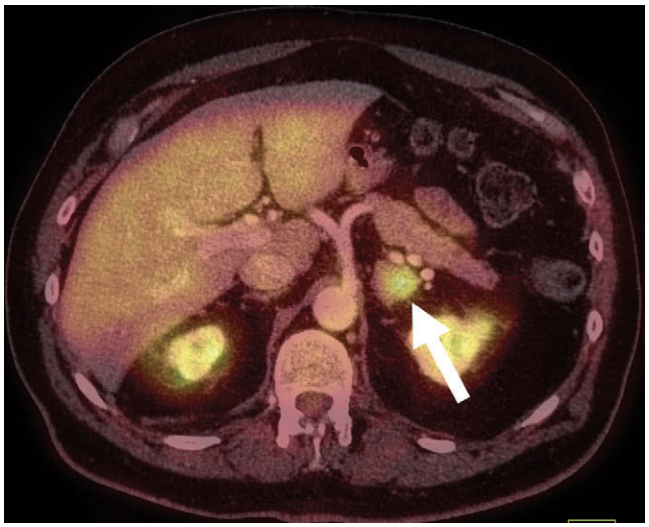
Color plate 74.1 Microphotographs of representative examples of core needle biopsy (biopsy) and fine needle aspiration (cytology) specimens frequently available for histology diagnosis of advanced lung cancer. In lung tumors, the diagnosis of the histology is the first step. In tumors with poorly differentiated histology and with negative immunohistochemistry (IHC) markers, the diagnosis of non-small-cell lung cancer not otherwise specified (NSCLC-NOS) is performed. However, a more specific histology diagnosis should be reached by using a limited panel of IHC: neuroendocrine markers (NEs) are needed for the diagnosis of large cell neuroendocrine carcinoma (LCNEC) histology; TTF1 is a marker of adenocarcinoma histology; and p63 and p40 are markers of squamous cell carcinoma histology. After assessment of tissue quality for molecular testing, the sample should be submitted for a panel of molecular tests. In lung adenocarcinoma and NSCLC-NOS, the standard testing includes *EGFR* mutation, and *ALK* and *ROS1* fusions. When available, multiplexed assays can be applied to maximize the utilization of small-tissue and cytology samples, including the newer next generation of sequencing methodologies.



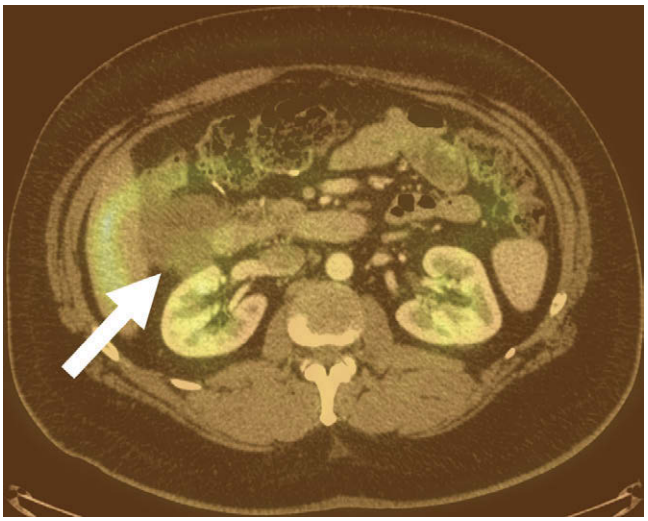
Color plate 131.1 A 70-year-old with a history of renal cell carcinoma treated with right nephrectomy. Positron emission tomography–computed tomography (PET–CT) confirms that the left renal mass does not demonstrate fluoro-deoxyglucose (FDG) avidity. Biopsy was positive for renal cell carcinoma.



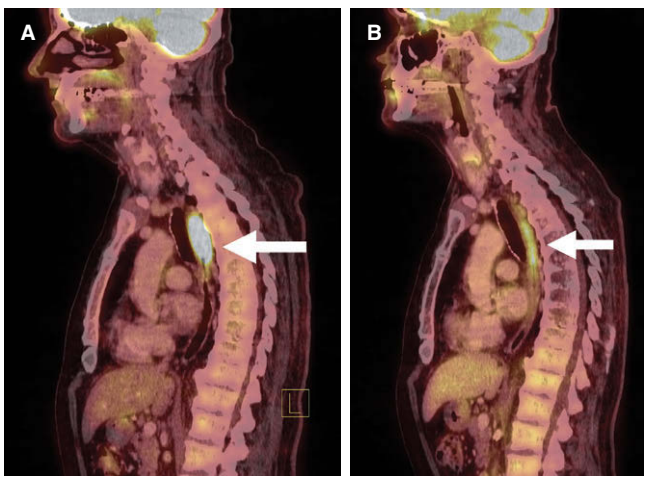
Color plate 131.2 A 65-year-old man 8 months post Whipple procedure for pancreatic cancer. (A) Positron emission tomography–computed tomography (PET–CT) demonstrated a mass at the resection margin with avid fluoro-deoxyglucose (FDG) uptake (arrow). Biopsy of this region was positive for actinomycosis. (B) After treatment with intravenous penicillin and vancomycin, the mass and FDG avidity resolved.



Color plate 131.3 A 45-year-old woman with a history of gastrointestinal stromal tumor (GIST). Positron emission tomography–computed tomography (PET–CT) found a fluoro-deoxyglucose (FDG)-avid left adrenal nodule (arrow). This nodule was stable for over 5 years and was consistent with a benign FDG avid adenoma.



Color plate 131.4 A 52-year-old man post right colectomy for colonic adenocarcinoma. Follow-up positron emission tomography–computed tomography (PET–CT) demonstrated a mass in the right upper quadrant (arrow) adjacent to the anastomosis, which did not demonstrate fluoro-deoxyglucose (FDG) uptake. Biopsy found atypical signet ring cells in a background of abundant mucoid acellular material, consistent with origin from an FDG-negative adenocarcinoma.



Color plate 131.5 A 67-year-old man with squamous cell cancer of the upper esophagus. Fluoro-deoxyglucose (FDG) positron emission tomography–computed tomography (PET–CT) (A) pre- and (B) one month post neoadjuvant chemoradiation shows a decrease in FDG avidity of the tumor (arrow). At resection, there was no residual viable carcinoma.