Pediatric Oncology

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Hematopoietic Cell Transplantation in Children with Cancer

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Editors
Franklin O. Smith, MD
Division of Hematology/Oncology
Department of Internal Medicine
University of Cincinnati College
of Medicine
University of Cincinnati Cancer Institute
Cincinnati, Ohio
USA

Judy M. Racadio, MD
Division of Hematology/Oncology
Department of Internal Medicine
University of Cincinnati College
of Medicine
Madeira, Ohio
USA

Gregory H. Reaman, MD
Division of Oncology
George Washington University
School of Medicine and Health Sciences
Children's National Medical Center
Washington, D.C
USA

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Preface

The evolution of hematopoietic cell transplantation (HCT) as a science, discipline, and treatment modality for malignant diseases in children is integrally linked to the dramatic improvement in outcomes for children with cancer that have occurred during the past four to five decades. The biologic concepts leading to early clinical investigation of the transplantation of bone marrow from a normal donor to a compromised recipient began in treatment-refractory acute leukemia and congenital immunodeficiency. However, the number of potential clinical indications for HCT within just the spectrum of malignant diseases in children has expanded considerably beyond leukemia to a number of solid tumors, including those situations utilizing autologous HCT as rescue from high, both myeloablative and sub-myeloablative, doses of chemotherapy. In addition, the number of investigational and accepted clinical indications for HCT in nonmalignant diseases, including primary and secondary marrow failure disorders, hemoglobinopathies, congenital and acquired immunodeficiency states, and glycogen and lipid storage disorders, may now well outnumber the oncologic applications, but are beyond the scope of this text.

Advances in transplant techniques, improved rates of engraftment, expanded donor sources beyond matched siblings or family members, and the decrease in serious complications, notably acute and chronic graft versus host disease, paralleled advances in the understanding of the normal human immune system. Subsequently, therapeutic manipulation of host immune responses resulted in improved clinical outcomes with HCT. Similarly, mechanical and pharmacological manipulation of harvested hematopoietic stem cells through deletion or enhanced selection of specific cell populations has refined therapeutic efficacy by enhancing graft versus tumor effects and targeted tumor cell elimination.

Similar to the experience with chemotherapy and radiotherapy, where long-term, longitudinal follow-up of survivors has demonstrated significant acute and long-term toxicities, as HCT becomes increasingly successful in contributing to the survivor base, specific late effects are expected and observed. The potential for still unanticipated late effects of HCT warrants a focused survivorship research agenda.

The field of HCT for children with cancer is replete with extraordinary basic science and clinical investigators from numerous disciplines from all over the world. They are represented by legendary giants, including those who have been recognized for their efforts as Nobel laureates as well as by

the many who continue to work tirelessly managing critically ill patients. It is an incredible honor to have been mentored by and to have collaborated with such dedicated professionals who have contributed enormously to establishing HCT as a pivotal treatment modality in childhood cancer.

As with all scientific discovery that ultimately leads to clinical practice, the important role of clinical research in this translation cannot be overstated. Countless children and adolescents have served as willing participants in clinical trials. Many have benefitted personally from these experiences, and many more have contributed to the ever-expanding pool of knowledge that will directly benefit only those children who will follow. It is to those children and their families that we humbly and thankfully dedicate this book.

Cincinnati, OH, USA — Franklin O. Smith, MD
Washington, D.C., USA — Gregory H. Reaman, MD
Madeira, OH, USA — Judy M. Racadio, MD

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The History of Pediatric Hematopoietic Cell Transplantation Around the World

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Jean E. Sanders, Peter F. Coccia, Dietrich Niethammer, Carmemm M. Bonfim, Peter J. Shaw, and Chi-Kong Li

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1.1 Introduction

The concept of modern-day hematopoietic cell transplantation (HCT) began in the 1950s with mouse studies demonstrating that the irradiated mouse would survive if the spleen was shielded, and in other studies the mouse could be protected by an infusion of spleen or marrow cells collected prior to irradiation. Early attempts at human marrow transplant failed except in syngeneic situations, but a few successful transplants in young patients with resistant leukemia demonstrated that lethal total body irradiation (TBI) followed by infusion of compatible marrow could lead to restoration of marrow function and control of the leukemia. Since then, a reasonable estimate is that more than 88,546 children <18 years of age have received hematopoietic cell transplant around the world through 2010. We present the story of how this has developed. While this chapter is not intended to be a complete international

J.E. Sanders, MD (✉)
Member Emeritus Fred Hutchinson Cancer Research Center, Professor Emeritus Pediatrics, University of Washington, Seattle, Washington, USA
e-mail: jsanders@fhcrc.org

P.F. Coccia, MD
Ittner Professor and Vice Chair Pediatrics, University of Nebraska Medical Center, Omaha, Nebraska, USA

D. Niethammer, MD
Professor of Pediatrics Emeritus, Department of Pediatrics, University of Tubingen, Tubingen, Germany

C.M. Bonfim, MD
Director Pediatric Blood and Marrow Transplant Program, Clinical Hospital, Federal University of Parana, Curitiba, Brazil

P.J. Shaw, MA
Head BMT Service, Oncology Unit, Children's Hospital at Westmead, Clinical Professor Pediatrics and Child Health, University of Sydney Medical Program, NSW, Australia

C.-K. Li, MBBS, MD
Chinese University of Hong Kong, Chairman Coordinating Committee in Paediatrics Hospital Authority Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

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history of pediatric HCT, it demonstrates the extent of complimentary international development of transplant programs and collaboration between pediatric transplanters and programs.

1.1.1 The Beginning

Modern-day hematopoietic cell transplantation had its beginning in the early 1950s with the studies of Jacobson who found that shielding the spleen of a mouse during otherwise lethal irradiation permitted the mouse to survive (Jacobson et al. 1949). Lorenz found that an intraperitoneal injection of spleen cells would achieve the same result (Lorenz et al. 1951). At that time, it was unclear whether this radiation protection was due to humoral factors or cellular reconstitution. Definitive experiments in favor of cellular reconstitution came from the observation of Main and Prehn that irradiated mice protected by an infusion of allogeneic marrow subsequently displayed tolerance of a donor skin graft (Main and Prehn 1955). Trentin was able to show that tolerance of the graft was specific for the marrow donor (Trentin 1956). This observation was followed by Ford's report that lethally irradiated mice protected by a subsequent marrow infusion showed marrow cytogenetic characteristics of the marrow donor (Ford et al. 1956).

1.1.2 Early Clinical Studies

In 1956, Barnes and Loutit reported the treatment of leukemic mice by supralethal irradiation followed by infusion of normal mouse marrow (Barnes et al. 1956). At almost the same time, attempts to treat human leukemia with total body irradiation (TBI) and a marrow infusion were reported, but the only successful transplants utilized syngeneic marrow (Thomas et al. 1957). In retrospect, the failure of these early allogeneic transplant attempts was due in part to lack of knowledge of human histocompatibility typing and the use of irradiation exposures too low to achieve the immunosuppression necessary for acceptance of a foreign graft. These failures were duplicated by other investigators, and in 1970, Bortin compiled a list of approximately 200 attempts at allogeneic marrow grafting, all of which had failed (Bortin 1970). Mathe achieved the first persistent allogeneic marrow graft in a patient with leukemia, but the patient died with many problems that were probably related to graft-versus-host disease (GVHD) (Mathe et al. 1965).

In 1959, Thomas et al. reported an identical twin with terminal leukemia who was given 850 R (748 cGy) TBI from opposing cobalt-60 sources and an intravenous infusion of marrow from the normal twin (Thomas et al. 1959b). This dose of irradiation would be expected to produce prolonged pancytopenia and death, but the patient showed prompt hematopoietic recovery and disappearance of leukemia for 4 months. This study showed that lethal irradiation followed by compatible marrow could have an antileukemic effect even in advanced leukemia. Most importantly, it showed that compatible marrow infused intravenously could restore marrow function in human beings after lethal irradiation.

During the 1960s, many of the problems of allogeneic marrow grafting were addressed in animal models. Thomas et al. carried out a series of studies of irradiation and allogeneic marrow grafting in the canine model (Thomas et al. 1959a; Thomas et al. 1962). They found that grafts between histocompatible littermate pairs (i.e., dog lymphocyte antigen [DLA] identical) demonstrated all of the problems that were soon to be recognized in human patients. These transplants were often successful with recipients becoming healthy chimeras.

By the end of the 1960s, developments in supportive care and in the knowledge of human histocompatibility typing led to renewed attempts at allogeneic marrow grafting in human patients. Gatti (University of Minnesota) reported on the first successful allogeneic marrow graft in a child with severe combined immunodeficiency (SCID) using a human leukocyte antigen (HLA)-matched sibling as donor (Table 1.1) (Gatti et al. 1968). Two similar cases were reported very shortly thereafter (De Koning et al. 1969; Bach et al. 1968). The first transplant carried out by the

Table 1.1 Key early transplant reports

Year	Disease	Donor	Reference
1968	SCID	Unrelated	Gatti et al. (1968)
1968	Immune Deficiency	Sibling	Buckley (1971)
1968	Wiskott Aldrich Syndrome	Sibling	Bach et al. (1968)
1968	SCID	Sibling	De Koning et al. (1969)
1971	Acute Leukemia	Sibling	Buckner et al. (1970)
1972	Aplastic Anemia	Sibling	Thomas et al. (1972)
1979	JMML [formerly JCML]	Sibling	Sanders et al. (1979)
1979	Acute Leukemia	Mismatched family	Clift et al. (1979)
1979	ALL remission	Sibling	Thomas et al. (1979)
1980	ALL remission	Unrelated	Hansen et al. (1980)
1980	Osteopetrosis	Sibling	Coccia et al. (1980)
1981	AML – CR 1	Sibling	Sanders and Thomas (1981)
1981	Hurler Syndrome (MPS I)	Sibling	Hobbs et al. (1981)
1982	ALL – glioblastoma second malignancy	Mismatched sibling	Sanders et al. (1982)
1982	Thalassemia	Sibling	Thomas et al. (1982)
1984	Sickle Cell Anemia	Sibling	Johnson et al. (1994)

Seattle team was in 1969. The demonstration that some patients with advanced leukemia could be cured with supralethal chemo-irradiation followed by an infusion of marrow from an HLA identical sibling donor rapidly led to the application of marrow grafting to patients with a variety of malignant and nonmalignant diseases having in common a high probability of failure with other forms of therapy (Buckner et al. 1970; Thomas et al. 1972; Thomas et al. 1975; Thomas et al. 1977; Santos et al. 1971).

The immunological basis of the GVHD reaction was originally described by Billingham and Brent in murine studies (Billingham et al. 1953), but the magnitude of the problem in human patients was not appreciated until consistent engraftment of donor marrow was achieved in the early 1970s. Even with an HLA-matched sibling donor and the use of prophylactic "long" course methotrexate (methotrexate given on days 1, 3, 6, 11, and weekly through 102 days post-transplant), acute GVHD occurred in up to half of the patients. Improved prevention of acute GVHD was achieved with the use of "short"-course methotrexate (days 1, 3, 6, and 11) and daily cyclosporine, decreasing the incidence of acute GVHD in matched sibling pediatric transplants to 20–30 % (Storb et al. 1986). With the increased use of alternative donors, such as matched and mismatched unrelated donors, cord blood donors, and haploidentical donors, acute GVHD incidence remains in the approximate 50 % range. Other agents used in cord blood and haploidentical transplant recipients include rabbit ATG (Thymoglobulin), mycophenolate mofetil, tacrolimus, and posttransplant in vivo T-cell depletion with cyclophosphamide (haploidentical transplants) (O'Donnell et al. 2010). Early publications that helped establish "proof of principle" in pediatric transplantation are listed in Table 1.1.

1.2 Pediatric HCT in the United States and Canada

Jean E. Sanders and Peter F. Coccia

As can be seen in Tables 1.2a and 1.2b and Fig. 1.1, there were few pediatric marrow transplants performed in North America before 1975, and those performed were all from matched sibling donors. It was after publication of the "100 patient" paper (Thomas et al. 1977) that Dr. Mark Nesbit came to Seattle to discuss with Dr. Thomas the plans for a multi-institution study in

Table 1.2a Total and cumulative numbers of pediatric transplants in the United States and Canada by year

Year	ALLO	AUTO	Total	Cumulative total
1968–1974	158	0	158	158
1975–1980	533	25	558	716
1981–1985	957	52	1,009	1,725
1986–1990	1,627	673	2,300	4,025
1991–1995	3,423	1,870	5,293	9,318
1996–2000	4,646	2,166	6,812	16,130
2001–2005	5,216	2,152	7,368	23,498
2006–2010	5,822	2,271	8,093	31,591

ALLO allogeneic, *AUTO* autologous

Table 1.2b Total number of pediatric transplants in the United States and Canada by disease

Disease	ALLO	AUTO
ALL	7,051	345
AML	4,763	731
CML	981	11
MDS	1,349	19
Lymph	582	1,476
Solid	208	6,482
AA	1,892	0
Immune	2,099	0
Other	3,457	145

ALLO allogeneic, *AUTO* autologous

the Children's Cancer Group (CCG). This study was the first study comparing the outcome of children with acute myelogenous leukemia (AML) in first remission who were to subsequently be treated with an allogeneic marrow transplant if an HLA-matched sibling donor were available or be randomized to one of two chemotherapy maintenance regimens (CCG-251) (Nesbit et al. 1994). A total of 508 previously untreated children were entered, and among the 381 who achieved first remission, survival at 3, 5, and 8 years showed a significant difference in favor of marrow transplant ($p<0.05$). Following this study, the CCG Marrow Transplant Committee was formed in June 1982 with Peter Coccia as the initial chair. One of the major functions of this committee was the development of criteria for programs desiring to transplant patients using CCG protocols. The recommended criteria for performance of marrow transplant published by the American Society of Hematology (ASH) in *Blood* and by the American Society for Blood and Marrow Transplantation (ASBMT) in the *Journal of Clinical Oncology* (JCO) in 1990 were essentially identical and were readily adopted by CCG as the criteria for performance of CCG transplant. Jean Sanders was the chair of the CCG Marrow Transplant Committee from 1990 to 2000 until the time of the consolidation of the CCG and POG to form the Children's Oncology Group (COG). The Transplant Committee did not perform studies independent of the major disease disciplines, but rather transplantation was incorporated into the treatment protocol primarily for newly diagnosed patients with AML and neuroblastoma. A major AML study [CCG-2891] evaluated intensively timed versus standard-timed remission induction regimens followed by matched sibling allogeneic transplantation or randomization between autologous transplant and chemotherapy in the first complete remission (Neudorf et al. 2004; Woods et al. 1993). Results demonstrated that the impact of the remission induction regimen also had an influence on relapse rate and disease-free survival after matched sibling transplant. That is, those receiving intensively timed remission induction had superior survival after transplant compared to those receiving standard-timed therapy. Autologous transplant outcome was not significantly different from chemotherapy.

A neuroblastoma trial established that outcome after purged autologous marrow transplant was equivalent to HLA-matched allogeneic marrow transplant following myeloablative therapy for high-risk neuroblastoma (Matthay et al. 1994). Prior to 1991, all studies evaluating intensive chemotherapy, radiation therapy, and an immune biologic modifier had been Phase II studies. From 1991 to1996, a prospectively randomized study of patients with high-risk neuroblastoma evaluated the role of intensive chemotherapy as compared to autologous transplant and then the role of posttransplant 13-c*is*-retinoic acid. Results demonstrated superior event-free survival for those receiving autologous transplant, and treatment with 13-c*is*-retinoic acid was found to be beneficial when administered after chemotherapy or transplantation (Matthay et al. 1999).

John Graham-Pole was the initial chair of the Pediatric Oncology Group (POG) Marrow

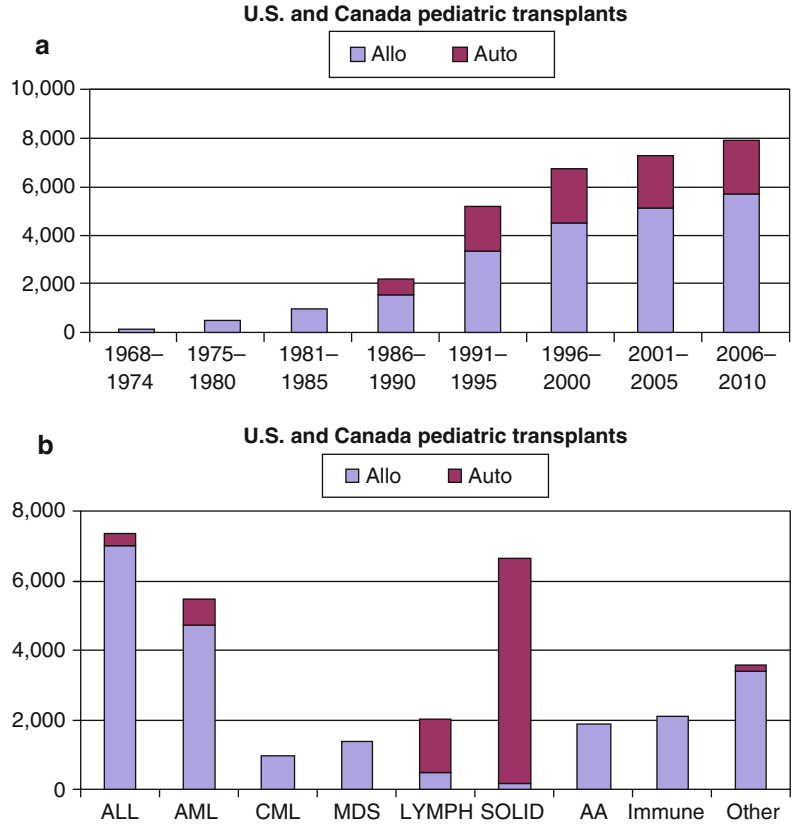


Fig. 1.1 The data illustrated represents pediatric (<18 year old) transplants performed during each time period in North America 1968–2010. The data were obtained from Fred Hutchinson Cancer Research Center (FHCRC) and Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR data are confidential and represent a preliminary review of data submitted to them. The analysis has not been reviewed or approved by Advisory or Scientific Committees of CIBMTR. Data from FHCRC were combined with CIBMTR data to construct the graph

Transplant Committee. He was followed by Jeffrey Lipton who was POG Marrow Transplant Committee chair from 1990 to 2000 and during that time developed cooperative group-wide criteria for performance of a POG transplant. There were two important studies performed by POG during this time. The POG 8821 AML study incorporated allogeneic transplant for those with a matched sibling donor and a randomization to either autologous transplant in first remission or chemotherapy. Results were similar to that observed in CCG 2891, which was that there were no differences in outcome between chemotherapy and autologous transplant, but superior survival for those receiving matched sibling allogeneic transplant in first remission (Neudorf et al. 2004; Woods et al. 1993; Ravindranath et al. 1996). A pivotal study compared results of transplantation for children with acute lymphoblastic leukemia (ALL) in second remission as reported to the International Bone Marrow Transplant Registry (IBMTR) with children who received chemotherapy treated by POG. The results demonstrated that those who received matched sibling transplants had fewer subsequent relapses and superior leukemia-free survival (Barrett et al. 1994).

The COG was formed in 2000 as a result of the merging of CCG, POG, the National Wilm's Tumor Study Group, and the International Rhabdomyosarcoma Study Group, thus making one pediatric oncology cooperative group in North America. Jeffrey Lipton and Jean Sanders were initial co-chairs of the newly formed COG hematopoietic cell transplant discipline. It was determined that in order to enroll children onto a COG study incorporating transplantation, the institution must be a member in good standing of COG and the transplant program must achieve Foundation for Accreditation of Cellular Therapy (FACT) accreditation. The next COG AML studies focused on dose-intensive rather than intensive-timing strategy and did not ask specific transplant questions, but they did permit children with suitably matched family member donors to receive an allogeneic transplant in first remission. Results indicated that

disease-free survival was superior for those receiving an allogeneic transplant in first remission (Cooper et al. 2012). Subsequent AML studies addressed the highest-risk patients and transplantation for those individuals. Neuroblastoma trials continue to evaluate the use of intensive chemotherapy for high-risk patients along with surgery, myeloablative chemotherapy, autologous peripheral blood stem cell (PBSC) transplants (PBSCT) and posttransplant immune modulation with 13-c*is*-retinoic acid, and use of anti-GD2 monoclonal antibody. A prospective ongoing Phase III study has just been completed evaluating the impact of tandem versus single autologous PBSC transplants on disease-free survival.

Cooperative group leukemia and solid tumor transplant questions were always tied to the primary remission induction chemotherapy protocol and as such took a long time to develop, write, complete accrual, and analyze. The pediatric transplant physicians were also interested in transplant approaches for patients with nonmalignant diseases. Thus, the Pediatric Blood and Marrow Transplant Consortium (PBMTC) was formed. Initially this group struggled because of limited funds and no reliable way to collect data. The meetings were held in conjunction with COG meetings, where some investigators with nonmalignant disease transplant protocols openly made information available and others presented proposed new studies. Eventually, arrangements were made to work with COG for data collection. Currently, the PBMTC has a pediatric program (day) at the tandem Center for International Blood and Marrow Transplant Research (CIBMTR) meetings, which is followed by the annual PBMTC business meeting.

1.3 Pediatric HCT in Europe

Dietrich Niethammer

The history of pediatric HCT in Europe began in 1949, with a report from the University of Lvov, Poland, about the therapeutic intramedullar transfusion of bone marrow in children with leukemia and other blood diseases (Raszek-Rosenbusch 1949). The modern history of pediatric HCT began in Europe in 1965 in Leiden, the Netherlands, when a child with SCID (at that time called Swiss-type agammaglobulinemia) received bone marrow cells that had been depleted of T cells by density gradient centrifugation from a "matched" unrelated donor. The child died 2 weeks after the bone marrow transplant (BMT) due to *Pneumocystis carinii* pneumonia (Dooren et al. 1968). In 1968, a successful BMT in a child with SCID was also performed in Leiden (De Koning et al. 1969). In the following years, further successful (C. Griscelli, Paris) and unsuccessful attempts at BMT in SCID patients were documented in other centers. In the United Kingdom (UK), the first successful allograft was performed in a child with mucocutaneous candidiasis by the Westminster Children's Hospital Bone Marrow Team (Valdimarsson et al. 1972). Given the success of allogeneic BMT in patients with aplastic anemia in Seattle during the 1970s, some European countries initiated similar transplant programs (Table 1.3). In most countries, the programs were initially managed by Internal Medicine services or collaborations between pediatric and adult hematologists. Leiden had an independent pediatric program from 1971, and in the United Kingdom pediatric transplantation developed de novo from pediatric oncology programs and was hence independent of Internal Medicine.

In 1974, the European Bone Marrow Transplantation Group (EBMT) was founded

Table 1.3 Examples of the initiation of combined bone marrow transplantation programs in some European countries for diseases other than immunodeficiency

Country (city)	Year
Switzerland (Basel)	1973
Finland (Helsinki)	1974
(Turku)	1981
Germany (BRD) (Munich and Ulm)	1975
(DDR) (Jena)	1980
Sweden (Stockholm/Huddinge)	1975
France (Paris)	1975
Italy (Pescara)	1976
(Genoa)	1978
Poland (Warsaw)	1984
(Poznan) – only pediatrics	1989
Turkey (Istanbul)	1989

with the goal to promote all aspects associated with the transplantation of hematopoietic stem cells. During the following years, several special Working Parties (WP) were established, but only the Inborn Errors WP was linked specifically to pediatric disease. All other WPs pooled data relating to adults and children. In the 1970s and early 1980s, patients with aplastic anemia were transplanted with increasing success. When the transplantation of adult patients with end-stage leukemia began, most pediatric centers decided to avoid BMT in end-stage patients because they had already been heavily treated with chemotherapy, and their leukemia proved to be very resistant to further treatment. However, transplanting patients with relapsed leukemia early after remission induction proved to be a more promising and logical approach. In Europe, most pediatricians treat patients with chemotherapy as well as care for them through HCT, so discussion of a combined approach soon followed. The first cooperative trial of BMT in relapsed ALL of the Berlin-Frankfurt-Münster (BFM) and CoALL groups in Germany showed the benefits of this treatment strategy for children with early relapse after the initial intensive treatment (Dopfer et al. 1991). Other trials followed with pediatricians from several European countries collaborating, which confirmed the value of this approach.

Although the pace of HCT technology increased rather rapidly in western European countries, progress was not so fast in eastern European countries for various reasons. Therefore, in 2001, the EBMT in collaboration with the European School of Hematology (ESH) developed an outreach program supporting emerging projects and transplant centers in countries with limited resources and/or experience. A report describing this program summarized the results of stem cell transplantation in 2,342 children performed in eastern European countries between 1985 and 2004 (Wachowiak et al. 2008).

In the 1990s, the number of transplants in children and adolescents increased steadily within Europe (Fig. 1.2a). Nevertheless, the EBMT-registry, as well as the WPs, continued to report data on patients with the same diagnoses independent of their age. This became increasingly problematic for pediatricians because the characteristics of the underlying leukemia, as well as their primary chemotherapy treatments and outcomes, were very different from adults. It took several years for pediatricians to convince their EBMT WP colleagues from Internal Medicine that it was important to perform analyses according to age rather than in a broad diagnostic category. In addition, an increasing number of children were transplanted for diseases not found in adults, such as inborn defects of hematopoiesis or the diverse groups of autoimmune and metabolic diseases. In 1984, the group in Pesaro, Italy, published the first positive results of BMT in children with thalassemia (Lucarelli et al. 1984). Progressively, some of the established combined centers separated due to recognition of the different needs of adult and pediatric patients. In many countries, new centers for HCT were established, and the majority no longer combined the treatment of adults and children.

Finally, in 1995, the Board of the EBMT agreed to create the WP Pediatric Diseases (PDWP). The first chair was Dietrich Niethammer from Tübingen, Germany, followed by Giorgio Dini from Genoa, Italy. Currently, the WP is chaired by Chris Peters from Vienna, Austria. The WP meets regularly during the annual meeting of the EBMT and separately every second year in varying locations. As a consequence, international courses on bone marrow transplantation in children were created. During the second course, a consensus concerning the indications for transplantation in childhood leukemia was reached within the WP (Dini et al. 1996). These and other activities led to a dramatic increase in collaboration, such as multicenter trials, discussions about the standardization of conditioning regimens, treatment of GVHD, and quality of care. Logically, the accreditation of established transplant units became a topic for discussion. It was clear to pediatricians from the beginning of BMT that the needs of children are very different from those of adults. The delivery of high-quality, safe, child-appropriate care in the best environment, where the child's and family's experience is of paramount importance, is as critical as good outcomes. However, it took 5 years of negotiation

until this was finally accepted by the European committee responsible for the assessment and accreditation of hematopoietic stem cell transplant programs (Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and EBMT-Joint Accreditation Committee (JACIE)) (Cornish 2008). The first dedicated Pediatric JACIE Training Course was run in December 2011 in Barcelona, and such was its success that others will follow, serving the whole of Western, Eastern, and Middle Europe.

Following the establishment of the PDWP, the registry of the EBMT finally began separate analyses of results in children and adolescents.

During the 1970s, only a small number of children and adolescents received stem cell transplants in Europe. However, the number of these procedures has grown steadily since the 1980s (Fig. 1.2a). Initially, only matched sibling donors were used for transplantation, but since the mid-1980s, an increase in the use of matched and later on of mismatched family donors, especially haploidentical parents, has been documented. During the 1990s, an increase in the use of unrelated donors followed. At the same time, the use of cord blood as a source of stem cells also emerged. The largest program using unrelated donors in HCT

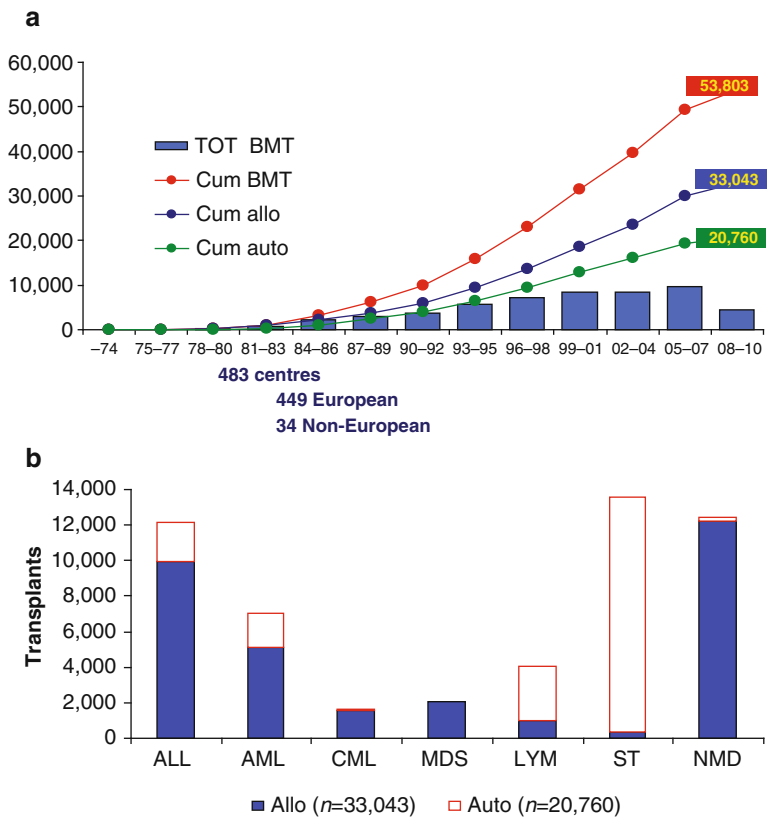
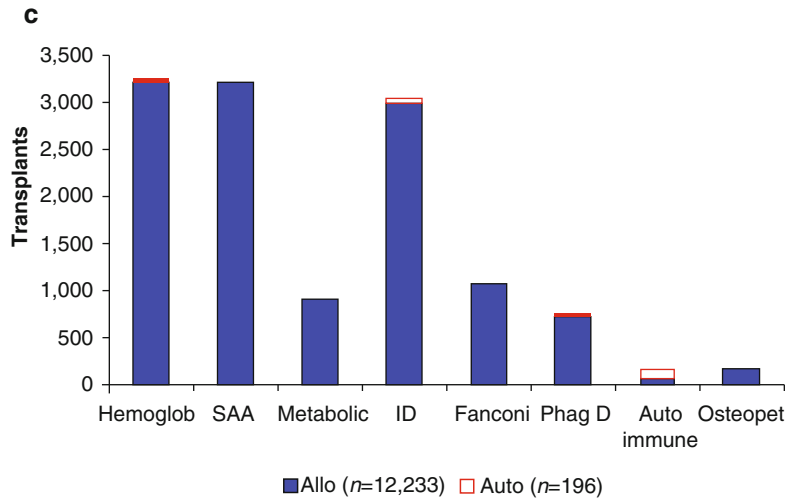


Fig. 1.2 (a) Annual and total numbers of HSCT in patients ≤ 18 years (From the EBMT-Registry and the EBMT Working Party Pediatric Diseases). (b) Number of transplants by disease in patients ≤ 18 years of age (From the EBMT-Registry and the EBMT Working Party Pediatric Diseases) *ALL* Acute Lymphoblastic Leukemia, *AML* Acute Myelogenous Leukemia, *CML* Chronic Myelogenous Leukemia, *MDS* Myelodysplastic Syndrome, *LYM* Lymphoma, *ST* Solid Tumors, *NMD* Nonmalignant Disease. (c) Number of HCT in patients ≤ 18 years by disease in NMD (From the EBMT-Registry and the EBMT Working Party Pediatric Diseases). *Hemaglob* Hemoglobinopathies, *SAA* Severe Aplastic Anemia, *ID* Immune Deficiency, *Fanconi* Fanconi Anemia, *Phag D* Phagocytic Disease, *Autoimmune* Autoimmune Diseases, *Osteopet* Osteopetrosis

Fig. 1.2 (continued)



for children was initiated in Bristol, UK (Cornish 2005; Harvey et al. 2012).

In autologous transplantation, stem cells were collected from peripheral blood from 1995 to the present, whereas for allogeneic transplantation, bone marrow continues to be the main source of stem cells in children and adolescents. Figure 1.2b shows the number of transplants by disease and demonstrates that autologous stem cell transplantation has been performed in solid tumors and to some extent in cases of acute leukemia and lymphoma. Figure 1.2c summarizes the patients with nonmalignant diseases. Of interest are the HCTs in children with autoimmune diseases after the efficacy of this approach was demonstrated in some treatment-resistant diseases (Brinkman et al. 2007; Daikeler et al. 2009). The original guidelines for this approach, published in 1997, have recently been revised (Snowden et al. 2012). The transplant-related mortality (not shown) has decreased as a result of the growing experience of the centers over the years as well of the improvement of treatment and supportive care strategies.

During the last decade, various multicenter trials in pediatric oncology containing HCT as one arm of the treatment strategy have been initiated on national, European, and even international scales. An example of this extremely productive collaboration for the treatment of children is the ALL-SCT-BFMi trial, which is an extension of the ALL-SCT-BFM 2003 trial for patients with high-risk ALL in first remission, or after first or subsequent relapse (Schrauder et al. 2008). Strict rules define HLA typing, now at high resolution, which aids in donor selection. There are also rules regarding conditioning regimen, GVHD prophylaxis, and therapy as well as standards of supportive care all designed to reduce transplant-related mortality. There is also an assessment for minimal residual disease (MRD) (Bader et al. 2009). The importance of the detection of MRD for a successful outcome has been shown by the group from Bristol (Knechtli et al. 1998), and its value for the treatment stratification of childhood ALL was also shown in an international multicenter trial (Flohr et al. 2008). Additionally, chimerism-guided, preemptive immunotherapy plays a well-defined role in the pediatric transplant setting to treat impending relapses (Rettinger et al. 2011). HCT currently has an established position in the treatment of childhood leukemia in Europe.

The first reports about HCT in children with Fanconi anemia (FA) from Paris and Leiden showed a very early-onset toxic reaction in 4 of 5 patients in each center, which at that time was considered to be very acute severe GVH reaction (Gluckman et al. 1980). Later, it became clear that the conditioning regimen had to be reduced in these patients to prevent lethal toxicity. Since these early trials, almost a thousand children with FA have been transplanted in Europe (Fig. 1.2c).

Finding an appropriate unrelated donor remains a challenge in the multiethnic context of Europe, as it is often not possible to find a donor in a timely manner. This explains why the use of haploidentical donors, of which the parents are almost always available, was investigated. The group in Ulm demonstrated that in children with SCID, it was possible to reconstitute the immune system with HCT without inducing life threatening GVHD by performing rigorous T-cell depletion using soybean agglutinin and rosette formation with sheep red blood cells (Friedrich et al. 1984). In recent years, various methods of T-cell depletion have been used. The next important step was the use of highly purified CD 34+ mobilized stem cells (Handgretinger et al. 2001), which led to a near absence of GVHD. However, delayed immune reconstitution remains a problem. This might be overcome by new methods of T-cell depletion (CD3+/CD19+ depletion), which retain large numbers of NK cells, monocytes, dendritic cells, and other myeloid cells in the graft.

In summary, continuous development and evolution of pediatric HCT in Europe has been evident since the early 1970s, leading to its establishment as a standard therapeutic procedure with a defined place in pediatric hematology and oncology treatment strategies. The early foundation of the EBMT, wherein physicians performing pediatric transplants found a platform for fruitful debate and discussion, was fundamentally invaluable. The majority of these pediatricians had their primary activities in the very early days based in pediatric oncology. Extrapolating from experiences in this field, they already understood that close national and international collaboration was the only way to resolve many problems associated with childhood illnesses that are appropriate for consideration of a HCT procedure.

1.4 Pediatric HCT in South and Latin America

Carmem M. Bonfim

The field of HCT is expanding rapidly in South and Latin America, and tremendous improvement has been observed during the past 35 years. The first BMT was performed in Colombia in 1976 as a lifesaving procedure for a young woman with aplastic anemia/paroxysmal nocturnal hemoglobinuria. The bone marrow was obtained from her identical twin, and the transplant was successful (Restrepo 1985).

The idea of setting up a HCT unit according to international parameters began in 1976 when Euripedes Ferreira came back from Duke University and organized a Histocompatibility Laboratory at the Federal University of Parana (Curitiba, Brazil). Rebecca Buckley and Bernard Amos from Duke University were invaluable in the development of this area in Brazil. Together with Ricardo Pasquini and a dedicated multidisciplinary staff, they initiated the first HCT Program in South America, and in October 1979 the first patient was transplanted. This patient had severe aplastic anemia and died from infectious complications before engraftment, but this initial experience enabled the development of HCT in Brazil and other countries in South America. The first 62 patients were reported in 1985 with encouraging results (Ferreira et al. 1985). The chronological initiation of HCT programs in Latin America is described in Fig. 1.3.

It was only in 1981 that the first child was transplanted in South America. This 15-year-old boy had acute leukemia and received a bone marrow from his HLA identical sibling in Curitiba, Brazil. In that same year, a very important collaboration was established with Fred Hutchinson Cancer Research Center (FHCRC) (Seattle, USA). This collaboration stands today, and many physicians and nurses as well as data managers and other allied health professionals from Brazil and other countries in Latin America receive part of their training at FHCRC.

The first years of transplantation in South and Latin America were marked by many challenges and very limited resources. Most of the children transplanted had acute leukemias in advanced phases, but in December 1985, the first patient with primary immunodeficiency (X-linked SCID) was transplanted in Costa Rica at the Hospital Nacional de Ninos (Fasth 2009). This was, again, the result of a long-standing collaboration with the European School for

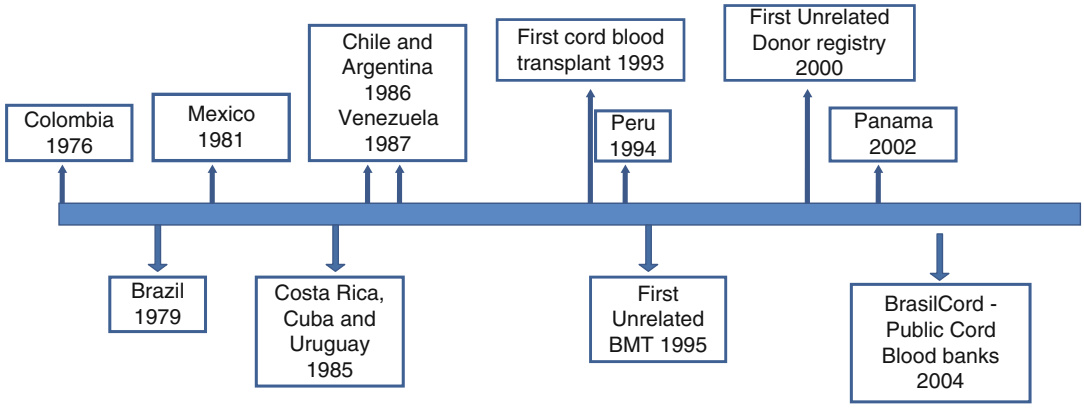


Fig. 1.3 Chronology of initiation of HCT programs in Latin America

Primary Immunodeficiencies (ESID) and the Working Party of Inborn Errors and Primary Immunodeficiencies of the EBMT. Transplants for primary immunodeficiencies (PID) are challenging, especially for developing countries, due to the delay in diagnosis, high cost of the procedure, and lack of specialized HCT units. In 2009, the Latin American Society for Primary Immunodeficiencies (LASID) was founded with the major goal of increasing awareness of these diseases and improving the outcome of patients (Leiva et al. 2011). Argentina, Brazil, and Chile are the most active countries, but the number of transplants is low when compared to developed countries. All South and Latin American countries give neonatal BCG for prevention of endemic tuberculosis, and babies with SCID are usually transplanted with disseminated disease. HCT for babies with SCID have worse outcome when compared to developed countries, but the outcome in patients with Wiskott-Aldrich is similar to that reported in the literature.

The first HCT for a patient with an inborn error of metabolism (IEM) was performed in Curitiba, Brazil, in 1988. This 5-year-old girl had mucopolysaccharidosis type III (Sanfilippo) and received a bone marrow from her HLA identical sibling. She engrafted promptly without any transplant-related toxicity but without effect on the progression of her disease; her disease progressed, and she became severely disabled (Lange et al. 2006). Only in 1999, with the expertise gained at the University of Minnesota, a new HCT program for genetic diseases was initiated in Brazil. During the past decade, intense interaction between Latin American HCT centers and the Working Party of IEM and PID of the EBMT and the pediatric HCT program at Duke University provided the basis for the opening of the first pediatric unit designated for babies with genetic diseases in Latin America. Together, the HCT centers in Latin America have transplanted less than 50 patients with IEM, most of them with the diagnosis of X-linked adrenoleukodystrophy and mucopolysaccharidosis. Delayed diagnosis, late referral to a HCT center, as well as lack of reimbursement by the government may account for the low number of patients transplanted in this region.

In the beginning of the 1990s, the first related cord blood transplant was performed in Latin America (Curitiba, 1993). The 2-year-old child transplanted with AML in second clinical remission (CR2) is now a healthy young adult, and the use of cord blood as an alternative stem cell source expanded the use of HCT in Latin America. Three years later, in 1995, a 6-year-old girl with AML in CR3 received the first unrelated bone marrow transplant (Curitiba). Collaboration with international registries, such as the National Marrow Donor Program (NMDP), the Anthony Nolan Registry, the New York Cord Blood Bank, Eurocord, and the German Donor Registry (DKMS), was very important but insufficient to find donors with adequate compatibility for the majority of our patients. In 2000, the Brazilian Unrelated Donor Registry (REDOME) was created, initially with only 12,000 donors. From

2000 to 2009, the Brazilian government invested over 375 million dollars to expand the donor pool and now REDOME is the third largest registry in the world with almost 3 million donors, and 60–70 % of unrelated BMT in Brazil are being performed with Brazilian donors. The three other volunteer donor registries in South and Latin America are in Mexico, Argentina, and Uruguay. The numbers are small, but these registries are growing rapidly, and they will reduce the cost of unrelated HCT as well as speed up the search for unrelated donors in our population. The 17 public cord blood banks in South and Latin America are 12 in Brazil, 3 in Mexico, 1 in Chile, and 1 in Argentina.

1.4.1 Transplant Activity in South and Latin American Countries

HCT activity in the Americas has been recently updated as part of an effort from the Worldwide Network for Blood and Marrow Transplantation (WBMT) to report global activity in all regions. HCT is now considered a standard procedure for many diseases, and it is not restricted only to countries with high income (Gratwohl et al. 2010). In Latin America, the number one indication for HCT in children is acute leukemia, and the local government usually pays for HLA identical sibling transplant. Unfortunately, in some countries, unrelated HCT is restricted to patients with private insurance due to the high cost of the procedure and lack of adequate reimbursement by federal funds.

Presently, there are 70 transplant centers in Brazil with a median of 2,000 transplants/year, and 80 % are located in public hospitals, and the government pays for related and unrelated transplants. Most of the transplants are from related donors, and 50 % are allogeneic. Approximately 300 pediatric transplants are performed every year, and the major indications are acute leukemia and bone marrow failure syndromes. Infectious complications after HCT are common, and different microorganisms are prevalent in South and Latin America. Therefore, the study of neglected tropical diseases is very important for this population (Machado et al. 2009). There is also a comprehensive program for the treatment of FA patients with more than 250 patients having been transplanted in Curitiba (Bonfim et al. 2007).

Chile is also a very active country in pediatric transplantation. The Pontificia Universidad Catolica has transplanted more than 200 children, among which 30 % were unrelated and most were cord blood. The Hospital Calvo Mackenna has transplanted 160 children and recently published their experience in haploidentical transplantation (Palma et al. 2012). In Mexico, there are five pediatric HCT centers, and the government pays for transplants in children with leukemia. All other indications are usually covered by private insurance. Approximately 50–60 transplants are performed in children every year in Mexico, and approximately 80 % are allogeneic. Many HCT centers use reduced intensity regimens for the preparatory regimen in children (Ruiz-Arguelles and Gomez-Almaguer 2008).

HCT activity in the pediatric population is increasing rapidly in other Latin American countries. Colombia has 14 HCT units and 50 % of those transplant pediatric patients, while in Peru 25 % of the transplant activity is related to children (10–15 transplants/year). In Cuba there is one pediatric HCT unit where the majority of children have been transplanted since 1986 (Dorticos-Balea et al. 2011). Costa Rica has one pediatric HCT center, and approximately five to six transplants/year are performed. Venezuela has two active HCT units and both transplant pediatric patients. According to INCUCAI (Instituto Nacional Central Único Coordinador de Ablacion e Implante), Argentina has 53 HCT centers that performed almost 700 transplants during the year of 2010 (68 % were autologous). Most of the pediatric transplants are performed at Hospital Garrahan, but activity in this area is not restricted to this hospital. In Uruguay, the first child was transplanted in 1997, and the country is well organized with an unrelated donor registry and an active pediatric HCT unit.

One of the most important factors for the development of HCT in South and Latin America was the possibility of joining international registries. Since 1985, Brazil has been reporting its

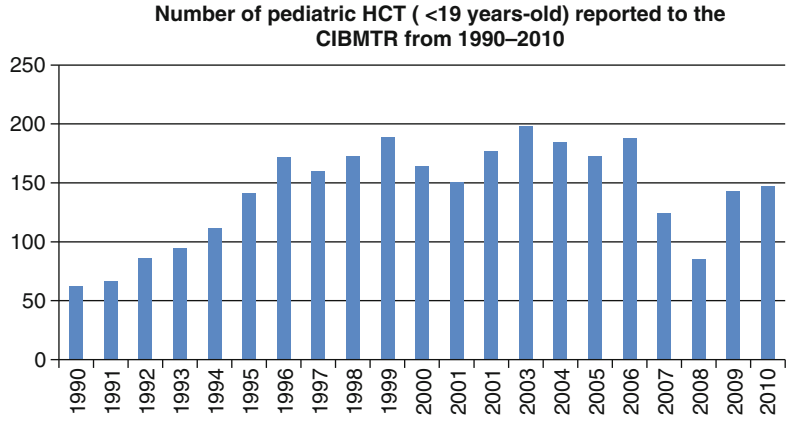


Fig. 1.4 Pediatric HCT activity in Latin America reported to the CIBMTR (Data reported by HCT centers in Argentina, Brazil, Costa Rica, Colombia, Chile, Cuba, Peru, and Uruguay from 1990 to 2010. The data presented in this figure are preliminary and were obtained from the Statistical Center of the Center for International Blood and Marrow Transplant Research. The analysis has not been reviewed or approved by the Advisory or Scientific Committees of the CIBMTR)

data to the CIBMTR. Now 11 HCT units in South and Latin America report to this registry. The creation of an international working committee by the CIBMTR was of utmost importance because it opened a special forum for discussion of HCT for countries outside the United States. A few centers in Latin America also report to the EBMT and the Eurocord registries, and this has enabled many opportunities for research. Data registered by Latin American countries to the CIBMTR is illustrated in Fig. 1.4 and reflects the transplant activity in the region. Autologous HCT are likely underreported. Most of the children were transplanted below the age of 11 (63 %) and received bone marrow from HLA identical siblings. The major indications were acute leukemia in 40–50 % of patients, and bone marrow failure syndrome in 25 % of the cases reported to this registry (Pasquini 2012 CIBMTR Data).

Another international institution that has played a major role in the development of pediatric oncology in South and Latin America is the St. Jude International Outreach Program (Memphis, USA). More than 100 physicians and nurses from almost every country in Latin America have participated in training at this institution. St Jude Children's Research Hospital has an official program with Chile (Hospital Calvo Mackenna) and with the Federal University of Parana in Curitiba, Brazil.

HCT is an expensive procedure, and access to this treatment is still limited in developing countries. In Latin America, most of the transplant centers are supported by the local government, and federal funds will be needed to develop better units as well as unrelated donor registries and public cord blood banks. With support from the WBMT as well as the CIBMTR, the Latin American Blood and Marrow Transplant Society will be created in 2012, and it will join the other international transplant societies. A better assessment of HCT activity in Latin America is urgently needed, and further integration between transplant centers may help improve outcome of HCT in this geographical area.

1.5 Pediatric HCT in Australia and New Zealand

Peter J. Shaw

When compared with many other countries, Australia and New Zealand (ANZ) are big countries with small populations. Provision of specialized medical services is always an issue when the population is spread over such a vast area for the area of Australia is similar to that of the United

States, but has a population about 1/15th the size. Much of the population is centered in the main coastal cities of Adelaide, Brisbane, Melbourne, Perth, and Sydney in Australia and Auckland in New Zealand. These six cities have seven major pediatric referral hospitals that account for all of the pediatric allogeneic HCT activity in Australia and New Zealand.

The development of pediatric HCT in ANZ was influenced by three main elements: the earlier development of pediatric oncology centers, the pioneer centers for BMT in Europe and the United States, and the parallel thoughts of developing BMT expertise in adult hospitals. Even in the first years of existence of the pediatric oncology units, younger members of the faculty were encouraged to go to European and US centers to gain experience in this new exciting field. Early transplants were often for nonmalignant conditions, such as aplastic anemia, and so initial series from adult units included some pediatric age patients (Biggs 1980). Marcus R. Vowels returned from his fellowship in Glasgow via Boston and San Francisco to Prince of Wales Children's Hospital (now Sydney Children's Hospital). After a visit to Seattle, he established a combined adult and pediatric program for transplantation of patients with leukemia using TBI. They first transplanted such a patient in 1975 and subsequently transplanted the first pediatric case with sustained remission in Australia in 1979 (Vowels et al. 1982) F. Leonard Johnson was a fellow at the Royal Alexandra Hospital for Children (RAHC) in Sydney and subsequently trained in Seattle, where he was involved in some of their earliest pediatric publications (Johnson et al. 1976). He was instrumental in Michael Stevens completing a fellowship in Seattle and then returning to RAHC, then at Camperdown. One of the cobalt machines at the nearby Royal Prince Alfred Hospital was modified to deliver TBI for the first patient transplanted there in 1980. Eight transplants for nonmalignant disease were performed at Royal Children's Hospital in Melbourne between 1973 and 1980, but it was only after Henry Ekert encouraged Karin Tiedemann to spend some time at Great Ormond Street Hospital in London with Judith Chessels and Roland Levinsky that they commenced transplant for leukemia in 1981. In Perth, the concept of "Total Therapy" was brought to Western Australia with the arrival of Michael Willoughby from the United Kingdom in 1983. The Total Care Unit at the Princess Margaret Hospital came into being, with their first allogeneic bone marrow transplant being performed later that same year. In Adelaide, the development of pediatric BMT at Adelaide Children's Hospital in the early 1980s was heavily centered on what was happening next door at the Royal Adelaide Hospital with Dr. Chris Juttner and other adult hematologists. This included some of the earliest experience in the use of peripheral blood stem cell collection in children (Juttner et al. 1990).

The second wave of pediatric transplant physicians also showed strong overseas influence in their training. Peter J. Shaw came from the United Kingdom, where he had worked with John Barrett in leukemia and John Hobbs in metabolic disease at Westminster Children's Hospital, London, and Tom Revesz had worked in a variety of centers, in particular Utrecht in the Netherlands. Ian Toogood returned to Adelaide after training with Mark Nesbit in Minneapolis. A strong North American relationship between the unit in Perth and Vancouver still continues after Cathy Cole and later Tina Carter returned to Perth from fellowships in Canada. More recently, the Minnesota influence persists with both Tracey O'Brien (Sydney Children's Hospital) and Chris Fraser (Royal Children's Hospital Brisbane) undertaking fellowships there. The European links also continue, with Francoise Mechinaud, previously in charge of the HCT program in Nantes, France, joining and now heading the unit in Melbourne.

In New Zealand, the very first allogeneic bone marrow transplant was performed in 1976 in Auckland, again a combined adult and pediatric initiative. However, only small numbers of pediatric transplants were performed prior to Lochie Teague returning from training Melbourne in 1992.

In the years since, in particular in the main capitals in the larger states of New South Wales (Sydney), Victoria (Melbourne), and Queensland

(Brisbane) in Australia and Auckland in New Zealand, the centralization of pediatrics into the major centers has promoted development of well-established pediatric HCT units, providing the full array of transplant types to children of all ages and with all diagnoses. A particular area of interest and expertise in ANZ is cord blood transplantation. In the decade 2001 to 2010, unrelated cord was used in 60 % of unrelated procedures in pediatric patients (Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) annual data summary 2010). Some of the first cord blood transplants in the world were done in ANZ (Vowels et al. 1993). The leading role played by Marcus Vowels' early interest in cord blood transplant led to establishment of the Sydney cord blood bank in 1995, which has since grown into the federally funded Auscord, operating three coordinating banks in Australia with an inventory in excess of 25,000 units – one of only seven countries with more than 20,000 units, giving Australia the third highest rate of cord units available per capita (Bone Marrow Donors Worldwide (BMDW) annual report 2010). Our early collective experience in pediatric cord blood transplant has been published (Petterson et al. 2009).

Because HCT is such a small specialized area, in particular in pediatrics, not only do many of the centers rely on specialists whose training is completed overseas, but also in order to improve results in the future, collaboration is vital.

Within ANZ, the Pediatric Oncology Group (currently known as the Australia and New Zealand Children's Haematology Oncology Group, ANZ CHOG) initially established informal groups for those with a shared passion, and HCT was one of these. Since all centers were required to report their raw transplant data to the national registry, the Australasian BMT Recipient Registry (ABMTRR), a mechanism was developed to share this data, and this led to publication of our national pediatric data in 2009 (Moore et al. 2009). Data was pooled on the first 136 cord blood transplants done in the pediatric centers (Petterson et al. 2009). Further retrospective studies are underway using this national database as a starting point.

In addition to continued international retrospective collaborations, such as within CIBMTR and EBMT, the ANZ centers have also recognized the necessity to participate in international prospective studies. The early years of the ANZ CHOG group allowed collaborative studies to be performed and published, including transplantation studies (White et al. 1994; McCowage et al. 1995; O'Brien et al. 2002). But, in exactly the same way that CCG and POG came together to form COG, the Australasian centers recognized that future prospective studies needed to be larger, and, for countries with so small a population as Australia and New Zealand, this meant international collaboration. Thus, all the seven pediatric oncology centers referred to here are part of COG. Several also participate actively in PBMTC studies, and all the centers have embraced the need for FACT accreditation as a measure of quality, a requirement of continued HCT activity within COG, and as an avenue to further prospective study participation through the partnership between PBMTC and Blood and Marrow Transplant Clinical Trials Network (BMT-CTN). Continued collaboration remains the only way forward, and this includes our closer neighbors in the Asia-Pacific region, as well as Europe and North America. Many of the units have assisted in training fellows who have returned to their own countries in Asia and maintain close contacts with them.

1.6 Pediatric HCT in China

Chi-Kong Li

HCT in China was started in 1981 (Wu and Lu 2008) and was initially performed by adult hematologists in adult BMT units, but also included older children with acute leukemia. There are now over 100 HCT units in China, and 2,000 transplants are performed annually, but mostly for adults (Lu 2009). With the development of pediatric hematology and oncology in children's hospitals and general hospitals, a few pediatric BMT units started to appear in the late 1980s. However due to high treatment

costs and unsatisfactory transplant outcomes, the development was rather slow. Some centers might only perform a few cases per year, or even suspend the service for some years. Since the early 2000s, more pediatric BMT units have been established across the country. These are mainly concentrated in the big cities such as Beijing, Shanghai, and Guangzhou. The centers are set up in the university hospitals with strong pediatric hematology backgrounds (e.g., Beijing Children's Hospital, Shanghai Children's Medical Center, Sun Yat-sen Memorial Hospital, and Naval General Hospital). There are a number of challenges here in establishing a pediatric transplant unit. Donor availability is one of the major limiting factors as the "one-child" policy has been in place since the 1970s. Most families only have one child, thus an unrelated donor is always required in pediatric HCT. The Chinese Marrow Donor Program (CMDP) was initiated in 1992 and started service for the public in 2001. The number of registered voluntary donors in the early years of the registry was low, thus the chance of finding a matched donor was low. The cost of procuring unrelated donor stem cells (bone marrow or cord blood) from overseas is very expensive, and few families can afford it. Taiwan Tzu Chi Stem Cell Center provides help to search for Chinese donors for patients in mainland China; so far 748 donations have been sent to 41 hospitals (Yang et al. 2009). In recent years, there has been a rapid development of the CMDP and the registered donors now number over one million. CMDP under the Chinese Red Cross Society has 30 branch registries, 25 HLA laboratories, 3 high-resolution HLA laboratories, and 1 quality control laboratory. This has much improved the chance of finding a matched unrelated donor in China.

The establishment of an unrelated umbilical cord blood bank in China is another important milestone in pediatric HCT activities. There are now eight cord blood banks in the large cities, namely, Beijing, Tianjin, Shanghai, Guangzhou, and Jinan. The Ministry of Health issued licenses to accredited cord blood banks and oversees the operation. Unrelated cord blood is now an important source of stem cells for transplant in children.

Haploidentical donor transplant is more commonly performed in China due to lack of compatible sibling donors. Parents are usually selected as donors and donate bone marrow and/or peripheral blood stem cells for their children. Ex vivo T-cell depletion is not performed due to strict requirements on technology. Intensive in vivo T-cell depletion by antithymocyte globulin (ATG) and other immunosuppressive treatment have been adopted with encouraging results (Dong et al. 2011). Haploidentical transplant is performed more commonly in adult transplant units, but also includes pediatric patients. In one recent report, out of 181 family haploidentical donor transplants, 37 % were performed in patients under age of 20 years; only 16 % of these were below age of 10 years (Dong et al. 2011).

High treatment cost is another inhibitory factor for development of HCT in China. The health insurance system is not well developed, and families have to pay for the transplant cost of RMB 200,000 to 300,000 (USD $30,000 to $50,000) for an uncomplicated transplant. For a family with the average annual income of RMB 40,000, it is a great financial burden. With the rapid economic development and also the tradition of helping relatives in extended families, more patients can now afford the transplant. Charity organizations also contribute funds to help patients with the treatment costs. Recently, the government set up an insurance system to cover some serious diseases in children including acute leukemia, and more patients can now receive appropriate treatment including HCT.

The pediatric conditions treated by HCT in China are similar to other countries. ALL and AML are the two most common conditions treated with HCT. Aplastic anemia appears to be more common in China and the reason is not clear. Congenital immunodeficiencies and inborn errors of metabolism are also treated by HCT in a few centers that have special interest in these hereditary diseases. Autologous HCT is performed mainly for solid tumors, especially stage 4 neuroblastoma. However, the indications for HCT may be quite variable and depend on the center's policies. For example, minimal residual disease methodology is not standardized in ALL, but it may

be applied as an indication for transplant in first complete remission. Adult transplant physicians might have different definitions of very high-risk ALL, and some children might be treated with HCT instead of intensive chemotherapy. Due to the unsatisfactory chemotherapy results in AML, some centers adopt the general approach of unrelated donor HCT for AML in first complete remission. Similarly, some centers also advocate early HCT for newly diagnosed severe aplastic anemia because of encouraging results of matched unrelated donor HCT in this disease. Conditioning for HCT is also variable, and total body irradiation is less commonly included. With the heterogeneity of disease statuses, conditioning regimens and experience of the HCT centers, the results of HCT may be quite variable.

In the recent 5 years, collaborative work in pediatric hematology and HCT has been established in China. The Chinese Children Leukemia Group (CCLG) has been formed, and an ALL study has been started. The study has delineated clear HCT indications for childhood ALL. Under the Hematology Committee of Chinese Pediatric Society, a working group on HCT was also formed. The working group concentrates on two areas, the HCT registry and guidelines for HCT. By 2009, the registry collected data from 13 pediatric HCT units in 7 cities from 1998 to 2008 (personal communication with Dr. Zuo Luan). A total of 505 transplants were performed, from 5 transplants initially in year 1998 to 111 transplants in year 2009. The conditions treated by HCT included hematologic malignancies (280), solid tumors (135), thalassemia (75), aplastic anemia (65), autoimmune diseases (15), and immunodeficiencies (19). For leukemias, 96 % were allogeneic transplants of which unrelated donors constituted 62 % and haploidentical donors 11 %. Umbilical cord blood has now become a major source of unrelated donors for HCT in leukemia, constituting 54 %. Bone marrow donation is uncommon in both sibling and unrelated donor settings; most of the donors choose peripheral blood stem cell (PBSC) donation. The traditional belief of precious bone marrow directs most people towards PBSC. The above statistics only included information submitted by pediatric HCT units on a voluntary basis, and the pediatric transplants performed in adult HCT units are not included.

As China has a pediatric population of approximately 200 million, there is a great demand for HCT service. With the expanding number of registered voluntary donors in the donor registry and the rapid increase in the number of cord blood unit storage centers, matched unrelated donors are now more readily available. More families can now afford the financial burden of HCT, but the insurance system needs further improvement to extend the coverage. The hospital management is supportive in the physical set up of HCT units because it is considered a reputable high standard of care in their hospitals. However, the training of HCT personnel is of utmost importance for the success of a HCT center. Sending medical, nursing, and laboratory to some established centers in China, Hong Kong, and overseas is arranged, but there is no formal training program yet.

Hong Kong reintegrated with China in 1997, but their pediatric HCT service started in 1991. With the two pediatric HCT centers serving a population of 7 million, about 50 HCT are performed every year. The Hong Kong Bone Marrow Donor Registry was set up in 1991, and the public cord blood bank was established in 1998. Unrelated donor HCT is becoming the major activity as the family size is now getting small. One of the important sources of unrelated donors is Taiwan, as both are Chinese communities. The Buddhist Tzu Chi Stem Cell Center (BTCSCC, formerly Tzu Chi Bone Marrow Donor Registry) was established in 1994, and there were over 320,000 volunteer donors by the end of 2008. Cord blood banks were also established, including nonprofit organizations, such as BTCSCC and Sun Yat-Sen Cancer Center Cord Blood Bank, as well as commercially run cord blood banks (Chen et al. 2009).

1.7 Summary

Clearly, pediatric hematopoietic cell transplant has come a long way since the late 1960s and 1970s. Over the past four decades, improvements

in supportive care and HLA typing have contributed substantially to improved outcomes. Throughout this time, children with hematologic malignancies and many different types of nonmalignant disorders have benefited and been cured of their underlying diseases with this procedure. Similarly, expanding the acceptable sources of hematopoietic stem cells has permitted this procedure for an even larger number of children. Later chapters will report outcomes for specific diseases and descriptions of late effects resulting from the intensive transplant preparative regimens used to date. Although none of us has a crystal ball, future pediatric studies will no doubt be directed toward decreasing the early and late toxicities through application of non-myeloablative regimens. Some nonmalignant diseases may benefit from gene therapy approaches.

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Donor Sources and Donor Selection for Hematopoietic Cell Transplant

2

Ann E. Woolfrey and Vanderson Rocha

Contents

Hematopoietic stem cells (HSCs) may be obtained by collection of bone marrow, mobilization and collection of peripheral blood stem cells (PBSCs), or collection of umbilical cord blood (UCB). The choice of HSC product depends upon the disease being treated, the availability of a suitable donor, and, to a certain extent, donor size. Donors of either PBSC or marrow rarely develop serious complications, although there are qualitative differences in the types of adverse events associated with either procedure (Rowley et al. 2001).

2.1 Autologous Hematopoietic Stem Cells

Autologous HSC provides a readily obtainable reservoir of cells for reconstitution of hematopoietic function after high-dose therapy without risk of graft-versus-host disease (GVHD). The indications for autologous hematopoietic cell transplant (HCT) are limited to high-risk lymphoma or certain solid tumors, such as high-risk neuroblastoma. Autologous HSC may also serve as the source of cells for gene transfer for correction of single-gene defects, such as X-linked severe combined immunodeficiency (SCID) or Fanconi anemia (Cavazzana-Calvo et al. 2000; Tolar et al. 2011). Autologous grafts have the potential disadvantage of tumor cell contamination and lack immune-mediated graft-versus-tumor effects, which may contribute to relapse of malignancy after transplant (Rill et al. 1994). In the late 1980s, the procedure of autologous HCT was advanced

A.E. Woolfrey (✉)
Fred Hutchinson Cancer Research Center, Seattle, WA, USA
e-mail: awoolfre@fhcrc.org

V. Rocha
EUROCORD, Hospital Saint Louis, Paris, France

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significantly by use of hematopoietic growth factors to stimulate circulation of large numbers of HSC that could be collected from the peripheral blood. PBSC has largely replaced marrow as the preferred product for reconstitution of autologous hematopoiesis because recovery of peripheral blood counts is more rapid. Consequently, compared to marrow recipients, PBSC recipients have fewer platelet and red cell transfusions, days of antibiotic use, and days in hospital (Theilgaard-Monch et al. 1999; Schmitz et al. 1996). Marrow and PBSC differ quantitatively and qualitatively in the number of CD34+ cells as well as other cell subsets, including a tenfold increase in number of CD3 cells in PBSC. CD34+ and CD3 cells obtained by granulocyte colony-stimulating factor (G-CSF) mobilization may be functionally different, and together with differences in types of accessory cells, the two products may not be equivalent in types of immune cells reinfused or the kinetics of immune reconstitution (Arpinati et al. 2000).

Private banking of autologous UCB has increased over the past 10 years, with approximately 2,000,000 units stored worldwide. To date, few of these units have been used for autologous HCT. One reason is that there are a limited number of indications for autologous HCT, and in these settings the goal is generally to achieve rapid recovery of hematopoiesis after high-dose conditioning. Therefore, the potential benefit of avoiding tumor cell contamination in the cord unit may be counterbalanced by the slow engraftment kinetics of UCB. Secondly, the limited cell dose of most UCB units restricts the option to young children. Nonetheless, there have been several case reports of successful autologous HCT. Therefore, if available, it could be considered, particularly in cases in which a graft-versus-leukemia effect is not required (Hayani et al. 2007; Rosenthal et al. 2011).

2.2 HLA-Identical Related Donors

Allogeneic HCT requires availability of a suitable donor, determined by human leukocyte antigen (HLA) compatibility and physical fitness for the procedure. The inheritance pattern of HLA haplotypes results in the potential for matching HLA antigens at the genetic level among full siblings (HLA genotypic identity). Donor-recipient HLA genotypic identity confers the lowest risk for immunologically mediated complications, graft rejection and GVHD (Beatty et al. 1991; Anasetti et al. 1989). When an HLA genotypically identical donor is available, the choice of marrow or PBSC depends upon the patient's disorder, as well as suitability of donor for the procedure. Randomized trials have found faster recovery of peripheral blood cells without significant increase in the incidence of acute GVHD among recipients of PBSC compared to marrow (Schmitz et al. 1998; Bensinger et al. 2001). Allogeneic PBSCs are associated with a lower risk for relapse and increase the probability of relapse-free survival, suggesting that the higher dose of T cells may contribute an important graft-versus-leukemia (GVL) effect. The superiority of PBSC in treatment of patients with hematologic malignancies cannot be extrapolated to patients with nonmalignant conditions, as the risk of chronic GVHD is higher with PBSC grafts (Flowers et al. 2002).

2.3 Alternative Donors

Most patients referred for allogeneic HCT lack an HLA-matched sibling; thus, an alternative donor must be identified. Possible sources for an alternative donor include unrelated volunteer donors (URD), unrelated cord blood units, or extended family members. The suitability of each donor source depends upon the disease being treated, the urgency of the transplant procedure, and the available protocols. To date, there have been no randomized studies comparing outcome of the various donor sources that could guide selection of an alternative donor. The best possible alternative donor will be HLA matched with the recipient; however, a less well-matched donor may be appropriate for patients with aggressive malignancies in the interest of shortening the time to HCT.

Large studies comparing outcome of HCT using HLA-matched sibling donor (MSD) grafts

compared to other donor sources have necessarily been retrospective analyses. Therefore, caution should be taken in the interpretation of these studies, particularly those with small numbers, as the results may be affected by selection bias or other confounding factors. As discussed in more detail below, high-resolution typing has improved the ability to select donors matched for HLA alleles. Although matching for HLA-A, HLA-B, HLA-C, and DRB1 (8/8) alleles has been shown to improve outcome of unrelated HCT, it is not clear whether this level of matching can be viewed as equivalent to an HLA-MSD (Petersdorf et al. 2004; Lee et al. 2007). A prospective, genetically randomized trial conducted by the French Society of Bone Marrow Graft Transplantation and Cell Therapy (SFGM-TC) found that disease-free survival (DFS) was not statistically different for patients given unrelated donor grafts matched for HLA-A, HLA-B, HLA-C, DRB1, and DQB1 ($n=55$) compared to patients given HLA-MSD grafts ($n=181$) (Yakoub-Agha et al. 2006; Hansen et al. 1998). However, larger, albeit retrospective, studies have shown that even very well-matched unrelated donor (MUD) grafts are not the equivalent of MSD grafts. In a study of patients with chronic myelogenous leukemia (CML) given myeloablative conditioning, Weisdorf and colleagues from the Center for International Blood and Marrow Transplant Research (CIBMTR) found that DFS was superior for those given MSD grafts ($n=450$) compared to 8/8 HLA-MUD grafts ($n=667$) (hazard ratio (HR) 1.89, 95 % confidence interval (CI) 1.59–2.25, $p<0.0001$) (Weisdorf et al. 2009). Another CIBMTR study of adults with hematologic malignancies found that DFS was lower for 8/8 MUD recipients with acute myeloid leukemia (AML, $n=340$) compared to MSD recipients ($n=1,271$), although no difference was observed for patients with acute lymphoblastic leukemia (ALL, $n=483$ MSD versus 189 MUD) or CML ($n=1,401$ MSD versus 412 MUD) (Petersdorf et al. 1998; Ringdén et al. 2009). In this analysis, the significantly greater incidence of acute or chronic GVHD among MUD recipients did not appear to result in a reciprocal significant reduction in relapse.

These studies primarily or exclusively include patients with chronic phase CML, not commonly diagnosed in pediatric patients, and now considered treatable with tyrosine kinase inhibitors, such that HCT is no longer considered frontline therapy. For this reason, a single-center retrospective study was conducted in 1,448 patients with advanced hematologic malignancies to determine whether the outcome of HCT with very well-matched (10/10) MUD grafts could approach that of MSD (Woolfrey et al. 2010). The risk for mortality and relapse was similar between the two groups; however, patients given 10/10 MUD had a significantly higher risk for acute GVHD grades 2–4 (odds ratio (OR) 1.77, 95 % CI 1.33–2.36, $p=0.0001$) and for clinical extensive chronic GVHD (adjusted HR 1.34, 95 % CI 1.12–1.60, $p=0.001$). Despite a higher incidence of chronic GVHD, there was no significant difference in the performance scores, suggesting that quality of life was not appreciably different. There was, however, an effect of cell source that was apparent among patients with intermediate-risk disease, defined as acute leukemia in remission, CML in accelerated phase, or refractory anemia with excess blasts (RAEB). Specifically, patients given PBSC grafts from 10/10 MUD had significantly higher risk for mortality compared to patients given MSD grafts or MUD marrow grafts (HR 1.62, 95 % CI 1.21–2.17, $p=0.001$).

Taken together, these retrospective studies support several concepts. First, despite matching for HLA by high-resolution typing at 8 or 10 alleles, MSD grafts remain the "gold standard" and therefore should be preferred over MUD when available. Second, if a suitable MSD is not available, an 8/8 or 10/10 MUD graft will result in nearly similar outcome. Third, the effect of using an alternative donor is mainly seen in patients with low-risk disease, and there is little difference in outcome for those with more advanced leukemia. Finally, the source of MUD cells (i.e., peripheral blood or marrow) may have an effect on outcome, particularly for patients with less advanced disease.

2.4 Selection of Unrelated Donors

Several factors should be considered in selection of the optimal URD in order to reduce transplant-related mortality (TRM), the most important of which is the degree of HLA match. Within the past decade, high-resolution typing techniques have been developed to allow identification of the polymorphic alleles of class I HLA-A, HLA-B, and HLA-C antigens and class II HLA DRB1 and DQB1 antigens. Retrospective studies have shown that only half of patient-donor pairs otherwise matched for HLA-A and HLA-B by serologic typing, and matched for the DRB1 alleles, will be matched at the allele level for all five loci (HLA-A, HLA-B, HLA-C, DRB1, DQB1), and approximately 25 % will be mismatched for multiple alleles (Petersdorf et al. 1998). The ability to distinguish allele-level mismatches has allowed investigation of the relevancy of patient-donor mismatching. These studies show that the impact of patient-donor mismatching depends on the disease being treated, and within disease risk groups depends upon the degree of HLA mismatch and the locus of HLA mismatch.

Initial studies of HLA matching based on retrospective high-resolution typing suggested that both the number and the location of the allelic mismatch were associated with outcome. The Seattle group found an increased risk for graft failure when donors had multiple mismatches that involved at least one class I allele, but the highest risk for severe acute GVHD was observed with multiple mismatches involving at least one class II allele (Petersdorf et al. 1998; Petersdorf et al. 1997; Sasazuki et al. 1998; Petersdorf et al. 2001). The effect of HLA mismatching appeared to be greater for patients with low-risk diseases, such as CML, compared to those with more aggressive leukemias (Petersdorf et al. 2004). An important limitation of the Seattle studies was that patients were mainly of Caucasian ethnicity, so results may not be transferable to other ethnic populations. For example, studies conducted with the Japan Marrow Donor Program (JMDP) found that mismatching of HLA-A and HLA-B, but not class II HLA, decreased survival (Sasazuki et al. 1998).

Retrospective HLA-allele typing of patient and donor pairs performed by the National Marrow Donor Program (NMDP) has allowed analysis of larger donor-recipient cohorts, which has helped to distinguish the contribution of both number and locus of the HLA mismatch to outcome. Of most use for clinicians is an understanding of the effects of HLA mismatching on overall mortality. The initial study by Flomenberg employed multivariate modeling to determine the independent effects of HLA mismatching detected by high-resolution typing of 1,874 donor-recipient pairs (Flomenberg et al. 2004). Donor-recipient disparity of class I HLA loci HLA-A, HLA-B, and HLA-C was found to be independently associated with an increase in the risk for mortality. In this study, class I HLA mismatches that could be detected only with high-resolution typing (allele-level mismatch) did not appear to increase the risk for poor outcome, nor did mismatches at HLA-DQ. The subsequent 2007 NMDP/CIBMTR study included 3,857 patients and incorporated subset analyses in order to determine whether there were specific HLA locus effects (Lee et al. 2007). In this large cohort of patients with hematologic malignancies given myeloablative conditioning, mortality increased proportionately with the number of mismatches involving HLA-A, HLA-B, HLA-C, or DRB1, but again not HLA-DQ. Furthermore, the effect of an allele-level mismatch appeared to be similar to that of an antigen-level mismatch. The risk of mortality was 1.25-fold higher for patients given a single HLA-mismatched (7/8 match) graft and 1.65-fold higher for those given a double mismatched graft (6/8 match) compared to a fully matched (8/8 match) graft. Mismatches at HLA-A and DRB1 appeared to have a greater negative effect on mortality compared to mismatches at HLA-B or HLA-C. In these studies, the negative effects of HLA mismatching on survival were due to higher incidence of both acute and chronic GVHD; negative effects on relapse and graft rejection were not discerned.

Although marrow is more commonly used as the graft source for pediatric patients, PBSC grafts have become the predominant source for adult patients. Because the previous studies were

confined almost entirely to recipients of marrow grafts, the CIBMTR conducted a separate analysis of HLA matching in patients given PBSC grafts for treatment of hematologic malignancies (Woolfrey et al. 2011). Similar to the Lee study, matching for HLA-A, HLA-B, HLA-C, and DRB1 alleles (8/8 match) was associated with better survival at 1 year (56 % versus 47 %) compared with 7/8 HLA-matched pairs. Mismatches involving the HLA-C antigen were associated with increased mortality. In the PBSC dataset, neither allele-level mismatches nor mismatches at antigens other than HLA-C had a significant effect on mortality. The increase in mortality associated with HLA-C mismatching held for recipients given either myeloablative or reduced-intensity conditioning. The analysis also indicated that in the case of an HLA-C antigen mismatch, switching from PBSC to marrow as the source did not mitigate the negative effect.

The studies discussed above were confined to patients treated for hematologic malignancies; therefore, the results may not be valid for patients with nonmalignant disorders. A recent CIBMTR study addressed this question by analysis of a separate cohort of 663 patients with nonmalignant disorders, including aplastic anemia (which comprised around half of the cohort) (Horan et al. 2012). Again, survival was not affected by mismatching at either HLA-DQ or HLA-DP. Higher mortality was associated with mismatch of a single HLA antigen or two mismatches, but not with mismatch at a single HLA allele. In contrast to the findings in patients with hematologic malignancies, in this study HLA mismatches were not associated with acute or chronic GVHD, but were strongly associated with graft failure, with two- to fourfold increased risk of graft failure depending on the number of mismatched loci. Most likely the lack of association with GVHD is because almost all patients in this cohort were given anti-T-cell antibody, such as antithymocyte globulin (ATG), and many were given T-depleted grafts.

Taken together, these studies support donor identification strategies that limit HLA mismatch. Because the numbers of donor-recipient pairs in the PBSC study and the nonmalignant disease study were smaller than in the 2007 NMDP study, it should be assumed that mismatch at the allele level must be identified by high-resolution typing and avoided if possible. These studies together also suggest that, in the instance when a mismatch is unavoidable, a tolerable mismatch will depend upon the ethnicity of the recipient, the type of graft (PBSC or marrow), and the disease (Table 2.1). Among Caucasian recipients, mismatch at HLA-DQB1 appears most tolerated, followed by mismatch at HLA-B. In contrast, in Japanese recipients, HLA-A or HLA-B mismatches fare the worst. These data do not define tolerable mismatches for other ethnic groups, due to insufficient patient numbers and diverse HLA haplotypes.

Consideration of other donor-related factors is justified when more than one donor of equivalent HLA match has been identified. The source of the cell product has not been considered to affect outcome, and as noted above, PBSC has become the predominant source of unrelated hematopoietic stem cells. The recently completed

Table 2.1 General guidelines for selection of an unrelated donor

Primary donor selection criteria
HLA-A, HLA-B, HLA-C, DRB1 (8/8) match by high-resolution HLA typing
If no 8/8 donor
Avoid mismatch defined by donor-specific HLA antibody
For patient with nonmalignant disease: avoid HLA-C antigen mismatch
For patient with malignant disease:
Avoid HLA-C antigen mismatch with a PBSC donor
Avoid HLA-A or HLA-DRB1 mismatch with a marrow donor
Secondary donor selection criteria
(Apply when there are >1 potential donors with equivalent HLA match)
Younger age
ABO match
Other considerations:
CMV match
Male donor for male patient

CMV cytomegalovirus, *HLA* human leukocyte antigen, *PBSC* peripheral blood stem cells

NMDP/CIBMTR randomized study of unrelated marrow versus PBSC, which included pediatric patients, found that indeed there was no significant difference in mortality between recipients of PBSC compared to marrow. However, the incidence of chronic GVHD was approximately 55 % in PBSC compared to 40 % in marrow recipients ($p < 0.014$) (C. Anasetti, personal communication). Based on these results, marrow should be the preferred source for pediatric patients, unless infectious comorbidities exist that would benefit from the faster neutrophil recovery associated with PBSC grafts.

The contribution of donor age or gender to TRM may be important for certain diseases. The 2001 NMDP analysis, which included 6,978 patients, found that both male gender and younger age were independently associated with lower risk for GVHD and younger age with improved survival (Kollman et al. 2001). Importantly, the study suggested that these factors may be more important in the situation wherein the donor is HLA mismatched. In subsequent retrospective studies focused on the impact of high-resolution mismatches, donor age and gender were not found to be independently associated with survival; however, age and ABO incompatibility have been found to be associated with risk for mortality in a recent analysis of a larger cohort of patients (C. Kollman, personal communication). Earlier studies supported matching patients and donors for cytomegalovirus (CMV) serostatus (Bowden et al. 1993; Ljungman et al. 2003); in the current era, with early polymerase chain reaction (PCR) detection methods and effective drugs for treatment of CMV reactivation, the CMV status of the donor does not affect mortality (M. Boeckh, personal communication) (Lee et al. 2007). Several other variables have been associated with outcome, such as cell dose or time between collection and infusion; however, these factors are typically not under control of the physician caring for the patient (Collins et al. 2010; Lazarus et al. 2009).

Selection of the optimal URD must also consider whether the donor has been sensitized to HLA. Screening recipient serum against a panel of reactive antibodies (PRA) will detect potential anti-HLA antibodies (Anasetti 1991). Crossmatch studies, which detect antibodies in recipient serum directed against proteins expressed by donor cells, are used to determine whether the antibody is specific or nonspecific. The importance of a positive crossmatch was demonstrated in a study of 522 patients in which there was a ninefold greater incidence of graft rejection among crossmatch-positive compared to crossmatch-negative recipients (Anasetti et al. 1989). More recent technology uses solid surfaces or beads coated with purified HLA molecules to detect donor-specific antibodies (DSA), resulting in enhanced sensitivity and specificity compared to cell-based assays. Bead-based technology used in a prospective study of 604 patients given 8/8 or 7/8 matched URD grafts detected DSA in 1.4 % of patients, primarily directed against donor HLA-DPB1 (Ciurea et al. 2011). The presence of DSA was correlated with the risk for graft rejection ($p = 0.0014$). Recommendations for HLA-antibody studies are shown in Table 2.2. Determination of the HLA specificity of the antibody is important, as avoiding a donor with the sensitizing HLA may require typing of HLA-DPB1.

Table 2.2 Indications for donor-specific antibody assay

PRA result	HLA match[a]	DSA assay
Positive	Match or mismatch	Required
Negative	Match	Not required
Negative	Mismatch	Required

DSA donor-specific antibody, *PRA* panel reactive antibody

[a]HLA match is defined by high-resolution typing for HLA-A, HLA-B, HLA-C, and DRB1

Significant advances have been made in understanding the role of natural killer (NK) cell activity after marrow grafting; however, the value of selecting an NK alloreactive donor has not been established. Killer immunoglobulin-like receptors (KIR) present on NK cells interact with specific HLA class I molecules, particularly HLA-C, to regulate NK cell activation. Several studies have evaluated the impact of KIR ligand mismatching, defined as the absence of one donor KIR ligand class I allele in the recipient. A study of 130 patients treated at three European centers

and conditioned with myeloablative conditioning and thymoglobulin found a significant decrease in mortality ($p=0.0006$) among patients given a KIR ligand mismatched graft. In contrast, retrospective analyses from Japan and Minnesota evaluated 1,449 and 175 URD transplants, respectively, and found no benefit for KIR ligand incompatibility (Davies et al. 2002; Morishima et al. 2003). Although most of these latter patients did not receive T-cell depletion, though necessary for promoting NK alloreactivity, another study of 190 patients, most of whom received ATG, also showed no benefit; in fact, survival was lower and TRM higher among recipients of KIR ligand mismatched grafts (Schaffer et al. 2004). Thus, the value of KIR ligand mismatching in URD selection remains undetermined. More promising results have come from studies of KIR genotyping and categorization of donors into those who possess "favorable" or ≥2 B gene motifs (Cooley et al. 2009). In a retrospective study that included 1,409 patients, those with AML who received their graft from a "favorable" KIR genotype had significantly lower mortality and lower relapse (Cooley et al. 2010). A prospective study is currently under way to test the hypothesis that donor KIR haplotype has an independent effect on mortality.

2.5 Selection of Umbilical Cord Blood Units

Umbilical cord blood (UCB) characteristically differs from marrow in a number of ways. The median doses of total nucleated cells (TNC), CD34+ cells, and CD3+ cells in UCB unit are approximately ten times lower than that of a bone marrow graft (Moscardo et al. 2004; Barker and Wagner 2003). Reduced cell numbers may be offset by a higher capacity for replication, as indicated by higher cell cycle rates and longer telomeres in UCB progenitor cells (Lewis and Verfaillie 2000; Mayani and Lansdorp 1998). Immune mediator cells in UCB have been characterized as relatively immature compared to marrow cells, including less mature T- and B-cell phenotypes, reduced response to alloantigen, and lower capacity to generate inflammatory cytokines (Mayani and Lansdorp 1998; Garderet et al. 1998; Risdon et al. 1994; Risdon et al. 1995; Bradley and Cairo 2005). These biologic differences have significant effect on outcome following UCB transplant and as well influence the selection of a UCB unit.

Diminution of immunologic activity has allowed greater freedom to transplant HLA-mismatched UCB units. Conventionally, the degree of HLA match between recipient and UCB has been determined according to serologic typing at HLA-A and HLA-B along with high-resolution typing to distinguish DRB1 alleles. Hence, a UCB unit matched by serologic typing at HLA-A and HLA-B and matched for DRB1 allele has been considered a full or 6 of 6 locus match. This definition of matching ignores mismatches at HLA-C and DQB1 as well as allele-level mismatches at HLA-A and HLA-B loci. Not surprisingly, around one-third of conventionally typed units will have at least one additional undetected HLA mismatch at HLA-A, HLA-B, HLA-C, DRB1, or DQB1 when retyped by high-resolution methods (Cornetta et al. 2005; Kogler et al. 2005).

Retrospective studies of HLA matching have shown an association with the risks for graft failure, TRM, and GVHD. Initial observations reported for 65 UCB transplants by the Eurocord registry in 1997 and 562 transplants by the New York Blood Center (NYBC) in 1998 found HLA mismatch to be associated with lower probability of neutrophil and platelet recovery and, in the latter study, a higher probability of acute GVHD and lower probability of survival (Gluckman et al. 1997; Rubinstein et al. 1998). The subsequent NYBC analysis of 607 UCB transplants found the degree of HLA mismatch correlated directly with the probability of TRM (Abstracts and summary of the 4th Annual International Umbilical Cord Blood Transplantation Symposium 2006). Particularly among patients who did not develop acute GVHD, HLA mismatch was associated with high risk of death from infection, implying a potential negative effect on immune reconstitution. A Minnesota group study of 152 UCB transplants showed that

survival after transplant of a UCB unit matched at 4 of 6 loci was significantly worse compared to those matched at 5 or 6 loci (Wagner et al. 2002). In contrast, the subsequent Eurocord report, which analyzed 550 patients, confirmed the association of HLA mismatch with probability of neutrophil engraftment and acute GVHD grades III–IV, but showed an association with lower probability of relapse and thus no apparent effect on survival (Gluckman et al. 2004). More recently the relevance of matching the UCB unit based on high-resolution HLA typing was analyzed in a retrospective analysis of 803 recipients of UCB transplants registered at Eurocord-European Group for Blood and Marrow Transplantation, Netcord, and the CIBMTR (Eapen et al. 2011). Addition of mismatch at HLA-C to a 6/6 or 5/6 conventionally matched unit was found to significantly increase the risk for TRM ($p=0.018$ and 0.029, respectively). Taken together, these studies indicate that HLA matching is an important factor in reducing the risk for TRM and improving outcome after UCB transplants. Although not all UCB units have been typed for HLA-C, if the information is available, it may help in selection of the optimal unit.

The cell dose of a UCB unit, a critical factor in determining success, was observed in the first large studies and correlated with probability of neutrophil engraftment and platelet recovery (Gluckman et al. 1997; Rubinstein et al. 1998). Based on the Eurocord results, the lower limit of an acceptable unit has generally been considered approximately 2×10^7 total nucleated cells (TNC) per kilogram recipient weight, as determined by TNC in the unit before cryopreservation (Migliaccio et al. 2000). In acknowledgement of the importance of cell dose, UCB banks subsequently made efforts to improve UCB volume at collection. However, until recently the problem of cell dose has limited UCB transplants to smaller patients; hence, most of the subsequent analyses have been performed in pediatric patients. These studies confirmed the association of cell dose and engraftment, and in the most recent Eurocord analysis that included 550 UCB transplants, TNC was found to be associated with risk for acute GVHD (Gluckman et al. 2004). Together these studies support a minimum TNC dose of around 2×10^7 per kilogram recipient weight. Furthermore, stepwise increases in TNC dose appear to correlate with reduction in TRM, and there does not appear to be an upper limit over which TNC dose seems detrimental (Michel et al. 2003).

The best method to measure UCB progenitor cell dose for unit selection has not been established. Several studies show superior predictive value using CD34+ cell dose compared to TNC (Wagner et al. 2002; Laughlin et al. 2001). In the Minnesota studies, the number of CD34+ cells per kilogram recipient weight was associated not only with graft recovery but also with TRM and survival. The doses of TNC and CD34+ measured after thawing may also have superior predictive value compared to values obtained before unit cryopreservation, although post-thaw assays have no practical value for unit selection. The lower limit of CD34+ cell dose has not been firmly established; however, a unit with less than 1.7×10^5 CD34+ cells per kilogram recipient weight has generally been considered inadequate (Wagner et al. 2002; Laughlin et al. 2001). UCB graft progenitor cell content, measured by colony-forming cell assay, has also been shown to correlate with engraftment; however, no association with survival has been suggested (Migliaccio et al. 2000). Current data supports the utilization of either TNC or CD34+ cell dose as measure of unit suitability.

The selection of an optimum UCB unit must take into account both cell dose and HLA match, and there continues to be debate about which factor, if either, should be considered more important. To address this question, Barker et al. analyzed 1,061 UCB recipients treated for hematologic malignancies (Barker et al. 2010). Similar to previous studies, lower TNC and greater HLA match were independently associated with mortality. Importantly, the analysis was able to elucidate interactions between cell dose and HLA match. Specifically, when the unit contained a TNC of at least 2.5×10^7/kg recipient weight, HLA matching became the more significant determiner of outcome. Thus, if a 5/6 unit has a

TNC above the threshold (e.g., TNC of 2.8×10^7/kg), selection of a 4/6 unit with higher TNC does not appear to improve outcome. In contrast, within a TNC range of 2.5–4.9×10^7/kg, survival appears to be better with a 5/6 compared to 4/6 matched unit. To continue the example, if the same 5/6 matched unit has a TNC below the threshold (e.g., 2.0×10^7/kg), then selection of a 4/6 unit with a TNC above the threshold appears to improve survival.

Consideration of cell dose in addition to HLA match has most profound implications for adult patients. While it is now possible to identify a 4/6 matched UCB unit for most pediatric patients, the number of usable units decreases markedly when cell dose is considered (Stevens et al. 2005). A prospective multicenter study of single unit UCB transplants found <10 % survival in the adult arm of the protocol, in part because the median TNC was 2.3×10^7 per kilogram recipient weight (Cornetta et al. 2005). These difficulties have prompted exploration of methods to enhance cell dose given to adult patients, such as transplant of more than one UCB unit or expansion of UCB progenitor cells. Addition of a second unit is a practical method to increase the overall TNC given to the patient, as demonstrated in a study of 21 adult recipients wherein the median TNC after two units was 4.0×10^6/kg (Ballen et al. 2007; Barker et al. 2005). Single-center studies of double UCB transplants in adults also report comparatively improved outcome. The observation that only one of the two CB units engrafts long term suggests a supportive role for the additional unit. Algorithms to aid in multiple unit selection have been devised, based upon HLA match and cell dose of each unit. One reasonable algorithm for selection of two CB units is shown in Table 2.3. Without large numbers of patients to analyze, ambiguity remains regarding the allowable minimum cell dose, HLA mismatch with recipient, and unit-to-unit HLA matching. Reports of supporting single CB transplant with third-party G-mobilized PBSC suggest that HLA matching between cell products may not be relevant (Magro et al. 2006). The degree of HLA match of the recipient to each UCB unit appears to be much more important, since either may become the engrafting unit (Barker et al. 2005).

Table 2.3 General algorithm for umbilical cord blood selection

Identify the best HLA match for HLA-A, HLA-B, and DRB1 with TNC dose of at least 2.5×10^7/kg recipient weight
Above this TNC threshold, prioritize 6/6 match > 5/6 match > 4/6 match
If there are no units above the TNC threshold of at least 2.5×10^7/kg, identify the unit with the highest TNC dose between 1.5 and 2.4×10^7/kg
A second unit should be considered if the TNC is $<2.5 \times 10^7$/kg for any level of HLA match
A second unit should be considered if the best HLA match is 4/6
Selection of a second unit should follow the same criteria as the first unit

Recipient sensitization to alloantigen is more difficult to assess prior to UCB transplant, since donor cells are not available for crossmatch assays. A reasonable approach is to screen UCB recipients for HLA antibodies by PRA assay, discussed in the previous section. Recipients with a positive PRA can be tested for further for HLA-antibody specificity to determine whether DSA is present. A recent single-center analysis of 73 recipients of double UCB transplants found that the presence of DSA was significantly associated with graft rejection, delayed neutrophil engraftment, and mortality. Patients at most risk for graft rejection were those with DSA to both units.

Thus, if DSA is detected in the recipient, it is prudent to avoid units with the identified HLA whenever possible (Cutler et al. 2011).

Aside from HLA matching and cell dose, recent studies have suggested other potential factors to consider in selection of the optimal UCB unit(s). A retrospective study that included 218 recipients of UCB grafts from the Eurocord group suggested that NK alloreactivity may play a role in GVL effects (Willemze et al. 2009). NK cells are essential effector cells of the innate immune system that, without prior activation, recognize and lyse target cells. NK cell cytolytic activity is regulated by the balance of inhibitory and activating signals generated by binding of NK cell surface receptors, or KIRs. Negative

regulation occurs when inhibitory KIR bind to specific HLA class I molecules; hence, target cells expressing the appropriate HLA class I molecules are protected from NK cell cytolysis (a mechanism termed "missing self") (Ljunggren and Kärre 1990; Lanier 1998). In the setting of allogeneic HCT, NK cell alloreactivity can occur when the recipient lacks the inhibitory ligand for donor KIR. Class I HLA epitopes involved in NK cell allorecognition include the Bw4 epitope, present on approximately 40 % of HLA-B alleles, and the allelic HLA-C1 and HLA-C2 epitopes, one of which is present on all HLA haplotypes and which have approximately equal frequencies (Biassoni et al. 1995; Colonna and Samaridis 1995) In the Eurocord study, KIR ligand incompatibility was defined as absent expression in the recipient of a predicted KIR ligand for the donor (i.e., absence of HLA-C group 1, HLA-C group 2, or HLA-B24 allele group), which would correlate with NK alloreactivity. KIR ligand incompatible UCB grafts were found to confer improved leukemia-free survival, in particular for patients with AML.

Investigators have speculated that exposure to noninherited alloantigen during pregnancy might induce a level of tolerance that could be exploited in selection of UCB grafts as well as haploidentical donors. Indeed, long-term presence of very small numbers of fetal cells can be detected in about 80 % of mothers and maternal cells in about 65 % of offspring, consistent with transference of maternofetal tolerance. Several groups have investigated the role of matching for noninherited maternal antigens (NIMA). Theoretically, placental blood cells could develop tolerance to noninherited maternal HLA, which might translate to tolerance of mismatched HLA of the recipient (van Rood et al. 2009). An analysis of 1,121 recipients of single UCB grafts found that mortality was significantly lower among recipients of grafts with a NIMA match. NIMA match also was correlated with improved neutrophil recovery and reduced risk for relapse. Rocha and colleagues have also found NIMA match to be associated with lower mortality and improved leukemia-free survival (V. Rocha, personal communication). Taken together, the studies above suggest that, in the future, the selection of CB units will require consideration of factors other than HLA match or TNC.

2.6 Selection of Haploidentical Donors

A haploidentical donor is defined as sharing one distinct inherited haplotype (genetically identical) with the patient; the unshared haplotype may be HLA matched (phenotypically identical) or mismatched at one or more HLA loci. Most patients have an HLA-haploidentical donor available, typically a parent or sibling. At the current time, guidance on the selection of the optimal HLA-haploidentical donor is not as clear as that for URD or UCB donors. The rapid development of novel regimens, posttransplant immune suppression strategies, and cellular manipulation has outpaced the ability to perform large retrospective analyses to evaluate factors important in HLA-haploidentical donor selection. Furthermore, previously published retrospective studies of HLA-haploidentical graft recipients did not evaluate high-resolution HLA typing; therefore, the limit of tolerable HLA mismatches has not been defined with certainty.

Published studies have examined outcome risks associated with HLA mismatch defined by serologic typing for HLA-A and HLA-B plus identity for DRB1 alleles. The contribution of mismatching at HLA-C or DQB1, or of allele-level mismatching at HLA-A or HLA-B, is thus unknown. Nonetheless, these studies provide some guidance for selection of haploidentical donors. An analysis of 1,199 recipients of marrow grafts found a sixfold increase in graft failure among recipients of grafts from HLA-haploidentical relatives mismatched for 0 to 3 HLA-A, HLA-B, and DRB1 antigens of the nonshared haplotype compared to those who received grafts from an HLA-identical sibling (genetically HLA identical) (Anasetti et al. 1989). The relative disparity between donor and host histocompatibility antigens, determined by the vectors of HLA incompatibility, also affects engraftment (Fig. 2.1). Specifically, recipients who were

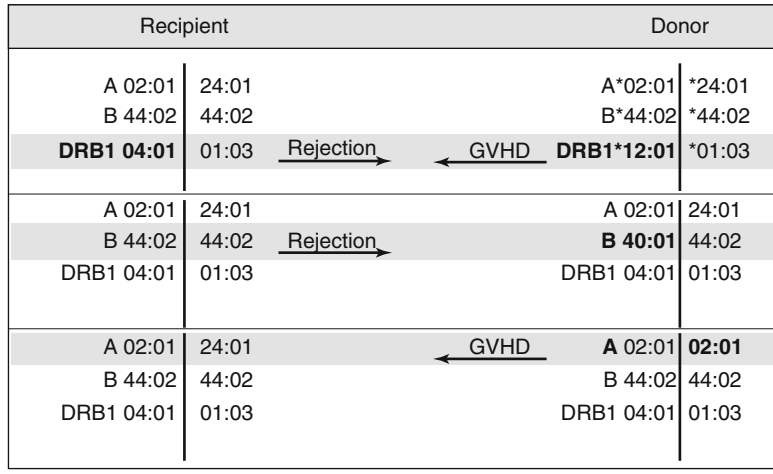

Fig. 2.1 Alloreactivity vectors. The vector for graft-versus-host disease (GVHD) or graft rejection depends upon whether the recipient or donor is homozygous at the locus of mismatch. HLA typing is shown for a potential recipient (*left side*) and for three potential donors (*right side*). In the *top panel*, both recipient and donor are heterozygous at the mismatched HLA-DRB1 locus; therefore, the mismatch will generate alloreactivity in both the GVHD and the rejection vectors. In the *middle panel*, the recipient is homozygous at the mismatched HLA-B locus; therefore, the mismatch will generate an alloreactivity reaction only in the direction of rejection. In the *bottom panel*, the donor is homozygous at the mismatched HLA-A locus; therefore, the mismatch will generate an alloreactivity reaction only in the direction of GVHD

homozygous at one or more mismatched loci had a threefold increase in the risk for graft failure compared to heterozygous recipients. Thus, when selecting a haploidentical donor, it is desirable to avoid the situation in which the number of HLA mismatches in the direction of host-versus-graft is not counterbalanced by the same number of HLA mismatches in the direction of GVH (Woolfrey and Anasetti 1999). The historic analyses also showed that disparity of multiple HLA loci resulted in a prohibitive incidence of GVHD when the graft was not depleted of T cells (Ash et al. 1991; Tomonari et al. 2002; Speiser et al. 1997). These studies, together with knowledge gained from analyses of URD transplants, support the use of high-resolution typing to discriminate haploidentical donors potentially mismatched for HLA-A, HLA-B, HLA-C, DRB1, or DQB1 locus.

Our current understanding of the important role of hematopoietic stem cell dose in HLA-haploidentical grafts is based on animal models. Early murine models demonstrated that engraftment of allogeneic marrow required tenfold higher number of cells compared to syngeneic marrow (Gengozian et al. 1969). Similar models showed that host alloreactivity conferred by the presence of residual (or experimentally added-back) host T cells could be overcome by increasing the number of donor cells, presumably by manipulating competition for marrow space in favor of the donor stem cells (Lapidot et al. 1989). In HLA-histoincompatible models, engraftment of T-cell depleted marrow was shown to require greater numbers of donor marrow cells compared to non-T-cell depleted grafts (Lapidot et al. 1990; Lebkowski et al. 1990). Stem cell dose also appeared to be the critical factor in determining engraftment of T-cell depleted HLA-histoincompatible marrow when intensity of immunosuppression was held constant (Bachar-Lustig et al. 1995; Rachamim et al. 1998). The benefit of mobilized PBSC to attain high cell dose was reported by Aversa and colleagues in studies of HLA-haploidentical grafts for treatment of hematologic malignancies (Aversa et al. 1994; Aversa et al. 1998). After 2–4 apheresis procedures followed by CD34+ selection or T-cell depletions, the PBSC graft contained a median CD34+ cell dose of $13.9–16 \times 10^6$ per kilogram

recipient weight and a median CD3+ cell dose of $0.27–1.43 \times 10^5$ per kilogram recipient weight, resulting in 95 % engraftment rate. Correlation of CD34+ cell dose with risk for graft failure has been confirmed by other groups after different conditioning regimens (Peters et al. 1999). The requirement for maximal CD34+ cell dose guides donor selection toward a preference for adult donors able to tolerate multiple apheresis procedures. In contrast, if a marrow graft instead of PBSC is planned, studies suggest that younger donor age may be preferable (Godder et al. 2000).

Studies by the Perugia group suggest that, in the absence of T cells, NK cell alloreactivity may play an important role in outcome of haploidentical grafts (Biassoni et al. 1995). The existence of potential donor alloreactive NK cells can be deduced through comparison of donor and recipient HLA class I type. This "missing self" model of NK alloreactivity presumes that there exist NK clones in the donor capable of activation provided the recipient lacks the inhibitory ligand. The "missing self" model is an oversimplification of NK cell receptor-ligand biology, as some individuals do not have the inhibitory KIR gene anticipated based on the HLA typing. Velardi and colleagues screened the KIR genotype of 162 patients and found that prediction of NK alloreactivity based solely on KIR ligand incompatibility would be invalid for 3 % of donors who do not possess KIR2DL1 receptor for group 2 HLA-C alleles and 6 % of donors who lack the gene for HLA-Bw4 inhibitory receptor KIR3DL1 (Ruggeri et al. 1999; Ruggeri et al. 2002; Ruggeri et al. 2004a; Velardi et al. 2003; Ruggeri et al. 2004b). This group also showed that direct identification of NK alloreactive clones in the donor was useful for optimum donor selection. Potentially relevant to selection of haploidentical donors is the "missing ligand" model of donor NK activity, which takes into consideration that alloreactive donor NK clones may develop after transplant, provided the recipient lacks at least one KIR ligand. In contrast to the "missing self" model, there is no requirement for a mismatch of the class I HLA ligand between donor and recipient. Hence, the "missing ligand" model would potentially encompass two-thirds of recipients, who will lack one or more of the class I HLA ligands for KIR. In this model, KIR genotyping is essential in order to identify a donor with potential to express an alloreactive KIR.

The Perugia group demonstrated the potential role for NK alloreactivity in protecting against relapse after T-cell-depleted HLA-haploidentical grafts for patients with myeloid malignancies (Ruggeri et al. 1999; Ruggeri et al. 2007). In an analysis of 112 patients, with AML, NK alloreactive clones were detected before transplant in all KIR epitope mismatched donors whose recipients did not express HLA-C group ligands and two-thirds whose recipients did not express HLA-Bw4 alleles, whereas none were detected in donors whose recipients expressed the class I HLA groups present in the donor. Multivariate analysis confirmed that donor-versus-host KIR "ligand mismatch" was an independent factor for survival, associated with a twofold reduction in death or relapse among all patients ($p < 0.001$), including those with relapsed disease at time of HCT (DFS 30 % versus 6 %, $p = 0.04$). In contrast, when the analysis took into consideration patients who lacked expression of at least one KIR ligand, for whom there was potential for NK alloreactivity according to the "missing ligand" model, no survival advantage was discerned. Although these results have not been confirmed by others (Bishara et al. 2004), they suggest that the search for HLA-haploidentical donors should be extended beyond immediate family members, guided by KIR genotyping (Ruggeri et al. 2005).

2.7 Selection of the Optimal Donor

Optimization of the donor graft, whether URD, UCB, or HLA haploidentical, takes into consideration data derived from multivariate analyses of large numbers of transplants. In contrast, there are no randomized studies that address the question of selection between the various donor

sources. Studies that seek to compare outcome between any donor type, whether HLA-matched sibling, HLA-matched URD, UCB, or haploidentical donors, have been retrospective; therefore, consideration of the results must take into account the problem of selection bias, wherein poor-risk patients die before HCT can be performed. In general, time lapse between the decision to undergo HCT and donor identification is greater for recipients of alternative donor grafts, increasing the probability that poor-risk patients will not be included in these groups. In counterbalance, perception of an increased risk associated with alternative donor HCT may drive physicians to withhold referral of patients until the disease has progressed to an advanced stage.

Registry studies have provided comparative information about outcome among different alternative donor groups. The Eurocord group reported outcomes separately for pediatric and adult patients with acute leukemia given unrelated UCB compared to URD marrow transplants. The first large study reported by the Eurocord group analyzed outcome of pediatric patients given UCB or URD grafts between 1994 and 1998 (Rocha et al. 2001). The adjusted analysis showed lower DFS and a twofold increase in TRM among the UCB recipients compared to URD ($p<0.01$), with most of the mortality risk within the first 100 days. In contrast, no difference in survival was reported for adult patients in the Eurocord comparison of 98 single UCB unit recipients to 584 recipients of 6 of 6 HLA-matched URD marrow grafts, reported to the registry between 1998 and 2002 (Rocha et al. 2004). An International Bone Marrow Transplant Registry study reported around the same time found that recipients of UCB or mismatched URD marrow had a higher risk for death from any cause ($p<0.001$, HR 1.66, 1.53, respectively) compared to recipients of HLA-matched URD marrow (Laughlin et al. 2004). The increasing awareness of cell dose and advent of the double UCB unit transplant procedure have improved outcome in adult patients, and two recent retrospective studies that compared outcome of double UCB grafts and URD grafts in adult patients with hematologic malignancies found no significant difference in outcome. In patients with hematologic malignancy given myeloablative conditioning, the source of the donor graft (i.e., double UCB or HLA-matched URD or HLA-mismatched URD or HLA-identical sibling) was not found to be significantly associated with mortality (Brunstein et al. 2010). Donor source was also not found to be associated with outcome after reduced-intensity conditioning (Brunstein et al. 2012).

Most importantly, all comparative studies of URD, haploidentical donors, and mismatched cord blood grafts have shown that phase of disease at time of transplant is the most significant predictor of survival (Gluckman et al. 2004; Speiser et al. 1997; Sierra et al. 1997; Aversa et al. 2005; Lu et al. 2006). Therefore the most important variable to consider at the start of the donor search is the urgency of the transplant procedure. Thus, optimal donor selection balances the risk of disease progression against the time required to identify the best donor (Woolfrey et al. 2002). Pragmatically, the time to disease progression or relapse (which depends upon the available therapies that presumably improve over time) should be estimated and donor identification should proceed accordingly. Advances in determining the biologic markers for disease progression should improve ability to decide in favor of HCT with an alternative donor (Bruggemann et al. 2006; Zhou et al. 2007). Table 2.4 shows a useful guideline which we use in our center to select the "optimal" donor based on the predicted urgency of the need for transplant. By employing a strategy that identifies an acceptable donor in the shortest period of time, and that subsequently refines the search to optimize donor characteristics, we can meet our goal to move to transplant at the time most appropriate for the patient, knowing that we have identified the best donor within the appropriate time frame.

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Table 2.4 General algorithm for donor selection

Algorithm according to disease severity	Search parameter (identify donors meeting the following criteria)
Standard timeline	
1. Initial search parameter – identify best HLA match	Unrelated donor matched for HLA-A, HLA-B, HLA-C, DRB1 Unrelated PBSC donor: mismatched at a single HLA-A, HLA-B, allele (high resolution)
2. Review patient status and search results every 8 weeks. Upgrade to Urgent Algorithm if clinically indicated	
Urgent timeline (transplant goal within 2–4 months)	
1. Initial search parameter – identify first available donor meeting criteria	Unrelated donor matched for HLA-A, HLA-B, HLA-C, DRB1 Unrelated donor mismatched at a single HLA-A, HLA-B, or DRB1 Umbilical cord blood matched for 4–6 HLA-A, HLA-B, DRB1
2. Continue to search for more optimal donor if time allows	
3. Review patient status and search results every 4 weeks. Upgrade to Critical Algorithm if clinically indicated	
Critical timeline (transplant goal within 1–2 months)	
1. Prioritize first available donor	Unrelated donor matched for HLA-A, HLA-B, HLA-C, DRB1 Unrelated donor mismatched at a single HLA-A, HLA-B, HLA-C, or DRB1 Umbilical cord blood matched for 4–6 HLA-A, HLA-B, DRB1 HLA-haploidentical donor Consider: Unrelated donor mismatched involving two separate loci
2. Review patient status within 4 weeks	

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Preparative Regimens

3

John E. Levine, Peter J. Shaw, and Franklin O. Smith

Contents

J.E. Levine, MD, MS (✉)
Pediatric BMT Program, University of Michigan, Ann Arbor, Michigan
e-mail: jelevine@med.umich.edu

P.J. Shaw, MD
Children's Hospital at Westmead, Sydney, Australia

F.O. Smith, MD
Division of Hematology/Oncology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

3.1 Considerations in Preparative Regimen Agent Selection: Overview

It is important to keep in mind that preparative regimens in hematopoietic cell transplant (HCT) are typically disease specific and have undergone prospective investigation and validation in clinical trials before becoming widely used. Thus, the choice of a specific preparative regimen is usually the result of selecting from a series of regimens that have been shown to be effective for a given disease. Within the group of recommended regimens, consideration should be given to the status of the disease at time of the HCT (more intensive regimens are usually preferred for disease states with high relapse risk) and the patient's overall health condition (less-intensive regimens are usually preferred for patients with comorbid conditions or to avoid late effects, like infertility). Novel preparative regimens are not recommended outside of a prospective clinical trial. Another important issue in pediatric HCT is that there have been few randomized trials comparing regimens to assess superiority. Thus, the clinician has to exercise their own judgment when choosing which preparative regimen to use from the list of acceptable regimens. Another important consideration for allogeneic HCT is to determine whether non-chemotherapy immunosuppressive agents should be administered as part of preparative regimens to help prevent graft rejection. In the next sections, we will briefly review each of these broad considerations and then focus on the common preparative regimens for specific diseases.

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3.1.1 Preparative Regimen Intensity

Comorbid conditions and/or advanced age can be a relative or absolute barrier to using high intensity, myeloablative preparative regimens. To assist clinicians in assessing the risk of allogeneic HCT when comorbid conditions are present, Sorror et al. published a HCT comorbidity index score (Sorror et al. 2005), which has been validated for pediatric patients (Smith et al. 2011). In the pediatric study of 252 children, median age 6 years, an increasing HCT comorbidity index score was associated with higher risk of non-relapse death and worse survival. Children with the highest scores experienced a cumulative incidence of non-relapse mortality at 1 year of 28 %. When myeloablative preparative regimens are contraindicated, reduced intensity preparative regimens may be a suitable alternative. Controversy persists as to what truly constitutes a reduced intensity regimen, although attempts at developing a consensus have been published (Giralt et al. 2007; Bacigalupo 2004; Bacigalupo et al. 2009). A working definition for a reduced intensity regimen is any regimen that results in low non-hematologic toxicity and produces mixed donor-recipient chimerism in a substantial proportion of patients in the early posttransplantation period (Giralt et al. 2007). Non-myeloablative regimens are reduced intensity regimens that do not require stem cell support for hematopoietic cell recovery. The Center for International Blood and Marrow Transplant Research (CIBMTR) defines myeloablative regimens as any preparative regimen with total body irradiation (TBI) single doses of ≥500 cGy or fractionated doses totaling ≥800 cGy, busulfan doses of >9 mg/kg, or melphalan doses of >150 mg/m^2 given either as single agents or in combination with other drugs; all other regimens are considered reduced intensity. More recently, myeloablative regimens with a low incidence of toxicity, such as fludarabine in combination with myeloablative doses of busulfan, have been termed reduced toxicity (de Lima et al. 2004). Ultimately, clinicians need to be aware of the wide variation in drugs and dose intensity within these broad groups of myeloablative and reduced intensity preparative regimens when comparing outcomes and especially when substituting one regimen for another.

Most clinical experience with reduced intensity preparative regimens comes from adult HCT studies, as children generally do not have the comorbid conditions that preclude the use of myeloablative regimens. However, it is clear that the presence of comorbidities and other clinical considerations also impact pediatric HCT outcomes. In some cases, the patient's underlying disease dictates the use of a reduced intensity regimen. For example, the DNA repair defect in Fanconi anemia predisposes these patients to excessive regimen-related toxicity, including treatment-related malignancies, and thus reduced intensity regimens are preferred (Wagner et al. 2007). The Pediatric Blood and Marrow Transplant Consortium (PBMTC) tested low-dose busulfan in combination with fludarabine and thymoglobulin in 47 children with hematologic malignancies who were deemed poor candidates for myeloablative preparative regimens, most often due to a previous myeloablative HCT. Successful neutrophil engraftment was achieved in 89–94 % of patients across a range of stem cell sources including related donors, unrelated donors, and unrelated cord blood. The 2-year cumulative incidence of transplant-related mortality was 11 % and 2-year survival was 45 %, demonstrating that for selected children, reduced intensity preparative regimens are efficacious (Pulsipher et al. 2009). There has yet to be a consensus developed for when to select a reduced intensity preparative regimen for children based on organ function. The PBMTC criteria are listed in Table 3.1.

Another possible indication for selecting a reduced intensity preparative regimen is to avoid late HCT-related effects, such as infertility. Interest in reduced intensity regimens for this purpose has focused on patients with nonmalignant disease, as concern for long-term sequelae can be a barrier to curative allogeneic HCT for conditions such as sickle cell disease. The potential reduction in development of late effects when reduced intensity regimens are used has not been sufficiently quantified to recommend their use

Table 3.1 Pediatric Blood and Marrow Transplant Consortium (PBMTC) organ dysfunction criteria for reduced intensity preparative regimens

Lung	Carbon monoxide lung diffusion capacity (DLCO), forced expiratory volume in 1 s (FEV1), or forced vital capacity (FVC) between 30 and 60 %
Kidney	Creatinine clearance less than 60 mL/m /1.73 m^2 or requiring dialysis
Liver	Transaminases between 4 and 10 times institutional upper limit of normal *OR* total bilirubin between 2.0 and 3.0 mg/dL
Heart	Ejection fraction between 30 and 50 %

outside of a clinical trial. The feasibility of this approach for nonmalignant conditions has been demonstrated, although graft rejection when mismatched donors or unrelated donors, including unrelated cord blood, are used as the stem cell source remains a challenge (Kamani et al. 2012; Satwani et al. 2008; Law et al. 2012; Veys 2011).

3.1.2 Immune Ablation

Graft rejection is most commonly mediated by recipient T cells, although animal models support a possible role for natural killer cells (Murphy et al. 1987). Thus successful donor cell engraftment requires that the preparative regimen sufficiently ablate recipient T cells. The intensity of immune ablation in the preparative regimen to reliably facilitate donor cell engraftment depends on the clinical context. For example, patients with malignancies with extensive exposure to chemotherapy prior to the HCT already have an induced immunodeficiency and thus may require less-intense regimens. Alternatively, patients with nonmalignant diseases may have fully intact T-cell function at the time of the preparative regimen and their graft rejection risk is accordingly much higher (Satwani et al. 2013; Olsson et al. 2013). Other risk factors for rejection include major histocompatibility antigen mismatches (Teshima et al. 2005; Petersdorf et al. 2001; Olsson et al. 2013), use of donors other than human leukocyte antigen (HLA)-identical siblings (Weisdorf et al. 2002; Satwani et al. 2013; Aversa et al. 2005), the use of ex vivo T-cell depletion (Olsson et al. 2013; Boelens et al. 2007), and reduced intensity conditioning regimens (Olsson et al. 2013).

3.1.2.1 Chemotherapy- or Radiation-Based Immune Ablation

Because busulfan is not particularly immunosuppressive for host T cells, the combination of busulfan with other agents allows an evaluation of their immunoablative potential. For pediatric preparative regimens, cyclophosphamide (total dose 200 mg/kg) has proven to be sufficiently immunoablative to facilitate reliable engraftment after sibling HCT in combination with busulfan (Neudorf et al. 2004). Lower doses of cyclophosphamide (total dose 120 mg/kg) have been shown to be sufficient for engraftment in adult HCT (Kashyap et al. 2002; Tutschka et al. 1987), but there is a paucity of data for this regimen in pediatric patients. When alternative donors, such as unrelated adult donors or unrelated cord bloods, are used, cyclophosphamide has not been considered to be sufficient to facilitate engraftment without the use of additional immunoablation, but this premise has not been rigorously evaluated. Fludarabine as a substitute for cyclophosphamide has been used in adult sibling (de Lima et al. 2004) and unrelated donor (Nakane et al. 2011) HCT and, to a lesser extent, in children (Tse et al. 2009) without the use of any other immunoablating agents in the preparative regimen. In almost all other settings, immunoablation does not rely on a single agent. Fractionated TBI 10 Gy or higher is highly lymphotoxic (Altschuler et al. 1989) and when used in combination with chemotherapy agents such as cyclophosphamide or etoposide results in engraftment following sibling or unrelated donor HCT (Gassas et al. 2006). In the adult non-myeloablative setting, low doses of TBI (2 Gy) have been sufficient to prevent graft rejection (Gyurkocza et al. 2010), but that approach has not been sufficiently tested in children to recommend its use. However, antibody-mediated host T-cell depletion is frequently included in preparative regimens, especially when alternative donors are used as the stem cell source.

3.1.2.2 Antibody-Based Immune Ablation

Antibodies that target T cells play an important role in pediatric allogeneic HCT preparative regimens. As noted above, in the sibling donor setting, antibodies are not always used to prevent graft rejection, but they are commonly incorporated when unrelated donors or cord blood are used as the stem cell source. In these scenarios, the anti-T-cell therapy also may be used for graft-versus-host disease prevention, but that is not discussed in this chapter. There are two primary anti-T-cell products used to prevent graft rejection – antithymocyte globulin and alemtuzumab. Antithymocyte globulin, which consists of polyclonal sera derived from inoculated animals, was introduced into the HCT arena first and has a very good track record for ensuring engraftment for both malignant and nonmalignant diseases when alternative donors are used (Remberger et al. 2001; Veys et al. 2012) and with umbilical cord blood (Geyer et al. 2011; Wall et al. 2005). There are different preparations of antithymocyte globulin, and each is dosed differently. In the absence of prospective randomized trials, one cannot recommend any of the antithymocyte globulins over the others. An alternative to antithymocyte globulin is alemtuzumab, a monoclonal antibody that binds to CD52, an antigen that is expressed on virtually all lymphocytes (Flynn and Byrd 2000). Alemtuzumab has been used successfully to promote engraftment in a variety of pediatric HCT settings (Law et al. 2012; Marsh et al. 2010; Shenoy et al. 2005; Veys et al. 2012), although the optimal dosing and schedule has yet to be determined. Randomized trials comparing antithymocyte globulin to alemtuzumab have not been performed. Selection of a particular anti-T-cell antibody to use in a given preparative regimen is influenced by other factors, such as access, the side effect profile, cost, graft-versus-host disease (GVHD) risk, and clinician preference.

3.2 Preparative Regimens for Myeloid Leukemias

A full discussion about preparative regimens used for AML can be found in Chap. 9. Given the initial experience with TBI in acute leukemia, the first reports emanating from the Fred Hutchinson Cancer Research Center in Seattle for transplantation of myeloid diseases used TBI-based conditioning (Thomas et al. 1977; Clift et al. 1987). One of the first randomized HCT studies included patients with acute myeloid leukemia (AML) and illustrated the difficulties with designing preparative regimens that persist to this day: in a cohort of patients with AML randomized to 12 Gy or 15.75 Gy of TBI, the higher dose of radiation significantly reduced the rate of relapse, but this was counterbalanced by higher transplantation-related mortality (TRM) (Clift et al. 1990). The ablative therapy that kills leukemia also increases toxicity.

Consistent with adult practice, early pediatric AML studies used TBI with cyclophosphamide (CY) (Feig et al. 1987; Johnson et al. 1988). Early rat experiments revealed the myeloablative potential of busulfan (Bu) and, as with TBI, it was successfully combined with CY in the BuCY200 (200 mg/kg) regimen. The original cohort of study patients included some pediatric patients (Santos et al. 1983). Because of concerns of toxicity in adult practice, the CY dose was often reduced to BuCY120 (120 mg/kg), but in pediatric practice the full dose of CY200 was often preferred. Indeed, half of the long-term survivors of BuCY200 from this original cohort were 18 years or less at the time of HCT (Bolanos-Meade et al. 2006). In the French experience, first remission patients who received BuCY200 fared better than those who received BuCY120. TRM was lower for BuCY200 (5 %) and BuCY120 (0 %) compared to TBI (10 %), while the relapse rate, which was comparable for TBI and BuCY 200, was much higher for BuCY120 (Michel et al. 1994). Thus, as children tolerate the higher dose of CY better, pediatric transplant physicians have tended to use this dose for AML. Even the earliest reports from pediatric cooperative group studies included some use of BuCY200 (Feig et al. 1987). This regimen has been retained in all successive studies of the Children's Oncology Group (COG) until the most recent iteration, which replaced CY with fludarabine. In summary, the BuCY200 regimen is commonly used for children with AML who are undergoing matched family donor HCT (Horan et al. 2008), although TBI has most often been used for

children with more advanced disease requiring an unrelated donor transplant (Bunin et al. 2008).

3.2.1 Comparisons Between Total Body Irradiation and Busulfan

TBI and Bu combined with CY have differing profiles of toxicity and efficacy. It took until the 1990s for 4 randomized studies to directly compare the efficacy and toxicity of BuCY against CY-TBI. Although these trials included predominately patients with myeloid disease, they were conducted almost exclusively in adults (Blaise et al. 1992; Clift et al. 1994; Devergie et al. 1995; Ringden et al. 1994; Dusenbery et al. 1995). These studies found that BuCY is associated with more sinusoidal obstruction syndrome (veno-occlusive disease (VOD)), hemorrhagic cystitis, and alopecia, but fewer cataracts long term. In terms of disease control, CY-TBI exhibited equal or better control of AML, especially for advanced disease. A chemotherapy-only regimen, such as BuCY, offers a real advantage in terms of logistics and resource utilization over TBI-containing regimens. With a starting point of BuCY and CY-TBI, there are a variety of methods to try and improve results. Table 3.2 summarizes the preferred treatment options for pediatric AML and, when HCT is indicated, what appears to be the best of the published preparative regimens, if such a distinction can be made.

3.2.1.1 Intensifying the Regimen

There have been several attempts to increase the dose of TBI. The early Fred Hutchinson Cancer Research Center study of 12 Gy versus 15.75 Gy of TBI highlighted the problems with this approach. However, a more modest dose increase (i.e., 1,320 cGy) has been associated with good results in AML, with a 75 % 5-year survival in complete remission (CR)2 (Brochstein et al. 1987). The complex schedule of irradiation in this report is most often simplified to delivering a total dose of 1,320 cGy in 8 fractions over 4 days. This dose, although never tested directly with 1,200 cGy in 6 fractions, is used widely in many current clinical trials (e.g., NCT00412360). In a recent publication using unrelated donor HCT, higher dose TBI produced similar results to lower dose TBI and indeed to standard BuCY (Uberti et al. 2011). Another way to target delivery of radiotherapy to the hematopoietic system is with radiolabeled antibodies, but to date such trials have been in advanced disease and mainly in adults (Pagel et al. 2009; Schulz et al. 2011).

3.2.1.2 Optimizing the Combination

The initial report using BuCY reported 51 patients with AML and matched sibling donors given 16 doses of 1 mg/kg Bu and 4 doses of 50 mg/kg CY (Santos et al. 1983). Ten are long-term survivors (Bolanos-Meade et al. 2006). The regimen was quite toxic: acute GVHD and cytomegalovirus (CMV) interstitial pneumonitis were the major causes of death, and hemorrhagic cystitis and hepatic VOD were common causes of morbidity associated with BuCY. A relationship between high Bu area under the curve (AUC – a measure of systemic exposure to the drug) and the development of VOD was reported by Grochow et al.

Table 3.2 Preferred options for pediatric myeloid diseases

Disease	First-line therapy	Published best HCT option	In current use
AML standard risk	Chemotherapy	UKAML12 (Gibson et al. 2011)	Chemotherapy
AML high risk (of relapse)	HCT	CY-TBI (Bunin et al. 2008), BuCY (Horan et al. 2008)	CY-TBI, BuCY, other
JMML	HCT	BuCY-MLP (Locatelli et al. 2005)	HCT
CML CP1	TKI	Myeloablative (Weisdorf et al. 2002) Reduced intensity TreoFlu (Casper et al. 2004)	TKI
CML, beyond 1st CP	HCT or 2nd generation TKI	Myeloablative (Weisdorf et al. 2002)	HCT, 2nd generation TKI, both

Abbreviations: *HCT* hematopoietic cell transplant, *AML* acute myeloid leukemia, *JMML* juvenile myelomonocytic leukemia, *CML* chronic myelogenous leukemia, *CP* chronic phase, *TKI* tyrosine kinase inhibitors, *CY* cyclophosphamide, *Bu* busulfan, *MLP* melphalan, *TBI* total body irradiation, *Treo* treosulfan, *Flu* fludarabine

(1989). In this original cohort of patients given BuCY200, 5 of the 6 patients who developed VOD had a busulfan AUC value greater than the mean. In a subsequent study, VOD occurred in 6 of 8 patients with busulfan AUCs above 1,500 micromolar.min (for each dose) but in only 1 (of 27) patients with AUCs below 1,500 micromolar.min (Grochow 1993). Thus, targeting of busulfan AUC has been in widespread clinical practice ever since. In the meantime, studies of adult patients found that reducing the CY dose from a total of 200 mg/kg to 120 mg/kg reduced the incidence of interstitial pneumonitis and VOD in AML patients without compromising the antileukemic effect (Tutschka et al. 1987). The relationship between Bu levels and relapse has been shown in adult patients with chronic myelogenous leukemia (CML) who get 120 mg/kg of CY administered over 2 days rather than 200 mg/kg administered over 4 days. Slattery et al. studied 42 patients with CML conditioned with 16 doses of 1 mg/kg Bu and 2 doses of 60 mg/kg CY (Slattery et al. 1997). Patients with Bu Css (steady state trough – another measure of systemic exposure) less than median had a higher relapse rate. There was no relation between Bu Css and non-relapse mortality or graft rejection, perhaps because of the lower dose of CY. They recommended targeting a high Bu level to minimize the chance of relapse, without an increased risk of severe regimen-related toxicity. In a subsequent series of 131 HLA-matched family donors with the same conditioning, Bu pharmacokinetics were analyzed after the first dose and, if necessary, dose adjustments were then made after days 1 and 2, targeting a higher exposure. This series of patients had an excellent outcome and there was no relationship between Bu level (again expressed as the median of all the Bu Css measures) and outcome and no comment on any toxicity with this regimen (Radich et al. 2003).

In children, Bu was optimized after realizing that younger children were systematically under dosed when compared to older transplant patients (Vassal et al. 1992; Yeager et al. 1992). Body surface area (BSA)-based dosing and weight-based nomograms are routinely used to establish the starting dose of Bu, which is subsequently modified based on measures of systemic exposure.

More recently, there has been a shift to intravenous (IV) busulfan. This switch was associated with a clear improvement in outcome and a modest reduction in the variability of exposure, perhaps a 3–4-fold variation rather than 5–6-fold as commonly seen with oral busulfan (Andersson et al. 2000; Hassan et al. 2002; Shimoni 2003; Sobocinski et al. 2004; Zwaveling et al. 2005; Kashyap et al. 2002; Lee et al. 2005; Thall et al. 2004; Bartelink et al. 2008). This switch to the IV formulation also facilitated a move to single daily dosing, even though some centers had been using this with the oral preparation (Shaw et al. 1994). A major advantage of the single daily dosage is that with a few blood samples, the actual clearance of the drug is measured (i.e., the pharmacokinetics is measured rather than estimated, as was often done with dosing every 6 h) (Nath and Shaw 2007).

Recent data has suggested that the problems of low exposure and relapse (or non-engraftment for nonmalignant disease) and high levels and TRM can be minimized by targeting a midrange of Bu AUCs. A recent pediatric study found a clear association between exposure, toxicity, and event-free survival: lower exposure was associated with increased rates of relapse and graft failure, while higher exposure was associated with increased toxicity and TRM. This suggested that the therapeutic window, even with IV Bu, still appears quite narrow (Bartelink et al. 2009). It must be accepted that much of the past data is based on Bu-based combinations that are less often used (BuCY and BuCY-melphalan), but current studies are based on a planned cumulative exposure to busulfan.

3.2.1.3 Substituting a More Active Agent

For AML, there is a rationale for substituting CY with an agent that has greater activity against myeloid leukemia. Thus, there are several publications using a combination of Bu and melphalan (Martino et al. 1995; Matsuyama et al. 1998). Melphalan has been used as monotherapy for pediatric autologous HCT in AML (Tiedemann et al. 1993). A backbone of Bu-melphalan was used in a cooperative group cord blood transplant study that included many children with myeloid leukemias (Wall et al. 2005).

3.2.1.4 Adding a Third Drug

It took years and large numbers of patients to delineate the toxicity profiles and the comparative ability to control disease in myeloid leukemias with BuCY or CY-TBI in a randomized way. It is not surprising then that there is no literature that convincingly demonstrates that the addition of a third drug is equal or superior to BuCY or CY-TBI. There has been broad experience using an aggressive 3-drug combination of BuCY and melphalan, in particular in juvenile myelomonocytic leukemia (JMML) and myelodysplastic syndrome (MDS) (Locatelli et al. 2005; Strahm et al. 2011). This combination appears to provide good disease control but is quite toxic (TRM 13–20 %) even in experienced pediatric centers. Given the data with Bu-melphalan alone, one could question whether the 3-drug combination of BuCY-melphalan offers any advantage. However, the published data generally indicate that using this 3-drug combination is probably better than using a predominately TBI-based regimen (Locatelli et al. 2005; Smith et al. 2002).

In contrast to combining Bu-melphalan with CY, a backbone of Bu-fludarabine (Flu) has been combined with melphalan for high-risk diseases, such as JMML (Yabe et al. 2008). We await further data on the more widespread use of BuFlu in higher risk myeloid malignancies to assess whether a more potent, but potentially more active, combination such as BuFlu-melphalan is warranted or whether the short- and long-term toxicities of TBI in this group of patients must be tolerated. It is noteworthy that our ability to avoid the use of TBI in the preparative regimen for children with JMML would suggest that as pediatricians, our goal of avoiding TBI in all growing children may be achievable, at least for some myeloid diseases.

3.2.1.5 Substituting a Less Toxic Agent into the Combination

In pediatric HCT centers, the mortality rate associated with the BuCY200 regimen is low, in the range of 3–5 %. However, as our non-transplant treatments improve, this rate of TRM may become unacceptably high and influence the risk-benefit ratio when considering transplant or non-transplant alternatives. Going forward, current clinical trials are assessing the safety and efficacy of newer, potentially less toxic drugs, including treosulfan. If successful, this may allow the substitution of busulfan with treosulfan, fludarabine for cyclophosphamide, and eventually, novel, potentially less toxic combinations of these drugs.

3.2.2 Reduced Intensity

There are numerous conditioning regimens that are not myeloablative, many of which do not find a role in pediatric HCT. Historically, it was thought that the main purpose of the conditioning regimen for myeloid malignancy was to provide high-dose antileukemia therapy; the patient needs the reinfusion of cells with hematopoietic potential to rescue them from the marrow toxicity of the high-dose therapy. However, even in these early days of transplantation, it was clear that allogeneic HCT has an allogeneic effect, in that the foreign cells mediate a graft-versus-leukemia (GVL) as well as a GVHD reaction (Horowitz et al. 1990). This was particularly true for CML in relapse after HCT, where donor lymphocyte infusions (DLI) were able to induce a remission (Kolb et al. 2004). And if a new immune system can mediate a potent antileukemia effect, then for those patients who are not fit enough to tolerate the rigors of a fully myeloablative conditioning regimen, a highly immunosuppressive regimen could temporarily suppress the patient's own immune system to allow them to accept an allograft; these reduced intensity regimens have wide acceptance in adults with myeloid disease requiring allogeneic HCT. One of the reasons commonly cited as an indication for a reduced intensity conditioning has been comorbidity that may limit HCT, but as has already been noted, this is less often the case in pediatrics. More often, pediatric transplant physicians are looking for an effective, ablative procedure, but with less toxicity. Thus, in pediatric myeloid leukemias, rather than reduced intensity, the goal is to reduce the toxicity associated with BuCY (and CY-TBI).

The two most widely used regimens in this situation are BuFlu and more recently, the investigational combination of treosulfan and fludarabine (TreoFlu).

3.2.3 Reduced Toxicity

A number of reports have described single institution experience in using BuFlu in pediatric patients (Horn et al. 2005; Dalle et al. 2003; Kletzel et al. 2006; Tse et al. 2009; Lee et al. 2011; Styczynski et al. 2011). A recent prospective study demonstrated a graft-failure rate of <5 % and no difference was found with stem cell source, with most children receiving unrelated donor cord blood. The cumulative Bu exposure was targeted at 85–95 mg/L.h (20,700 to 23,200 micromolar.min; the total exposure over the course of the 4 days of treatment), and all patients had full donor chimerism after day +30. Within this study, a cohort of BuFlu patients was compared with a prior cohort of BuCY (+/− melphalan) patients, both having the same targeted Bu exposure with similar indications and cell sources. The duration of neutropenia and the number of transfusions were significantly less with BuFlu (Boelens et al. 2012). Thus, BuFlu seems to be a well-tolerated and active combination and is being substituted for BuCY in front-line cooperative group AML protocols, including that of the current COG Phase III AML study (AAML1031).

One of the first reports of a treosulfan-based regimen was reported by Casper et al. (2004) and soon after used by de Lima et al. (2004). A low rate of organ toxicity and TRM was seen in the original studies of treosulfan combined with CY and Flu in adults ineligible for standard myeloablative conditioning (Beelen et al. 2005; Casper et al. 2004). In a more recent cohort, an 8 % 2-year non-relapse mortality was seen in a group of 60 adult and pediatric patients with hematological malignancy at high risk of relapse or TRM (Nemecek et al. 2011). Treosulfan-based regimens have also been well tolerated for second transplant procedures (Danylesko et al. 2012). The use of the treosulfan-Flu combination in preference to treosulfan-CY is justified by the absence of VOD in the treosulfan-Flu arm, in keeping with our knowledge of the impact of CY metabolites and liver toxicity (McDonald et al. 2003). Treosulfan has been widely used in Europe, and a recent analysis of over 700 pediatric HCT patients confirmed its acceptable safety profile, including in the high-risk second transplants setting (Bernardo et al. 2008; Wachowiak et al. 2011).

One area where a truly reduced intensity conditioning may have advantages in pediatrics is in CML. Today, as a result of the successful development of tyrosine kinase inhibitors (TKI), very few adult and pediatric patients with CML undergo HCT. In current practice, HCT for children and adults with CML is reserved for patients with advanced stages of disease and for those patients who cannot tolerate TKI therapy. However, in spite of this practice, there remains a debate in the pediatric transplant community about the impact of long-term TKI use in children with CML and the role of HCT (Cwynarski et al. 2003; Thornley et al. 2003; Andolina et al. 2012). As discussed above, CML was the first disease where it was clearly demonstrated that an allogeneic immune effect could be curative unto itself. Thus, in the case of a CML patient in chronic phase with a good molecular response to a TKI who wants to pursue potentially curative HCT, a non-myeloablative regimen is theoretically possible. However, initial reports of attempts at using reduced intensity regimens in adults with CML showed mixed results (Qazilbash et al. 2004). The best results were seen with the original reduced intensity regimen of Slavin's group (1998) or a modification of this regimen (Giralt et al. 1997; Or et al. 2003; Ruiz-Arguelles et al. 2005). However, results from MD Anderson Cancer Center in patients with higher risk disease were not encouraging (Kebriaei et al. 2007). Pediatric data are very limited and still favor upfront TKI therapy over HCT (Suttorp et al. 2011). However, if a patient is considered for allogeneic HCT based on lack of response to TKI or intolerance to treatment with these agents, consideration should be given to the enrollment of these children on clinical trials of

novel, reduced intensity conditioning regimens such as treosulfan-based regimens (Casper et al. 2004).

3.3 Preparative Regimens for Acute Lymphoblastic Leukemia

A full discussion of preparative regimens used for HCT in children with ALL can be found in Chap. 8. As noted above, there has been significant evolution in the development of non-TBI-based and reduced-intensity preparative regimens in children undergoing allogeneic transplantation for myeloid leukemias. In contrast, despite significant attempts, current data suggest little improvement in outcomes as a result of modifications to TBI-based preparative regimens in children with ALL undergoing allogeneic transplantation (reviewed in: (Hahn et al. 2005)). In fact, current evidence suggests that non-TBI-based regimens may result in worse outcomes.

Currently, there is only one prospective randomized clinical trial examining TBI-based versus non-TBI-based regimens in children with ALL (Bunin et al. 2003). In this Pediatric Blood and Marrow Transplant Consortium study, 43 children were randomized to receive busulfan, etoposide, and cyclophosphamide ($n=21$) or TBI at a dose of 1,200 cGy plus etoposide and cyclophosphamide ($n=22$). Patients received both related and unrelated donor transplants. Transplant-related mortality was higher in patients who received busulfan. At a median follow-up of 43.3 months, the 3-year event-free survival (EFS) was 58 % in children who received the TBI-based regimen versus 29 % ($p=0.03$) for the busulfan-based regimen.

In a large, retrospective analysis of data from the former International Bone Marrow Transplant Registry (now the CIBMTR), children with ALL undergoing matched sibling donor transplants were analyzed based upon several general classifications of cyclophosphamide and TBI- ($n=451$) or non-TBI-based preparative regimens based on busulfan and cyclophosphamide ($n=176$) (Davies et al. 2000). This large retrospective study suggested that 3-year leukemia-free survival was better in children who received CY-TBI-based regimens (50 % vs. 35 %; $p=0.005$), transplant-related mortality was higher in patients receiving the BuCY-based regimens (23 % vs. 15 %; $p=0.02$), while the risk of relapse was similar. Other single institution studies have shown similar patterns (Carpenter et al. 1996; Granados et al. 2000; Weisdorf et al. 1994).

As discussed in Chap. 8, this continued reliance on TBI in the preparative regimens for children with ALL undergoing allogeneic transplantation is particularly concerning in infants and young children, despite several studies that suggest similar toxicity profiles (Sanders et al. 2005) and long-term developmental outcomes (Eapen et al. 2006).

Conclusion

Almost six decades of clinical research have demonstrated the importance of the pre-transplant conditioning regimen on the ability to kill tumor cells and provide immune suppression of the host in order to allow for engraftment of HLA-disparate stem cells. It is well recognized that higher doses of chemotherapy and TBI enhance both tumor kill and immune suppression, but with increasing toxicity. Therefore, a vast number of studies have been performed attempting to preserve tumor kill and immune suppression, while minimizing short- and long-term toxicities. In myeloid malignancies, this work has resulted in our ability to develop effective myeloablative and non-myeloablative regimens, including those that do not require TBI. In contrast, progress in ALL, despite great effort, has not shown similar success, with most children continuing to receive TBI-based myeloablative regimens.

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Graft Versus Host Disease: From Basics to the Clinic

4

Eva C. Guinan and Margaret L. MacMillan

Contents

E.C. Guinan, MD (✉)
Departments of Radiation Oncology and Pediatric Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA

Harvard Medical School, Boston, MA, USA
e-mail: eva_guinan@dfci.harvard.edu

M.L. MacMillan, MD
Blood and Marrow Transplant Program, Department of Pediatrics, University of Minnesota Medical School, 420 Delawar Sr. S.E., Minneapolis, MN, USA

4.1 Graft Versus Host Disease

The transfer of allogeneic tissues from one individual to another is complicated by the exquisite specificity and cellular and mechanistic diversity of the immune system. Thus, recognition of donor tissues by host immune cells (host versus graft) and host tissues by donor immune cells (graft versus host, GVH) is an obligate event after HCT, although there is dramatic variation in the manifestations of these responses. While host versus graft reactions are quite effectively addressed by the immunosuppressive and ablative effects of pre-HCT conditioning on host immunity, GVH disease (GVHD) remains a significant barrier to successful HCT. GVHD is associated with both short- and long-term morbidity and mortality and may itself be of limited or unlimited duration. Despite diverse prophylactic and treatment approaches, it has been estimated that GVHD remains the major contributor to death in some 15–30 % of patients and a cause of morbidity in approximately half of those undergoing HCT (Ferrara et al. 2009).

Although recognition of host tissues by donor T cells remains the overarching paradigm guiding efforts to understand and address GVHD, investigation of GVHD pathophysiology and treatment has been broad in scope. Animal models, most commonly murine or canine, have been used to explore the relevance of various factors to the initiation, perpetuation, and resolution of GVHD; these factors include intrinsic donor and recipient characteristics (e.g., major and minor

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human leukocyte antigen [HLA] match and mismatch), physiologic responses (e.g., innate and adaptive immune reactivity), and management decisions (e.g., type of conditioning regimen and supportive care) (Ferrara et al. 2009; Socie and Blazar 2009; Schroeder and DiPersio 2011; Shlomchik 2007; Welniak et al. 2007). These models have helped delineate the complexity of GVHD, define the consequences of specific clinical strategies, and suggest new therapeutic and prophylactic approaches. However, as reviewed by Socie and Blazar (2009), the discordance between the very characteristics that make mouse experiments feasible and interpretable, such as inbred genetics and controlled environment, and the highly diverse circumstances reflected in human recipient-donor pairs has limited the direct applicability of such observations. Some problems, such as chronic GVHD and treatment-refractory GVHD, have proven difficult to model (Shlomchik 2007), and the particular issues of GVHD in children have gone largely unexplored due in part to the difficulties of creating relevant model systems.

The alternative approach to animal modeling is to study GVHD pathophysiology directly in humans. Just as animal models have provided seminal insights, data from human samples has been critical in advancing our understanding of this protean syndrome. For example, histopathologic assessment helped to establish the target-tissue characteristics of GVHD (Sale et al. 1977, 1979; Sloane et al. 1980) and has remained critical to elucidating new diagnostic and mechanistic issues related to GVHD (Shulman et al. 2006; Penack et al. 2011). Because demographic data is frequently available on donors, recipients, and volunteers, human sample data indexed to age has been used to shed light more specifically on GVHD in children (Geyer et al. 2011; Goddard et al. 2010; Hosseini et al. 2010).

Human clinical sample analysis has benefited greatly from technologic advances, of which improvements in histocompatibility antigen typing may be the most dramatic example of innovation that has impacted GVHD. Indeed, demonstrating the relationship of higher-resolution HLA matching of unrelated donor-recipient pairs with subsequent decreased GVHD risk in both adult and pediatric recipients is an excellent example of such clinically impactful correlative laboratory work (Giebel et al. 2003; Perez 2011). HCT population studies of potential biomarkers for inflammation or immune responsiveness have in large part moved from single analyte assays to multi-analyte techniques (Paczesny et al. 2009; Weissinger et al. 2007). The translational value of such technologies has recently been demonstrated by the efficacy of a 6 biomarker panel in predicting therapeutic response of GVHD (Levine et al. 2012).

Despite limitations such as discussed above, laboratory-based analyses of both animal models and human clinical samples have contributed greatly to the current understanding of GVHD pathophysiology. The following is not a comprehensive review of the extensive literature, but rather focuses primarily on those areas which have had the greatest clinical impact to date.

4.2 Host Microenvironment

Before immunologically active donor cells are ever infused into the recipient, myeloablative and, to lesser degree, non-myeloablative conditioning regimens damage host tissues, with results that influence subsequent GVHD. Preconditioning characteristics of the host microenvironment, such as infection, may also exert important influences. In the 1970s, mouse models revealed a critical role for the microbiome in the evolution and severity of acute GVHD occurring after radiation-based conditioning (van Bekkum and Knaan 1977; van Bekkum et al. 1974). These ideas gained significant momentum in the 1990s with the promulgation of the hypothesis that a cascade of inflammation-driven events ("cytokine storm") following HCT conditioning contributed significantly to GVHD (Antin and Ferrara 1992; Hill and Ferrara 2000; Nestel et al. 1992; Feinstein et al. 2001). Critical components of this conditioning effect were felt to include (1) direct tissue damage leading to expression of cell surface proteins, including HLA and adhesion molecules, that help to activate host antigen

presentation and initiate and amplify donor T-cell alloreactivity; (2) innate immune activation consequent to leakage of microbial pathogens and their associated toxins from the gastrointestinal (GI) lumen to the systemic circulation; and (3) release of cytokines and other inflammatory mediators from both fixed tissue and donor and recipient lymphohematopoietic cells that amplify these effects and modulate effector T-cell function (Blazar and Murphy 2005; Ferrara et al. 2009; Hill and Ferrara 2000; Vogelsang et al. 2003). The soluble mediators implicated in GVHD pathophysiology, many of which play an active role in innate and/or adaptive immunity, have recently been reviewed (Ball and Egeler 2008; Castor et al. 2012; Holler 2009).

Endotoxin (lipopolysaccharide, LPS) is perhaps the innate immune motif most strongly associated with acute GVHD. LPS is found uniquely in the outer membrane of Gram-negative bacteria (Raetz and Whitfield 2002). LPS leakage from a chemoradiotherapy-damaged GI lumen into the peripheral circulation has been postulated to be a major contributor to the cytokine storm and demonstrated to have a relationship to GVHD in model systems (Nestel et al. 1992). Humans undergoing myeloablative conditioning regimens become endotoxemic and develop disordered LPS-related innate immunity (Levy et al. 2003; Sauer et al. 2003; Guinan et al. 2011). Both animal models and human correlative data have suggested that LPS-induced TNF-α production, as well as other determinants of TNF-α production and responsiveness, contributes to acute GVHD and early HCT mortality (Cooke et al. 1998; Hill and Ferrara 2000; Cavet et al. 1999; Ordemann et al. 2002; Holler et al. 1993; Remberger et al. 1995). Single nucleotide polymorphisms (SNPs) in several important innate immune molecules have also been associated with the occurrence and, in some cases, the severity of acute GVHD (Holler et al. 2008; Dickinson and Holler 2008; Penack et al. 2010). In aggregate, these observations contributed to the adoption of reduced-intensity conditioning and to the development of preclinical and/or clinical trials of agents modifying innate immunity. The use of either TNF-α antagonists (Holler et al. 1995; Cooke et al. 1998) or LPS-receptor blockade (Cooke et al. 2001), or of animals with deficient TNF-α (Hill and Ferrara 2000) or LPS responsiveness (Cooke et al. 1998), has led to significant amelioration of acute GVHD, as has immunization against LPS prior to HCT (Abdul-Hai et al. 2006). As the pathophysiologic role of innate immunity becomes better understood and the number of agents active in these pathways increases, clinical trials in GVHD are likely to increase (Shin and Harris 2011; Penack et al. 2010; Holler 2009).

A completely different consideration in relation to GVHD and the host microenvironment is the functional status of the thymus. The thymus is both a GVHD target and, by the nature of its T-cell output, a modulator of GVHD (Krenger and Hollander 2010). The thymic contribution to T-cell regeneration after HCT is more effective in children, which may contribute to faster recovery of immunocompetence and an associated decrease in severity of GVHD (Chidgey et al. 2007). Moreover, recovery from GVHD-mediated damage to the thymus, which damage further impedes immunologic recovery, has been shown to be faster and more complete in children (Clave et al. 2009).

4.3 T cells and Their Target Antigens

Elegant studies in a variety of murine models established the critical role of alloreactive T cells in the generation of acute GVHD (reviewed in Schroeder and DiPersio 2011; Shlomchik et al. 2007; Socie and Blazar 2009). Depending largely upon the specific HLA disparities between recipient and donor, acute GVHD could be engineered to be dependent upon either CD4 or CD8 T cells or both (Sprent et al. 1988). Translation of these observations to human HCT has produced clinical trials in GVHD prophylaxis that have ranged from global immunosuppression to selective or complete T-cell depletion (Potter and Moore 2008). More recently, studies have demonstrated that specific CD4 and CD8 cell subsets may have differential activity in the pathophysiology of both acute

and chronic GVHD. These relationships have generally been inferred from genetically manipulated murine models in which various immune cell subsets have been eliminated (reviewed in Coghill et al. 2010). While naïve cells uniformly appear able to initiate GVHD in such model systems, the GVHD-inducing capability of memory T-cell subsets has been less clear and consistent (Zhang et al. 2005; Coghill et al. 2010; Socie and Blazar 2009; Chen et al. 2004; Anderson et al. 2003). The increasingly well documented cross-reactivity of pathogen-specific naïve and memory cells with alloantigens (D'Orsogna et al. 2012) makes these issues even more difficult to dissect in the complex human setting where exposure to pathogens occurs before, during, and after HCT. Moreover, the vagaries of donor-recipient HLA "matchedness" further confound the issue of T-cell receptor promiscuity. Nonetheless, recent studies have already demonstrated that expanded (memory) populations of pathogen-specific cells can be administered with minimal risk of GVHD (Melenhorst et al. 2010; Cruz et al. 2010; Doubrovina et al. 2012).

The targets of T-cell responses in GVHD have been shown to be model dependent and include not only Class I and Class II major histocompatibility molecules but also minor histocompatibility antigens (so-called mHag or MiHA) and other non-HLA antigens such as those associated with the Y-chromosome or certain polymorphic cell surface molecules (reviewed in Shlomchik 2007; Hansen et al. 2010). An increasing number of human mHag are being identified (Kamei et al. 2009), and relationships between mismatch at both major and minor histocompatibility antigens with human GVHD have been demonstrated in numerous studies (Goulmy et al. 1996; Vogt et al. 2002; Maruya et al. 1998; Woolfrey et al. 2011; Petersdorf 2008). Technical tools such as HLA-restricted, antigen-specific tetramers are enabling detailed experiments that explore the role of different T-cell populations in acute GVHD generation and expression (Kamei et al. 2009) and the role of tissue restriction of mHag as a factor in organ-specific GVHD.

In addition to acute GVHD-inducing and effector populations, T cells also contribute regulatory populations (Treg) to the complex immune milieu that characterizes GVHD. These cells may have particular importance in the occurrence and persistence of chronic GVHD. In mouse models, depletion of CD4+CD25hi Treg is associated with increased rates and severity of acute GVHD (Hoffmann et al. 2002; Taylor et al. 2002). Early clinical trials of Treg administration or in vivo expansion have been encouraging and suggest further exploration of this approach with in both acute and chronic GVHD (Koreth et al. 2011; Di Ianni et al. 2011; Brunstein et al. 2011).

4.4 Other Cell Populations

The science of GVHD has also revealed a great deal about the contributions to other cells and pathophysiologic mechanisms. However, the translation from bench to bedside has generally not yet proceeded to the same degree as the above areas (Socie and Blazar 2009; Welniak et al. 2007). For example, the roles of host and donor antigen-presenting cells demonstrated in elegant murine systems have proven difficult to translate to human therapeutic interventions, although they have provided frameworks for better understanding physiology (Shlomchik et al. 2007; Socie and Blazar 2009; Schroeder and DiPersio 2011). An exception to this general statement is the identification of B cells as active participants in both acute and chronic GVHD (Shimabukuro-Vornhagen et al. 2009), an observation perhaps predicted by their importance in solid organ graft rejection. In turn, the burgeoning number of B-cell-directed therapeutics for lymphoproliferative and plasma cell dyscrasias has become a somewhat unexpected source of potential GVHD therapeutics. For example, both rituximab, a monoclonal antibody directed against CD20, and bortezomib, developed as an anti-plasma cell agent, have moved into clinical GVHD trials. Improved understanding of the potential role of natural killer (NK) cells in acute GVHD has led to clinical exploration of both the number of NK cells in the graft and the relative match of NK cell surface receptors between donor and recipient. Both parameters appear to have some influence

(Bryson and Flanagan 2000; Socie and Blazar 2009; Ruggeri et al. 2006). The efficacy of mesenchymal cells (MSC), derived from a variety of sources, in the prophylaxis or treatment of GVHD continues to be explored clinically, based on extensive in vitro data demonstrating immunosuppressive effects (reviewed in Tolar and Tolar 2012; Kebriaei and Robinson 2011; Francois and Galipeau 2012; Auletta et al. 2010). While Health Canada recently approved the use of a specific MSC product for children with severe, steroid-refractory GVHD, the US Food and Drug Administration (FDA) has yet to approve the same agent for the same indication. Additional information will be necessary to determine the optimal MSC source and what role, if any, this therapy will play in GVHD.

The clinical advances achieved by studying animal models and individuals undergoing HCT have been many. Rates of severe acute GVHD in children and adults have diminished with time. Some of this improvement is a direct reflection of what has been learned about GVHD pathophysiology: the importance of finer HLA matching in unrelated donor HCT, the need to reconsider the toxicity of conditioning regimens, and the potential of cellular therapies to impact outcomes without inciting further GVHD. A review of current thinking that reflects these advances in relation to recognition and management of acute and chronic GVHD follows.

4.5 Approach to Clinical GVHD

Despite many advances in HCT over the last several decades, acute and chronic GVHD remain major causes of morbidity and mortality (Weisdorf et al. 1990a; Martin et al. 1990; MacMillan et al. 2002b; Lee et al. 2003a). The pathophysiology and manifestations of these two types of GVHD are different and unique. Classically, acute GVHD was thought to occur before day 100 after HCT and chronic GVHD after day 100. It is now apparent that these timeframes are neither accurate nor fixed. Additionally, patients can have active acute GVHD while developing chronic GVHD, an entity known as "overlap syndrome." In 2005, the National Institutes of Health (NIH) Consensus Working Group for Diagnosis and Staging established standardized criteria for the diagnosis of chronic GVHD and proposed tools for scoring GVHD organ involvement and assessing overall severity (Filipovich et al. 2005). The NIH working group also better defined the categories of acute and chronic GVHD as outlined in Table 4.1.

Table 4.1 Categories of acute and chronic GVHD as defined by NIH working group (Filipovich et al. 2005)

Category	Time of symptoms after HCT	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤100 days	Yes	No
Persistent, recurrent, or late-onset acute GVHD	>100 days	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

"Classic acute" GVHD is defined by the presence of acute GVHD manifestations prior to day 100 after HCT. Acute GVHD manifestations occurring more than 100 days after HCT are classified as "persistent," "recurrent," or "late-onset" acute GVHD depending on whether acute GVHD occurred prior to day 100. "Classic chronic" GVHD is defined by diagnostic manifestations of chronic GVHD without acute GVHD. "Overlap" GVHD is a subtype of chronic GVHD in which both acute and chronic GVHD manifestations are present. Overlap GVHD is associated with worse overall survival and higher non-relapse mortality than classic chronic GVHD (Pidala et al. 2011). Importantly, there is no time limit set for the diagnosis of either acute or chronic GVHD (Filipovich et al. 2005).

It is imperative that GVHD is diagnosed accurately and in a timely fashion to ensure appropriate and hopefully effective therapy. The diagnosis and treatment of acute and chronic GVHD will be discussed separately.

4.6 Acute GVHD

Acute GVHD (of any grade) occurs in 30–70 % of patients who receive an allogeneic HCT (Martin et al. 1990; Weisdorf et al. 1990a; MacMillan et al. 2002b, 2009). Acute GVHD usually develops within the first 60 days after allogeneic HCT but can occur later, especially after non-myeloablative HCT (Mielcarek and Storb 2005). Factors associated with higher risk of acute GVHD include older recipient age (Kollman et al. 2001; Weisdorf et al. 1991), unrelated donor grafts (Kernan et al. 1993), HLA disparity (Beatty et al. 1985; Kernan et al. 1993; Weisdorf et al. 1991; Flowers et al. 2011), cytomegalovirus (CMV) seropositivity (Weisdorf et al. 1991), the use of a female donor for a male recipient (Flowers et al. 2011), and the use of total body irradiation in the preparative regimen (Clift et al. 1990; Flowers et al. 2011). Lower rates of acute GVHD are observed after single umbilical cord blood (UCB) transplants compared to unrelated bone marrow or peripheral blood stem cell (PBSC) transplants (Wagner et al. 1996; Laughlin et al. 2004; Eapen et al. 2007). The use of two UCB units has been associated with a higher risk of moderate GVHD compared to a single UCB unit, but with no increase in transplant-related mortality (MacMillan et al. 2009).

4.6.1 Clinical Manifestations

Acute GVHD is manifested by fevers, skin rash, GI and/or liver involvement. The typical appearance of cutaneous GVHD is that of an erythematous, maculopapular skin rash, which often starts on the dorsal surfaces of the extremities and may involve the palms and soles. Rash on the palms and soles is an almost pathognomonic finding. Other commonly affected areas include the face, back of the ears, and neck. While cutaneous GVHD may involve only a small portion of the skin, as it progresses, the rash can involve the full limbs and trunk. Over time the rash may become confluent. In cases of severe acute GVHD, bullae may form.

Acute GVHD of the gut may involve the upper and/or lower GI tract. Upper GI acute GVHD causes persistent nausea with or without vomiting. Patients are often intermittently nauseated after an allogeneic HCT, but the nausea and vomiting characteristics of upper GI GVHD are more persistent throughout the day. Lower GI acute GVHD causes voluminous watery diarrhea with frequency, urgency, tenesmus, and often abdominal cramping. In contrast to many other types of diarrhea, acute GVHD is a secretory diarrhea and therefore resting the gut does not substantially decrease the volume. In severe GI GVHD, the diarrhea can be grossly bloody. As GI GVHD can be complicated by occurrence of an ileus, it is important to distinguish between therapeutic response and decreased motility when a decrease in stool volume is observed. Acute GVHD of the liver causes cholestasis with hyperbilirubinemia, often accompanied by elevation of serum alkaline phosphatase. Transaminitis can also be seen and may be marked.

4.6.2 Diagnosis, Staging, and Grading of Acute GVHD

The clinical manifestations of acute GVHD may be mimicked by signs and symptoms of other posttransplant complications including those attributable to regimen-related toxicity, infections, medications, veno-occlusive disease, cholelithiasis, and hemolysis. Therefore, in order to accurately diagnose acute GVHD, biopsies of suspicious sites should be performed for confirmatory histological diagnosis and, most importantly, to rule out other potential causes for rashes, diarrhea, nausea, and hyperbilirubinemia. Because liver biopsies are more invasive and liver GVHD rarely occurs in isolation (MacMillan et al. 2002b), liver biopsies are not routinely performed if biopsies from other sites confirm the diagnosis of GVHD. Duodenal biopsies should be performed cautiously due to the potential risk for nonhealing ulcerations and intramural hematomas. Interpretation of biopsies can be particularly difficult early after HCT as cellular injury from chemoradiotherapy can be indistinguishable

Table 4.2 Clinical stage of acute GVHD

Stage[a]	Skin	Liver	Lower GI tract	Upper GI tract
1	Maculopapular rash <25 % body surface	Bilirubin 2.0–3.0 mg/dl	Diarrhea 500–1,000 ml/day or 280–555 ml/m^{2b}	No protracted nausea and vomiting
2	Maculopapular rash 25–50 % body surface	Bilirubin 3.1–6.0 mg/dl	Diarrhea 1,000–1,500 ml/day or 556–833 ml/m^2	Persistent nausea, vomiting, or anorexia
3	Maculopapular rash >50 % body surface	Bilirubin 6.1–15.0 mg/dl	Diarrhea >1,500 ml/day or >833 ml/m^2	
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin >15.0 mg/dl	Severe abdominal pain, with or without ileus, or stool with frank blood or melena	

[a]Assign stage based on *maximum* involvement in an individual organ system
[b]For pediatric patients, stool volume calculated as ml/m^2

Table 4.3 Acute GVHD grading systems

Grade[a]	Skin[b]	Liver	LGI	UGI
Minnesota (Weisdorf et al. 1990b; Przepiorka et al. 1995; MacMillan et al. 2002b)				
I	1–2	0	0	0
II	3	1	1	1
III	–	2–4[d]	2–3[d]	
IV	4	–	4	
Consensus (Przepiorka et al. 1995; Weisdorf et al. 1990b)				
I	1–2	0	0	0
II	3	1	1	1
III	–	2–3	2–4	
IV	4	4	–	
CIBMTR (Rowlings et al. 1997)[c]				
A	1	0	0	0
B	2	1–2	1–2	1
C	3	3	3	
D	4	4	4	

[a]Each grade is based on *maximum* stage for each involved organ
[b]Each column identifies *minimum* organ stage for overall grade
[c]Modified as shown to include UGI GVHD
[d]Consensus Grading differs from Minnesota Grading only by assigning stage 2–4 LGI as grade III and stage 4 liver as grade IV (Przepiorka et al. 1995)

from acute GVHD (Shulman et al. 2007). In 2006, the NIH Pathology Consensus Committee established guidelines for the interpretation of biopsy results to assist pathologists and clinicians (Shulman et al. 2006).

Once the diagnosis is made, the stage and grade of GVHD need to be determined. Although biopsies provide a histological grade, treatment is determined by the overall clinical grade, which is in turn based upon the constellation of clinical symptoms and their severity. Each organ is staged according to the degree of clinical involvement, and the overall grade of GVHD is then determined based upon the involvement and stage in each organ as shown in Table 4.2. The three most popular grading systems used are the consensus/modified Glucksberg criteria (Przepiorka et al. 1995; Weisdorf et al. 1990b; MacMillan et al. 2002b), the Minnesota grading system (MacMillan et al. 2002b), and the Center for International Blood and Marrow Transplant Research (CIBMTR) GVHD organ stage-derived grading system (Rowlings et al. 1997) as shown in Table 4.3.

Several grading conventions have arisen with time. Skin GVHD is staged based upon the extent of the rash as determined by the affected body surface area (BSA). However, if bullae are present, it is always considered stage 4 skin GVHD, regardless of the extent of the rash. If upper GI GVHD occurs, it is classified as stage 2 GI GVHD. Lower GI GVHD staging is based upon volume of stool, requiring accurate measurements of stool volumes. Finally, liver GVHD is staged according to bilirubin levels. The overall GVHD grade is determined by the stage of each organ according to a grading system. The Minnesota (MacMillan et al. 2002b) and Consensus (Przepiorka et al. 1995; Weisdorf et al. 1990b) systems are similar except for the liver and lower GI staging criteria for grades III and IV GVHD. The CIBMTR index (Rowlings et al. 1997) is different and tends to give a higher GVHD score for a given combination of GVHD stages (MacMillan et al. 2002b).

4.6.3 Treatment of Acute GVHD

Grade I GVHD is considered mild GVHD and is essentially a skin rash over <50 % BSA (i.e., stage 1–2 skin GVHD). Such limited skin GVHD is treated with topical steroid creams or ointments (e.g., 0.1 % triamcinolone to the body and 1 % hydrocortisone to the face and groin, applied 3–4 times daily). If skin GVHD extends beyond 50 % BSA or if there is any GI or liver involvement, it is at least grade II GVHD and systemic therapy is required. Grade III–IV acute GVHD is referred to as severe because it is difficult to treat and is associated with high rates of morbidity and mortality.

Corticosteroids remain the primary systemic therapy for acute GVHD (Martin et al. 2012b). Corticosteroids are lympholytic and decrease the inflammatory cascade that propagates acute GVHD. Conventionally, patients receive 48 mg/m^2 (or 2 mg/kg) of intravenous methylprednisolone or oral prednisone equivalent (Weisdorf et al. 1990b; Martin et al. 1990; MacMillan et al. 2002b). Some centers choose to treat patients with a lower starting dose (usually 1 mg/kg prednisone), predominantly for lower initial grade GVHD (Mielcarek et al. 2009). Practices in relation to tapering the steroid dose vary widely. However, once the GVHD has been effectively treated, steroids are most often gradually tapered over several weeks; the steroid taper often begins at least 3–7 days after initiation of therapy, and the dose is usually decreased by 10 % every 5–7 days. If a flare of GVHD occurs, the taper is held and either the dose increased or additional therapy added to treat the GVHD.

Approximately half of patients will respond to initial therapy with steroids with approximately 18–30 % experiencing a durable response and the remainder requiring second-line therapy (MacMillan et al. 2002b; Martin et al. 1990; Weisdorf et al. 1990a, b). Patients with lower GI involvement (± other organ involvement) have lower response rates (MacMillan et al. 2002b; Martin et al. 1990). Efforts are now being made to better identify patients at diagnosis who are less likely to respond to initial steroid therapy and warrant alternative initial therapy. In a recent analysis by the Minnesota group of 864 patients with acute GVHD, high-risk initial GVHD was defined as either skin stage 4, lower GI stage ≥3, or skin stage 3 and lower GI or liver stage ≥2 GVHD (MacMillan et al. 2012). Patients with this high-risk GVHD at initial diagnosis were less likely to respond to steroid therapy and had a twofold increased risk of transplant-related mortality compared to patients with standard risk GVHD. Promising studies suggest that it may be possible to use GVHD biomarker panels to predict therapy-responsive GVHD and adjust therapy accordingly (Levine et al. 2012; Harris et al. 2012). To date, higher-dose steroids or the addition of other therapies to upfront steroids, including novel proteins (Levine et al. 2008), antithymocyte globulin (ATG) (Cragg et al. 2000), and monoclonal antibodies (Couriel et al. 2009; Lee et al. 2004), have not been shown to yield improved results. However, the poor outcome of patients with high-risk severe GVHD at onset warrants alternative initial therapy, providing a focus of well-designed, novel therapeutic trials (Martin et al. 2012b).

Importantly, all patients with GVHD regardless of grade require close monitoring. If GVHD worsens after 4 days of treatment or does not improve after 7 days of treatment, second-line therapy is required. Timely introduction of second-line therapy has been shown to be associated with improved survival (MacMillan et al. 2002a). Patients being treated for severe GVHD may require repeat endoscopies and biopsies to differentiate between active ongoing GVHD requiring additional therapy and persistent symptoms in the face of a healing gut. Management of steroid-resistant acute GVHD is difficult. As recently thoroughly reviewed by Martin et al. on behalf of the American Society of Blood and Marrow Transplantation (Martin et al. 2012b), there is no consensus as to the best second-line agent. Many novel agents reported in the literature have been tested in small, less than optimal trials that provide little therapeutic guidance (Martin et al. 2012a). Even the most effective agents produce only a 25–30 % success rate. Novel approaches to the prevention and treatment of acute GVHD are being explored based upon new insights from basic immunology, preclinical models, and phase I clinical trials (Blazar

et al. 2012). It is imperative that these new agents be tested in well-designed trials to accurately determine their safety and efficacy (Martin et al. 2012a).

4.7 Chronic GVHD

Chronic GVHD occurs in 10–70 % of patients who receive an allogeneic HCT and is the leading cause of morbidity and non-relapse mortality in patients beyond 2 years from HCT (Lee et al. 2003b; Arora et al. 2003; Rocha et al. 2000). Symptoms usually have an insidious onset and generally present 4–6 months after HCT, although they can occasionally first manifest beyond a year after HCT. Risk factors for chronic GVHD are fairly similar to those for acute GVHD with the additional and strongest risk factor being a prior history of acute GVHD (Flowers et al. 2011; Lee et al. 2003b). The vast majority of patients have a history of acute GVHD, with only 10–20 % having de novo chronic GVHD (Lee et al. 2003b). Risk factors associated with chronic GVHD include having undergone mobilized PBSCT and older patient age (Flowers et al. 2011).

4.7.1 Clinical Manifestations of Chronic GVHD

Chronic GVHD is characterized by immune dysregulation, decreased organ function, and impaired quality of life. Chronic GVHD is a chronic multisystem disorder with characteristics of several autoimmune diseases and can involve one or more organs, including the skin, nails, hair, eyes, oral mucosa, GI tract, liver, lungs, muscles, joints, genitals, and hematopoietic and immune systems.

4.7.2 Diagnosis, Classification, and Staging of Chronic GVHD

The diagnosis of chronic GVHD can be challenging due to the insidious onset of signs and symptoms and the difficultly of distinguishing their association with chronic GVHD from other diagnoses. A thorough detailed history and physical exam with selected labs and tests are essential to accurately diagnose chronic GVHD. The NIH working group has recommended that the diagnosis of chronic GVHD be based on at least 1 diagnostic manifestation of chronic GVHD or at least 1 distinctive manifestation with the diagnosis confirmed by pertinent biopsy, laboratory tests, or radiological findings as outlined in Table 4.4 (Filipovich et al. 2005). Diagnostic features include poikiloderma; sclerosis; morphea; hyperkeratotic plaques; lichen planus-like lesions on the skin or in the mouth or vagina; stenosis of the mouth, upper GI tract, or vagina; esophageal webs; bronchiolitis obliterans; fasciitis; joint stiffness; and contractures. Distinctive features include depigmentation, dystrophic nails, alopecia, oral ulcers and atrophy, sicca syndrome, and myositis (Filipovich et al. 2005). Biopsies of affected sites should be performed to assist in the diagnosis and to rule out infections or other causes for the symptoms. An excellent diagnostic guide by Carpenter has been recently published (Carpenter 2011).

The NIH working group also recommended a new chronic GVHD clinical staging system (0–3) to score individual organ severity and functional impact (Filipovich et al. 2005). Eight organs are assessed including skin, mouth, eyes, GI tract, liver, lungs, joints and fascia, and genital tract. As shown in Table 4.4, global staging of chronic GVHD severity (none, mild, moderate, and severe) is determined and replaces the former "limited" versus "extensive" classification. Although this staging system is relatively new, early assessments show good correlation with outcomes (Arai et al. 2011; Kim et al. 2010; Inamoto et al. 2012; Pidala et al. 2011; Mitchell et al. 2011).

4.7.3 Treatment of Chronic GVHD

Treatment of chronic GVHD is usually less aggressive and more prolonged than that of acute GVHD. Mild chronic GVHD involves only one or two organs with a score of 1 and can be treated

Table 4.4 Signs and symptoms of chronic GVHD from NIH guidelines (Filipovich et al. 2005)

Organ or site	Diagnostic[a]	Distinctive[b]	Other features[c]	Common[d]
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)[e]		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes[e] Ulcers[e]		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes[f] Cicatricial conjunctivitis Keratoconjunctivitis sicca[e] 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[e] Fissures[e] Ulcers[e]		
GI tract	Esophageal web Strictures or stenosis in the upper to mid-third esophagus[e]		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)

Liver				Total bilirubin, alkaline phosphatase >2× upper limit of normal[e]
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with pulmonary function tests and radiology[e]		Bronchiolitis obliterans organizing pneumonia (BOOP)
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis[f]	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (autoimmune hemolytic anemia and immune thrombocytopenic purpura)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

[a]Sufficient to establish the diagnosis of chronic GVHD
[b]Seen in chronic GVHD but insufficient alone to establish a diagnosis of chronic GVHD
[c]Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed
[d]Seen with both acute and chronic GVHD
[e]In all cases, infection, drug effects, malignancy, or other causes must be excluded
[f]Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes)

with local therapy. Topical steroids or calcineurin inhibitor can be applied to areas of localized skin involvement. Cyclosporine or tacrolimus eye drops, punctual plugs, or Boston scleral lenses can help alleviate symptoms associated with dry eyes. Dexamethasone oral rinses may be used for oral hypersensitivity.

The NIH guidelines suggest systemic therapy if 3 or more organs are involved or if any single organ has a severity score of 3. Most patients requiring systemic therapy are treated with a calcineurin inhibitor (cyclosporine or tacrolimus) and steroids. The starting corticosteroid dose is usually 0.5 mg/kg administered daily or every other day. In patients with persistent symptoms, another agent, including azathioprine (Sullivan et al. 1988), thalidomide (Chao et al. 1996; Arora et al. 2001), or mycophenolate mofetil (MMF) (Martin et al. 2009), is often added, although they have not been demonstrated to provide benefit. If chronic GVHD fails to improve or progresses, a third-line agent is needed. A variety of agents have been used with varying success. Choice of agents depends upon the clinical manifestations, end-organ function, and treating physician preference. Once chronic GVHD is under control, immunosuppressive agents are tapered. Steroids are usually tapered first, and if chronic GVHD manifestations remain stable, the other immunosuppressive agents are tapered slowly. The decision as to the timing and order of taper varies by center. Patients must be followed carefully for signs of chronic GVHD flares.

In a prospective study of 298 patients at 5 centers, the NIH global severity scores were found to be associated with both non-relapse mortality and survival. Two-year non-relapse mortality was 3 % for mild, 9 % for moderate, and 32 % for severe global severity chronic GVHD (Arai et al. 2011). Factors associated with poor survival in patients with chronic GVHD have been reported to include older recipient age, HLA mismatch, progressive onset of chronic GVHD, lower performance score at diagnosis, receiving corticosteroids at onset, gut involvement, elevated bilirubin, thrombocytopenia, lichenoid skin changes, and >50 % BSA skin involvement (Jacobsohn et al. 2011).

4.8 Supportive Care

GVHD is in itself immunosuppressive as is its treatment. Therefore it is not surprising that opportunistic infections are the major cause of the death for patients with acute or chronic GVHD. Physical predispositions for infection include the frequent reliance upon central venous catheters during GVHD therapy, thus increasing the risk for bacteremia, and the breakdown of natural epithelial barriers, including the upper and lower GI tract, skin, and cornea. High-dose steroids increase the risk for viral reactivation, most notably CMV, and invasive mold infections (Nichols et al. 2001; Marr et al. 2002). Patients may require antiviral prophylaxis depending on CMV and herpes simplex virus serostatus; at-risk patients also require serial monitoring for CMV reactivation. Varicella reactivation is common as well. All patients require monitoring for reactivation of Epstein-Barr virus, human herpes virus 6, and adenovirus, and specific testing is generally indicated in the face of febrile episodes. Patients require antibiotic prophylaxis both for the functional hyposplenia that accompanies GVHD and for *Pneumocystis carinii* pneumonia prophylaxis. Broad spectrum intravenous antibacterial and antifungal therapy should be administered when patients become febrile or acutely ill. Patients with active GVHD should not receive immunizations because they will not mount an adequate response and may become quite ill with live vaccines. An exception to this rule is the injectable form of influenza vaccine, which should be administered to all patients annually as well as to their household members. The inhaled live attenuated form of influenza should not be given to patients or household members because there is a theoretical risk of shedding.

Conclusion

Acute GVHD is considerably better understood than it was several decades ago, in terms of its manifestations, pathophysiology, management, and implications. While the same is true for chronic GVHD, our comprehension of this latter condition lags in all of these parameters. Nonetheless, newer technologic

platforms and more sophisticated computational analyses are bringing the field closer to the goal of a defining signature for these syndromes, thus enabling more targeted and less generic therapeutic interventions. These will be both pharmacologic and cellular and will require the conduct of carefully constructed, multicenter clinical trials.

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Pulmonary and Hepatic Complications of Hematopoietic Cell Transplantation

5

Gregory A. Yanik, Kenneth R. Cooke,
Vincent T. Ho, and Paul G. Richardson

Contents

G.A. Yanik, MD
Blood and Marrow Transplant Program,
University of Michigan Cancer Center,
Ann Arbor, MI 48109, USA
e-mail: gyanik@umich.edu

K.R. Cooke
Pediatric Blood and Marrow Transplantation Program,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
e-mail: kcooke5@jhmi.edu

V.T. Ho
Department of Medical Oncology,
Dana-Farber Cancer Institute,
Boston, MA 02215, USA
e-mail: vincent_ho@dfci.harvard.edu

P.G. Richardson, MD (✉)
Department of Medical Oncology,
Jerome Lipper Multiple Myeloma Center,
Dana-Farber Cancer Institute, Boston, MA 02215, USA
e-mail: paul_richardson@dfci.harvard.edu

5.1 Introduction

Significant advances have been made in allogeneic transplantation for both adult and pediatric transplant recipients over the past 20 years, corresponding with dramatic declines in treatment-related mortality (TRM). The cumulative incidence of TRM at 1 year following unrelated donor transplants has decreased from 40 to 15 % between 1987 and 2006 for children with acute leukemia, the primary indication for transplant in the pediatric population (MacMillan et al. 2008). Improvements in conditioning regimen, supportive care, and human leukocyte antigen (HLA) testing have all been associated with incremental improvements in survival during this period. In particular, the management of both infectious and noninfectious organ complications has changed dramatically, with improved sensitivity for diagnostic testing for pathogens and tremendous improvements in our understanding of organ complications. Two organ complications in particular, pulmonary and hepatic, have been a major focus of investigation over the past several decades. The introduction of tumor necrosis factor (TNF) inhibitors for the management of acute, noninfectious lung injury and the introduction of an endothelial stabilizing agent (defibrotide) for the management of hepatic veno-occlusive disease have been major advances in the field.

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5.2 Pulmonary Complications

5.2.1 Overview

Pulmonary toxicity, both infectious and noninfectious, develops in 25–50 % of hematopoietic cell transplant (HCT) recipients, accounting for nearly 50 % of all transplant-related deaths (Clark et al. 1999; Crawford and Hackman 1993; Weiner et al. 1986; Quabeck 1994; Crawford et al. 1993; Kantrow et al. 1997; Afessa et al. 2001). Despite advances in treating opportunistic organisms, infectious lung injury remains a significant problem, particularly in patients with graft-versus-host disease (GVHD) or in individuals with delayed immune reconstitution. On the other hand, noninfectious lung injury can be either acute or chronic depending upon the time of occurrence posttransplant and the rate of disease progression. Acute lung injury may be alloreactive or non-alloimmune, secondary to cardiogenic shock or chemoradiotherapy effects. Chronic lung injury may be obstructive or restrictive in nature, depending upon the pathogenesis of the lung injury pattern (Holland et al. 1988; Schultz et al. 1994; Crawford et al. 1995; Sullivan et al. 1992; Sanchez et al. 1997; Badier et al. 1993; Quigley et al. 1994). This section will review the definitions, risk factors, and pathogenesis of lung injury occurring after HCT.

5.2.2 Diagnostic Evaluation

Because respiratory distress can progress rapidly once established, the timely coordination of care between the hematology-oncology, pulmonary, and often intensivist teams is essential to optimizing outcomes. Determination of the severity of respiratory dysfunction, including an assessment of the need for supplemental oxygen support, overall fluid balance, renal function, and cardiac output should be followed by radiographic imaging. In general, an initial chest x-ray or CT scan will identify the presence of lobar, multilobar, or diffuse pulmonary infiltrates (Fig. 5.1). While such findings may impact the decision-making process, they are nondiagnostic in and of themselves. In the absence of obvious cardiac failure or iatrogenic fluid overload, bronchoscopy with bronchoalveolar lavage (BAL) should be considered when infiltrates are present. BAL samples should be sent for a number of diagnostic tests to determine the potential presence of community or hospital acquired and opportunistic infections. Besides bacterial, fungal, and cytological stains, quantitative cultures should be performed on BAL fluid for diagnostic purposes. In addition, direct fluorescent antibody stains, centrifugation cultures (shell vial), or polymerase chain reaction (PCR) assays may also be very useful in isolating/identifying various viral pathogens.

The role of BAL in HCT recipients remains a matter of debate, with the diagnostic yield ranging from 31 to 67 % in various reports (Huaringa et al. 2000). In many cases, patients are referred for BAL after several days of symptoms and only after empiric antibiotic therapy has been well established. Empiric antibiotic management has been reported to provide inadequate coverage in over 40 % of patients with pathogens identified on subsequent BAL (Ascioglu et al. 2002; Prasoon et al. 2004). Furthermore, prolonged empiric antibiotics may diminish growth of potential pathogens, limiting the subsequent utility of bronchoscopic procedures. In a retrospective study of 598 patients who underwent BAL within the first 100 days post-HCT at MD Anderson Cancer Center, the overall yield of BAL was 55 %, with the yield 2.5 times greater among patients in whom a BAL was performed within the initial 4 days of clinical presentation. In addition, pneumonia-associated deaths were three times higher (18 % vs. 6 %) in those patients undergoing late bronchoscopy, following 4 days of clinical symptoms (Shannon et al. 2010). Yanik and colleagues examined 444 bronchoscopy procedures completed on 300 patients who received HCT at the University of Michigan from 2001 to 2007 (Yanik et al. 2008a). Only 13 % of BAL specimens collected in the first 30 days of HCT were positive for infection, with the diagnostic yield increasing to 33 % between days 31 and 100. Hence, while the majority of HCT patients requiring BAL

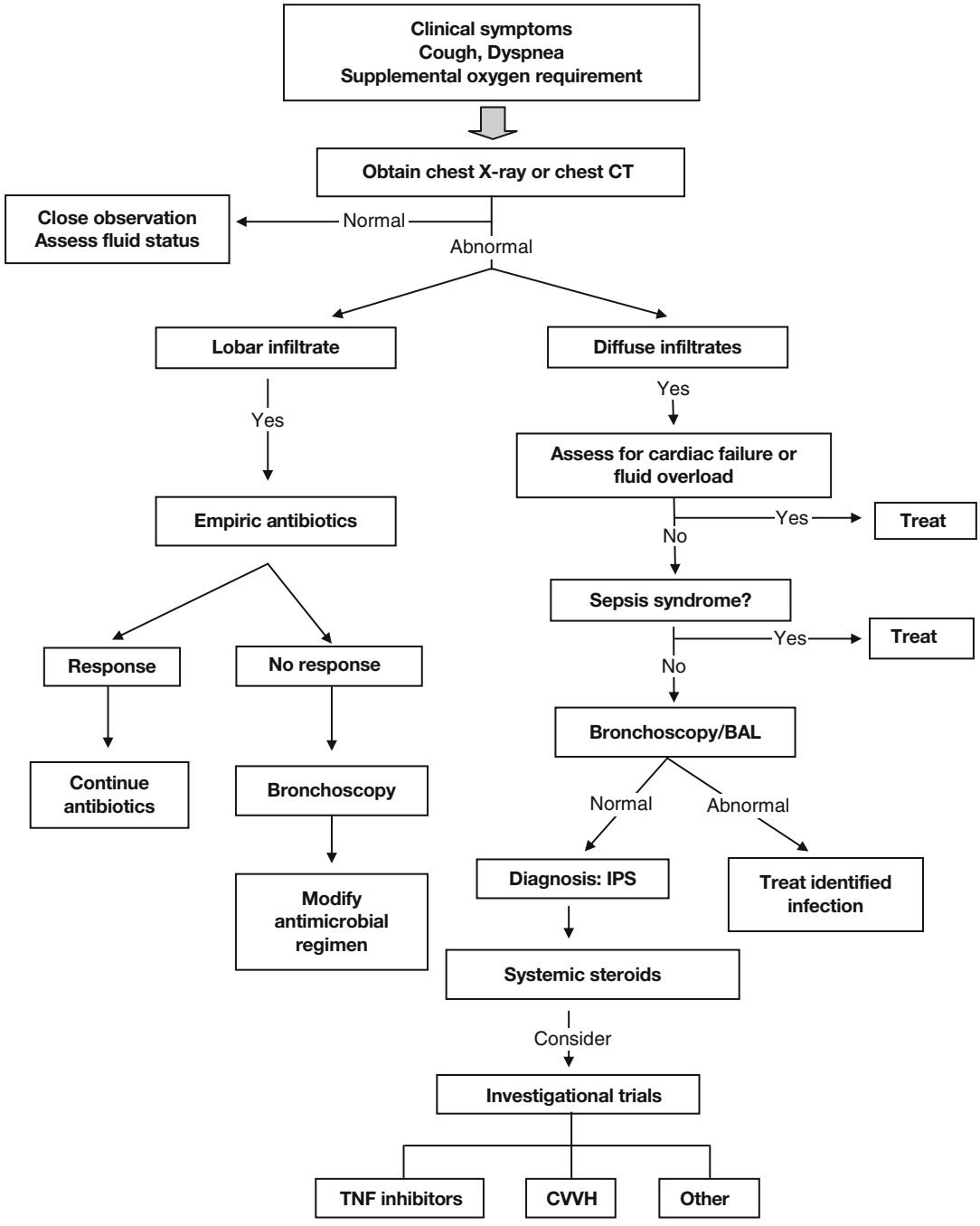


Fig. 5.1 Evaluation of a patient with respiratory dysfunction (*Abbreviations*: *CT* computed tomography, *BAL* bronchoalveolar lavage, *IPS* idiopathic pneumonia syndrome, *TNF* tumor necrosis factor, *CVVH* continuous veno-venous hemofiltration)

within the first 100 days may be categorized as having idiopathic pneumonia syndrome (IPS), a significant number of individuals will have evidence for infection. BAL resulted in changes in medical management in approximately 60 % of cases.

5.2.3 Infectious Lung Injury

Factors contributing to infectious pneumonitis following HCT may include suppression of laryngeal or cough reflexes, impaired removal of respiratory secretions due to decreased mucociliary clearance or airway obstruction, and impaired humoral and cellular defense mechanisms. Quantitative and/or qualitative defects in neutrophil or lymphoid function allow nonpathogenic organisms to ultimately become both invasive and pathogenic. With the lungs of a 10 kg child exposed to approximately 2,000 liters of inhaled air every 24 hours, the number of organic and inorganic particles and potential pathogenic organisms processed by our respiratory tract each day is countless. A fine balance exists between those organisms that become true pathogens and those that remain commensurate and often depends upon the quantity of inoculum received and host-defense factors outlined above.

Infectious pneumonitis may be subdivided into those associated with either interstitial or parenchymal involvement. Common pathogens that cause interstitial pneumonitis include community-acquired respiratory viruses (e.g., parainfluenza, respiratory syncytial virus (RSV), influenza, metapneumonia), mycoplasma, and opportunistic pathogens such as *Pneumocystis jiroveci* (PCP), whereas bacterial and fungal pathogens are more frequently associated with parenchymal changes.

CMV pneumonitis remains a significant cause of morbidity and mortality following allogeneic HCT. In the absence of a CMV prevention strategy (e.g., preemptive monitoring of CMV by plasma PCR for antigenemia or universal prophylaxis), CMV pneumonitis may develop during the first 100 days following HCT with a peak incidence at approximately 8 weeks. In the current era, most CMV infections occur after the monitoring or prophylaxis period ends. CMV pneumonitis in patients with chronic GVHD has also been well documented (Boeckh and Ljungman 2002; Osarogiagbon et al. 2000). With the availability of improved antiviral therapy, the mortality rate associated with CMV pneumonitis has declined significantly in recent years (Reusser 1991). Risk factors for the development of CMV disease include the presence of acute GVHD, recipient CMV seropositivity, transplantation for a hematologic malignancy, and the use of antithymocyte globulin during the transplant process (Osarogiagbon et al. 2000; Ljungman et al. 2003). Radiological manifestations of CMV range from diffuse interstitial opacities to widespread air space consolidation (Shimada et al. 2004). Histopathology remains the gold standard for identification of CMV pulmonary disease. Though molecular techniques have an excellent sensitivity for detection of infection, they may be less specific in regards to identifying CMV pneumonitis. The potential for polymicrobial superinfections is another concern in the transplant patient with CMV pulmonary disease, given the multiple issues often involved in patients with active CMV infections, including the concurrent use of systemic corticosteroids and prolonged empiric antibiotic usage.

Respiratory syncytial virus (RSV) is a single-stranded, enveloped RNA virus that presents as a self-limiting upper respiratory tract infection in immunocompetent individuals or a potentially fatal pneumonitis in immunocompromised patients (Ebbert and Limper 2005). Outbreaks in patients undergoing allogeneic HCT have been associated with mortality rates as high as 78 % (Englund et al. 1988; Harrington et al. 1992). In the United States, the onset of RSV infections typically begins in November and continues for approximately 24 weeks. The organism is highly contagious, with transmission occurring primarily through surfaces contaminated with viral-laden nasal or oral secretions. Even in immunocompetent patients, native memory responses are incomplete, allowing for repeated infections. The overall virulence of this agent places the immunocompromised patient at particular risk for fatal lower respiratory tract infections during the seasonal period (Ebbert and Limper 2005). Radiographically, patchy alveolar or diffuse interstitial infiltrates may be seen. Clinically, affected patients may exhibit profound dyspnea and hypoxemia, with or without concurrent upper respiratory tract symptoms. Less than 50 % of patients with lower tract involvement have preceding or concurrent

nasopharyngeal symptoms (Ebbert and Limper 2005; Harrington et al. 1992). The use of aerosolized ribavirin (6 g/day) using small particle generators has resulted in a decrease in RSV shedding, but clinical efficacy has not been proven (Ebbert and Limper 2005; Boeckh et al. 2007). Palivizumab may be considered as prophylaxis option in adults with lower respiratory tract disease (Hynicka and Ensor 2012).

The clinical impact of recently described viruses including human metapneumovirus and non-SARS human coronaviruses is not yet clear. Human metapneumovirus (hMPV) is a paramyxovirus recently recognized as the first human pathogen within the genus *Metapneumovirus* (van den Hoogen et al. 2004). The virus was first identified in the Netherlands in 2001 and was recently reported as a potential pathogen in allogeneic transplant recipients (Englund et al. 2006). In the bone marrow transplant setting, infected patients typically present within the first 50 days posttransplant and exhibit clinical and radiographic findings similar in appearance to IPS. Rapid progression of respiratory symptoms may occur, with a median of 4 days reported between initiation of oxygen support and death (Englund et al. 2006). The clinical spectrum of hMPV as a cause of interstitial pneumonia posttransplant remains ill defined, with issues such as the frequency of asymptomatic shedding, improved detection methods, and treatment strategies all under investigation.

The reactivation of latent viruses, especially herpes family and adenovirus, may also clinically mimic interstitial pneumonitis (Shields et al. 1985). However, in the vast majority of cases, clinical symptoms related to systemic involvement are manifested by signs of disease in other organs, including abdominal pain, elevation of serum hepatic transaminases with CMV, varicella zoster virus, or adenovirus, and oral mucosal involvement with herpes simplex viruses.

Bacterial pneumonia typically presents as alveolar and parenchymal filling infiltrates, with concurrent fever and clinical symptoms (chest pain, tachypnea, cough). Pneumonias due to bacteria are common in the pre-engraftment period, including infections from both Gram-positive (*Staphylococcus* and *Streptococcus* species) and a wide range of Gram-negative organisms. Factors that impact the risk of early bacterial pneumonia include oral-pharyngeal mucositis, focal or diffuse enteritis, aspiration risk due to the influence of opiates and sedatives, and catheter-related risks. Pneumonias due to Gram-negative organisms *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Acinetobacter*, *Escherichia coli*, and *Enterobacter* have all been commonly reported within the first 100 days posttransplant, of particular concern in patients with concurrent gastrointestinal GVHD (Martin-Pena et al. 2011). Later onset bacterial pneumonias (following day 100 post-HCT) are not uncommon in patients with concurrent chronic GVHD, especially prominent in patients with bronchiolitis obliterans syndrome (BOS) or those on systemic corticosteroids for chronic GVHD management.

Fungi are historically classified as either yeasts (*Candida*, *Trichosporon*, *Cryptococcus*) or molds, with molds subdivided by septate hyphae (*Aspergillus*, *Scedosporium*, *Fusarium*, *Histoplasma*, *Penicillium*) or aseptate hyphae (*Mucor*, *Rhizopus*). Fungi rarely cause acute infections in the immunocompetent host. *Candida* species, for example, are commensal flora of the nasopharyngeal tract and skin, rarely causing lower respiratory tract invasion in the immunocompromised host. Candidal infections and candidemia are commonly seen when breakdowns in epithelial and mucosal barriers occur in conjunction with concurrent use of empiric antibacterial agents that eradicate normal bacterial flora. Tissue cultures are required to establish the diagnosis of invasive *Candida*, with both bronchoalveolar lavage and sputum cultures poor predictors of invasive pulmonary candidal infections. In contrast, invasive fungal infections from pathogenic molds are a common cause of pneumonia in the posttransplant setting, with invasive *Aspergillus* infections occurring in 10–15 % of allogeneic transplant recipients. *Aspergillus* pneumonia has been reported at a median 92 days posttransplant, and overall survival from invasive *Aspergillus* has been reported at less than 30 % (Grow et al. 2002). Risk factors for the development of *Aspergillus* pneumonia include prolonged corticosteroid usage (≥1 mg/kg/day), history of recent

cytomegalovirus (CMV) infection, and prolonged neutropenia (Grow et al. 2002; Garcia-Vidal et al. 2008). The combination of neutropenia, impaired T-cell function, and abnormal glucose metabolism is an additive risk for invasive fungi. Definitions of invasive fungi were established in 2002 to distinguish colonization from actual infection. Invasive fungal infections are now classified as proven, probable, or possible. Proven infections require histologic confirmation or a positive tissue culture. Probable infections require both a host factor and clinical and/or fluid cultures consistent with an invasive fungus (De Pauw et al. 2008). Currently available tests for the serum fungal markers beta-glucan and galactomannan could also be useful to differentiate colonization from invasive infections with *Candida* and *aspergillus* species, respectively. Radiographic features of invasive fungi are heterogenous, with small and large nodules, ground-glass opacifications, cavitary lesions, tree-in-bud appearance, and halo signs can be observed on chest radiograph or computed tomography (CT). Treatment of invasive fungi makes use of the unique biology of the organism. Fungi contain a cell membrane with ergosterol and a cell wall with beta-glucan, both targets for antifungal therapy. Voriconazole provides effective therapy for a wide range of pathogenic fungi, excluding *Mucor* species. Both posaconazole and lipid formulations of amphotericin B provide coverage for *Mucor*, in addition to coverage for *Aspergillus* and *Candida* species. The clinician initiating voriconazole or other antifungal "azole" therapy should be mindful of its impact on cytochrome p450-dependent drugs, including the calcineurin inhibitors tacrolimus and cyclosporine and the mTor inhibitor sirolimus. When voriconazole is initiated, doses of tacrolimus and cyclosporine should be reduced by 50 %, with even greater dosing reduction (90 %) for sirolimus if being given in conjunction with voriconazole.

5.2.4 Noninfectious Lung Injury

Noninfectious lung injury may be mediated by either alloimmune or non-alloimmune mechanisms. Common alloimmune lung complications post-HCT include IPS, transfusion-related lung injury (TRALI), diffuse alveolar hemorrhage (DAH), or peri-engraftment respiratory distress syndrome (PERDS), existing as a subset of IPS, with both DAH and PERDS existing as a subset of IPS. Non-alloimmune conditions may include the direct cytotoxic effects of conditioning therapy and cardiogenic causes of pulmonary edema.

5.2.4.1 Chemotherapy-Related Pneumonitis

Initially described in the 1970s, chemotherapy-associated pulmonary toxicity has been reported in association with multiple chemotherapeutic busulfan agents, including BCNU, busulfan, cyclophosphamide, and melphalan. In particular, BCNU-related lung injury is acute in onset and develops within the first 3 months following HCT in 10–40 % of patients receiving this therapy (Aronin et al. 1980). Clinically, BCNU-related lung injury is associated with a nonproductive cough with increasing dyspnea in the context of rapidly progressing, bilateral, interstitial infiltrates on both chest radiographs and CT. Pulmonary function testing reveals a restrictive pattern of lung injury, with diminished forced vital capacity and total lung capacity noted (Lane et al. 2012). The pathogenesis of BCNU-related lung injury has been ill defined, though increased production of fibrogenic factors such as platelet-derived growth factor-β, insulin-like growth factor I, and transforming growth factor-β1 has been implicated (Shen et al. 2004). Treatment with pulsed doses of corticosteroids early in the clinical course significantly decreases the morbidity and mortality associated with this condition and is key for successful outcomes; if untreated or recognized late in its clinical course, severe pulmonary fibrosis may develop (Shen et al. 2004).

Busulfan, either alone or in combination with other cytotoxic agents, has also been implicated in posttransplant lung dysfunction. However, the use of pharmacokinetic targeting of busulfan dosing has decreased the incidence of acute lung injury. Similar to BCNU administration, increased pulmonary toxicity has been noted in patients receiving prior mediastinal radiotherapy, following either autologous or allogeneic HCT (Bolling et al. 2009).

5.2.4.2 Transfusion-Related Acute Lung Injury (TRALI)

TRALI is one of the leading causes of mortality following infusions of plasma-containing blood products, estimated to occur in 1:1,000 to 1:5,000 transfusions (Silliman et al. 2003; Kopko et al. 2002). All plasma-containing blood products, including whole blood, packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets, cryoprecipitate, granulocytes, immune globulin infusions, and stem cell products, have been linked with the development of TRALI, with albumin the sole exception (Swanson et al. 2006). The diagnosis is based upon clinical symptoms with acute onset of dyspnea and respiratory distress typically occurring 1–6 hours after transfusion. Chest radiographs reveal diffuse pulmonary infiltrates reflecting edema from increased pulmonary vascular permeability. Pathologically, neutrophil infiltrates and overexpression of neutrophil-related cytokines and chemokines have been linked to its development. With mortality rates approximating 5–10 %, TRALI accounts for 47 % of all transfusion-related deaths. Treatment is generally supportive. Discontinuation of the blood product, corticosteroid administration, forced diuresis, and respiratory support results in recovery within 3–4 days in the majority of patients. In over 70 % of cases, donor antibodies directed against HLA class I or II epitopes on recipient hematopoietic cells have been identified as the primary cause of the TRALI event, but in rare cases the antibody may be present in the recipient's plasma and may be directed against transfused donor leukocytes (Kopko et al. 2003; Kao et al. 2003) The use of high plasma volume blood products from alloimmunized donors, including apheresis stem cell products and platelets, is associated with high risk for the development of TRALI (Reesink et al. 2012).

5.2.4.3 Idiopathic Pneumonia Syndrome

IPS refers to an acute lung injury that occurs post-HCT, associated with diffuse alveolar damage in the absence of lower respiratory tract infection. In 1993, a National Institute of Health (NIH) workshop proposed a broad definition for IPS, the definition recently updated by an American Thoracic Society research statement (Table 5.1) (Clark et al. 1993). IPS encompasses a spectrum of disorders, including diffuse alveolar hemorrhage (DAH), peri-engraftment respiratory distress syndrome (PERDS), acute idiopathic interstitial pneumonitis, and chemotherapy-related lung injury. The diagnosis, however, is often one of exclusion, with infectious pneumonitis, sepsis syndrome, cardiac

Table 5.1 Idiopathic pneumonia syndrome: diagnostic criteria

I. Diffuse alveolar injury
(a) Diffuse infiltrates on chest radiograph or computed tomography
(b) Clinical signs of pneumonia (cough, dyspnea, tachypnea)
(c) Evidence of abnormal pulmonary physiology
1. Increased alveolar to arterial oxygen difference
2. New or increased restrictive pulmonary function test abnormality
II. Absence of infectious pneumonitis, as determined by
(a) Bronchoalveolar lavage negative for significant bacterial pathogens, including acid-fast bacilli, *Nocardia*, and *Legionella* species.
(b) Bronchoalveolar lavage negative for pathogenic nonbacterial organisms
1. Viral and fungal culture
2. Shell vial culture for cytomegalovirus (CMV) and respiratory syncytial virus (RSV)
3. Cytology for viral inclusions, fungi, and Pneumocystis jiroveci
4. Direct fluorescence staining with antibodies against CMV, RSV, herpes simplex virus (HSV),varicella zoster virus (VZV), influenza virus, parainfluenza virus, adenovirus, and other organisms
(c) Other organisms/tests to consider
1. Polymerase chain reaction (PCR) for human metapneumovirus, rhinovirus, coronavirus, and human herpesvirus (HHV)6
2. PCR for *Chlamydia*, *Mycoplasma*, and *Aspergillus* species
3. Serum galactomannan ELISA for *Aspergillus* species
(d) Transbronchial biopsy, if condition of the patient permits
III. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Adapted from Panoskaltis-Mortari et al. (2011)

failure, and iatrogenic fluid overload all potentially exhibiting similar clinical presentations.

The cumulative incidence of IPS in the first 120 days after allogeneic HCT ranges between 2 and 15 %, with a median onset 14–42 days post-HCT and mortality rates 50–80 % within 28 days of diagnosis (Panoskaltsis-Mortari et al. 2011; Fukuda et al. 2003; Sakaguchi et al. 2012; Yanik et al. 2008b). IPS has been reported in 8.0 % of pediatric allogeneic transplants, with median onset at 67 days posttransplant (Sakaguchi et al. 2012). Long-term survival for affected children is poor, with TRM significantly higher in affected than non-affected patients (5-year TRM: 52 % vs. 13 %, $p = 0.001$) (Sakaguchi et al. 2012).

Diffuse alveolar hemorrhage (DAH), a subset of IPS, generally develops at the time of neutrophil recovery in the early post-HCT period in the immediate post-HCT period and is characterized by progressive shortness of breath, cough, and hypoxemia with or without fever (Afessa et al. 2001; Robbins et al. 1989; Lewis et al. 2000; Metcalf et al. 1994). Classically, DAH is defined by the demonstration of progressively bloodier aliquots of BAL fluid on successive saline lavages, but frank hemoptysis is rare (Robbins et al. 1989). Mortality from DAH may be as high as 75 % despite aggressive treatment with systemic corticosteroids, with death usually occurring within weeks of diagnosis (Lewis et al. 2000). A small case series has suggested that high dose solumehol (1 gm/day) could be an effective treatment of DAH (Chao et al. 1991). A retrospective study has suggested that the addition of aminocaproic acid to high dose corticosteroids could be of benefit in the treatment of DAH (Wanko et al. 2006). Some patients with DAH can have microorganisms isolated from blood, BAL fluid, or tracheal aspirate within 1 week of alveolar hemorrhage. Majhail and colleagues compared patients with DAH and infection-associated alveolar hemorrhage who presented with similar clinical and radiographic findings in the setting of progressively bloodier BAL fluid following allogeneic HCT (Majhail et al. 2006). Alveolar hemorrhage from either infectious or noninfectious causes has extremely poor outcome following therapy with conventional agents, including steroids (Majhail et al. 2006).

Peri-engraftment respiratory distress syndrome (PERDS) also falls within the definition of IPS (Afessa et al. 2001). PERDS is characterized by fever, dyspnea, and hypoxemia that, by definition, occurs within 5–7 days of neutrophil engraftment (Capizzi et al. 2001; Wilczynski et al. 1998; Bhalla et al. 2000). Although PERDS after autologous HCT appears similar to IPS after allogeneic HCT with respect to clinical presentation and time of onset, PERDS/IPS following autologous transplantation differs sharply from PERDS/IPS in the allogeneic setting, with significantly improved outcomes in the autologous setting (Kantrow et al. 1997; Yanik et al. 2002; Cahill et al. 1996; Capizzi et al. 2001).

Potential etiologies and risk factors for IPS include direct toxicity from HCT conditioning regimen, occult pulmonary infections, and immunologic factors related to acute GVHD (Crawford et al. 1993; Weiner et al. 1989; Kantrow et al. 1997; Atkinson et al. 1991; Della Volpe et al. 2002; Crawford and Hackman 1993; Sakaguchi et al. 2012). In particular, the cumulative incidence of IPS is significantly less following the use of reduced intensity conditioning regimen when compared to conventional, myelo-ablative regimen (Fukuda et al. 2003). Acute GVHD often precedes IPS, suggesting a possible causal relationship between the two disorders (Crawford and Hackman 1993; Bortin et al. 1989; Beschorner et al. 1978; Weiner et al. 1986; Crawford et al. 1993; Kantrow et al. 1997; Afessa et al. 2001). However, although IPS may correlate with the presence of acute GVHD, it does not necessarily correlate with the severity of GVHD, consistent with clinical reports of IPS in allogeneic HCT recipients whose signs and symptoms of GVHD were mild or absent (Yanik et al. 2002; Schultz et al. 1994; Curtis et al. 1995; Clark et al. 1987; Holland et al. 1988; Schwarer et al. 1992).

Historically, the lung has not been recognized as a classic target organ for GVHD, and the specific role of alloreactive donor T-lymphocytes in the pathogenesis of IPS is under considerable debate. Epithelial apoptosis is usually attributed to T-cell-mediated injury and is considered pathognomonic for acute GVHD. Although identified in the lungs of many patients with IPS

(Yousem 1995; Beschorner et al. 1978), epithelial apoptosis has not been consistently observed in allogeneic HCT recipients with lung dysfunction. Based upon murine models, the pathogenesis of IPS appears to be a complex interplay between soluble inflammatory mediators (Th1 cytokines, lipopolysaccharide (LPS), inflammatory chemokines), donor-derived effector T cells, accessory cells (myeloid, pulmonary macrophages), and resident epithelial and endothelial cells. Significant increases in the total number of lymphocytes, macrophages, and neutrophils in the bronchoalveolar space (Cooke et al. 1996), increased vascular permeability, plus elevated levels of TNFα and inflammatory cytokines have been noted in the lung tissue and BAL fluid in both murine models and from clinical samples from patients with IPS (Clark et al. 1998; Shankar and Cohen 2001; Cooke et al. 1996, 2000b; Piguet et al. 1989a). A direct role for TNFα in the development of IPS has been established using strategies that either neutralize its effects (Piguet et al. 1987; Cooke et al. 2000b) or use TNFα-deficient mice as HCT donors (Cooke et al. 2000a; Hildebrandt et al. 2004). Administration of rhTNFR-Fc, a soluble, dimeric, TNF-binding protein at the time of endotoxin challenge in mice, effectively prevents IPS-associated lung injury in this setting (Cooke et al. 2000b). Studies using genetically altered mice have shown that IPS is dependent upon donor-derived, rather than host-derived, TNFα. While TNFα from both donor accessory cells (macrophage/monocytes) and T cells significantly contributes to lung injury, the T-cell component (of TNFα) predominates (Hildebrandt et al. 2004).

TNFα likely contributes to the development of IPS through both direct and indirect mechanisms. In addition to being directly cytotoxic, TNFα increases expression of inflammatory chemokines (Hildebrandt et al. 2004) and major histocompatibility complex (MHC) antigens, modulates leukocyte migration, and facilitates cell-mediated cytotoxicity, including endothelial cell injury, a common feature of IPS (Gerbitz et al. 2004). Strategies that neutralize TNFα in experimental models do not completely abrogate lung injury (Piguet et al. 1987, 1989b; Cooke et al. 2000b; Clark et al. 2000; Hildebrandt et al. 2004), suggesting that other inflammatory and cellular mechanisms besides TNFα may also contribute to the development of IPS. For example, IL-1β, nitric oxide, and reactive oxygen species have also been implicated in the development of lung injury after HCT, particularly in the setting of myelo-ablative conditioning (Haddad et al. 1999; Panoskaltsis-Mortari et al. 1997; Qureshi et al. 2004). An analysis of plasma and BAL fluid protein profiles in patients with IPS showed that in addition to increases in the levels of TNFα and its soluble receptors (TNFR1), significant elevations in other Th1 cytokines (γ-interferon, IL-6) and proteins involved in the LPS cascade (sCD14, LBP) along with several inflammatory chemokines (IL-8, MCP-1, MIG) that regulate leukocyte recruitment to sites of inflammation were also evident (Yanik et al. 2008b).

Treatment options for IPS have historically combined supportive care measures, including supplemental oxygen support, diuretics, broad-spectrum antimicrobial agents, and intravenous corticosteroids (Kantrow et al. 1997; Yanik et al. 2002, 2008b; Tizon et al. 2012). High-dose corticosteroid therapy (>2 mg/kg/day of methylprednisolone equivalent) has not been shown to improve outcome when compared to lower doses of corticosteroids (≤2 mg/kg/day) (Fukuda et al. 2003). More recently, the role for TNF inhibition in the management of IPS has been under investigation. A pilot study from the University of Michigan examined the use of a soluble TNF-binding agent, etanercept, in the treatment of patients who met the diagnostic criteria for IPS. A 4-week course of therapy was given, with a strict definition used to define response (complete cessation of all oxygen support within 28 days of therapy onset). Responses were noted in ten (67 %) subjects, with survival 73 % within the therapy period (Fukuda et al. 2003; Yanik et al. 2008b). A retrospective review of 39 patients treated with either corticosteroids alone ($n=22$) versus corticosteroids plus etanercept ($n=17$) similarly noted high response rates in the etanercept arm. Overall survival was significantly higher in those patients treated with

corticosteroids plus etanercept, both at 28 days (88.2 % vs. 36.4 %, <0.001) and 2 years (18 % vs. 9.1 %, $p=0.003$) following onset of IPS (Tizon et al. 2012). Advances in supportive care, including the early institution of continuous veno-venous hemofiltration, may provide additional help in improving survival, but prospective studies addressing the treatment of IPS with clinical trials are in progress. Based upon these encouraging results, larger phase II (pediatric) and phase III (adult) trials have recently been completed within the Bone Marrow Transplant Clinical Trials Network (phase III) and the Children's Oncology Group (phase II).

5.2.4.4 Bronchiolitis Obliterans Syndrome

Bronchiolitis obliterans syndrome was initially described in the 1980s as a form of chronic lung injury following allogeneic transplant and remains one of the most perplexing posttransplant conditions to manage (Holland et al. 1988; Crawford et al. 1995). The clinical course is highly variable, ranging from a gradual decline in lung function over years to a rapid deterioration over several months. The incidence of BOS has varied from 2 to 25 % following allogeneic HCT, the wide range likely reflecting the nonuniform diagnostic criteria used to define the condition (Afessa et al. 2001; Williams et al. 2009). The disorder is associated with airflow obstruction on pulmonary function testing (PFT) with declines in forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC) ratio required for diagnostic purposes. In early stages, BOS is characterized by small airway inflammation with lymphocytic bronchitis, ultimately progressing to fibrinous obliteration of bronchiolar lumen (Schwarer et al. 1992; Urbanski et al. 1987; Cooke and Yanik 2009).

Respiratory symptoms include cough, dyspnea, and wheezing, but many patients remain asymptomatic despite showing signs of moderate to severe airway obstruction on PFTs (Clark et al. 1987; Holland et al. 1988). Chest radiographs are most often normal except for signs of hyperinflation (Curtis et al. 1995; Holland et al. 1988; Schwarer et al. 1992). Likewise, chest CT findings range from normal early in the course of disease to extensive peribronchial inflammation and bronchiectasis with significant air trapping and diffuse parenchymal hypoattenuation at later time points (Schultz et al. 1994; Ooi et al. 1998). One study has demonstrated that on high resolution CT scanning, BOS is characterized by central airway dilation, the degree of which correlates with decrement in lung function, and is distinct from the central airway narrowing observed with emphysema or asthma (Gazourian et al. 2013). The clinical course of BOS varies from mild to severe with necrotizing bronchiolitis and a rapid decline in respiratory function (Holland et al. 1988; Schultz et al. 1994; Sullivan et al. 1992; Sanchez et al. 1997; Curtis et al. 1995; Clark et al. 1989).

In 2005, a NIH Consensus statement on the diagnosis and staging of chronic GVHD included strict diagnostic criteria for BOS, with subsequent proposed modifications for improved identification of BOS patients (Williams et al. 2009; Filipovich et al. 2005) (Table 5.2). Studies published prior to the 2005 publication used various definitions of disease and response to therapy, making it difficult to translate previous results in the current era. The Fred Hutchinson Cancer Research Center recently utilized the NIH criteria to identify the incidence, risk factors, and mortality from BOS following allo-

Table 5.2 NIH bronchiolitis obliterans syndrome (BOS) diagnostic criteria

No active infection
FEV_1 <75 % predicted or >10 % decline from pre-HCT value
Signs of obstruction
FEV_1/FVC ratio <0.7 or FEV1/SVC ratio <0.7
RV >120 % predicted
RV/TLC >120 %
HRCT with evidence of air trapping
Another manifestation of chronic GVHD in another organ

Adapted from Williams et al. (2009)
NIH National Institutes of Health, *GVHD* graft-versus-host disease, *FEV1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *SVC* slow vital capacity, *RV* residual volume, *TLC* total lung capacity, *HRCT* high-resolution computed tomography

geneic HCT (Au et al. 2011). The overall incidence of BOS was 5.5 % and as high as 14 % in patients with chronic GVHD. The median time to diagnosis was 439 days post-HCT, with chronic GVHD present in 100 % of patients identified with BOS. Lower baseline FEV1 (<80 %) and circulating IgG levels were predictive of BOS onset. Previously reported risk factors for BOS, including busulfan-based regimen, peripheral stem cells as the donor source, methotrexate for GVHD prophylaxis, viral pneumonitis post-HCT, HLA mismatch, disease status, and the use of a myelo-ablative regimen, were not predictive of BOS in this report (Holland et al. 1988; Schultz et al. 1994; Clark et al. 1987, 1989; Chien et al. 2003, 2005). Unfortunately, whereas risk factors for BOS have been identified, no clear predictors of outcome have been reported.

Therapy for BOS remains challenging, with no recognized standard therapy. Once established, the prognosis of BOS is very poor, with 5-year survival rates of 15 % (Chien et al. 2010). Even answers to seemingly basic questions have yet to be determined. At what point should therapy be started? Are BAL, transbronchial, or surgical lung biopsies required prior to starting treatment? How should response be defined? A European GVHD consensus conference (2009) summarized diagnostic criteria and treatment options for pulmonary manifestations of chronic GVHD, with a particular focus on BOS (Hildebrandt et al. 2011). PFTs were recommended pre-HCT, every 3 months for the first 2 years posttransplant, and every 6 months thereafter. When obstructive changes are noted on PFTs, then high-resolution computed tomography (HRCT) with inspiratory and expiratory images is recommended to assess for radiographic signs of BOS, including air trapping, bronchial wall thickening, and bronchiectasis (Fig. 5.2). The degree of obstructive changes (decline in FEV1) that would warrant a HRCT was not specified, though at many centers a 10 % decline in FEV1 would typically initiate a HRCT, especially if the FEV1 was <80 % predicted.

Systemic and topical (inhaled) corticosteroids, mTOR inhibitors, extracorporeal photopheresis (ECP), imatinib, azithromycin, montelukast, and combination topical corticosteroid-bronchodilators have all been utilized with varying degrees of success (Hildebrandt et al. 2011). Few BOS treatment options have been based upon prospective clinical trials (Ratjen et al. 2005; Khalid et al. 2005; Couriel et al. 2006; Yanik et al. 2012). Systemic and topical corticosteroids have become commonplace in managing BOS, supported by small case reports and observational studies (Ratjen et al. 2005; Ishii et al. 2000; Bergeron et al. 2007; Bashoura et al. 2008). Three retrospective studies support the use of inhaled corticosteroids

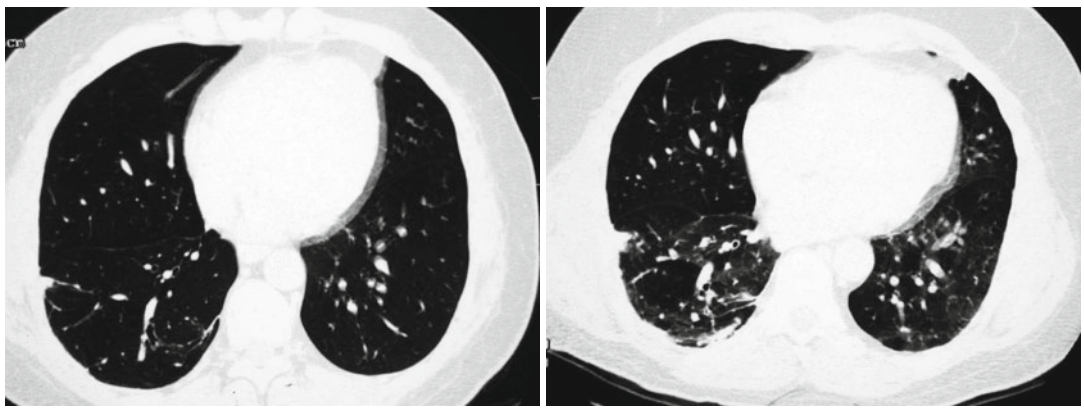


Fig. 5.2 Computed tomography (CT) of bronchiolitis obliterans syndrome (BOS), inspiratory and expiratory films. Note bronchiectasis on both inspiratory and expiratory images

(Bergeron et al. 2007; Bashoura et al. 2008; Norman et al. 2011). The combination of systemic plus inhaled corticosteroids has been examined in a few studies. In one trial, repetitive courses of oral methylprednisolone (10 mg/kg/day) plus inhaled budesonide led to disease stabilization in 7 of 9 patients (Ratjen et al. 2005). The combination of an inhaled steroid plus long-acting bronchodilator (budesonide/formoterol) was reported in 13 patients with BOS, with clinical improvement noted in all 13 patients; responses were seen at a mean 2.3 months following onset of therapy (Bergeron et al. 2007). In another case series, the use of inhaled fluticasone, azithromycin, and montelukast (FAM) therapy was useful in "sparing" systemic corticosteroid usage in eight patients with BOS (Norman et al. 2011). The Chronic GVHD Consortium has begun enrolling patients into a clinical trial investigating the use of FAM therapy for newly diagnosed BOS (NCT01307462).

The use of macrolide antibiotics (azithromycin) for frontline therapy of BOS is widespread in the transplant community, though based upon a single report of eight HCT patients receiving a 12-week course of therapy (Khalid et al. 2005). Subjects did not undergo pre-therapy BAL, thus questioning whether subsequent responses were secondary to anti-inflammatory or antimicrobial effects of the agent. There are no published reports justifying the use of azithromycin for BOS prevention. In an observational study of 81 patients with BOS following lung allografts, 24 of 81 (30 %) experienced an improvement in FEV1 after 6 months of azithromycin therapy (Gottlieb et al. 2008). The presence of neutrophilia in pre-therapy BAL was not only a positive predictor for subsequent response but also suggested a mechanistic role for azithromycin in this clinical setting (Gottlieb et al. 2008). The published reports on the benefits of ECP for BOS following HCT are even less compelling (Couriel et al. 2006; Lucid et al. 2011; Child et al. 1999), with only one focusing on patients with BOS post-HCT (Lucid et al. 2011). Stabilization in FEV1 was reported in six of nine patients in this retrospective report, comparing FEV1 values prior to and during ECP therapy (Lucid et al. 2011).

A phase II clinical trial using etanercept for the treatment of chronic lung injury post-HCT was reported in 2012 (Yanik et al. 2012). Etanercept was administered to 31 patients with either BOS ($n=22$) or restrictive lung disease ($n=9$), with NIH Consensus Criteria used to define the cohort of patients with BOS. For subjects with BOS, response was defined as a $\geq$10 % improvement in FEV1 within 4 weeks of therapy completion. Responses were noted in 7 of 22 (32 %) patients with BOS, with no differences in response based upon the severity of pulmonary disease at study onset. Therapy was well tolerated, with few infectious complications. Estimated 5-year OS was 90 % (95 % CI, 73–100 %) for patients who responded to therapy (Yanik et al. 2012). The study deserves particular notice for its use of strict eligibility and response criteria. All patients underwent pre- and post-therapy BAL, HRCT, plasma biomarker analysis, and PFTs, with additional PFTs performed monthly during therapy. No changes in adjuvant immune-suppressive therapy were allowed within the initial 28 days of therapy (Yanik et al. 2012).

The lack of defined response criteria greatly limits our ability to compare therapy strategies for BOS. Does a 10 % improvement in FEV1, as used in the etanercept BOS trial, even equate to improved performance? Are FEV1 and FEV1/FVC the best measures of airway obstruction (and response), or would changes in FEV1/slow vital capacity (SVC) serve as a better indicator of response in small airway disease (Au et al. 2011)? Should quality of life (QOL) assessments be included in the response analysis? The etanercept trial was unique in that validated quality of life (QOL) instruments were additionally used to assess patient performance during therapy. However, no difference in QOL outcome measures (pre-therapy vs. post-therapy) was noted in subjects that responded or did not respond to therapy (Yanik, unpublished observations).

The development of BOS likely involves an initial insult to lung parenchyma followed by an ongoing inflammatory process involving immune effector cells and the resident cells of the pulmonary vascular endothelium and interstitium. Much of our knowledge regarding the pathogenesis of BOS is based upon observations made in lung allograft recipients and from data generated in murine tracheal transplant models. Strong Th1 immune responses have been noted in rat heterotopic lung allografts, the Th1 response present even after fibrosis and airway obliteration was complete (Boehler et al. 1999). Several groups have shown enhanced expression of TNFα, IL-8, TGFβ, and IL-1β during lung allograft rejection (Belperio et al. 2002; Elssner et al. 2000; Fattal-German et al. 1998; El-Gamel et al. 1999) and additionally revealed critical roles for both RANTES and MCP-1 in the development of experimental BOS (Belperio et al. 2000, 2001). Ultimately, advances in the management of BOS will require improvements in our understanding of the basic pathophysiology of the disorder. A murine model for BOS has been reported, with peribronchiolar inflammation and airway resistance in the mice mimicking the human model (Panoskaltsis-Mortari et al. 2007; Srinivasan et al. 2012). The potential benefits of this murine model remain to be elucidated, in terms of improving our understanding of this enigmatic disorder and designing optimal treatment strategies.

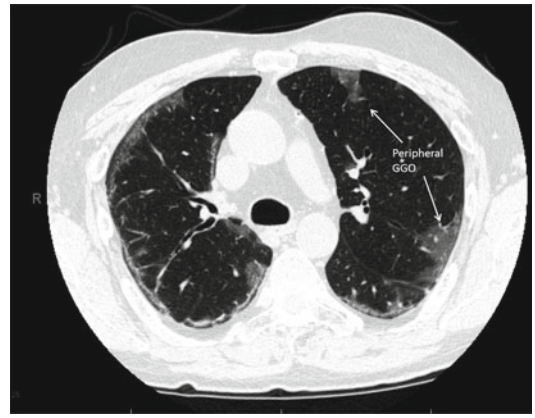


Fig. 5.3 Computed tomography of bronchiolitis obliterans organizing pneumonia (BOOP), with presence of peripheral ground-glass opacification (GGO, *arrows*). Reprinted with permission from Current opinions in oncology. 2013, Vol 25:187–194, Walters Kluwer Health. Lippincott Williams and Wilkins

5.2.4.5 Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) was first described in allogeneic HCT in the early 1990s, presenting as acute bilateral airspace disease within the first 2–6 months post-transplant (Thirman et al. 1992; Mathew et al. 1994) (Fig. 5.3). In contrast to BOS, in which bronchiolar damage predominates, BOOP is primarily an alveolar disorder. The disorder is characterized by extensive infiltration of granulation tissue within alveoli, with fibroblasts and a matrix of loose connective tissue deposits. The pathophysiology is poorly understood, though a strong association with acute and/or chronic GVHD (Freudenberger et al. 2003; Jinta et al. 2007), a possible link to HLA B35 (Yotsumoto et al. 2007), and decreased incidence following T-cell-depleted HCT (Ditschkowski et al. 2007) are all supportive of an alloimmune mechanism. To avoid confusion with BOS, the disorder has been renamed cryptogenic organizing pneumonia (COP) in the pulmonary community.

Though consensus diagnostic criteria are lacking, the incidence of BOOP is estimated at 1–2 %, based upon single institution reports (Freudenberger et al. 2003; Jinta et al. 2007). In contrast to IPS and BOS, BOOP typically presents with fever, dyspnea, and a nonproductive cough, with PFTs revealing a restrictive defect (FVC <80 %, FEV1/FVC ≥80 %) (Table 5.3). HRCT reveals peripheral air space consolidation, with ground-glass and nodular opacities commonly identified (Lee et al. 1994; Pipavath et al. 2012). Given the clinical presentation and radiographic findings, infectious etiologies must be ruled out in all patients. Despite the collective support for the diagnosis of BOOP based upon clinical findings and radiographic presentation,

Table 5.3 Idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans syndrome (BOS), and bronchiolitis obliterans organizing pneumonia (BOOP)

Characteristic	IPS	BOS	BOOP
Incidence	2–15 %	4–8 %	1–2 %
Clinical features	Dyspnea Cough	Dyspnea Cough Wheezing	Dyspnea Cough Fever
Risk factors	Full intensity regimen Acute GVHD	Chronic GVHD Hypogammaglobulinemia ↓ FEV1 pre-HCT	TBI regimen Active GVHD
Consensus criteria	Yes	Yes	No
PFTs	↓ TLC ↓ DLCO	FEV1 <75 % FEV1/FVC <0.7 RV >120 %, RV/TLC >120 %	FVC <80 % FEV1/FVC ≥70 % TLC <80 %, ↓ DLCO
Radiographic features	Diffuse infiltrates	CXR: Hyperinflation, normal	Consolidation
Computed tomography	Diffuse interstitial infiltrates	Air trapping, bronchiectasis, septal thickening	Peripheral ground-glass or nodular opacities
Treatment	Systemic corticosteroids TNF inhibitors	Systemic corticosteroids Inhaled corticosteroids Other immune suppressants	Corticosteroids

Adapted from Yanik and Kitko (2013)
GVHD graft-versus-host disease, *PFTs* pulmonary function testing, *TLC* total lung capacity, *DLCO* diffusion lung capacity for carbon monoxide, *FEV1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *RV* residual volume, *CXR* chest radiograph, *HCT* hematopoietic cell transplant, *TBI* total body irradiation, *TNF* tumor necrosis factor

transbronchial or surgical lung biopsy approaches are still considered the gold standard for diagnosis (Alasaly et al. 1995; Wells 2001).

There is no standard treatment for BOOP, and no clinical trials are currently listed on *clinicaltrials.gov*. Based on limited retrospective reviews, systemic corticosteroids (1.0 mg/kg/day) would be considered the treatment of choice, with prolonged treatment courses recommended secondary to high rates of recurrence during taper (Thirman et al. 1992; Mathew et al. 1994; Freudenberger et al. 2003; Jinta et al. 2007). Reported response rates are 50–60 %, with overall survival approximately 50–70 % (Freudenberger et al. 2003; Jinta et al. 2007).

Our overall understanding of BOOP is limited, with no consensus diagnostic criteria, a lack of prospective trials and minimal understanding of the underlying pathophysiology. All three disorders IPS, BOS, and BOOP are postulated to be caused by alloimmune injury. However, why such alloreactivity would selectively target the interstitium and broncho-alveoli in IPS, bronchiolar structures in BOS, and the alveoli in BOOP remains poorly understood.

5.3 Hepatic Veno-occlusive Disease/Sinusoidal Obstruction Syndrome

5.3.1 Incidence of Veno-occlusive Disease/Sinusoidal Obstruction Syndrome

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication after HCT. Hepatic VOD/SOS affects both adult and pediatric populations and both allogeneic and autologous graft recipients, with a higher incidence in the allogeneic setting (Richardson et al. 2012; Carreras 2012). The onset of VOD/SOS is well described within the first 30 days after HCT

(Richardson et al. 2012), though later occurrences have been reported. It is characterized by clinical features including hepatomegaly, jaundice, weight gain, and ascites (Carreras et al. 2011; Coppell et al. 2010). VOD/SOS is reported to occur in 8–14 % of patients following HCT (Carreras et al. 2011), although incidence rates may be as high as 60 % in higher-risk patients (such as those with underlying liver disease and certain specific drug exposures, including gemtuzumab ozogamicin and sirolimus), and depending upon the diagnostic criteria used (Carreras et al. 2011; Coppell et al. 2010). Severe VOD/SOS is typically associated with multiorgan failure (MOF) and high mortality rates (>80 %) (Carreras et al. 2011; Coppell et al. 2010). Even among patients with moderate VOD/SOS, the mortality rate is still estimated at approximately 20 % (McDonald et al. 1984).

5.3.2 Pathogenesis of VOD/SOS

VOD/SOS is thought to be triggered by activation of and damage to the sinusoidal endothelial cells (SECs) in zone 3 of the hepatic acinus due to conditioning regimen-mediated injury (Guglielmelli et al. 2012). As shown in Figure 5.4, exposure of SEC's to conditioning radiation or toxic metabolites of chemotherapy leads to SEC injury and activation. Activated SECs express cytokines (e.g., TNFα and IL-1β) and adhesion molecules (e.g., ICAM-1 and VCAM-1) resulting in activation of proinflammatory pathways that further damage the endothelium (Coppell et al. 2003). This leads to the loss of endothelial wall fenestrae and formation of gaps between SECs (Panel B) (Carreras 2012). Consequently, red blood cells, leukocytes, and cellular debris extravasate into the space of Disse, causing progressive extraluminal compressive narrowing of the sinusoids (Carreras 2012; Coppell et al. 2003; Bearman 1995) and dissection of the endothelial cells, which could further embolize downstream and occlude the sinusoid (Panel C) (Carreras 2012). In addition, injury to the SECs of the sinusoids is also associated with a procoagulant and hypofibrinolytic state that contributes further to fibrin deposition, clot formation in situ, and narrowing of the sinusoids (Guglielmelli et al. 2012; Coppell et al. 2003; Bearman 1995). Together, these effects reduce hepatic venous outflow, leading to post-sinusoidal hypertension, central venular occlusion, hepatic enlargement with capsular distension, and, in more severe cases, portal venous flow reversal and hepatorenal syndrome, leading to multiorgan failure (MOF) and death (Carreras 2012) (Fig. 5.4).

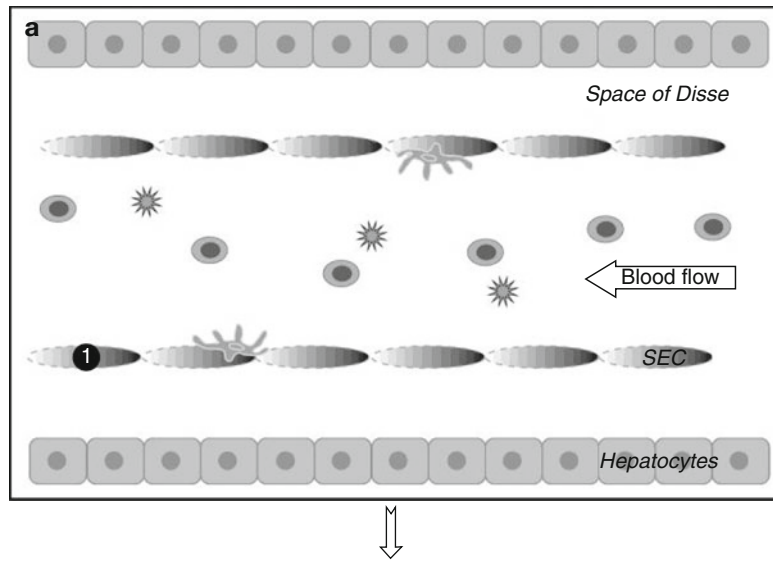
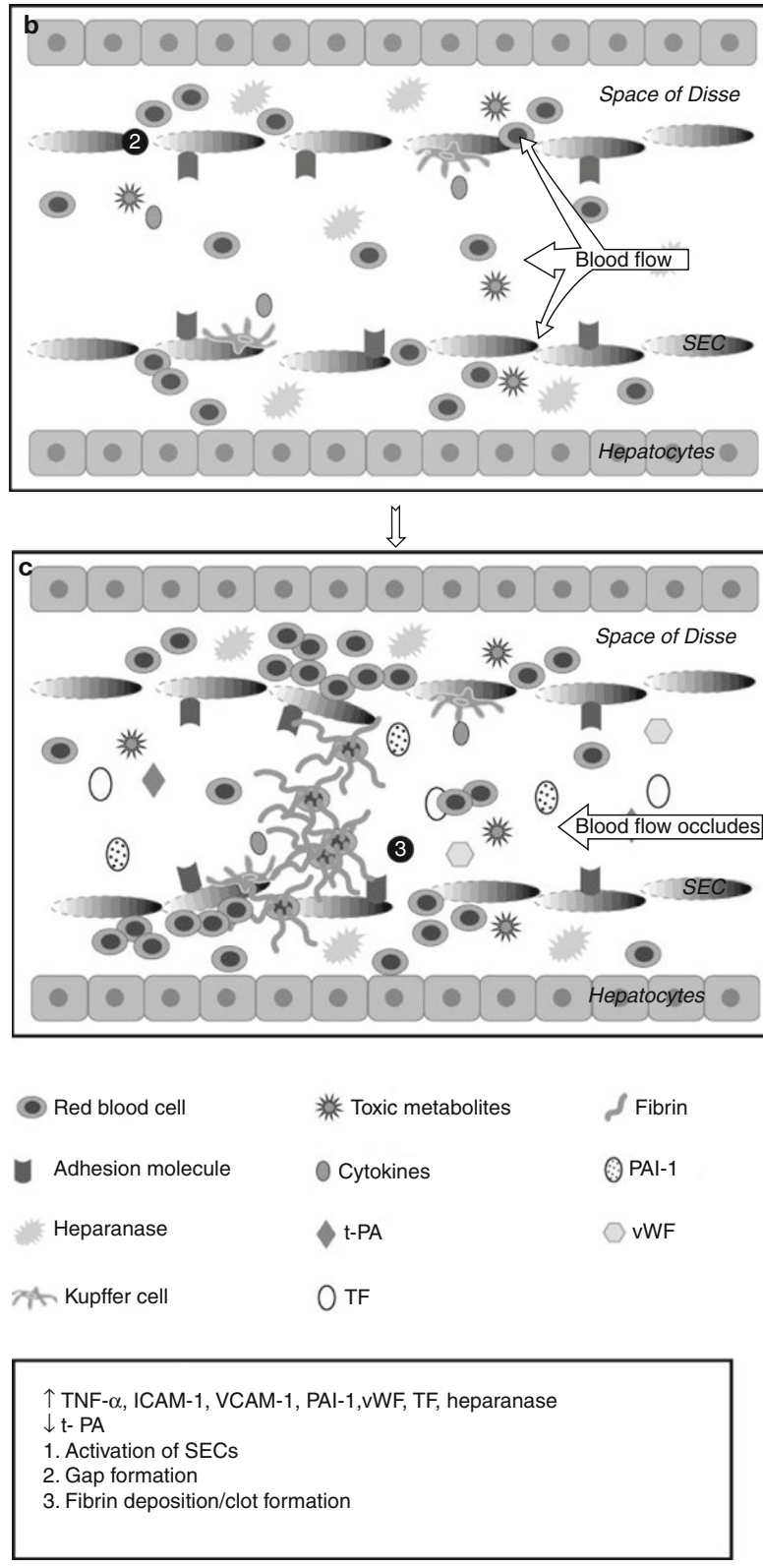


Fig. 5.4 Mechanisms of action of defibrotide (DF) (Adapted with permission from Richardson et al. (2013))

Fig. 5.4 (continued)



5.3.3 Diagnosis and Prognosis of VOD/SOS

The diagnosis of VOD/SOS is made based on clinical criteria with two established systems, the Seattle criteria (Bearman 1995) and the Baltimore criteria (Corbacioglu et al. 2012; Jones et al. 1987; Richardson et al. 1998). The Seattle criteria require at least two or more clinical features including jaundice, painful hepatomegaly or ascites, and/or unexplained weight gain within 30 days of transplantation (Bearman 1995; Corbacioglu et al. 2012). The Baltimore criteria specify an elevated bilirubin level of at least 2.0 mg/dL and two or more of the following characteristics: hepatomegaly, ascites, or at least 5 % weight gain by day +21 post-HCT, with the Baltimore criteria validated according to both histopathologic features as well as outcome (Bearman 1995; Jones et al. 1987).

VOD/SOS presents with a wide clinical spectrum and is conventionally divided into mild, moderate, and severe disease (McDonald et al. 1993). Mild VOD/SOS is considered disease that meets diagnostic criteria, does not require specific treatment for fluid excess or medication for hepatic pain, and has a self-limiting course. Moderate VOD/SOS reveals evidence of liver injury with need for active treatment for fluid excess or medication for hepatic pain but usually resolves completely. Severe VOD/SOS is defined in association with MOF and severe hyperbilirubinemia with rapid weight gain and has very high mortality rate (DeLeve et al. 2009). Although several biomarkers of endothelial injury have been described in the literature, including plasminogen activator inhibitor type-1 (PAI-1) (Nurnberger et al. 1998; Salat et al. 1994), no laboratory marker has been validated as a diagnostic marker of VOD/SOS. From retrospective analyses, the presence of multiorgan failure has emerged as the most useful marker for VOD/SOS severity to date. The Bearman model, developed in the 1990s, estimates the risk of developing severe VOD/SOS based on bilirubin level, percentage weight gain, and a designated time frame from HCT; this model has demonstrated some utility for predicting VOD/SOS severity. However, as the Bearman model was developed in a cohort of patients who developed VOD/SOS within 17 days of HCT after specific conditioning regimens, its general applicability to other conditioning regimens and later time frames post-HCT is limited (Carreras et al. 2011; Coppell et al. 2010; Bearman et al. 1993). In this context, sensitive and specific biomarker assays are needed that could guide disease prognostication and management, with some candidate markers under study but none yet defined.

5.3.4 Treatment Options and Patient Management for VOD/ SOS

Current management of VOD/SOS consists primarily of supportive care, with fluid management, adequate oxygenation, and transfusional support given to minimize ischemic liver injury, plus avoidance of known hepato-/nephrotoxins (DeLeve et al. 2009; Richardson et al. 2010). The use of tissue plasminogen activator with or without heparin has been evaluated in a number of studies. However, results have generally been disappointing. Approximately one-third of patients show response to thrombolytic therapy, although severe hemorrhages are common with therapy and can be life threatening with no survival advantage apparent (DeLeve et al. 2009) (Table 5.4).

Although there are no agents to date approved for the treatment of VOD/SOS either in the USA or Europe, the investigational drug defibrotide (DF) has shown the most promising results in clinical trials to date. DF has now been used in more than 1,800 patients worldwide and has demonstrated significant safety and tolerability, with low rates of drug-related hemorrhage (ref Gentium Announces Submission of a Marketing Authorization Application for Defibrotide to the European Medicines Agency, 2011). DF is a polydisperse oligonucleotide with fibrinolytic properties (but no significant systemic anticoagulation) and has shown protective effects on micro- and macrovascular endothelium. The use of DF for the

Table 5.4 t-PA with or without heparin for the treatment of VOD

Author	No. of patients	Dose (mg/day)	Duration (*d*)	Heparin (yes/no)	No. of responses	Life-threatening hemorrhage
Baglin et al. (1990)	1	50	4	No	1	0
Bearman et al. (1997)	42	5.4–120	2–4	Yes	12	10
Leahey et al. (1996)	9	5–10	2–4	Yes	5	0
Goldberg et al. (1996)	1	20	4	Yes	1	0
Higashigawa et al. (1995)	1	2–5	4	Yes[a]	1	0
Lee et al. (1996)	3	10–20	7–14	Yes	3	0
Yu et al. (1994)	3	0.25–0.5[b]	4	No	2	0
Schriber et al. (1999)	37	30–40	1–25	Yes	13[c] (2)[d]	13
Kulkarni et al. (1999)	17	10	1–12	Yes[e]	6	0

[a]Patient also received PGE
[b]Dose reported as mg/kg
[c]In patients who were suspected of VOD
[d]In patients who were diagnosed with VOD
[e]12 patients received heparin

Table 5.5 Prior clinical trials of defibrotide (DF) in the treatment of severe hepatic veno-occlusive disease (sVOD)/multiorgan failure (MOF)

Phase; pts	Condition	Design	Key end points	Other results
Phase I (Richardson et al. 1998) *N* = 19	sVOD post-HCT	Compassionate use: DF: 5–60 mg/kg/day (intra-pt dose escalation, until response/toxicity)	CR: 42 % No severe hemorrhage related to DF	Day +100 survival: 32 %
Phase I/II (Richardson et al. 2002) *N* = 88	sVOD post-HCT	Emergency use: DF: 5–60 mg/kg/day (intra-pt dose escalation, until response/toxicity)	CR: 36 %	Day +100 survival: 35 % No serious AEs attributed to DF
Phase II (Richardson et al. 2010) *N* = 149 (DF)	sVOD post-HCT	Randomized, dose-finding; Arm A: DF 25 mg/kg/day Arm B: DF 40 mg/kg/day For ≥14 days or CR, VOD progression or unacceptable toxicity	Overall CR: 46 % Effective dose 25 mg/kg/day	Day +100 survival: 42 % Treatment-related AEs incidence: 8 % (greater at 40 vs. 25 mg/kg/day)
Phase III (Richardson et al. 2009) *N* = 102 (DF) *N* = 32 (HC)	sVOD with MOF post-HCT	Nonrandomized, comparison to HC; DF: 6.25 mg/kg IV q6h (25 mg/kg/day) for ≥21 days	Day +100 CR DF 24 % HC 9 % ($p < 0.05$)	Day +100 mortality: DF 62 %; HC 75 % ($p = 0.051$) Hemorrhagic AEs: DF 65 %; HC 69 %

Designated an orphan drug by the FDA and EMA
Pt(*s*) patient(s), *HC* historical control, *q6h* every 6 hours, *CR* complete response, *IV* intravenous, *AEs* adverse events

treatment of VOD/SOS is supported by a number of large clinical trials showing that DF improves both complete response (CR) and survival, with a recent multicenter randomized phase II study establishing an effective DF dose of 25 mg/kg/day, given in divided doses intravenously every 6 hours (Richardson et al. 2010) (Table 5.5).

The efficacy of DF for the treatment of VOD/SOS was initially demonstrated in a retrospective study of 19 patients with VOD/SOS plus MOF, showing complete resolution of VOD/SOS in eight patients (42 %), six of whom survived for longer than 100 days with no significant bleeding observed (Richardson et al. 1998). A number of

trials have subsequently confirmed the efficacy of DF, with a European multicenter compassionate-use study demonstrating a 55 % CR rate in 40 treated patients (Chopra et al. 2000). A pivotal phase III trial of DF in 102 patients with VOD/SOS plus MOF showed a superior 100-day CR rate in the DF group when compared with historical controls treated without DF (24 % vs. 9 %, respectively; adjusted $p=0.015$) and a lower 100-day mortality rate (62 % vs. 75 %, respectively; adjusted $p=0.051$). In 2007, the FDA permitted access to DF in the USA through an investigational new drug (IND) expanded access treatment protocol for patients with VOD/SOS plus MOF. An analysis of 269 patients enrolled between December 2007 and March 2011 at 67 US centers on this compassionate-use study revealed a 32 % CR rate by day 100 post-HCT, with a day 100 overall survival of 50 % (Richardson et al. 2011).

The promising results observed with DF in VOD/SOS treatment trials have led to investigation of its use as prophylaxis for VOD/SOS following HCT. A number of prospective historically controlled trials have reported benefits with DF prophylaxis in pediatric patients at high risk of developing VOD/SOS (Cappelli et al. 2009; Corbacioglu et al. 2006; Qureshi et al. 2008). These studies are also supported by the recent prospective multicenter phase II/III study in Europe (Corbacioglu 2012). In this trial, 360 children (<18 years) who were undergoing myelo-ablative HCT were randomized to receive either prophylactic DF from conditioning to 30 days post-HCT or no prophylaxis (as a control group). In an intent-to-treat analysis, there was a 40 % reduction in VOD/SOS by day 30 post-HCT in patients receiving prophylactic DF when compared with control (12 % vs. 20 %; $p=0.051$). Of note, the mortality at 100 days was four times higher in patients who developed VOD/SOS compared to those without VOD/SOS (25 % vs. 6 %; $p<0.0001$). Interestingly enough, the incidence of acute GVHD was also significantly lower in the DF prophylaxis arm, an observation consistent with similar findings in treatment studies (Richardson et al. 2010).

5.3.5 Future Directions

Despite the promising results from clinical trials with DF as treatment and prevention of VOD/SOS, day 100 mortality from VOD/SOS remains unacceptably high. The importance of early intervention is key, with recent clinical observations indicating that delays in the initiation of VOD/SOS treatment are associated with worse outcomes (Richardson et al. 2011). The role of DF in VOD/SOS management may, in fact, be optimized with its use in early disease or as prophylaxis. Additional prospective studies in VOD/SOS prevention are now planned in adult HCT populations and specific high-risk settings. Elevations of von Willebrand factor, thrombomodulin, E-selectin, and soluble ICAM-1 before and early after allogeneic transplantation may be useful in predicting VOD/SOS in patients receiving sirolimus (Cutler et al. 2010) as GVHD prophylaxis and could lead to preemptive treatment or prevention trials based on these and other biomarkers (Richardson et al. 2012). Finally, additional therapies, such as low molecular weight heparin, N-acetyl cysteine, antithrombin III, and other novel antithrombotics may warrant further investigation in combination with DF (Richardson et al. 2012; Ho et al. 2008).

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Opportunistic Infections in Pediatric Blood and Marrow Transplantation

6

Christopher C. Dvorak and William J. Steinbach

Contents

C.C. Dvorak, MD (✉)
Division of Pediatric Allergy, Immunology, and Blood & Marrow Transplantation, Benioff Children's Hospital, University of California San Francisco, 505 Parnassus Ave., M-659, San Francisco, CA 94143-1278, USA
e-mail: dvorakc@peds.ucsf.edu

W.J. Steinbach, MD
Division of Pediatric Infectious Diseases, Duke University Medical Center, 427 Jones Building, Research Drive, Durham, NC 27710, USA
e-mail: bill.steinbach@duke.edu

6.1 Introduction

Advances in supportive care have led to significant improvements in hematopoietic cell transplant (HCT) outcomes over the last decade. The one-year transplant-related mortality (TRM) rate for children with acute leukemia and unrelated donor HCT performed prior to 1995 approached 40 %. More recently, rates from 2003 to 2006 have fallen by more than half to approximately 15 % (MacMillan et al. 2008). This has led to performance of significantly more alternative donor HCTs for a wide variety of nonmalignant diseases, including T-cell and phagocyte primary immunodeficiencies, hemoglobinopathies, bone marrow failure syndromes, and metabolic syndromes. However, these children often have relatively intact immune systems at the time of HCT and thus require increased pre-HCT immunoablation to prevent graft rejection. This often leads to delays in post-HCT immune reconstitution, which in turn is associated with significant opportunistic infections. In addition to causing significant morbidity and prolonged hospitalizations, opportunistic infections cause a staggering 37–40 % of TRM following allogeneic HCT (Pasquini and Wang 2010).

There is also evidence that certain opportunistic infections may play a role in the triggering of alloreactivity and graft-versus-host disease (GVHD). For example, animal models have suggested that administration of probiotics may alter the intestinal microflora and decrease inflammation in mesenteric lymph nodes, thereby abrogating GVHD (Gerbitz et al. 2004). A randomized trial of fluconazole versus

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placebo demonstrated less severe GVHD of the intestinal tract in the fluconazole recipients, possibly due to decreased intestinal antigenic stimulation (Marr et al. 2000). Some data suggest that both cytomegalovirus (CMV) and human herpesvirus-6 (HHV-6) reactivations can trigger the development of GVHD (Lönnqvist et al. 1984; Pichereau et al. 2012). Since GVHD is another significant component of TRM following allogeneic HCT, further understanding of the interplay between opportunistic infections and initiation of GVHD may provide another avenue towards making HCT a safer procedure with improved overall outcomes.

6.2 Epidemiology of Opportunistic Infections After HCT

Although opportunistic infections do occur following autologous HCT, the much more profound and ongoing T-cell dysfunction that occurs before and after allogeneic HCT makes opportunistic infections far more likely to occur in this population. Multiple therapy-induced alterations of host defenses contribute to this risk (Lehrnbecher et al. 1997). The three major contributors to the development of an opportunistic infection are (1) breakdown in natural barriers (such as indwelling central venous catheters [CVCs] and mucositis), (2) defects in cell-mediated immunity (lymphopenia from corticosteroids and other anti-T-cell cytotoxic agents), and (3) deficient numbers of phagocytes (due to myeloablative chemotherapy). Classically, three phases of risk for opportunistic infections occur after HCT, as shown in Fig. 6.1 (Tomblyn et al. 2009). Knowledge of the timing of the variety of infections that can occur following HCT allows clinicians to develop rational approaches to antimicrobial prophylaxis, diagnostic monitoring for infections, and earlier treatment of proven infections.

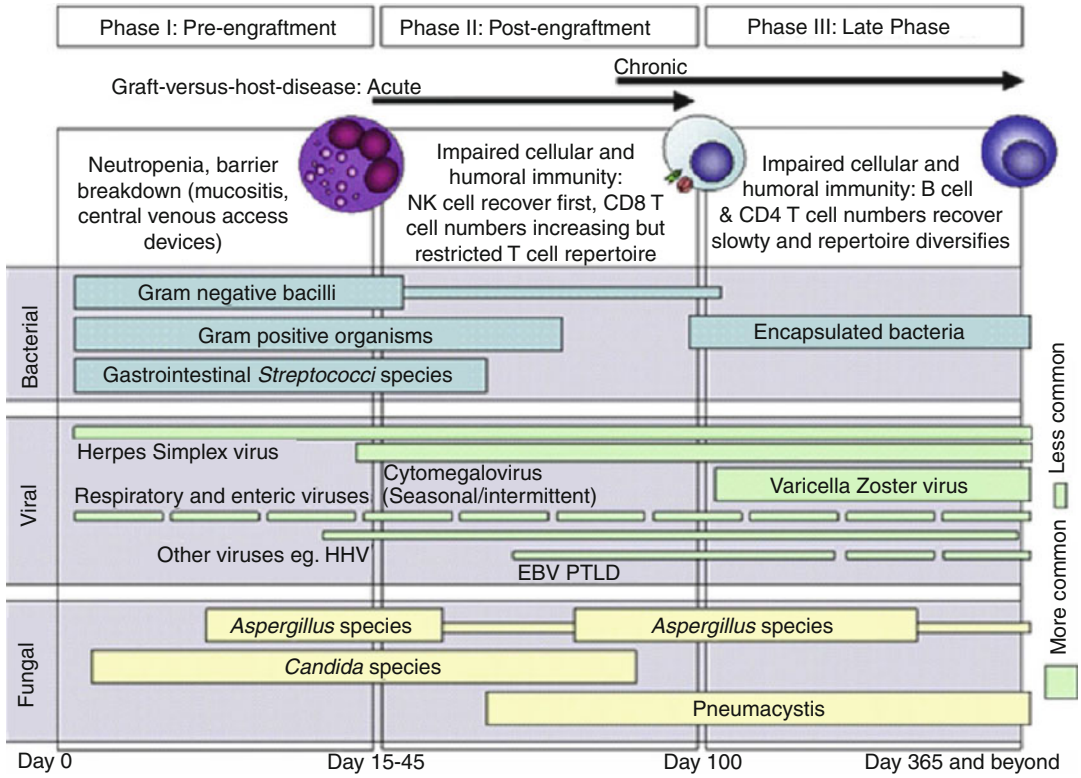

Fig. 6.1 The phases of opportunistic infections following allogeneic HCT. *NK* natural killer, *HHV-6* human herpesvirus-6, *EBV* Epstein-Barr virus, *PTLD* posttransplant lymphoproliferative disease (Reprinted from Tomblyn et al. (2009). Copyright (2009), with permission from Elsevier)

6.3 Phase I: Pre-engraftment (<30 Days)

Infections in phase I are similar to those seen with other forms of profoundly myelosuppressive chemotherapy and include Gram-positive and Gram-negative bacteremia, candidemia, invasive aspergillosis (IA), reactivation of oral herpes simplex virus contributing to mucositis, and community-acquired viruses such as influenza. Administration of granulocyte colony-stimulating factor (G-CSF) during this period will shorten the time to recovery of neutrophils by several days and may decrease rates of documented infections (Dekker et al. 2006). However, there is less evidence that G-CSF improves infection-related or transplant-related mortality, and it may increase the incidence of acute GVHD (Trivedi et al. 2009). Therefore, only about 60 % of HCT centers utilize G-CSF routinely (Lee et al. 2008).

6.3.1 Bacterial Infections

6.3.1.1 Classic Gram-Positive and Gram-Negative Bacteria

Bacterial infections following HCT most commonly divide into Gram-positive organisms originating from the skin or gastrointestinal (GI) tract and Gram-negative organisms translocating from the GI tract. The period of highest risk for bacterial bloodstream infections, especially with enteric Gram-negative rods, is the pre-engraftment period (Castagnola and Faraci 2009), during which the incidence of bacteremia can range from 21 to 34 % and 21 to 58 % for patients undergoing autologous and allogeneic HCT, respectively, although some studies report no difference between the two groups (Busca et al. 1999; Castagnola et al. 2008a, b; Mullen et al. 2000; Cappellano et al. 2007). In HCT patients, bloodstream infections prior to engraftment are a significant independent predictor of mortality (Poutsiaka et al. 2007; Almyroudis et al. 2005). Several studies have demonstrated that either host or donor polymorphisms in genes responsible for immunity may contribute to the risk of bacterial infections (Rocha et al. 2002; Azarian et al. 2008; Lee et al. 2007; Chien et al. 2008; Mensah et al. 2009; van der Velden et al. 2009).

Given the significant risk of developing bacteremia, it is surprising that there is little evidence that routine antibacterial prophylaxis plays a role in management of pediatric HCT recipients. In adult patients undergoing HCT, there is general consensus regarding the utility of a prophylactic quinolone with antipseudomonal activity (Tomblyn et al. 2009). This derives from data generated by a large contemporary trial of levofloxacin prophylaxis in which 45 % of enrolled patients were undergoing autologous HCT. The rates of fever and bacteremia were significantly reduced in those patients receiving levofloxacin, but prophylaxis did not impact mortality (Bucaneve et al. 2005). Similar results have been reported using ciprofloxacin and vancomycin as a prophylactic regimen for autologous HCT patients (Eleutherakis-Papaiakovou et al. 2010). Unlike autologous HCT, there are no contemporary large randomized trials of the use of antibiotic prophylaxis versus no prophylaxis in allogeneic HCT patients. Most existing studies in HCT patients have included small patient numbers and have compared two prophylactic regimes, as opposed to prophylaxis versus no prophylaxis, and have given rise to variable results (Guthrie et al. 2010; Kroschinsky et al. 2002; Perez-Simon et al. 2004; Slavin et al. 2007; Solano et al. 2005). Since all of these studies were done in adult patients, caution must be used in applying the specific results to pediatric HCT recipients.

Other approaches to antibacterial prophylaxis utilize nonsystemic treatments to potentially avoid medication toxicities and the development of resistant organisms. Chlorhexidine gluconate (CHG) is an antiseptic bactericidal to Gram-positive and Gram-negative bacteria, including multidrug-resistant organisms. The mechanism of action involves bacterial membrane disruption; its onset is relatively rapid and the effect is persistent. A 2 % CHG-impregnated cloth product has been studied as a skin-cleansing product in the adult critical care setting where it has been shown to decrease risk of central line associated infections by at least 50 % and new acquisition of

multidrug-resistant organisms by 30–50 % (Bleasdale et al. 2007; Climo et al. 2009; Popovich et al. 2009; Vernon et al. 2006). Currently, there are no peer-reviewed published studies on the effect of CHG bathing on prophylaxis of bloodstream infections in children undergoing HCT. Similarly, since many cases of bacteremia are seen in the setting of CVCs, the use of ethanol lock solutions may potentially decrease CVC colonization without the concern of resistance from antibiotic locks. A randomized, double-blind study in adults receiving chemotherapy or HCT demonstrated the benefit of ethanol locks versus heparin (Sanders et al. 2008). Studies of prophylactic ethanol locks in pediatric HCT recipients are currently lacking.

When patients develop a fever early posttransplant, empiric antibacterial treatment is usually started. While a variety of different regimens exist, they are generally tailored to cover *Streptococcus* species (spp.), *Staphylococcus* spp., and enteric Gram-negative organisms, based on local susceptibility patterns.

6.3.1.2 *Clostridium difficile*

Although hardly unique to the pediatric HCT population, the widespread use of broad-spectrum antibiotics for empiric therapy of febrile neutropenia has led to *C. difficile*-associated diarrhea. In adults, up to 15 % of patients may develop this complication within 30 days of HCT (Arango et al. 2006), though pediatric-specific data is relatively lacking. Prevention of *C. difficile* may potentially be accomplished through the administration of certain strains of probiotics (McFarland 2006). It is not yet clear that this practice is safe in the immediate post-HCT phase, where a combination of neutropenia and compromised intestinal integrity could theoretically lead to the development of bacteremia from the ingested strain (Hammerman et al. 2006). Treatment of *C. difficile*-associated diarrhea in the pediatric HCT patient is similar to that of the general population, with metronidazole or oral vancomycin, although caution must be utilized during the conditioning phase of HCT when metronidazole can enhance toxicities from radiation or busulfan (Gulbis et al. 2011).

6.3.2 Fungal Infections

Although bacteria represent the most common infection following HCT, invasive fungal infections (IFI) account for a significant amount of posttransplant mortality. Several retrospective reports on the development of IFI in pediatric HCT patients have been published, with a 1-year incidence as high as 13–20 % and mortality as high as 58–83 % (Hovi et al. 2000; Benjamin et al. 2002; Dvorak et al. 2005; Safdar et al. 2007). The most commonly identified invasive fungal organisms following HCT are *Candida* spp. and *Aspergillus* spp. Patients who are considered to be the highest risk for developing an IFI following HCT are those who undergo transplant from either an unrelated donor (including umbilical cord blood) or a partially matched related donor, or for treatment of a malignancy, bone marrow failure syndrome, or congenital immunodeficiency (Marr et al. 2000; Mikulska et al. 2009; Tomblyn et al. 2009; Burgos et al. 2008; Dvorak et al. 2005; Kontoyiannis et al. 2010).

There is currently near-universal use of antifungal prophylaxis in HCT patients. Empiric therapy directed against resistant *Candida* or molds generally commences after approximately 72 h of prolonged fevers despite administration of broad-spectrum antibacterials. One surprising feature to note from the original prophylactic fluconazole studies is that, even in the placebo arm, >80 % of HCT patients did not develop an IFI, though these studies did include lower-risk autologous HCT recipients (Goodman et al. 1992; Slavin et al. 1995). This suggests that there must be other explanations for the development of IFI post-HCT. Researchers are now finding that either host or donor polymorphisms in genes responsible for immunity appear to play a significant role in IFI risk (Kesh et al. 2005; Seo et al. 2005; Zaas et al. 2008; Bochud et al. 2008; Mezger et al. 2008; Cunha et al. 2010; Granell et al. 2006). Most of these proposed genetic risk factors still require validation in a prospective multicenter cohort, but the future possibility of having different prophylactic strategies based on an a priori risk of developing an IFI is promising.

6.3.2.1 *Candida*

Invasive candidiasis tends to occur during the neutropenic period immediately following HCT, although later cases can occur in the setting of GVHD and prolonged immunosuppression, especially when CVCs are still in place. Typically, invasive candidiasis originates from endogenous *Candida* spp. colonizing patients' GI tracts (Cole et al. 1996). Pediatric patients appear to have relatively more invasive infections caused by *Candida parapsilosis* and less infections caused by *Candida glabrata*, as compared to adults (Malani et al. 2001). Two placebo-controlled trials from the early 1990s, performed in patients greater than 12 years of age undergoing autologous or allogeneic HCT, demonstrated that prophylactic administration of fluconazole significantly decreased IFIs (Goodman et al. 1992; Slavin et al. 1995). Long-term follow-up of allogeneic HCT patients given fluconazole prophylaxis supports a survival benefit (mortality 20 % in the fluconazole arm vs. 35 % in the placebo arm; $p = 0.004$), postulated to be at least partly due to less severe GVHD of the GI tract in the fluconazole recipients from decreased intestinal antigenic stimulation (Marr et al. 2000). The classic duration of fluconazole prophylaxis administration is during the high-risk period until 75 days post-HCT (Marr et al. 2004b; Marr et al. 2000). Because fluconazole does not cover *C. krusei* and has variable activity against *C. glabrata*, alternative agents should be considered for patients known to be colonized with these species. Reasonable options include extended-spectrum triazoles, echinocandins, and lipid formulations of amphotericin B (LFAB), all of which also have some coverage of *Aspergillus* spp.

When patients develop invasive candidiasis post-HCT, the most common site of infection is the bloodstream. In addition to initiation of appropriate antifungal agents, the standard practice is to discontinue all CVCs in patients with candidemia (Raad et al. 2004). Less common, but more perplexing, disseminated *Candida* infections of the liver, spleen, and/or lungs can often be blood culture negative and may require tissue biopsy in order to establish a diagnosis. Serum beta-glucan (BG) levels will be very useful for identifying cases of possible invasive candidiasis once the assay has been optimized for use in children (Smith et al. 2007). Furthermore, in patients with disseminated candidiasis, a formal ophthalmologic evaluation is recommended to rule out *Candida* endophthalmitis, which may require intravitreal injection of antifungal agents to preserve vision (Riddell et al. 2011). For treatment of cases of invasive candidiasis, especially those that develop on fluconazole prophylaxis, the echinocandins are a class of antifungal agents that target β-(1,3)-D-glucan synthase and interrupt biosynthesis of the glucan polymers that make up fungal cell walls. Because mammalian cells do not possess cell walls, echinocandin administration to human patients has generally resulted in limited toxicity. Echinocandins possess fungicidal activity against *Candida* spp. (Ashley et al. 2006). In some settings, the echinocandins may be superior to fluconazole (Reboli et al. 2007) or amphotericin B (Mora-Duarte et al. 2002) for treatment of invasive candidiasis.

6.3.2.2 *Aspergillus*

In adult HCT recipients, *Aspergillus* infections have a bimodal distribution, with a first peak at a median of 16 days and the second at a median of 96 days post-allogeneic HCT (van Burik and Weisdorf 1999; van Burik et al. 2007). This second peak may be less pronounced in children (Castagnola et al. 2008a). IA can be one of the most devastating infections to occur following allogeneic HCT. In a multivariate analysis of risk factors for mortality among a modern cohort of pediatric patients with IA, the major risk factor for death was the development of IA after an allogeneic HCT (Burgos et al. 2008). Although treatment options for IA have increased in recent years, significant attention has also been paid to preventing IA infections. Although fluconazole prophylaxis has been shown to reduce the risk of IFI relative to placebo, fluconazole lacks activity against *Aspergillus* spp. Given this lack of antimold activity, several trials have compared fluconazole to mold-active agents in hopes of decreasing rates of IA. The first of these trials compared fluconazole to low-dose conventional

amphotericin B deoxycholate (D-AMB) (Wolff et al. 2000). However, D-AMB did not show benefit over fluconazole and resulted in a higher adverse event rate. Several trials, including one in children (Roman et al. 2008), have evaluated the LFAB (often given only three times per week) for antifungal prophylaxis in HCT and acute leukemia patients (Mattiuzzi et al. 2003; Kelsey et al. 1999; Penack et al. 2006). However, like D-AMB, LFAB has not been shown to be superior to fluconazole in overall success and typically demonstrates increased side effects.

Extended-spectrum triazoles such as itraconazole, voriconazole, and posaconazole do possess anti-*Aspergillus* activity (Ashley et al. 2006); however, there are clear limitations to each as a potential prophylactic agent. Several trials of itraconazole versus fluconazole have been performed, and a meta-analysis showed significantly less IFI (Vardakas et al. 2005), but because of its common gastrointestinal side effects, greater drug interactions, and poor tolerability (Marr et al. 2004b), itraconazole prophylaxis has generally been abandoned in children. The results of a multicenter, double-blinded trial showed that voriconazole was not superior to fluconazole in the prevention of IFI, though the safety profile was similar (Wingard et al. 2010). Given voriconazole's broader spectrum of activity, this result was surprising but may have been due to an incomplete understanding of the complex pharmacokinetics of voriconazole. In adults and children over the age of 12 years, voriconazole has nonlinear pharmacokinetics with relatively well-established dosing regimens. Even in adults, however, recent studies have questioned standard dosing regimens and have proposed dosing based on serum drug levels (Trifilio et al. 2007; Smith et al. 2006; Pascual et al. 2008), although the optimal goal serum voriconazole level is still unclear. Part of this variability may be due to allelic polymorphisms of the gene encoding for CYP2C19, which can result in an increase or decrease in voriconazole metabolism (Pascual et al. 2008). In children, the situation is further complicated by linear voriconazole kinetics, so that younger children may need significantly higher dosages of voriconazole (Karlsson et al. 2009; Neely et al. 2010; Friberg et al. 2011). Voriconazole also has significant drug interactions with commonly used agents in a pediatric HCT population. Voriconazole is a substrate of CYP2CP (major), 2C19 (major), and 3A4 (minor) and an inhibitor of 2C9 (moderate), 2C19 (weak), and 3A4 (moderate) (Cronin and Chandrasekar 2010). Proton pump inhibitors increase voriconazole levels, while voriconazole increases serum levels and/or toxicity of corticosteroids, imatinib, and many other medications (Cronin and Chandrasekar 2010). The approved voriconazole label reports that concomitant use of voriconazole can cause a 1.7- to 3-fold increase in cyclosporine or tacrolimus levels and recommends that the dosing of cyclosporine be decreased by 50 % and the dosing of tacrolimus be decreased by 66 % of the normal dose. In a recent study of 27 adult HCT patients receiving voriconazole, 100 % of patients required multiple tacrolimus dose reductions to achieve a safe target level (Trifilio et al. 2010). Furthermore, the use of voriconazole with sirolimus is officially contraindicated, and when its use has been reported, investigators have recommended dropping the levels of sirolimus to 90 % of original dosing at the time of initiation of voriconazole (Marty et al. 2006).

Posaconazole is a triazole with broad coverage of most fungi, including the agents of mucormycosis (previously called zygomycosis) (Ashley et al. 2006). In a trial of adult patients with neutropenia, posaconazole prophylaxis was superior to fluconazole or itraconazole but was also associated with an increased risk of serious adverse events (Cornely et al. 2007). In a trial of teenagers and adults receiving treatment for acute or chronic GVHD, posaconazole was superior to fluconazole at preventing breakthrough IFI and death from IFI, with similar rates of toxicity (Ullmann et al. 2007). Unfortunately, this did not translate to improved overall survival. Factors limiting the use of posaconazole in children include the lack of pharmacokinetic data in children less than 13 years of age, the current lack of an intravenous formulation (since these children typically have nausea, mucositis and poor oral intake during the highest risk period), and unreliable absorption in the setting of limited oral intake. Finally, posaconazole shares many of the same enzymatic

pathways and therefore drug interactions as voriconazole. Because of the CYP interactions, azole prophylaxis is generally started after the conditioning regimen is complete. For patients who enter the HCT period being treated for a preexisting IFI, discontinuation of azoles 72 h prior to the start of conditioning chemotherapy is often done in order to allow the CYP enzymes to return to baseline function, though some data suggest that fluconazole coadministration may actually help with cyclophosphamide metabolism and decrease toxicity (Upton et al. 2007).

Echinocandins possess fungistatic activity against *Aspergillus* spp. (Ashley et al. 2006). In a prophylactic antifungal trial, micafungin demonstrated reduced need for empiric antifungal therapy and an improved safety profile compared to fluconazole (van Burik et al. 2004). However, the number of pediatric subjects enrolled was small ($n=84$), and a reduction in the incidence of proven or probable IFI was not demonstrated. The lack of impact on IFIs may have been because the incidence of breakthrough IFIs in both groups was very low, likely due to the inclusion of low-risk patients (46 % autologous HCT recipients) and very few patients undergoing umbilical cord blood transplant ($n=30$). Caspofungin has been shown to be at least equivalent to itraconazole in the setting of antifungal prophylaxis (Mattiuzzi et al. 2006), with little caspofungin-related adverse events (Chou et al. 2007), although prospective trials in this population are lacking. The major disadvantages to widespread echinocandin use are cost and the lack of an available oral formulation.

If prophylaxis fails, the typical locations where IA develops following an allogeneic HCT are the lungs and sinuses, with fairly common seeding of the brain as well. It should be noted that children do not always display the "classic" radiographic findings seen in adults with IA, such as the air crescent or halo signs (Burgos et al. 2008), and a high index of suspicion must be maintained (Fig. 6.2a). Much attention has been focused on developing noninvasive tests for diagnosing IA. Galactomannan is a polysaccharide cell-wall component that is released by *Aspergillus* during growth. The Platelia EIA *Aspergillus* galactomannan (GM) assay was approved by the Food and Drug Administration in 2003 for use in adult patients (Pfeiffer et al. 2006). Early large-scale clinical testing included few children, but available data suggest that detection values for adult patients can be extrapolated to children (Steinbach et al. 2007; Hayden et al. 2008). Serum β-D-glucan (found in all fungi except *Cryptococcus* spp. and mucormycosis) can be detected using an approved diagnostic serum assay and has been found to have high specificity and high positive predictive values for the detection of IFI in adults (Ostrosky-Zeichner et al. 2005). However, data on the performance of this assay in children are limited (Smith et al. 2007). Ultimately, obtaining cultures through early bronchial alveolar lavage (BAL) can be incredibly useful in determining the etiology of pulmonary infiltrates, as the differential diagnosis can be quite broad (Table 6.1). In one study, over 50 % of BALs yielded an organism, and early identification and therapy modification were associated with less mortality (Shannon et al. 2010). In the cases where BAL does not identify a pathogen, tissue biopsy is the ultimate way to be certain of what organism is being treated since *Aspergillus* spp. can look different than other fungi (Fig. 6.2b-d). Speciation of the *Aspergillus* is also important if polyene therapy is planned, due to intrinsic resistance of *Aspergillus terreus* to amphotericin B (Dodds Ashley et al. 2006).

Based on a pivotal trial performed in teenagers and adults, voriconazole has become the standard therapy for patients with IA (Herbrecht et al. 2002). Because of the high mortality rate of IA in post-HCT patients, there has been great enthusiasm for potentially synergistic combination therapies, such as with a triazole and an echinocandin (Marr et al. 2004a). If amenable to a surgical approach, strong consideration should be made for resection of cases of IA, which has been shown to decrease mortality if disease is precariously located near a major vessel (Burgos et al. 2008). In patients who develop IA during the neutropenic period, transfusions of irradiated random donor granulocytes have been proposed as a method to improve outcomes, though conclusive proof that this laborious procedure is

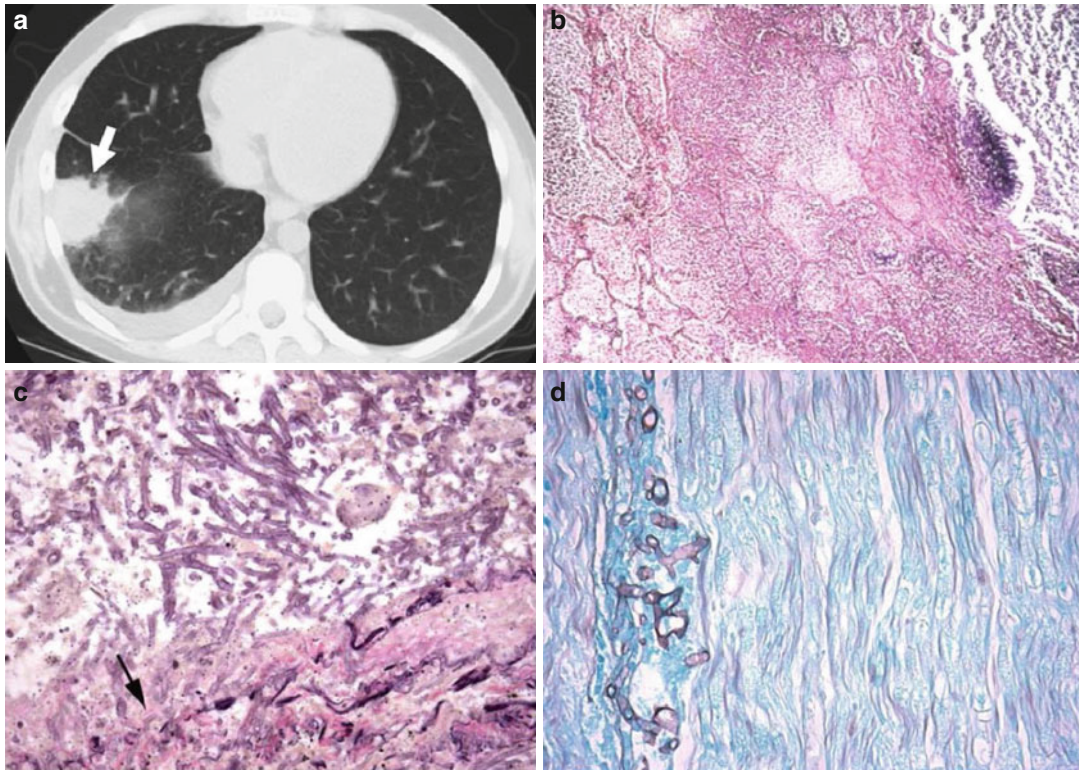

Fig. 6.2 (**a**) Invasive aspergillosis presenting as mass-like consolidation in a 15-year-old girl with acute lymphocytic leukemia and hematopoietic cell transplantation. Axial lung window CT image shows a pleural-based, mass-like consolidation (*arrow*) with mild surrounding ground-glass opacities in the right lower lobe. A small right pleural effusion is also seen. Subsequent surgical resection of this lung lesion confirmed *Aspergillus* spp. infection (With kind permission from Springer Science + Business Media: Yikilmaz A, Lee EY (2007) CT imaging of mass-like nonvascular pulmonary lesions in children. *Pediatric Radiology*, 37, 1253–63, Figure 17) (**b**) Biopsy specimens of pulmonary tissue involved with IA typically demonstrate necrotizing pneumonia with areas of hemorrhage and acute and granulomatous inflammation. Hematoxylin and eosin (With kind permission from Springer Science + Business Media: Kradin R (2010) The pathology of *Aspergillus* infection. In: Comarú Pasqualotto A, ed. *Aspergillosis: From Diagnosis to Prevention*, pp 87–104, Figure 14) (**c**) Identification of fungal angioinvasion (*arrow*) is enhanced with the aid of an elastin stain (With kind permission from Springer Science + Business Media: Kradin R (2010) The pathology of *Aspergillus* infection. In: Comarú Pasqualotto A, ed. *Aspergillosis: From Diagnosis to Prevention*, pp 87–104, Figure 11) (**d**) Gomori methenamine silver stains can also be useful, as they can help distinguish the acute angle dichotomous branching hyphae of *Aspergillus* spp. (not shown) from the broad pauciseptate hyphae of Zygomycetes as seen here (With kind permission from Springer Science + Business Media: Kradin R (2010) The pathology of *Aspergillus* infection. In: Comarú Pasqualotto A, ed. *Aspergillosis: From Diagnosis to Prevention*, pp 87–104, Figure 21)

beneficial is lacking (Seidel et al. 2008). Finally, exciting work has demonstrated the importance of adaptive immunity to fighting IA (Hebart et al. 2002). Based on this, work has been done on creating *Aspergillus*-specific T cells for use in adoptive immunotherapy. It has been demonstrated that a cohort of patients who developed IA after haploidentical HCT and who received *Aspergillus*-specific T cells had significantly better resolution of the IA than a similar cohort not given the specific T cells (Perruccio et al. 2005).

6.3.3 Viral Infections

Viral infections following pediatric HCT can be divided into two broad categories: DNA viruses that occur due to reactivation of a previous

Table 6.1 Differential diagnosis of pulmonary infiltrates in a pediatric HCT patient

Infectious causes		Noninfectious causes
Bacteria	Enteric Gram-negative rods *Staphylococcus aureus* *Legionella pneumophila* *Mycoplasma* spp. *Chlamydia trachomatis* Atypical mycobacteria	Idiopathic pneumonia syndrome Bronchiolitis obliterans with organizing pneumonia Bronchiolitis obliterans syndrome
Fungal	*Aspergillus* spp. *Candida* spp. Rare molds (e.g., mucormycosis) *Pneumocystis jirovecii*	
Viral	CMV Adenovirus Respiratory viruses (e.g., influenza, RSV, and parainfluenza) HHV-6	
Parasitic	*Strongyloides stercoralis*	

infection (and occasionally as a de novo infection) and community-acquired respiratory viruses. Other than donor and recipient serostatus, the major risk factor for a reactivation of a double-stranded DNA (dsDNA) viral infection post-HCT is the use of T-cell depletion, either ex vivo or in vivo via the use of serotherapy (Cohen et al. 2005; Myers et al. 2005; Park et al. 2009). Recently, a few polymorphisms in host immune response genes have also been shown to possibly contribute to the development of dsDNA viral infections following HCT (Jaskula et al. 2009; Bogunia-Kubik et al. 2006; Bogunia-Kubik et al. 2007).

6.3.3.1 Herpes Simplex Virus

Herpes simplex virus (HSV)-1 and HSV-2 infections post-HCT usually occur as a result of reactivations from a previously acquired latent virus. As such, pre-transplant serologies are very useful in identifying at-risk patients. Since acquisition of HSV occurs as patient's age, many pediatric HCT patients will be seronegative. In the era prior to routine prophylaxis of seropositive patients, reactivation rates were approximately 70–80 % and significantly contributed to post-HCT mucositis (Saral et al. 1981). Dissemination of HSV to the lungs, liver, or brain is also possible. Routine acyclovir prophylaxis is usually given during the period of mucositis and with this HSV reactivations are relatively rare (Gluckman et al. 1983). However, severely immunocompromised individuals can continue to develop reactivations for many months post-HCT, and thus some centers will continue prophylaxis for up to 6 months (Ljungman et al. 1986), a typical time period for development of T-cell reconstitution. This is not needed for patients that receive ganciclovir for CMV prophylaxis, since ganciclovir has activity against HSV as well (Goodrich et al. 1993). In addition, since some strains of HSV have become acyclovir resistance, patients with more severe than anticipated mucositis should have a lesion swabbed for HSV culture, and resistant strains should be treated with either foscarnet or cidofovir (Tomblyn et al. 2009).

There does not appear to be a role for routine acyclovir prophylaxis in HSV seronegative patients, though consideration of varicella-zoster virus (VZV) serostatus must also be taken into account. Furthermore, patients with B-cell immunodeficiencies may be unable to mount an antibody response to prior HSV infection and should be considered for prophylaxis, especially if close contacts such as the parents or siblings have a history of HSV infections.

6.3.3.2 Respiratory Viruses

Influenza

During seasonal outbreaks, HCT recipients are at risk for developing influenza infections from close contacts. Although upper respiratory tract symptoms are common, systemic symptoms such as fever or myalgias may be absent (Peck et al. 2007). Thus a high index of suspicion must be maintained during the peak season, since 20–50 % of influenza infections can rapidly progress to lower respiratory tract disease with hypoxemia and a risk of mechanical ventilation and death (Choi et al. 2011). A BAL may be needed in patients with evidence of lower respiratory tract symptoms, as highly immunosuppressed patients are at risk for harboring multiple pathogens. Preemptive treatment with neuraminidase inhibitors (the choice dependent upon that year's circulating strain) appears to be relatively efficacious at preventing progress to lower respiratory tract disease (Casper et al. 2010). Although the data are limited, combination regimens have been employed for patients with resistant strains or with respiratory failure. There is no parenteral agent that is commercially available in the United States, but several are under investigation and/or available through emergency use authorization (Casper et al. 2010). The use of moderate dosages of corticosteroids in order to reduce excessive inflammation is controversial (Casper et al. 2010), while other forms of immunosuppression should be lowered whenever possible.

Prevention strategies for influenza center around strict infection control practices, including hand-washing, isolation, and eliminating potential exposures via universal vaccination of health-care workers and patients' family members/caregivers. If a recent (less than 2 years or still immunocompromised) HCT recipient has a significant exposure to a confirmed case of influenza, prophylactic administration of a neuraminidase inhibitor is recommended. This strategy could also be considered if a nosocomial outbreak was to occur on a HCT unit. Vaccination of HCT recipients (with the inactivated strain) is highly recommended to continue for several years beginning at 6 months following HCT, before which time the majority of adult patients are unlikely to mount a response (Casper et al. 2010). However, pediatric data is limited, and a fixed 6-month rule fails to take into account the significant variation in immunologic recovery times that occurs between patients depending on stem cell source and presence of GVHD. It is not unreasonable to allow earlier vaccination for patients on tapering doses of immunosuppression (Tomblyn et al. 2009), even without documented B-cell function, since a T-cell response to influenza vaccine may also provide some protection (Avetisyan et al. 2008). Finally, efforts are under way to create influenza-specific T cells that can be given in a prophylactic fashion following HCT (Stadtmauer et al. 2011).

Respiratory Syncytial Virus

During seasonal outbreaks, upper respiratory tract infections from the RNA virus respiratory syncytial virus (RSV) are common in HCT recipients. Approximately 50 % of those infected will progress to involve their lower respiratory tract, especially those with GVHD or severe lymphopenia (Shah and Chemaly 2011). Untreated RSV pneumonia in HCT recipients has a mortality rate approaching 80 % (Shah and Chemaly 2011). Ribavirin, a guanosine analog, is available in aerosolized form for the treatment of RSV. Several potential regimens exist, including a continuous 18-h infusion and a 2–3-h infusion given three times per day. Due to concerns about potential teratogenicity, it is usually administered in a scavenging tent. Respiratory side effects from inhaled ribavirin are common and include potential bronchoconstriction. Despite its problems and costs, a comprehensive review of inhaled ribavirin treatment in adult HCT recipients suggests that initiation of ribavirin at the time of diagnosis of RSV upper respiratory tract infection can significantly decrease the risk of progression to lower respiratory tract disease and in those with lower respiratory tract disease can decrease the risk of death (Shah and Chemaly 2011). An oral formulation of ribavirin (used for treating hepatitis C) and an intravenous formulation (not available in the United States) have also been utilized for treating RSV. However, the data is not conclusive that these formulations are as effective as the inhaled ribavirin.

Palivizumab, an RSV-specific monoclonal antibody, is effective at preventing RSV infections

in very young high-risk children. Another potential immunomodulator is intravenous immunoglobulin (IVIG), which often contains anti-RSV antibodies, and may decrease RSV-mediated cytokine-induced pulmonary inflammation. A review of the available studies of immunomodulation plus inhaled ribavirin suggests that the combination is superior at preventing progression to lower respiratory tract disease and RSV-related death than inhaled ribavirin alone (Shah and Chemaly 2011). However, the report was unable to separate out those that specifically received palivizumab due to small numbers. Because of this, and the lack of any controlled trial, the use of the expensive palivizumab has been questioned. Even more controversial is the prophylactic use of palivizumab. Fortunately, the incidence of RSV infection in the first 100 days post-HCT is still relatively low at 5.8 % (Peck et al. 2007). However, based on decision-tree analysis, it has been estimated that in children undergoing HCT, the use of prophylactic palivizumab may increase the absolute survival rate from 83 % to 92 %, suggesting that 12 children would need to be treated in order to prevent one RSV-related death (Thomas et al. 2007). Clinical confirmation of this concept is lacking.

Even with "optimal" therapy of inhaled ribavirin plus an immunomodulator, the mortality attributable to RSV in HCT recipients with lower respiratory tract disease is approximately 25 %. Therefore, better treatments are desperately needed, and work is underway on higher-affinity monoclonal antibodies, high-titer RSV immune globulin, and antisense compounds (Shah and Chemaly 2011).

Other Respiratory Viruses

Other respiratory viruses, including parainfluenza virus (Srinivasan et al. 2011), human metapneumovirus (Englund et al. 2006), and rhinovirus (Milano et al. 2010), have been implicated in causing lower respiratory tract disease in HCT recipients. Risk factors for progression from upper respiratory tract infection to viral pneumonia include acquiring the infection early post-HCT, a low absolute lymphocyte count, and corticosteroid usage (Srinivasan et al. 2011). There is no FDA-approved antiviral agent with proven efficacy against these three viruses; however, identifying one of these viruses from the nasopharynx or bronchial washings can be useful in limiting empiric usage of potentially toxic agents to treat other infections, although these viruses often show up as co-pathogens. Some uncontrolled reports have suggested that inhaled ribavirin may be useful against parainfluenza (Chakrabarti et al. 2000), although others have questioned its utility (Nichols et al. 2001). Recently, a case report demonstrated possible efficacy of DAS18, an inhaled sialidase fusion protein, in a HCT recipient with severe parainfluenza infection (Chen et al. 2011). Ribavirin has in vitro activity against human metapneumovirus, and a recent report suggests that ribavirin may play a role in helping resolve lower respiratory tract disease (Shahda et al. 2011), although controlled comparisons are lacking. Clearly, the best strategy for dealing with respiratory viral infections following HCT is to avoid them through careful respiratory isolation.

6.4 Phase II: Early Post-engraftment (30–100 Days)

Some infections in phase II are caused by a combination of persistent defects in the function of the patients' phagocytes (partly from the administration of corticosteroids to treat acute GVHD) and retention of CVCs, which can lead to continue to lead to Gram-positive bacteremia and candidemia. Other infections are due to the ongoing relative and functional lymphopenia and involve reactivations of CMV and other double-stranded DNA viruses, *Pneumocystis jirovecii*, or certain parasitic infections. Finally, community-acquired viral infections continue to be a problem until full immune reconstitution has taken place.

6.4.1 Fungal Infections: *Pneumocystis jirovecii*

Pneumocystis jirovecii was previously referred to as *Pneumocystis carinii*, but that term now refers only to pneumocystis that infects rodents, and *Pneumocystis jirovecii* refers to the distinct

species that infects humans. The abbreviation PCP (or PJP) is often used to refer to Pneumocystis pneumonia. PCP reactivations or infections are generally thought to be preventable following HCT with administration of classic prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX). However, in the setting of alternative prophylaxis agents or TMP-SMX noncompliance, episodes of PCP do still occur beginning about 2 months post-HCT and continuing through recovery of T-cell functional immunity. TMP mechanism of action is by interference with the bacterial dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid and thus nucleic acid synthesis. Due to concerns about bone marrow toxicity, TMP-SMX is often held for several weeks following HCT until evidence of neutrophil recovery, although this practice has been challenged (Fontanet et al. 2011). The dose of TMP-SMX required to prevent PCP has not been well studied, and a variety of dosing regimens exist, with 2 or 3 days per week administration being the most common. Generally, TMP-SMX is continued for at least 6 months following an allogeneic HCT, though this should be lengthened for patients receiving ongoing immunosuppressive therapy (Tuan et al. 1992). In addition to possible bone marrow suppression, many patients have allergic or other reactions to TMP-SMX that induce clinicians to prematurely discontinue its use. However, the optimal second-line prophylactic agent is not well defined, and all options appear to be potentially less effective than TMP-SMX. Options that have been used include oral dapsone, intravenous or inhaled pentamidine, and oral atovaquone. Dapsone is inexpensive but has a high incidence of adverse events, especially in patients with glucose-6-phosphate deficiency (Sangiolo et al. 2005). Intravenous pentamidine given every 4 weeks has also been used, though inadequate protection has been noted in children under 2 years of age and those undergoing HCT (Kim et al. 2008), both of whom may need more frequent dosing. Aerosolized pentamidine is generally well tolerated other than occasional bronchospasm, but its effectiveness has been questioned (Vasconcelles et al. 2000). Atovaquone is generally well tolerated, but absorption can be limited in patients not eating diets containing fatty foods. In vitro, the echinocandin class of antifungal agents appears to have some activity against the cyst form of *P. jirovecii*. To date, no studies have evaluated the use of echinocandins as a solitary prophylaxis agent; however, a few case reports have described its potential utility in combination with TMP-SMX for the treatment of PCP (Beltz et al. 2006; Annaloro et al. 2006).

PCP must be suspected in HCT patients presenting with hypoxemia (often disproportionally more severe than the degree of hypercapnia), dyspnea, cough, fever, and bilateral infiltrates (Tuan et al. 1992; Shankar and Nania 2007), especially if noncompliance is suspected or alternative prophylaxis agents have been used. Although highly sensitive in patients with HIV, measuring the serum lactate dehydrogenase level is less useful in other immunocompromised patients due to low levels of sensitivity and specificity (Vogel et al. 2011). Serum BG levels could potentially be very useful for identifying cases of PCP once the assay has been optimized for use in children (Smith et al. 2007). Until then, the definitive diagnosis of PCP still requires identification of the organism on special stains or polymerase chain reaction (PCR) of induced sputum or BAL fluid (Shankar and Nania 2007). Once PCP is identified, the treatment of choice is high-dose TMP-SMX (15–20 mg TMP/kg/day divided every 6 h) (Shankar and Nania 2007). This high-dose TMP-SMX may be difficult to administer to a patient recovering from HCT with marginal bone marrow reserves. As such, some physicians have utilized folinic acid "rescue," analogous to what is used following methotrexate administration, with the hypothesis that bacteria are unable to take up the folinic acid from the environment and therefore only the host bone marrow cells are helped. Although no data exists in children undergoing HCT, caution should be taken with this approach as it has been associated with increased treatment failures in patients with HIV (Safrin et al. 1994). Although counterintuitive in a patient with poor T-cell function, TMP-SMX has been combined with a short course of corticosteroids, which appears to be beneficial in

preventing temporary worsening of hypoxemia due to inflammation from dying organisms. The recommended dose is 1 mg/kg/dose twice daily (maximum 40 mg twice daily) of prednisone (or the equivalent dose of methylprednisolone) tapered in half after 5 days and then again in another 5 days then discontinued after 21 days (Kaplan et al. 2009). It should be noted that this data derives solely from the adult HIV literature and it is unclear whether this approach is safe or beneficial in pediatric HCT patients.

6.4.2 Viral Infections

6.4.2.1 Cytomegalovirus

Historically, one of the most severe complications of allogeneic HCT was CMV reactivation in the bloodstream, which ultimately led to disease in the lungs (Fig. 6.3a), intestines, retinas, brain, and/or liver. On rare occasions, the blood will be negative for CMV by PCR, and further diagnostic interventions are required. BAL washings can be sent for both PCR and culture, as can tissue biopsies, which may show typical viral inclusion bodies (Fig. 6.3b). In the modern era, the use of PCR-based detection strategies has significantly reduced the incidence of CMV disease. Over 50 % of healthy adults in the United States are CMV seropositive, and the incidence increases with age, with 36 % of children age 6–11 years already exposed (Staras et al. 2006). With the use of CMV-negative blood products, the rate of de novo infection in CMV-seronegative donor/recipient (D-R-) pairs following HCT is as low as 2 % (Nichols et al. 2002). Thus, most infections occur as a result of reactivations, likely of host CMV, since infections are much less common in donor-positive, recipient-negative (D+R−) transplants than in those where the recipient is positive (D+R+ or D−R+) (Nichols et al. 2002). Other factors can alter the risk of reactivation in a CMV-seropositive HCT recipient. Following autologous HCT, CMV reactivations are not uncommon, but CMV disease is rare (Wingard et al. 1988), except in the setting of CD34 selection. T-cell depletion of donor cells in the allogeneic HCT setting is a major risk factor for reactivation, which may occur even prior to neutrophil engraftment (van Burik et al. 2007; Hertenstein et al. 1995). GVHD and its treatment with corticosteroids, and poor T-cell reconstitution even in the absence of GVHD, are all risk factors for CMV reactivation (Boeckh et al. 2003). Interestingly, even in the absence of

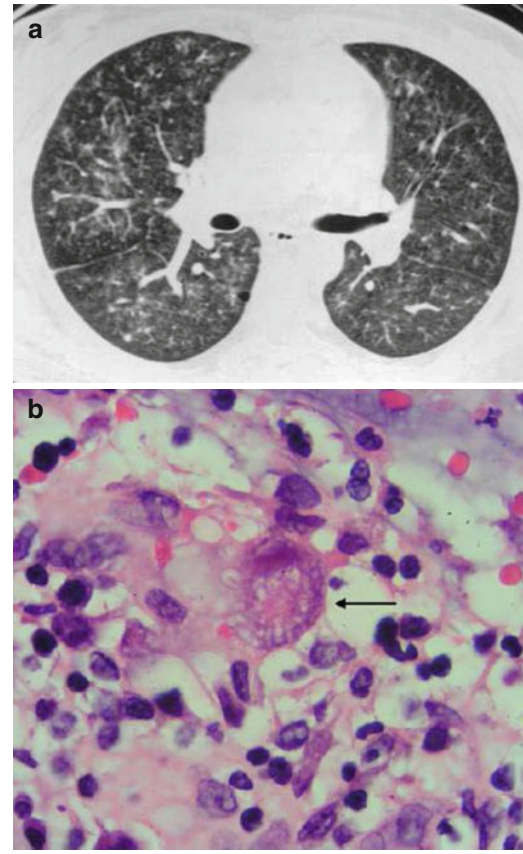

Fig. 6.3 (**a**) A patient with cytomegalovirus pneumonia after allogeneic hematopoietic cell transplantation. Thin-section CT scan demonstrates diffuse bilateral areas of ground-glass attenuation in a predominantly centrilobular distribution (With kind permission from Springer Science + Business Media: Franquet T (2004) Respiratory infection in the AIDS and immunocompromised patient. *European Radiology*, 14, E21–33, Figure 7) (**b**) Histology of cecum showing several enlarged cells with eosinophilic nuclear inclusion bodies typical of cytomegalovirus (*arrow*). Hematoxylin and eosin (With kind permission from Springer Science + Business Media: Yeh, Yu-Min (2009) Cytomegalovirus-related neutropenic enterocolitis with negative CMV antigenemia as the initial presentation in an acute myeloid leukemia patient. *Annals of Hematology*, 88, 279–80, Figure 1)

serotherapy, the choice of GVHD prophylaxis regimen may alter the risk of CMV reactivation. Sirolimus, an inhibitor of mTOR, appears to provide a protective effect against CMV when used in combination with tacrolimus and in place of other agents (Marty et al. 2007). It remains to be determined if this effect is due to direct inhibition of CMV viral replication from sirolimus or enhanced reconstitution of anti-CMV immunity (Marty et al. 2007). Overall, as many as 65 % of seropositive allogeneic HCT recipients will develop CMV reactivation if not given specific prophylaxis (Einsele et al. 2000).

Several agents have been used for CMV prophylaxis in at-risk patients (D-R- patients are typically excluded). Since acyclovir has some in vitro activity against CMV, high-dose acyclovir (500 mg/m^2/dose three times daily) has been shown to prevent CMV (Meyers et al. 1988). Due to its improved absorption, valacyclovir may be superior to high-dose acyclovir for the long-term prevention of CMV reactivation (Ljungman et al. 2002). Ganciclovir is the most commonly utilized CMV prophylactic agent (Tomblyn et al. 2009). Due to its marrow suppressive qualities, it is typically started after neutrophil engraftment (Boeckh et al. 1996; Winston et al. 1993), although some have suggested a role for a therapeutic window during the pre-HCT conditioning (Milano et al. 2011). In addition, ganciclovir use may partially inhibit recovery of both normal and CMV-specific T-cell function (Battiwalla et al. 2007). In patients at high risk for early CMV reactivation prior to neutrophil recovery, foscarnet has also been utilized due to its lack of significant marrow suppression (Bacigalupo et al. 1994). If prophylaxis is to be utilized, it is typically continued for 100 days post-HCT (Tomblyn et al. 2009), but longer courses may be indicated for patients with significantly impaired immune systems. All of these prophylactic strategies are generally used in combination with screening for reactivation by serum PCR (Tomblyn et al. 2009). An exciting potential new option, if the phase 2 results are confirmed, may be the utilization of an oral lipid formulation of cidofovir (CMX-001), which promises to have lower rates of renal and bone marrow toxicity than the parent compound (Marty et al. 2012). Not only could this potentially prevent CMV reactivation but might also lower rates of other double-stranded DNA viruses. Pediatric-specific testing of CMX-001 for this indication has yet to be performed.

Since all of the currently approved anti-CMV agents have some degree of toxicity, the alternate strategy to prophylaxis is preemptive treatment based on detection of CMV viremia. A randomized trial comparing prophylaxis versus preemptive management of CMV showed similar outcomes (Boeckh et al. 1996). Patients are screened at least once weekly for CMV DNA, and specific antiviral therapy is begun once a threshold amount of virus has been detected. Ganciclovir is the most common front-line agent utilized (Tomblyn et al. 2009), although foscarnet can be considered in patients with poor marrow reserve (Reusser et al. 2002). Even in patients with good marrow function, ganciclovir can cause neutropenia, and its use requires monitoring of neutrophil counts and often support with G-CSF (Tomblyn et al. 2009). Typically, ganciclovir is given twice daily for a minimum of 2 weeks or longer for patients whose viremia is still detectable after 2 weeks (Boeckh et al. 1996). Daily maintenance ganciclovir therapy has also been used in patients at high risk for a second reactivation due to poor immune recovery. The duration of maintenance therapy can vary from 4 weeks after first negative PCR or up to day 100. Oral valganciclovir has become more widely used for preemptive therapy, either as front line or to replace intravenous ganciclovir at the time of switching to maintenance therapy (Einsele et al. 2006).

Early in the treatment course, CMV viral loads may rise, but in antiviral-naïve patients, this is typically not a sign of resistance. However, continuing increases in viral loads after 2 weeks of therapy or signs of CMV disease should raise suspicion for a resistant strain of CMV. Mutations in the CMV UL97 phosphotransferase gene typically only cause resistance to ganciclovir, so that foscarnet and cidofovir remain alternative agents (Cesaro et al. 2005; Drew 2010). Mutations in the UL54 viral DNA polymerase will cause resistance to both ganciclovir and cidofovir and

occasionally foscarnet (Drew 2010). For the patient who appears to be failing or intolerant of all three drugs, leflunomide is a third-line alternative (Ehlert et al. 2006). Leflunomide is an immunomodulatory agent that inhibits pyrimidine synthesis and results in both antiproliferative and anti-inflammatory effects. The active metabolite appears to inhibit replication of both CMV and human polyomavirus type I (BK) virus.

The role of CMV-specific antibodies, either in conventional gamma globulin products or high-titer products, is of debatable efficacy. On the other hand, efforts to produce donor-derived CMV-specific T cells have shown great promise in treating CMV disease (Einsele et al. 2002). Given the low rates of GVHD associated with these cells, they may be an upcoming preventative strategy (Perruccio et al. 2005). Furthermore, the techniques that enable generation of CMV-specific T cells can also be utilized to generate T cells active against Epstein-Barr virus (EBV) and adenovirus (Hanley et al. 2009). These so-called trivirus-specific cells represent an exciting avenue of adoptive immunotherapy in severely immunocompromised post-HCT patients.

6.4.2.2 Epstein-Barr Virus

EBV infection following HCT usually results from the reactivation of latent EBV in either residual host B cells or passively transferred donor B cells. As with other herpes-family viruses, pre-HCT serologies can help to identify at-risk patients, but since approximately 95 % of adults are seropositive (Bertrand et al. 2010), virtually all patients undergoing adult unrelated donor HCT are potentially susceptible. Unlike other herpes-family viruses, there is no clearly effective antiviral agent against EBV, and thus, no post-HCT prophylaxis strategy exists. Fortunately, the rate of EBV reactivation in patients receiving T-replete grafts is quite low. Conversely, patients who receive ex vivo T-cell-depleted stem cells, anti-T-cell serotherapy, and umbilical cord blood (UCB) grafts have an elevated risk (Gerritsen et al. 1996). EBV reactivation can lead to the development of posttransplant lymphoproliferative disease (PTLD), signs and symptoms of which can include fever, lymphadenopathy, fulminate sepsis, or mass lesions in lymph nodes, spleen, or central nervous system. Several different histologic subtypes exist, and all generally occur within the first 3–6 months of the posttransplant period. The first step to be undertaken once an EBV infection is suspected is to reduce immunosuppression whenever possible (Styczynski et al. 2009). If that fails, since EBV proliferates primarily within B cells, administration of rituximab is often times successful at eliminating the infection (Wagner et al. 2004). Copy numbers of EBV in the blood can be easily monitored post-HCT by PCR, and routine monitoring of high-risk patients is recommended (Tomblyn et al. 2009). Less clear, however, is exactly what threshold level should be utilized for the initiation of preemptive therapy, since some patients will have transient self-limited EBV viremia post-HCT (Wagner et al. 2004). Nevertheless, evidence suggests that preemptive rituximab for treatment of EBV viremia is more effective than initiation once PTLD is established (Styczynski et al. 2009). Some groups have established methods for enriching for EBV-cytotoxic T-lymphocytes, which can both prevent and treat EBV PTLD in high-risk patients, with little risk for causing GVHD (Melenhorst et al. 2010). For centers without access to specific donor T cells, the fact that most donors are EBV seropositive allows the use of unmanipulated donor lymphocyte infusion, which is often effective, albeit with a high risk of inducing GVHD (Heslop et al. 1994; O'Reilly et al. 1997).

6.4.2.3 Human Herpesvirus 6

HHV-6 is an ubiquitous pathogen that has infected the majority of people by the age of 2 years, and has been reported to reactivate in approximately 50 % of HCT recipients according to PCR-based monitoring (Zerr et al. 2005). The majority of these episodes of viremia appear to be self-limited and asymptomatic, significantly limiting recommendations regarding preemptive therapy. However, a variety of reports have linked HHV-6 reactivations to post-HCT fevers, rashes, hepatitis, pneumonia, and delayed engraftment (Tomblyn et al. 2009). HHV-6 also appears to be a rare cause of post-HCT encephalitis, typically

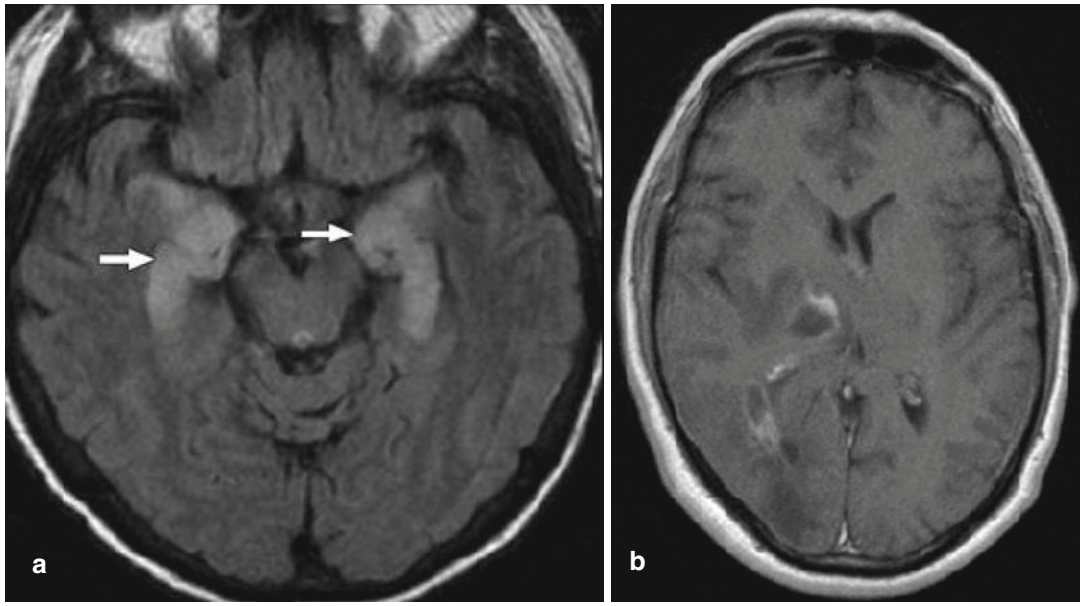

Fig. 6.4 (**a**) MRI of a patient with acute myelogenous leukemia after allogeneic hematopoietic cell transplantation. Axial FLAIR image shows bilateral limbic human herpesvirus 6 encephalitis with mesiotemporal (*arrows*) signal hyperintensities (With kind permission from the publisher. Sauter A, Ernemann U, Beck R et al (2009) Spectrum of imaging findings in immunocompromised patients with HHV-6 infection. *American Journal Roentgenology*, 193, W373–W380, Figure 4a) (**b**) MRI showing right thalamic lesion with patchy enhancement and considerable perilesional edema. Strands of abnormal tissue extend posteriorly, possibly along fibers of the internal capsule (Reproduced from: Yong, PFK, Post, FA, Gilmour, KC, et al (2008) Cerebral toxoplasmosis in a middle-aged man as first presentation of primary immunodeficiency due to a hypomorphic mutation in the CD40 ligand gene. *Journal of Clinical Pathology*, 61, 1220–1222, Copyright notice 2008, Figure 1)

manifested as memory loss, seizures, hyponatremia, cerebrospinal fluid (CSF) pleocytosis, and MRI abnormalities in the mesial temporal lobe (Fig. 6.4a) (Seeley et al. 2007; Gorniak et al. 2006). Patients manifesting these symptoms should have their CSF examined for HHV-6 by PCR. Recently, HHV-6 replication has been implicated in the initiation of GVHD (Pichereau et al. 2012). When HHV-6-associated disease is diagnosed, ganciclovir is typically the first-line agent utilized, although both foscarnet and cidofovir also have activity against HHV-6 (Zerr et al. 2002). If the HHV-6 viremia does not appear to be resolving with antiviral treatment, the possibility of chromosomally integrated virus must be considered (Jeulin et al. 2009). This can be determined by sending paired serum and whole blood PCRs and demonstrating that the copy numbers in the whole blood sample are relatively high, while the serum copy numbers are generally very low.

6.4.2.4 Adenovirus

A large number of serotypes of adenovirus have been implicated in causing human disease, and by the age of 5 years, most individuals will have been exposed to at least one serotype, thereby allowing latent virus to enter the system. Thereafter, reactivation during a period of intense immunosuppression results in the majority of cases of adenoviral viremia following HCT (Bruno et al. 2003). The major risk factor for adenoviral reactivation is the degree of immunosuppression experienced by the patient, especially among recipients of T-cell-depleted grafts or grafts from unrelated donors and those being treated for GVHD (Myers et al. 2005; Chakrabarti et al. 2002). Interestingly, for reasons that are not entirely clear, younger age also appears to be a risk factor (Bruno et al. 2003).

With the advent of PCR-based testing of blood and other body fluids, it has been demonstrated

that adenoviral reactivations occur in approximately 27–32 % of pediatric HCT recipients (Lion et al. 2003; Myers et al. 2005). Because of this high incidence, some centers have now adopted routine screening of blood by PCR for early detection of adenoviral reactivations in high-risk patients (Lion et al. 2003). When adenovirus viremia progresses to invasive disease, manifestations include pneumonia, hepatitis, enteritis, cystitis, and nephritis (Bruno et al. 2003). Adenoviral disease post-HCT has been associated with mortality rates as high as 78 % (Myers et al. 2005). The only currently available agent for treatment of adenoviral viremia or disease is intravenous cidofovir, typically given on a three times per week schedule (Hoffman et al. 2001). However, intravenous cidofovir has potentially significant toxicities to both the kidneys and bone marrow. This makes its use as a preemptive agent problematic, especially when some patients appear to spontaneously clear their viremia without treatment (Walls et al. 2005; Myers et al. 2005). An experimental oral liposomal formulation of cidofovir (CMX-001) may potentially be less toxic than the intravenous formulation and is currently being tested to determine if it can serve as a preemptive agent. Furthermore, since the major risk factor for the development of adenoviral infection is profound immunosuppression, rapid tapering or withdrawal of immunosuppression, whenever possible, may potentially play a role in the treatment (Chakrabarti et al. 2002). For patients who develop adenoviral infection after T-cell-depleted HCT, researchers are working on developing adenovirus-specific T cells for adoptive immunotherapy (Leen et al. 2009).

6.4.2.5 BK Virus

Human polyomavirus type I, commonly called BK virus (BKV), is a common asymptomatic infection in adults, 90 % of whom are seropositive (Knowles et al. 2003). Like other dsDNA viruses, it can reactivate during periods of intense immunosuppression, and between 50 and 80 % of HCT recipients will be found to shed BKV in their urine in the first several months post-HCT (Raval et al. 2011; Arthur et al. 1988). Much of the time, this viruria is asymptomatic, but BKV reactivation can be associated with the development of hemorrhagic cystitis (HC) in approximately 5–15 % of HCT recipients, typically 3–6 weeks following HCT (Bedi et al. 1995). The patients at highest risk for developing BKV-associated HC appear to be those who received cyclophosphamide-based conditioning regimens and T-cell-depleted grafts (Childs et al. 1998). Furthermore, BKV can also be found in the blood of some patients post-HCT, and high levels have been associated with the development of BKV-associated nephropathy (Haines et al. 2011), which can only be definitively diagnosed with a renal biopsy. Interestingly, fluoroquinolone antibiotics inhibit BKV replication in vitro, and some data suggest that their use as antibacterial prophylaxis post-HCT may also decrease rates of BKV-associated HC (Leung et al. 2005). Decreasing immunosuppression, whenever possible, is the first step towards treating BKV disease. If the BKV disease persists, cidofovir is the most commonly utilized antiviral agent, though leflunomide also appears to have some efficacy (Raval et al. 2011), and may potentially be better tolerated than cidofovir in patients with significant renal dysfunction.

6.4.3 Protozoa

6.4.3.1 *Toxoplasma gondii*

Since the majority of HCT programs have dietary counseling in place that eliminates most undercooked meat, toxoplasmosis post-HCT is generally caused by reactivation of previously acquired cysts. As such, serologic screening of HCT candidates can identify most patients at potential risk (excepting those with deficient antibody production) (Martino et al. 2005), although reports of transmission from white blood cells do exist (Jurges et al. 1992). In seropositive patients, PCP prophylaxis with TMP-SMX also provides excellent coverage against toxoplasmosis (Martino et al. 2005). Patients who cannot tolerate TMP-SMX need careful attention paid to the possibility of toxoplasmosis, as alternate PCP prophylaxis agents do not appear to provide

Table 6.2 Differential diagnosis of headache or mental status changes in a pediatric HCT patient

Infectious causes		Noninfectious causes
Bacteria	Rarely implicated	Hemorrhage
Fungal	*Aspergillus* spp.	Significant electrolyte imbalances
	Candida spp.	Pseudotumor cerebri
	Rare molds (e.g., mucormycosis)	Hypertensive crisis
Viral	CMV	Thrombotic microangiopathy
	HHV-6	Posterior reversible encephalopathy syndrome
	HSV	
	VZV	
	EBV PTLD	
Parasitic	Toxoplasmosis	

sufficient protection (Tomblyn et al. 2009). For these patients, clindamycin or pyrimethamine combinations can be used either as prophylaxis or as preemptive treatment based on PCR for reactivation (Tomblyn et al. 2009).

When toxoplasmosis occurs in a post-HCT patient, the general time frame is 2–6 months following HCT. Since the brain is the most commonly affected organ, fever plus focal neurologic signs, headaches, seizures, and/or altered mental status, are the typical symptoms that should prompt evaluation for toxoplasmosis and other causes (Table 6.2). Since brain MRI may not always show the characteristic ring-enhancing lesions (Fig. 6.4b), CSF confirmation should be obtained (Ionita et al. 2004).

6.4.3.2 *Strongyloides stercoralis*

Strongyloides stercoralis is endemic to the tropics and subtropics, including the southeastern United States. Transmission is usually via penetration of the larvae into exposed skin, from which it migrates into the intestines and possibly lungs. HCT candidates with intact immune systems may be asymptomatic or have only eosinophilia, and stool testing should be considered for anyone entering HCT with elevated eosinophil counts (Keiser and Nutman 2004). If positive, treatment with ivermectin is generally effective. Infected individuals may begin to show evidence of disseminated disease within 1–3 months following HCT. This can be manifested by diffuse pulmonary infiltrates, often with blood-tinged sputum, or colonic wall penetration, which leads to superinfection with Gram-negative enteric organisms.

6.4.3.3 *Cryptosporidium parvum* and *hominis*

Cryptosporidium spp. are enteric protozoa acquired from contaminated water supplies or livestock that infect intestinal epithelial cells. They cause seasonal transient non-bloody diarrhea and occasional systemic symptoms in healthy hosts, which is frequently mistaken for a viral gastroenteritis. In immunocompromised HCT recipients, however, cryptosporidiosis can cause a chronic severe diarrhea plus rare biliary tract disease. Multicenter incidence studies have never been performed, but based on one single-center prospective study, it may be as high as 4 % of all HCT recipients and 10 % of those with diarrhea (Legrand et al. 2011). Patients with B-cell deficiencies appear to be especially high risk (Legrand et al. 2011). In HCT recipients, the symptoms of a *Cryptosporidium* infection can easily be confused with that of intestinal GVHD, and testing for *Cryptosporidium* oocysts should be considered before initiation of additional immunosuppressants (Legrand et al. 2011). Therapy for *Cryptosporidium* is with paromomycin, azithromycin, or nitazoxanide. HCT recipients may need combination therapy, and decreases in systemic immunosuppression should be performed whenever possible (Legrand et al. 2011).

6.5 Phase III: Late Post-engraftment

Infections in phase III are generally caused by ongoing immunosuppressive therapy for the treatment of chronic GVHD (cGVHD), which also is

associated with a functional asplenia. As such, patients can develop infections with encapsulated bacteria and *P. jirovecii* and have ongoing problems with dsDNA viruses as well as community-acquired viral infections. There is also a second important peak of IA during this time.

6.5.1 Bacterial Infections

6.5.1.1 Encapsulated Organisms

Patients with cGVHD appear to have defects in their splenic function, and thus, encapsulated bacteria, such as *Streptococcus pneumoniae*, have been noted to cause significant mortality. Prophylaxis with penicillin appears to diminish this risk (Kulkarni et al. 2000), though the optimal duration of treatment is not yet defined. In patients with cGVHD, serum IgG levels should be monitored, and for patients with levels <400 mg/dL, administration of intravenous gamma globulin should be considered (Tomblyn et al. 2009).

6.5.1.2 Mycobacteria

Although less common than invasive fungal infections, infections with mycobacteria must always be considered in the differential diagnosis of pulmonary nodules following HCT. In developed countries, classic *Mycobacterium tuberculosis* infections are very rare in children undergoing HCT, although should always be considered in patients whose households have recently immigrated (Garces Ambrossi et al. 2005). More commonly encountered is environmental atypical nontuberculous mycobacterium (NTM), which can cause infections in the lungs, skin, lymph nodes, and bloodstream. Because of the relative rarity of NTM infections, there is a general paucity of literature in the HCT population. NTM infections have been reported to occur in as many as 9.7 % of T-cell depleted and 7 % of conventional allogeneic HCTs in adults, though the mortality rate was low (Weinstock et al. 2003). Pediatric HCT recipients have a somewhat lower rate of NTM infections (3.8 %), which occur at a median of 115 days (range 14–269 days) after HCT (Unal et al. 2006).

The exact risk factors associated with the development of NTM infections following allogeneic HCT are not well characterized. The protective immunity against NTM infections appears to be primarily driven by interferon (IFN)-γ production by T cells, as evidenced by the high rate of NTM infections in patients with IFN-γ deficiency (Haverkamp et al. 2006). Thus, T-cell depletion (ex vivo or with T-cell depleting antibodies) or treatment of GVHD with immunosuppressants that block IFN-γ might be expected to be risk factors for the development of NTM infections. Similarly, patients with an underlying T-cell immunodeficiency might be colonized with a NTM organism pre-HCT that puts them at risk for developing NTM disease following HCT. The optimal treatment of NTM infections is not clear. A wide variety of traditional antibiotics and anti-tuberculosis agents have some activity against NTM organisms, but reports vary on the number of agents that must be utilized in combination and the duration of optimal therapy. In patients with HIV, it is generally recommended to treat most cases of NTM infections for 12 months after establishment of negative cultures (Griffith et al. 2007). It is not clear that such a prolonged duration is required for HCT patients who, in the absence of cGVHD, tend to have improvement in, and even normalization of, their T-cell function over time.

6.5.2 Fungal Infections: Rare Fungi

Less frequently, infections occur with the agents of mucormycosis (*Mucor*, *Rhizopus*, and *Absidia* spp.), *Trichosporon* spp., *Fusarium* spp., and other saprophytic fungi (Marr et al. 2002). For these rare fungi, the key is to obtain culture identification, by biopsy if necessary, so that the optimal antifungal agent may be initiated. Posaconazole is a triazole with broad coverage of most fungi, including mucormycoses (Ashley et al. 2006), and as such may be the optimal treatment for many of these organisms, despite all of the caveats mentioned above regarding this agent. Recent work has demonstrated that *Mucorales*-specific T cells are generated following an infection

with this organism and thus might be useful as a diagnostic marker (Potenza et al. 2011), but also suggesting that generation of similar cells for treatment of *Mucorales* infections may one day be possible.

6.5.3 Viral Infections: Varicella-Zoster Virus

With the advent of routine vaccination against VZV at one year of age, the majority of immunocompetent patients entering HCT are seropositive for VZV. In the absence of prophylaxis, reactivations occur in approximately 30 % of patients following HCT (Boeckh et al. 2006). A double-blinded trial of acyclovir prophylaxis given for 1 year post-HCT demonstrated a significant reduction in VZV reactivations, although this duration of treatment was inadequate in patients who continued on immunosuppressive therapy for treatment of cGVHD (Boeckh et al. 2006). An unresolved question is whether pediatric HCT recipients who are VZV seropositive prior to HCT as a result of prior live-attenuated (LA) vaccination, rather than due to exposure to wild-type VZV, are at a high enough risk for reactivation to warrant long-term prophylaxis. Several case reports suggest that the LA-strain is capable of causing zoster and even disseminated disease in immunocompromised children (Chan et al. 2007; Levin et al. 2003). Therefore, until new data is available, the recommendation for acyclovir prophylaxis should be applied to all VZV-seropositive patients.

For post-HCT patients who are exposed to an individual with active wild-type VZV infection (including shingles) and who are not receiving prophylactic acyclovir or IVIG, passive immunization with varicella-zoster immune globulin should be initiated within 96 h of exposure (Tomblyn et al. 2009). There does not appear to be a significant rate of transmission of LA-vaccine strain VZV to immunocompromised individuals, and thus household contracts of HCT recipients are allowed to receive the vaccine, although optimally it should be given prior to the HCT whenever possible (Tomblyn et al. 2009).

According to the 2000 Center for Disease Control recommendations, patients who had received a HCT were instructed to not undergo vaccination with the LA strains of VZV, thereby placing previously naïve patients at long-term risk of developing a potentially serious infection. However, two reports have since demonstrated the safety and seroconversion rates of the LA-VZV vaccine when given to this patient population after first demonstrating of adequate T-cell immune reconstitution (Kussmaul et al. 2010; Chou et al. 2011).

6.6 Post-HCT Vaccinations

Although not "opportunistic" infections per se, it must be remembered that the performance of a HCT, especially from an allogeneic donor, involves the creation of a new immune system that lacks protective immunity to those vaccines received prior to the HCT. While some memory T and B cells may be passively transferred from the donor at the time of the cell infusion, the majority of the long-term immune system derives from newly generated naïve T and B cells. Therefore, all HCT recipients require revaccination following recovery of immune function. The major HCT and Infectious Disease groups, plus the Centers for Disease Control and Prevention, have published joint guidelines regarding the timing of vaccine administration (Tomblyn et al. 2009), but it has been argued that a "one-size-fits-all" approach, as utilized in generally healthy infants, is insufficient to produce protective immunity in many HCT recipients and that the vaccine schedule should be tailored to the individual kinetics of a patient's T- and B-cell recovery and followed by obtainment of titers to demonstrate adequate response (Small and Cowan 2011).

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7 Late Effects in Survivors After Hematopoietic Cell Transplantation in Childhood

K. Scott Baker, Anna Petryk, Vicki L. Fisher, Christine Duncan, and Paul A. Carpenter

Contents

K.S. Baker (✉) • P.A. Carpenter
Fred Hutchinson Cancer Research Center, Seattle, WA, USA
e-mail: ksbaker@fhcrc.org

A. Petryk
University of Minnesota, Pediatric Endocrinology, Minneapolis, MN, USA

V.L. Fisher
VLF Oncology & BMT Consultants, Medina, OH, USA

C. Duncan
Dana Farber Cancer Center, Boston, MA, USA

7.1 Introduction

Expansion of the number of indications for transplantation and improvements in the availability of appropriate alternative donor stem cell sources to patients with rare HLA types through the use of cord blood and haploidentical approaches is resulting in an ever-increasing number of hematopoietic cell transplants (HCT) performed annually in children. In conjunction with this, a reduction in the mortality secondary to relapse, infections, graft-versus-host disease (GVHD), and other acute transplant-related complications (Gooley et al. 2010) is leading to improved survival rates and thus an ever-increasing population of HCT survivors. Many of the late effects after HCT in childhood have been well described in the literature, but little is known about the specific pathophysiologic mechanisms that underlie their development, nor has there been much effort directed towards accounting for the cumulative impact of pre-transplant treatment exposures in addition to transplant exposures. It is hoped that the ongoing exploration of reduced-intensity conditioning regimens may, to an extent, mitigate the cumulative impact of the pre-transplant exposures. It will therefore be imperative that we continue to follow our HCT survivors on a long-term basis and continue research efforts to study long-term outcomes.

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7.1.1 Burden of Late Effects/Late Mortality

With longer and more coordinated follow-up of long-term survivors after HCT, we have discovered that in both the autologous and allogeneic transplant settings, HCT survivors experience mortality rates higher than the general population (Bhatia et al. 2005, 2007). One of the largest and most comprehensive studies of HCT survivors to date, the Bone Marrow Transplant Survivor Study (BMT-SS) (Bhatia et al. 2005, 2007), examined patients treated with HCT who were alive at least 2 years posttransplant and found that allogeneic HCT survivors had a 9.9-fold increased risk of premature death. Even 15 years after transplant, these patients continued to have mortality rates twice that of the general population (standardized mortality ratio = 2.2). While relapse of the primary disease and chronic GHVD were the leading causes of late mortality, 25 % of deaths were treatment related from causes that included second malignancies, late infections, cardiac, and pulmonary complications. Similar findings were recently published from the Seattle group where mortality rates in patients who survived for more than 5 years after HCT were four- to ninefold higher than the general population for at least 30 years after transplantation (Martin et al. 2010). In this analysis, second malignancies, late infections, cardiovascular or other vascular causes, and pulmonary complications were again the most frequent causes of mortality. This resulted in an absolute decrease in estimated residual life expectancy of 17.0 years for survivors at 20 years of age, to 6.4 years for survivors at 60 years of age, and a proportionate reduction in life expectancy of approximately 30 % regardless of attained age.

The most detailed analysis that has actually compared the risk of chronic health conditions between HCT survivors (from the BMT-SS), survivors who were treated with conventional chemotherapy (from CCSS), and a sibling control group was published recently (Armenian et al. 2011). Both groups had received their treatment during childhood and self-reported chronic conditions were graded with Common Terminology Criteria for Adverse Events (CTCAE) v3.0. HCT survivors were more likely to report severe/life-threatening conditions when compared to either siblings (relative risk [RR] 8.1, $p < 0.01$) or to CCSS survivors (RR 3.9, $p < 0.01$). Survivors after HCT were also more likely than CCSS survivors to report multiple adverse health conditions, functional impairments, and limitations in activity. In this study, recipients of unrelated donor HCT were at greatest risk.

7.2 System-Based Review

7.2.1 Cardiovascular

Late cardiovascular (CV) complications after HCT can be divided into three categories: (1) the development of heart failure most commonly attributed to exposure to anthracyclines; (2) structural abnormalities developing in valves, coronary arteries, or the conduction system from the direct impact of radiation exposure which can lead to a variety of different clinical outcomes; and (3) the premature development of conditions such as hypertension, diabetes, and hyperlipidemia that are known to increase the risk for CV-related events such as myocardial infarction, vascular disease, and stroke. As with many late effects, the risk for CV toxicities after HCT is cumulative, and one must account not only for pre-HCT treatment exposures but also the toxicity of chronic GVHD therapy, since most patients take at least 2 years to discontinue all immunosuppressive therapy (IST) after an initial diagnosis of chronic GVHD and 10 % require continued IST beyond 5 years (Stewart et al. 2004). Relevant pre-HCT exposures include cumulative doses of anthracyclines and exposure to radiation therapy that may have included the heart or mediastinum, as well as the transplant conditioning therapy. Anthracyclines impact the risk for cardiomyopathy in both a dose- and age-dependent manner, with the highest risk seen at doses ≥ 550 mg/m^2 in patients older than age 18 years and at doses ≥ 300 mg/m^2 in patients less than 18 years old at the time of treatment (Kremer et al. 2002a, b). However, higher risks are associated with anthracyclines combined

with exposure to radiation therapy. With HCT patients there is frequently the additional exposure to high-dose cyclophosphamide (CY), which has been described as a cause of acute cardiotoxicity, and to total-body irradiation (TBI). However, in practice, the CY/TBI regimen is one of the most commonly utilized, and the development of clinically evident cardiomyopathy is infrequent after HCT in patients who do not have significant pre-HCT exposure to cardiotoxic therapies.

A higher risk of CV mortality has been described in childhood cancer survivors, where the standardized mortality ratio for cardiac-related deaths was 8.2 (95 % CI: 6.4–10.4) among 5-year or longer survivors of childhood cancer and 3.8 (95 % CI: 1.5–7.6) for leukemia survivors (Mertens et al. 2001). As noted above, CV mortality is one of the leading causes of non-relapse mortality after HCT as well.

7.2.1.1 Metabolic Syndrome and Cardiovascular Risk

The metabolic syndrome (MS), comprised of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension, is associated with a substantially increased risk for type 2 diabetes mellitus and atherosclerotic cardiovascular disease (CVD) (Reusch 2002; Trevisan et al. 1998; Lakka et al. 2002). There is evidence to suggest that long-term childhood cancer survivors may be at high risk for premature development of characteristics associated with the metabolic syndrome (Nuver et al. 2002; Talvensaari and Knip 1997; Talvensaari et al. 1996). In one study, 23 long-term survivors (median age 20 years) who were 3–18 years after HCT for leukemia, 13 patients in remission from leukemia without HCT, and 23 healthy age-/sex-matched controls were evaluated for metabolic syndrome parameters. Hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, low HDL cholesterol, and abdominal obesity were more common among the HCT survivors than among the non-HCT group of leukemia patients or the healthy controls (Taskinen et al. 2000). Core signs of the metabolic syndrome were found in 39 % of HCT survivors versus 8 % of leukemia controls and 0 % of healthy controls. Fifty-two percent of HCT patients were found to have hyperinsulinemia, and 43 % had abnormal glucose metabolism, compared to none of the healthy controls ($p = 0.0002$ and 0.001, respectively). Variables associated with hyperinsulinemia in the HCT patients were time from transplantation ($p = 0.01$), presence of chronic GVHD ($p = 0.01$), and hypogonadism ($p = 0.04$). One pediatric study found that risk factors for later development of diabetes included a diagnosis of leukemia, non-Hispanic white ethnicity, family history of diabetes, and asparaginase toxicity (Hoffmeister et al. 2004). Another study in 34 children and adolescents after either autologous or allogeneic HCT compared to 21 age-/sex-matched controls found that the 18 patients who received TBI had a significantly higher first-phase insulin response and insulinemia/glycemia ratio on glucose tolerance testing as compared to patients who received only lymphoid radiation, no radiation, or controls (Lorini et al. 1995). These results suggest that TBI may play a role in the development of insulin resistance.

The BMT-SS evaluated selected CV risk factors and found that survivors of allogeneic HCT were 3.65 times (95 % CI: 1.82–7.32) more likely to report diabetes mellitus than siblings and 2.06 times (95 % CI: 1.39–3.04) more likely to report hypertension compared to siblings (Baker et al. 2007). Allogeneic HCT survivors were also more likely to develop hypertension (odds ratio (OR) = 2.31, 95 % CI: 1.45–3.67) than autologous recipients, and TBI exposure was associated with an increased risk of diabetes mellitus (OR = 3.42, 95 % CI: 1.55–7.52). This was a relatively young cohort (mean age at survey completion was 39.3 years); thus, the concern is that the higher risk of these outcomes at a relatively young age will lead to a higher than expected risk of premature heart disease (< age 55 years) and other CV events as these individuals mature. Long-term screening for the development of hypertension and diabetes mellitus, as well as screening for other CV risk factors such as lipid abnormalities and obesity, will be important for the long-term health of HCT survivors.

In ongoing studies of CV risk in survivors of HCT for hematologic malignancy (Baker et al. 2009), measures of insulin resistance, fasting glucose, insulin, lipids, anthropometry, blood pressure, and carotid artery compliance and distensibility were determined in 106 children and young adults (current mean age 26.6 years) who had received HCT for hematologic malignancy during childhood (mean age at HCT 9.9 years) and 72 healthy sibling controls. Sixty-two patients received TBI, 20 received cranial radiation prior to TBI (TBI + cranial radiation), and 24 received no TBI or cranial radiation (no XRT) before or during HCT. MS was present in 15/106 (14.2 %) HCT survivors and 4/72 (5.6 %) controls (OR 2.3, 95 % CI: 0.7–7.7, $p = 0.16$). However, two or more components of MS were present in 39/106 (37 %) survivors and only 10/72 (13.9 %) controls (OR, 2.7, 95 % CI: 1.2–5.9, $p = 0.015$). Compared to siblings, there were no differences between groups for glucose, body mass index (BMI), waist circumference, percent body fat, or blood pressure. However, HCT survivors who had undergone TBI or TBI + cranial radiation all had significantly higher total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and insulin. Those who received TBI + cranial radiation had significantly lower high-density lipoprotein (HDL) cholesterol and were also more insulin resistant. However, for the subjects who did not receive any radiation prior to or during HCT, there were no differences in any of the CV risk factors compared to controls. These findings are concerning and suggest that even at a relatively young age, and independent of obesity, survivors of HCT for childhood hematologic malignancies have increased CV risk factors which are associated with exposure to TBI +/− cranial radiation.

It remains unclear to what extent prolonged IST contributes to late morbidity or mortality by promoting components of MS in patients with chronic GVHD. However, improved survival and other benefits are observed in solid organ transplantation when key components of MS are addressed (Strippoli et al. 2004; Holdaas et al. 2003; Hingorani 2006). Because MS abnormalities may ultimately contribute to a higher risk of early CV morbidity and mortality, education, early screening, and management of modifiable CV and metabolic risk factors should be considered in HCT survivors (Majhail et al. 2009). It is helpful to consider each component of MS when developing a comprehensive management plan for patients with chronic GVHD. Management of diabetes in patients with chronic GVHD can be difficult, especially when caused or exacerbated by glucocorticoid therapy. Hyperlipidemia has been reported in 28–39 % of children as a late effect of HCT (Shalitin et al. 2006; Baker et al. 2007; Hoffmeister et al. 2004). HMG-CoA reductase inhibitors (statins) effectively reduce serum total cholesterol, are protective against premature cardiovascular disease, and improve survival in adults with a wide range of cholesterol levels whether or not they have a history of coronary artery disease (O'Rourke et al. 2004; Shepherd et al. 1995, 2002). Statins effectively lower serum lipid levels and have been associated with improved survival in solid organ transplant recipients (Holdaas et al. 2003; Hingorani 2006; Prasad et al. 2003). By extrapolation, it is reasonable to use statins to target lower LDL in HCT recipients when therapeutic lifestyle modifications are ineffective or not feasible. The lowest dose possible is used to minimize the potential for adverse drug interactions. Pleiotropic effects of statins may extend to improvement in renal function, hypertension, bone mineral density, reduced incidence of avascular necrosis, and even improved control of GVHD (Pritchett 2001; Tsiara et al. 2003; Fehr et al. 2004; Prasad et al. 2003; Wang et al. 2000) (for further discussion of hypertension, see Sect. 7.2.3).

7.2.2 Pulmonary

Please refer to Chap. 5 for a discussion of pulmonary complications after HCT.

7.2.3 Renal

Chronic kidney disease (CKD) is reported in up to 25 % of adults and children following HCT (Frisk et al. 2002; Kersting et al. 2007a; Abboud et al.

2009; Lawton et al. 1991; Van Why et al. 1991; Tarbell et al. 1990; Hingorani et al. 2007). A portion of these patients will progress to end-stage renal disease (ESRD) and are at increased risk for death compared to HCT patients who do not have ESRD (Butcher et al. 1999; Cohen et al. 1998; Thomas et al. 2004; Kist-van Holthe et al. 1998). CKD is most commonly detected 6 to 12 months following transplant but can develop as early as two months post-HCT (Hingorani 2006). Reported risk factors for the development of CKD include allogeneic transplant, conditioning regimen containing TBI or busulfan (Bu), acute or chronic GVHD, renal dysfunction in the early posttransplant period, and the use of calcineurin inhibitors (Abboud et al. 2009; Hingorani et al. 2007; Lawton et al. 1994).

7.2.3.1 Thrombotic Microangiopathy

Post-HCT thrombotic microangiopathy (TMA) has occurred in up to 21 % of patients after allogeneic or autologous HCT (Van Why et al. 1991; Changsirikulchai et al. 2009; Hingorani et al. 2007; Laskin et al. 2011). It is thought to result from endothelial damage and thrombus formation in the microcirculation, leukocyte adhesion, and increased vascular sheer stress (Fogo 2000; Ruggenenti et al. 2001). This is associated with platelet aggregation, consumptive thrombocytopenia, microangiopathic hemolytic anemia, and finally, ischemic organ injury (Changsirikulchai et al. 2009). Unlike in other settings, post-HCT TMA is not associated with von Willebrand factor or complement pathway abnormalities (Ruggenenti et al. 2001). Laboratory evidence of TMA includes the presence of schistocytes on routine blood smear, elevated serum lactate dehydrogenase (LDH), a greater than 50 % increase in baseline serum creatinine, and/or a 50 % or greater decrease in creatinine clearance without other identified etiology (Hingorani et al. 2007).

Thrombocytopenic purpura (TTP) is TMA presenting with extrarenal effects and typically presents in the early months after transplant with neurologic changes, bloody diarrhea, and fever. Hemolytic uremic syndrome (HUS) usually presents later than TTP and is present when TMA occurs with significant renal injury in the absence of significant extrarenal involvement, although patients can develop hypertension and seizure (Hingorani et al. 2007; Moake 2002; Ruggenenti et al. 2001). Risk factors for TTP and HUS include the use of calcineurin inhibitors or sirolimus, TBI, allogeneic HCT, sinusoidal obstruction syndrome, older age, and methylprednisone use (Hingorani et al. 2007; Fuge et al. 2001; Busca and Uderzo 2000; Uderzo et al. 2000; Ho et al. 2005; Cutler et al. 2005).

Despite multiple reported treatments for TMA, none is clearly efficacious. A first step is to discontinue potentially causative agents such as sirolimus or calcineurin inhibitors, which can be done with minimal risk assuming other appropriate IST can be provided (Choi et al. 2009). Therapeutic plasma exchange has been used successfully to treat TMA in non-HCT settings (Som et al. 2012; Clark 2012), but has not been reliably effective after HCT, and a 2005 consensus statement highlighted poor responses and unacceptable mortality rates based on the results of 11 studies (Roy et al. 2001; Ho et al. 2005; Sarkodee-Adoo et al. 2003; Fuge et al. 2001; Llamas et al. 1997). Anti-CD20 monoclonal antibody therapy with rituximab has been used in non-transplant TMA and to a lesser extent also for TMA after HCT (Marr et al. 2009; Carella et al. 2008; Au et al. 2007). Other reported therapies include HMG-CoA reductase inhibitors, antitumor necrosis factor (TNF) agents, allopurinol, and recombinant thrombomodulin (Batts and Lazarus 2007; Laskin et al. 2011; Sakai et al. 2010; Goldberg et al. 2010). The prognosis for patients with posttransplant TMA is guarded. TMA increases the risk of acute and chronic kidney disease resulting in heightened risk for ESRD and mortality (Kersting et al. 2007b; Laskin et al. 2011).

7.2.3.2 Nephrotic Syndrome

Rarely, adults and children with chronic GVHD have developed anasarca, hypoalbuminemia, and nephrotic range proteinuria (Lin et al. 2001; Markowitz et al. 2001). Transplant-associated nephrotic syndrome typically develops 8–14 months post-HCT in the setting of other system GVHD, often during recent periods of discontinuation of immunosuppression, and therefore is

thought to be a manifestation of GVHD (Akar et al. 2002; Rao 2005; Perrotta et al. 2005; Cruz et al. 1997; Hingorani et al. 2007; Hingorani 2006). Renal biopsy is advised, and the most common form of post-HCT nephrotic syndrome is membranous nephropathy that is thought to result from subepithelial deposition of antigen–antibody complexes (Rao 2005; Lin et al. 2001; Luo et al. 2011). Minimal change disease is the next most common pathology and is thought to be a T-cell-mediated entity (Rao 2005; Brukamp et al. 2006). Less frequently, renal histology has shown diffuse proliferative glomerulonephritis, antineutrophil cytoplasmic autoantibody (ANCA)-related glomerulonephritis, focal segmental glomerulosclerosis, and IgA nephropathy (Hingorani 2006; Chan et al. 2004; Oliveira et al. 1999; Suehiro et al. 2002; Nouri-Majelan et al. 2005). Treatment of nephrotic syndrome involves increasing the level of immunosuppression, typically with prednisone (Hingorani 2006; Reddy et al. 2006; Kim et al. 2010). Cyclosporine is also often included together with an angiotensin-converting enzyme inhibitor (ACEI), which helps reduce proteinuria that can be monitored serially and conveniently with spot urinary microalbuminuria to creatinine ratios. Prophylactic anticoagulation, particularly for membranous nephropathy, appears to be warranted on a case by case basis (Kamble et al. 2007).

7.2.3.3 Idiopathic Chronic Kidney Disease

Idiopathic chronic kidney disease (ICKD) occurs commonly after HCT and is diagnosed when the glomerular filtration rate (GFR) or creatinine is elevated at 6–12 months after HCT (Hingorani 2008). Its incidence has varied widely, 10–41 %, which is likely attributed to the broad definition (Hingorani 2008; Van Why et al. 1991; Lonnerholm et al. 1991; Kist-van Holthe et al. 1998; Gronroos et al. 2007; Berg and Bolme 1989). Risk factors include acute and chronic GVHD, acute renal failure and, after non-myeloablative regimens, the long-term use of calcineurin inhibitors and previous autologous HCT (Vincent et al. 2003; Hingorani 2006). It follows that calcineurin inhibitor serum trough levels are targeted to the low end of the normal range during chronic GVHD therapy. Although the role of hypertension in the development of ICKD is unclear, it is considered important to control blood pressure in patients with chronic GVHD on prednisone and a calcineurin inhibitor. Blockade of the renin–angiotensin axis using ACEIs alone or in combination with angiotensin II receptor blockers (ARBs) may be better therapy for hypertension in patients with ICKD than traditional long-acting calcium channel blockers based upon studies using ACEIs and ARBs in animal models of radiation-induced injury and on recent clinical experience (Vincent et al. 2003; Hingorani 2006). In addition to controlling blood pressure, ACEIs and ARBs may exert positive effects by reducing inflammation and inflammatory markers. In diabetics with albuminuria, treatment with ACEIs or ARBs slows the progression of CKD (Vincent et al. 2003; Hingorani 2006). Extrapolating from studies in the diabetic population raises the possibility that these agents might be beneficial after HCT where albuminuria was also recently found to be frequent (Strippoli et al. 2004). Controlled studies using ACEIs or ARBs to treat hypertension or microalbuminuria after HCT are needed.

Recommendations for screening post-HCT patients for renal dysfunction include blood pressure assessment at every clinic visit and laboratory assessment with BUN, creatinine, and urine protein at a minimum of every 6 months for the first year and annually thereafter (Majhail et al.). Patients at increased risk for renal dysfunction may be screened at more frequent intervals.

7.2.4 Gastrointestinal and Hepatic

Many of the late gastrointestinal complications of HCT are related to chronic GVHD. However, children may experience multiple gastrointestinal late effects not directly related to GVHD.

7.2.4.1 Esophageal, Gastric, and Intestinal Late Effects

Although less common in chronic GVHD relative to early after HCT, progressive dysphagia, with or without odynophagia, may signify chronic GVHD-associated esophageal erosions, strictures,

and web formation (McDonald et al. 1981, 1984; Minocha et al. 1997; Nakshabendi et al. 2000). However, some patients can develop esophageal stricture independent of chronic GVHD. In these situations, the stricture may be related to a history of severe mucositis, chronic gastroesophageal reflux, or viral infection. Repeated endoscopic dilatations by an experienced gastroenterologist may be required to allow for normal food intake. Topical glucocorticoid therapy can be helpful based upon results in analogous diseases (Aceves et al. 2007). Dysmotility associated with distal involvement of the esophagus may cause gastroesophageal reflux and is treated simultaneously with a proton pump inhibitor.

Children are at increased risk for squamous cell carcinoma of the esophagus following HCT (Borgmann et al. 2008; Gallagher and Forrest 2007; Yokota et al. 2012). Patients who had an allogeneic transplant, oral or esophageal GVHD, a history of human papilloma virus, or who were transplanted for Fanconi anemia are at heightened risk for esophageal cancers (Gallagher and Forrest 2007; Rosenberg et al. 2005; Atree et al. 1995).

Late stomach and intestinal complications of transplant are relatively uncommon after the first 100 days of transplant and are typically related to GVHD (Mielcarek et al. 2003). Other gastric and intestinal late effects are related to infections such as clostridium difficile, cytomegalovirus (CMV), adenovirus, giardia, and cryptosporidium (van Burik et al. 2001; Bobak et al. 2008; Neofytos et al. 2007; Sebastian et al. 2011). The classical "wasting syndrome" of untreated cGVHD is nowadays uncommon, and when gastrointestinal symptoms occur late after HCT, it is usually unclear whether these are due to cGVHD, infection, medication toxicity, or, infrequently, exocrine pancreatic insufficiency (Akpek et al. 2003). The temporal relationship of symptoms to the addition or tapering of IST could favor opportunistic infection or a flare of chronic GVHD, respectively. Common offending medications include high-dose oral magnesium supplements or mycophenolate mofetil. Antibiotic therapy may predispose to enteritis caused by *C. difficile* toxin, which should always be excluded by stool culture.

7.2.4.2 Hepatic Complications

Elevated serum transaminases, alkaline phosphatase, and bilirubin beyond 100 days after HCT are frequently due to chronic GVHD and often manifest during a taper of IST. When chronic GVHD is active at other sites, the diagnosis of liver GVHD involves excluding the toxic effects of triazole antifungal medications, calcineurin inhibitors, co-trimoxazole, or other hepatotoxic medications and biliary tract obstruction, or viral hepatitis with latent or transmitted hepatitis B or C, herpes family viruses, and possibly others. Iron overload may mimic an exacerbation of liver GVHD based on the observation that abnormal liver tests sometimes normalize after phlebotomy (see below) (Kamble et al. 2007). Liver biopsy is indicated when the diagnosis is unclear and chronic GVHD is not evident at other sites.

Iron overload is a relatively frequent hepatic complication before and after autologous or allogeneic HCT and is primarily related to red blood cell transfusions (Jastaniah et al. 2008; Chotsampancharoen et al. 2009; Lee et al. 2009; Altes et al. 2002; Majhail et al. 2008; Bae et al. 2012). The increased iron absorption that occurs in states of ineffective erythropoiesis, inflammation, and genetically inherited hemochromatosis may contribute to the problem (Majhail et al. 2008; Grigg and Bhathal 2001). Accumulation of tissue iron can lead to organ dysfunction; liver, heart, and endocrine tissue are the most commonly affected organs (Majhail et al. 2008). Serum ferritin is a sensitive screening test for iron overload, and elevated levels have been associated with increased transplant-related mortality (Altes et al. 2002; Pullarkat et al. 2008; Kim et al. 2008; Lee et al. 2009; Kanda et al. 2011). Clinically significant iron overload is rarely seen with ferritin levels below 1,000 ng/mL (Majhail et al. 2008), but because ferritin is not specific for iron overload, more accurate quantification of tissue iron should be considered when serum ferritin levels are greater than 1,000 ng/mL and the question of medical intervention is being addressed (Majhail et al. 2008; Armand et al. 2012; Armand et al. 2011). Liver biopsy is the traditional approach to measure tissue iron load; it may inform about other disease

processes like GVHD and infection and is the standard to which imaging studies are compared. The disadvantage is that liver biopsy involves risks of bleeding and infection (Olivieri and Brittenham 1997). Liver biopsy has been routinely replaced at some centers with noninvasive imaging, either superconducting quantum interference device susceptometry (SQUIDS) or T2* and R2 MRI scanning. SQUIDS uses the magnetic properties or iron and hemosiderin to estimate iron burden, and results correlate well with those of biopsy, but its availability remains limited (Brittenham and Badman 2003; Ali et al. 2012). T2* MRI is more readily available and also provides good correlation with liver biopsy (Wood et al. 2005; Carneiro et al. 2005; Rose et al. 2007). Iron burden greater than 7–15 mg per gram liver dry weight increases the risk of hepatic fibrosis and endocrine toxicity, whereas levels greater than 15 mg per gram are associated with cardiac disease and increased risk of death (Olivieri and Brittenham 1997). An elevated iron burden may also increase the risk for certain late infections such as mucormycosis and aspergillus in HCT patients (Gaziev et al. 1996; Kontoyiannis et al. 2007; Miceli et al. 2006).

The recommended screening for iron overload is a serum ferritin at 1 year after HCT in patients who received red blood cell transfusions. Biopsy or noninvasive imaging to quantify tissue iron is considered for those with significantly elevated ferritin levels (Majhail et al.). Treatment of iron overload with phlebotomy or chelation in long-term survivors is generally limited to those with a liver iron concentration greater than 7 mg per gram liver dry weight but can be done at lower levels when there is evidence of organ toxicity. Phlebotomy is effective and can be performed with minimal complications in patients with adequate vascular access and hemoglobin of at least 11.5 g%. Chelation with deferoxamine, deferiprone, or deferasirox is effective, although may be complicated by medication toxicities and issues of compliance.

Posttransplant transfusion-acquired viral hepatitis has declined over recent years with the increased safety of the blood supply in the USA and many other countries (Zou et al. 2012). In the USA, the risk of hepatitis C among all allogeneic blood donations is currently less than 1 per 1 million donations and that of hepatitis B is approximately 1 per 300,000 donations (Zou et al. 2012). Despite these safety improvements, patients remain at risk for viral infection and the complications associated with chronic infection. Long-term transplant survivors who have a history of hepatitis C infection, and who were typically asymptomatic during the early years of hepatitis C infection, have a higher rate of progression to cirrhosis than patients with hepatitis C who did not undergo HCT (Peffault de Latour et al. 2004; Strasser et al. 1999a; Strasser et al. 1999b). Therefore, regular monitoring of viral load by polymerase chain reaction (PCR) for patients with known hepatitis B or C is recommended, as well as consideration of liver biopsy 8–10 years post-HCT in those with chronic hepatitis C infection (Majhail et al.). Survivors of HCT who have chronic hepatitis C and B infection should also be screened for hepatocellular carcinoma annually starting at year 10 after transplant due to their increased risk for this complication (Ioannou et al. 2007).

Focal nodular hyperplasia (FNH) and nodular regenerating hyperplasia (NRH) are benign hepatic lesions that occur infrequently after transplant. NRH consists of multiple regenerative nodules, typically less than 10 mm in diameter, distributed throughout the liver and can cause portal hypertension, ascites, hepatomegaly, and hyperbilirubinemia (Sudour et al. 2009; Snover et al. 1989). FNH consists of confluent nodules greater than 10 mm in diameter associated with a central fibrous scar (Sudour et al. 2009). FNH is asymptomatic and is often identified as an incidental finding on imaging done for another clinical indication and does not require intervention (Cherqui et al. 1995; Mattison et al. 1987).

7.2.4.3 Pancreatic Complications

Pancreatitis and pancreatic insufficiency have been reported after HCT and may or may not be associated GVHD (Akpek et al. 2001; Jurges et al. 1991). Posttransplant pancreatitis is frequently viral or drug associated (Tomonari et al. 2006). Drugs used after transplant that can cause

pancreatitis in children are calcineurin inhibitors, glucocorticoids, trimethoprim-sulfamethoxazole, atovaquone, metronidazole, pentamidine, and acetaminophen (Versleijen et al. 2005; Sauleda et al. 1994; Bai et al. 2011). If the history suggests steatorrhea or carbohydrate intolerance and the diagnosis remains unclear, it is reasonable to screen for enzyme deficiency by examining the stool for reducing substances, fat microscopy, or formal collection to quantify fat. Due to the limited sensitivity of pancreatic screening tests, in milder cases a trial of pancreatic enzyme therapy is often reasonable and also diagnostic. Fat-soluble vitamin A, D, and E levels are low in severe cases, and replacement using water-soluble formulations may be necessary. Pancreatic insufficiency may be reversible after chronic GVHD has become inactive (Grigg et al. 2003).

7.2.4.4 Oral and Dental Complications

Disturbances in oral health may occur in children following HCT and include enamel hypoplasia, primary tooth retention, microdontia, hypodontia, tooth agenesis, root malformation, increased risk of caries, abnormal salivary function, and secondary oral cancers (van der Pas-van Voskuilen et al. 2009; Kaste et al. 2009). Regular oral examination and preemptive dental care are important elements to comprehensive transplant care. Children transplanted at less than 16 years of age are at risk for abnormal dental development with the risk being greater at lower ages at time of transplant (Uderzo et al. 1997). Chemotherapy and radiation damage tooth buds and cause jaw hypoplasia and can result in root abnormalities or agenesis, delayed dental eruption, and enamel hypoplasia (Holtta et al. 2005; Dahllof et al. 1994; Uderzo et al. 1997; Dahllof et al. 1988). Prospective studies of panoramic radiographs of children following transplant demonstrated significantly higher prevalence of tooth agenesis compared to normative data and common disturbances of dental root growth in the majority of pediatric patients, with the most significant abnormalities in patients less than 5 years at the time of HCT. Alteration of the craniofacial skeleton can result in hypoplastic jaw size and causes abnormal dental development (Dahllof 1998).

Salivary gland dysfunction and oral sicca syndrome due to GVHD, medications, chemotherapy, and/or radiation may result in mucosal injury, increased risk of dental caries, compromised quality of life, and decrease host responses to microbes (Bagesund et al. 2000b; Brand et al. 2009; Lin et al. 2008; van der Pas-van Voskuilen et al. 2009; Dahllof et al. 1997a; Dahllof et al. 1997b). Xerostomia due to conditioning often resolves in the early months after transplant but may be longer lasting (Jones et al. 1992). Chronic GVHD-associated salivary dysfunction develops in 75–85 % of patients with cGVHD and is due to lymphocyte-mediated attack on salivary duct and acinar tissues (Bagesund et al. 2000a); additional exam findings include mucosal erythema, oral atrophy, lichenoid changes, mucoceles, hyperkeratotic plaques, and oral sensitivity to foods and liquids previously tolerated (Nicolatou-Galitis et al. 2001; Treister et al. 2005; Balasubramaniam et al. 2009; Treister et al. 2008). Diminished and thickened saliva predisposes to recurrent infection, dental decay, and periodontitis. Pain avoidance may result in hesitancy to perform routine oral hygiene, restricted food choices, and suboptimal nutrition. Infection with herpes simplex virus, *Candida*, or other fungal and bacterial organisms may supervene and require treatment. Ancillary therapy for dry mouth might include sialogogues (in older children), frequent water drinking, oral moisturizers, and artificial saliva.

Squamous cell carcinoma and parotid gland cancers are frequent secondary solid tumors (Gallagher and Forrest 2007; Yokota et al. 2012), and risk factors for their development include oral acute and chronic GVHD, duration of GVHD therapy, and age at transplant (Demarosi et al. 2005a; Demarosi et al. 2005b; Curtis et al. 2005; Mawardi et al. 2011). Leukoplakia occurring > 2–3 years after HCT may be misdiagnosed as chronic GVHD and should periodically undergo biopsy to rule out malignant transformation. The "white lesion" of chronic GVHD usually resolves or softens after aggressive topical glucocorticoids but persistent or worsening leukoplakia does not. Due to the increased risk of caries and oral cancer, patients should practice good oral hygiene, and oral examination should

be done at one year and at least annually thereafter (Majhail et al.).

The opening diameter of the oral cavity should be monitored routinely for sclerosis of the perioral tissues, which mandates systemic immunosuppression with steroids, tacrolimus, azathioprine, cyclosporine, or ultraviolet therapy (Imanguli et al. 2006; Gurgan et al. 2012; Dignan et al. 2012) and stretching exercises to help to recover a functional orifice.

7.2.4.5 Ocular Late Effects

Posttransplant late effects in the eye include multiple ocular surface diseases, lens cataracts, and, less commonly, retinopathy; contributing etiologies include conditioning regimen and other pretransplant therapies, infection, and GVHD. Some form of ocular abnormality occurs in up to 50 % of children after HCT (Fahnehjelm et al. 2008; Suh et al. 1999).

Cataracts are one of the most common ocular late effects of transplant in children (Calissendorff and Bolme 1993; Frisk et al. 2000), and predisposing factors include cranial or total-body irradiation, chronic GVHD, corticosteroid therapy, and certain chemotherapeutic agents such as Bu (Aristei et al. 2002; van Kempen-Harteveld et al. 2000; Holmstrom et al. 2002; Hamon et al. 1993). The reported incidence of cataracts was up to 80 % when single-dose TBI was used but decreased when fractionated TBI became standard (Deeg et al. 1984; Bray et al. 1991; Suh et al. 1999); when the preparative regimen excludes radiation, the 12–20 % incidence of cataracts relates almost exclusively to glucocorticoid therapy (Benyunes et al. 1995; Deeg et al. 1998). The lag time from HCT to cataract formation is typically less than five years (Frisk et al. 2000; Suh et al. 1999; Dunn et al. 1993; Fahnehjelm et al. 2007). Cataract surgery is not required for all children who develop the complication. However, when surgery becomes necessary, it is preferably deferred until IST is discontinued, although it has been successful in patients receiving prednisone doses lower than 0.25 mg/kg. Surgery, when performed, is usually done 4 to 6 years from transplant and has excellent outcomes (Suh et al. 1999; Calissendorff and Bolme 1993).

Ocular surface diseases include dry eye syndrome (DES), blepharitis, infection, conjunctivitis, subconjunctival hemorrhage, corneal ulceration, keratitis, and keratoconjunctivitis sicca syndrome (KCS). DES is the most frequently reported ocular surface late effect in children, albeit less common than in adults, possibly due to more rapid regeneration of conjunctival epithelial cells in children compared to adults (Suh et al. 1999). Preverbal children may also be less likely to report symptoms of DES despite the fact that older children with tear abnormalities by fluorescein staining have few complaints of dry eye (Ng et al. 1999). Nonetheless, severe ocular GVHD can occur and lead to vision-threatening lesions including uveitis, corneal ulceration, and severe KCS. Severe KCS, or the presence of chronic GVHD in any other organ(s), mandates addition of systemic immunosuppression since untreated KCS may be associated with infection and irreversible corneal damage. Meticulous ocular hygiene, use of artificial tears, and follow-up with an ophthalmologist are essential. Potentially helpful ancillary and supportive care strategies include preservative-free artificial tears, long-acting lubricants, muscarinic agonists, cyclosporine, glucocorticoid, and even autologous serum eye drops. When tear production is markedly reduced, corneal wetting can often be improved by temporary plugging of nasolacrimal duct punctae. Severe KCS that is unresponsive to supportive care has been treated effectively with custom-fitted, fluid-ventilated, and gas-permeable scleral lenses that allow corneal resurfacing and have now been used in children below 13 years of age (Gungor et al. 2008).

Retinopathy is an uncommon posterior ocular segment complication associated with cranial radiation and TBI. It is less common with the use of fractionated TBI than when single-dose radiation is used. Other retinal complications include viral retinitis and bacterial corneal ulceration. The outcomes of patients with retinal complications tend to be worse than those with cataract or ocular surface diseases and may be associated with increased posttransplant mortality (Suh et al. 1999). Late retinitis is uncommon but should be considered in patients with chronic GVHD due to

infections caused by herpes zoster, *toxoplasma gondii*, and CMV, particularly in high-risk CMV seropositive patients after T-cell depletion or human leukocyte antigen-mismatched blood transplants (van Burik et al. 2007).

The overall prognosis for pediatric patients with ocular complications is good with appropriate medical and surgical therapy. Early diagnosis and intervention are important. Ophthalmologic examination is recommended three to six months after transplant and then annually thereafter (Majhail et al.).

7.2.5 Endocrine

7.2.5.1 Thyroid

The most common thyroid disorder after HCT is primary hypothyroidism, either subclinical (compensated) or overt. Other thyroid disorders, including central hypothyroidism, sick euthyroid syndrome, hyperthyroidism, thyroiditis, and thyroid nodules (both benign and malignant), are less common but can also occur after HCT (Afify et al. 2000; Sanders et al. 2009; Bailey et al. 2008; Berger et al. 2005; Ishiguro et al. 2004; Socie et al. 2000; Slatter et al. 2004; Kami et al. 2001; Tatevossian et al. 2004). Subclinical hypothyroidism (elevated thyroid-stimulating hormone (TSH) with a normal free thyroxine (T4)) is usually the first and most common manifestation of thyroid dysfunction, which may progress towards overt hypothyroidism (low free T4) if untreated or may be transient (Katsanis et al. 1990; Borgstrom and Bolme 1994; Thomas et al. 1993a).

The prevalence of hypothyroidism varies depending on the preparative regimen and other factors. TBI is a well-established risk factor due to high sensitivity of the thyroid gland to the effects of radiation, particularly in young patients (Boulad et al. 1995; Bailey et al. 2008; Ishiguro et al. 2004). The reported prevalence after a single-dose TBI is 21–73 % and after fractionated TBI 10–28 % (Bailey et al. 2008). Patients who received chemotherapy-only-based conditioning are also at risk for the development of hypothyroidism, although the incidence is lower than after TBI-based regimens, about 0–19 % (Bailey et al. 2008; Michel et al. 1997; Slatter et al. 2004). Regimens using only CY have a lower risk of thyroid dysfunction, whereas regimens containing Bu increase the risk (Sanders et al. 2009). Other factors that increase the risk of thyroid dysfunction are younger age (<10 years) at HCT, hematologic malignancy, particularly Hodgkin lymphoma, and HCT in second remission (Sanders et al. 2009; Ishiguro et al. 2004; Berger et al. 2005).

The mechanisms of hypothyroidism after HCT are not completely understood. While direct radiation to the thyroid gland in TBI-based regimens is clearly associated with hypothyroidism, thyroid dysfunction can also develop after chemotherapy-only conditioning. It has been proposed that viral infection or immune-mediated mechanisms may play a role, such as T-cell depletion, donor antibody transfer, or GVHD (Slatter et al. 2004; Marazuela and Steegman 2000; Lee et al. 2001). Consistent with the immune hypothesis is the observation that the risk of thyroid dysfunction is higher after unrelated donor marrow than after matched sibling HCT (Bailey et al. 2008). Both Hashimoto thyroiditis (Sanders et al. 2011; Slatter et al. 2004) and Graves' disease (Tolar et al. 2009) have been reported after HCT.

The interval between HCT and diagnosis of thyroid disease is 4 months to 28 years (Berger et al. 2005; Michel et al. 1997; Katsanis et al. 1990; Ishiguro et al. 2004; Bailey et al. 2008; Sanders et al. 2009). Although the latency period can be very long, the majority of patients develop hypothyroidism in the first 2 years after HCT, with the sick euthyroid syndrome being more likely during the first 6 months after HCT (Kami et al. 2001).

Thyroid tumors usually take longer to develop (a median of 10 years after HCT, range: 4.5–22 years) (Sanders et al. 2009; Cohen et al. 2001; Socie et al. 2000), occurring even 40 years after thymus irradiation (Shore et al. 1985). Although rare in absolute numbers, thyroid cancer is one of the most common second neoplasms after HCT along with brain cancer (Socie et al. 2000), with papillary thyroid cancer being more common than follicular thyroid cancer (Uderzo et al. 1994; Rovelli et al. 1997). The true incidence of thyroid cancer is difficult to determine because of the long latency period and inconsistent screening

practices. The reported prevalence range is between less than 1 % (Sanders et al. 2009; Socie et al. 2000) and 7 % when routine screening by thyroid ultrasonography is performed (Cohen et al. 2001). Importantly, in the latter study only one patient had a palpable nodule on physical examination. Some patients with thyroid cancer have been found to have abnormal thyroid function, but some have been euthyroid (Cohen et al. 2001; Sanders et al. 2009; Ishiguro et al. 2004). The vast majority of patients with thyroid tumors have a history of TBI or thoracoabdominal irradiation (TAI) (Ishiguro et al. 2004; Sanders et al. 2009). In children, a dose of radiation as low as 0.10 Gy has been associated with an increased risk of thyroid cancer (Ron et al. 1995; Socie et al. 2000).

Given the high incidence of thyroid disease after HCT, the recommended annual screening includes physical examination of thyroid, TSH and free T4 levels, thyroid antibodies if thyroid tests are abnormal, and thyroid ultrasound if thyroid nodule is palpated (Pulsipher et al. 2012), followed by surgical referral as needed. Annual screening by thyroid ultrasonography to identify thyroid nodules has been recommended by some authors, but has not been widely accepted as a standard of care (Cohen et al. 2001).

While there is agreement that patients with overt hypothyroidism should be treated with thyroid hormone replacement, treatment of patients with subclinical hypothyroidism remains controversial. The main rationale for treating these patients is to reduce the risk of thyroid cancer, although it has not been proven that an elevated TSH level actually increases the risk of thyroid cancer (Ishiguro et al. 2004; Cohen et al. 2001; Sanders 1991).

7.2.5.2 Puberty and Fertility

Hypogonadism is common after HCT (Sklar et al. 2001; Sanders 2008). In both boys and girls, hypergonadotropic hypogonadism (primary gonadal failure) is more common than hypogonadotropic hypogonadism (due to hypothalamic-pituitary dysfunction). In girls, ovarian failure is diagnosed by increased plasma follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH) concentrations. Ovarian failure is partial when plasma estradiol level is normal and complete when plasma estradiol is low (Laporte et al. 2011). In boys, seminiferous tubular dysfunction (tubular failure) is defined by an increased plasma FSH concentration, and Leydig cell failure by an increased plasma LH concentration, which can be partial when testosterone level is normal or complete when plasma testosterone concentration is low. Precocious puberty may also occur after HCT but is very rare (Frisk et al. 2004). In females, ovarian failure impairs both fertility and estradiol production. In males, however, fertility may be impaired, but testosterone production may be normal because testosterone production is independent of spermatogenesis.

The type of presentation depends on the pubertal status at the time of HCT. The earliest manifestation of impaired sex hormone production is delayed puberty in prepubertal patients, but older patients may show asynchronous or incomplete pubertal development, primary or secondary amenorrhea, and infertility due to azoospermia or premature menopause. Sex steroids are also required for the growth spurt during adolescence.

Delayed or incomplete puberty occurs in about 57 % of females and 53 % of males (Dvorak et al. 2011; Sanders et al. 2011; Sanders et al. 1985; Sanders 2008). The incidence varies depending on the conditioning regimen (16 % females and 14 % males after CY alone, 72 % females and 48 % males after Bu/CY, 57–71 % females and 58–81 % males after TBI depending on the dose).

Premature ovarian failure occurs in 65–84 % of females after HCT (Sanders et al. 1996; Salooja et al. 2001; Carter et al. 2006; Loren et al. 2011; Dvorak et al. 2011; Laporte et al. 2011). Risk factors include pubertal or postpubertal status at HCT, single-dose TBI, and Bu-/CY-based conditioning regimens. Ovaries are sensitive to gonadotoxic effects of chemotherapy and radiation. A dose as low as 4 Gy destroys about 50 % of oocytes (Mayer et al. 1999; Damewood and Grochow 1986). However, prepubertal patients are more resistant to gonadotoxic effects of CY and are more likely to retain or recover ovarian function (Leung et al. 2007). Young age at TBI and a fractionated protocol are also associated with increased ovarian recovery (Thibaud et al. 1998; Sanders et al. 1988), which

may take up to 7 years (Spinelli et al. 1994). However, probability of recovery is extraordinarily low or null in patients who received Bu/CY (Sanders et al. 1996; Michel et al. 1997; Afify et al. 2000). Pregnancy has been reported in women after HCT but much more commonly in those exposed to CY only (54 %) compared to Bu/CY (0 %) or TBI (1.3 %) (Sanders et al. 1996). Spontaneous abortion, preterm delivery, and low birth weight are more common than in the general population (Sanders et al. 1996).

Testicular failure occurs in 48–85 % males after HCT (Howell and Shalet 2005; Anserini et al. 2002; Sanders et al. 1996; Laporte et al. 2011; Sanders 2008). Younger age is somewhat protective in boys as well (Leung et al. 2007). Patients who are prepubertal at the time of HCT are at a lower risk of developing hypogonadism than older patients who are pubertal or postpubertal at the time of HCT. Those who were exposed to CY-only conditioning regimens are more likely to recover testicular function (24–90 %) than those exposed to Bu/CY (6.5–50 %) or TBI/TAI (1.3–17 %) (Sanders et al. 1996; Anserini et al. 2002). Recovery of spermatogenesis has been observed 1 year after HCT following CY but much later (4–9 years post-HCT) after regimens containing TBI/TAI (Anserini et al. 2002).

Germinal epithelium of the testis is more vulnerable to chemotherapy and radiation than Leydig cells (Michel et al. 1997; Sanders et al. 1996). Spermatogenesis can be impaired after 8 Gy, while Leydig cells are resistant to radiation dose up to 24 Gy (Mayer et al. 1999). Thus, even though spermatogenesis is frequently impaired (seminiferous tubular dysfunction), Leydig cell function and thus testosterone production may remain normal. Mildly elevated LH levels may also help to maintain normal production of testosterone in some patients (Mayer et al. 1999). These patients should continue to be monitored as testosterone levels may decline over time. Patients with seminiferous tubular dysfunction and germ cell damage can be expected to have lower testicular volume (Frisk et al. 2004; Mayer et al. 1999; Afify et al. 2000).

Pubertal stage should be assessed every 3–6 months until puberty and growth are completed. Annual laboratory screening should include estradiol, LH, and FSH starting at age 10 in females and testosterone, LH, and FSH starting at age 11 in males (Pulsipher et al. 2012). Inhibin B is also a useful marker of gonadal function and negatively correlates with FSH (Laporte et al. 2011). Anti-Müllerian hormone (AMH) is an indicator of the ovarian reserve, and its plasma level decreases as the number of follicles decreases with age. In boys, however, AMH is less useful because the plasma level decreases when testosterone increases at puberty. Semen analysis should be considered in males due to overall high incidence of azoospermia (Mayer et al. 1999). Ovarian failure should be treated with hormone replacement therapy. Boys with Leydig cell failure may require testosterone replacement. Methods of fertility preservation have been reviewed elsewhere (Dvorak et al. 2011).

7.2.5.3 Growth

Impaired linear growth after HCT is multifactorial in origin and can be due to growth hormone (GH) deficiency, hypothyroidism, hypogonadism, corticosteroid treatment as well as poor nutritional status, genetic factors, and metabolic status. Because of these confounding factors, the reported prevalence of growth impairment varies widely between studies (9–84 % of patients) (Huma et al. 1995; Giorgiani et al. 1995; Cohen et al. 1996; Sanders et al. 2005; Leung et al. 2007; Dvorak et al. 2008). On average, patients experience a loss of 0.9 to 2.1 standard deviation score (SDS) in height from the time of HCT to final height (Cohen et al. 1999; Sanders et al. 2005; Frisk et al. 2004; Clement-De Boers et al. 1996; Cohen et al. 1996). Previous cranial radiation therapy (CRT) and single-dose TBI result in most severe growth failure and have the most deleterious effect on the final height (Cohen et al. 1999; Bushhouse et al. 1989; Wingard et al. 1992; Brauner et al. 1997; Thomas et al. 1993b; Huma et al. 1995; Bozzola et al. 1993). Patients who received previous prophylactic CRT prior to HCT may manifest growth failure earlier, within 1 year after BMT, than patients who received chemotherapy and TBI alone (Bozzola et al. 1993; Giorgiani et al. 1995). The latter group may not manifest a decline in the rate of growth until the third year after HCT. Fractionated TBI and total lymphoid irradiation (TLI) can also reduce growth

velocity and final height, although the effect is less pronounced than after single-dose TBI (Bushhouse et al. 1989; Thomas et al. 1993b; Michel et al. 1997; Cohen et al. 1999). Growth failure associated with TBI may be due to direct radiation damage to the growth plates (Huma et al. 1995; Shalet et al. 1987; Probert and Parker 1975; Fletcher et al. 1994). Spinal growth may be preferentially affected, which is reflected in the sitting height SDS being lower than SDS for subischial leg length, which has been observed after both single fraction and fractioned TBI as early as 1 year after HCT (Thomas et al. 1993b; Shalet et al. 1987).

Growth failure after TBI may also be due to GH deficiency. The prevalence of GH deficiency after HCT ranges from 20 to 85 % (Sanders 2008; Brauner et al. 1997; Huma et al. 1995; Ogilvy-Stuart et al. 1992; Sanders et al. 2005; Leiper et al. 1987; Leung et al. 2007). Patients who received CRT prior to HCT are at greatest risk of GH deficiency (Huma et al. 1995), but TBI alone has also been associated with GH deficiency (Papadimitriou et al. 1991; Ogilvy-Stuart et al. 1992). GH deficiency has been diagnosed as early as 0.8 years and as late as 9.5 years after HCT (median of 1.3 years) (Sanders et al. 2005).

The impact of chemotherapy-only preparative regimens is less clear. Chemotherapy-only regimens usually do not adversely affect height (Afify et al. 2000; Giorgiani et al. 1995; Cohen et al. 1999; Cohen et al. 1996; Khoshniat et al. 2003; Shankar et al. 1996; Michel et al. 1997; Sanders et al. 2011), although there are rare reports of growth impairment and GH deficiency after Bu/CY (Wingard et al. 1992; Giorgiani et al. 1995; Manenti et al. 1989). In one study, growth in children who received Bu/CY was no better than in children treated by CY/TBI (Wingard et al. 1992). Patients who developed GH deficiency had higher plasma levels of Bu when compared with other children in one study (Giorgiani et al. 1995). Although Bu crosses the blood–brain barrier and can produce dose-related neurotoxicity, a direct causality between the dose of Bu and impaired GH secretion remains to be proven (Vassal et al. 1990; Khoshniat et al. 2003). Other risk factors include younger age at transplant (particularly <10 years), male sex, and chronic GVHD (Sanders et al. 2005; Cohen et al. 1999; Sanders et al. 1986; Brauner et al. 1993, 1997; Frisk et al. 2004).

Screening should include accurate measurement of height every 6–12 months until final height is achieved, as well as bone age X-ray and GH stimulation test if clinically indicated (Pulsipher et al. 2012). Insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3), which are frequently used as screening tests for GH deficiency, may not be reliable indicators of GH status after CRT (Brauner et al. 1997; Sklar et al. 1993). Patients who show growth deceleration should be referred to a pediatric endocrinologist for further management, which may include GH treatment.

Response to GH treatment has been variable (Thomas et al. 1993b; Papadimitriou et al. 1991; Brauner et al. 1997; Cohen et al. 1999). Some authors reported that patients who were treated with GH normalized their rate of growth, but did not exhibit catch-up growth (Thomas et al. 1993b; Brauner et al. 1997; Papadimitriou et al. 1991). However, differences in dosing regimens, monitoring practices, and duration of GH treatment make the interpretation of the effectiveness of GH treatment difficult. In a more contemporary study that included HCT survivors who did or did not receive GH (based on parental preference or treating endocrinologist's recommendation), GH treatment was associated with significantly improved final height (Sanders et al. 2005). Children who were treated with GH gained on average 0.9 standard deviation (SD) in height compared with untreated children. The effectiveness of GH treatment was inversely associated with patient age at the time of GH treatment and positively associated with the duration of treatment. Younger patients (<10 years) responded better to GH treatment than older patients, and females responded better than males, particularly if the indication for HCT was other than acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma (NHL). Interestingly, history of CRT did not have significant impact on the response to GH therapy. A beneficial effect of GH treatment on both short-term growth (Huma et al. 1995) and growth up to final height (Frisk et al. 2004) has also been reported by other authors.

Among 42 patients who received GH in one study, none developed recurrent leukemia (Sanders et al. 2005). The incidence of diabetes or second malignancy was not statistically different between those who were or were not treated with GH. However, the incidence of hypothyroidism and osteochondroma/exostosis was higher among GH-treated patients (Sanders et al. 2005).

7.2.5.4 Bone Health

Compared to other endocrine late effects after HCT, the impact of HCT on bone health in pediatric patients has been relatively understudied. The most common mode of evaluation of bone mineral density (BMD) is dual-energy X-ray absorptiometry (DXA) due to widely accessible normative data, low radiation exposure, and ease of administration. BMD is expressed as a *Z*-score in children and adolescents (ages 5–19 years) (Baim et al. 2008). *Z*-scores reflect the standard deviation from the mean with scores between −2 and +2 corresponding to the 5th to the 95th percentile and are matched for age, gender, and ethnicity (World Health Organization 1994; Kanis et al. 2008). The current recommendation of the International Society for Clinical Densitometry (www.iscd.org) is to avoid the terms osteopenia and osteoporosis in children but rather consider an areal BMD *Z*-score > −2 as normal and a *Z*-score > −2 as "low BMD," unless low BMD is accompanied by a history of fractures, in which case it may be referred to as osteoporosis (Gordon et al. 2008; Baim et al. 2008). Clinically significant fractures include a long-bone fracture of the lower extremities, vertebral compression fracture, or two or more long-bone fractures of the upper extremities.

While DXA has been used extensively in children, it is limited by its two-dimensional nature since the measurement is based on the mineral content per area of the image (g/cm^2) and does not take bone size into account. Thus, areal BMD tends to underestimate true volumetric BMD in short patients (Cummings et al. 2002; Kanis et al. 2008). This is particularly relevant to children who received HCT because they tend to be shorter than the general pediatric population. Quantitative computed tomography (QCT) allows measurement of trabecular and cortical volumetric BMD, providing more specific information about the bone geometry, but it is associated with higher doses of ionizing radiation than DXA.

Several studies have demonstrated that significant bone loss occurs during childhood and adolescence as early as 6 months after HCT (Carpenter et al. 2007; Prasad et al. 2008; Nysom et al. 2000; Daniels et al. 2003; Kaste et al. 2004; Perkins et al. 2007; Petryk et al. 2006) and that bone deficits can persist into adulthood (Frisk et al. 2011; Mostoufi-Moab et al. 2011; Ruble et al. 2010). Most studies were based on DXA except for two studies, which used QCT (Mostoufi-Moab et al. 2011; Kaste et al. 2004). Only one of these studies was prospective (Petryk et al. 2006), and the others were cross sectional. The reported bone deficits in children after HCT are usually mild, although the range is quite broad (mean total-body or lumbar BMD *Z*-score of about −1.0, range −5.2 to +2.3). The proportion of HCT recipients with BMD *Z*-scores between −1 and −2 (18–33 %) and even below −2 (6–21 %) is higher than in the general population (Perkins et al. 2007; Petryk et al. 2006; Kaste et al. 2004). It is important to note that long-term impact of below average BMD *Z*-score may be significant due to the fact that childhood and adolescence are critical periods for establishing adequate bone mass for the rest of the adult life. A recent study that utilized peripheral QCT scans demonstrated significant deficits in trabecular and cortical bone 3–16 years after pediatric HCT (Mostoufi-Moab et al. 2011). Notably, 8 out of 55 patients (15 %) in this study experienced fractures after HCT. Similarly, a high prevalence (20 %) of vertebral compression fractures was observed among survivors of pediatric HCT (Taskinen et al. 2007). Another study that included long-term survivors demonstrated a low bone mass in 33 % of survivors at a median of 18 years after HCT, consistent with at least doubling of the risk of fracture in one-third of HCT patients (Marshall et al. 1996; Frisk et al. 2011).

The cited risk factors for bone loss after HCT are numerous, including physical inactivity, Caucasian or Asian race, family history, young age, female sex, smoking, alcohol use, poor nutritional status, inadequate intake of calcium and/or vitamin D, TBI, previous CRT, the malignancy itself, corticosteroids, cyclosporine, granulocyte

colony-stimulating factor (G-CSF), growth hormone deficiency, hypogonadism, hypothyroidism or hyperthyroidism, GVHD or its treatment, direct effects of conditioning regimens on bone marrow stromal cells, cytokine release after HCT, and reduced production of growth factors (Weilbaecher 2000; Rodgers and Monroe 2007; McClune et al. 2011; Schulte and Beelen 2004; Schimmer et al. 2000; Banfi et al. 2001; Castaneda et al. 1997; Lee et al. 2004; Baker et al. 2004; Stern et al. 2001; Ebeling et al. 1999; Atkinson et al. 1998; Frisk et al. 2011; Taskinen et al. 2006; Mostoufi-Moab et al. 2011). TBI can reduce BMD by its association with hypogonadism and GH deficiency. In addition, myeloablative therapy can directly damage osteoprogenitor cells within the bone marrow stroma, independent of secondary effects on gonadal function and GH secretion (Baek et al. 2004; Galotto et al. 1999; Banfi et al. 2001). Since bone marrow stromal cells are of recipient origin, the ability to regenerate the osteoblastic compartment largely determines the recovery of bone formation post-HCT (Lee et al. 2002).

Studies in adult HCT recipients demonstrated that bone loss is due to a decrease in bone formation and an increase in bone resorption (Valimaki et al. 1999; Carlson et al. 1994; Lee et al. 2004; Baek et al. 2004; Kang et al. 2000). It is currently unknown whether similar changes in bone turnover occur in children after HCT as well because of paucity of prospective studies. Based on the levels of one marker, bone-specific alkaline phosphatase, it appears that bone formation may be similarly reduced in children (Petryk et al. 2006).

The recommendations for screening and follow-up are based on a general knowledge of risk factors and include annual monitoring of growth, thyroid, and pubertal development and DXA scan pre-HCT, 1 year after HCT, then once a year if BMD *Z*-score <-1 or every 5 years if BMD *Z*-score is normal (McClune et al. 2011; Wasilewski-Masker et al. 2008; Pulsipher et al. 2012; Bishop et al. 2008). Patients with a significant bone loss (BMD *Z*-score <-2), history of fractures, or endocrine deficiencies should be referred to a pediatric endocrinologist.

Hormonal deficiencies should be corrected if deemed appropriate based on age and the risk-to-benefit ratio. It is also recommended to provide adequate calcium and vitamin D supplementation, to encourage weight-bearing exercise, and to counsel about adverse effects of cigarette smoking, alcohol, and caffeine consumption. Although bisphosphonates can prevent bone loss after HCT in adult patients (Kananen et al. 2005; Grigg et al. 2006; Chae et al. 2009), their use in the pediatric HCT population has been limited. Although it is not known at present if bone resorption is increased in children after HCT, one retrospective study has shown that bisphosphonate therapy can improve BMD in pediatric HCT recipients as well (Carpenter et al. 2007). Prospective studies are needed to determine if the use of bisphosphonates can be recommended as a routine measure in children who received HCT and who either have low BMD or are at increased risk for continued bone loss. Potential concerns about the use of bisphosphonates in children should be taken into account when making treatment decisions (Ward et al. 2009).

7.2.5.5 Muscle and Joint Complications (Chronic GVHD Perspective)

Proximal myopathy after HCT is most frequently a complication of glucocorticoid therapy. Posttransplant fatigue contributes to inactivity that exacerbates muscle atrophy. Therefore, in addition to minimizing prolonged high-dose daily steroid therapy, it is important to encourage and gradually increase the level of physical activity to counter this vicious cycle. Less than 1 % of patients with chronic GVHD develop an inflammatory myopathy that resembles idiopathic polymyositis with regard to histology, electromyography, and response to immunosuppressive therapy (Stevens et al. 2003). Elevation of creatine phosphokinase, aldolase, and aspartate aminotransferase (AST) is common, and autoantibodies may be present.

Skeletal muscle cramps, sometimes with severe carpopedal spasms that disrupt sleep and may impair fine motor function, are not uncommon in patients with chronic GVHD. Their etiology is obscure. Cramps often manifest during the taper of glucocorticoids. It is useful to remember that secondary adrenal insufficiency may be present in this manner. Conventional muscle relaxants and analgesics are usually ineffective for severe cramping. Baseline interventions include good

hydration, correction of electrolyte imbalances (e.g., hypomagnesemia), and regular stretching. Anecdotal experience with titrated doses of clonazepam and baclofen can be moderately successful for this sometimes very bothersome problem.

Chronic GVHD involvement of fascia and tendons is initially associated with edema and an eosinophilic infiltrate, with later progression to fibrosis and joint contractures most commonly in wrists, fingers, ankles, shoulders, and elbows. Regular survey of the range of motion at all target joints is necessary to detect early and potentially reversible limitation of movement. Aggressive IST is necessary to prevent progression of contractures but is not usually effective at reversing established contractures, which are also not amenable to surgical release. Stretching exercises and deep myofascial massage are important to help improve range of motion of affected joints and restore functions of daily living (Couriel et al. 2006).

7.2.5.6 Avascular Necrosis

Avascular necrosis (AVN) develops in 4 % to 10 % of survivors at a median of 12 months (range 2 to 132 months) after allogeneic HCT and is suspected when pain persists or progresses at a typically affected joint in a patient at risk. The hip is most frequently affected, but multiple and bilateral joint involvement occurs and is more severe in glucocorticoid-associated AVN compared to idiopathic AVN (Tofferi and Gilliland 2006). MRI imaging offers high sensitivity and specificity for detecting early lesions of AVN and forms the basis of radiological staging. Early, and often asymptomatic, Stage I lesions (abnormal MRI or bone scan, normal radiograph or CT scan) and symptomatic Stage II (diagnostic MRI abnormalities and abnormal radiographs) are potentially reversible and more treatable stages of hip AVN. Stage III–VI lesions show varying degrees of femoral head collapse and even secondary osteoarthritis (Arlet 1992).

The exact pathogenesis of AVN is poorly understood, but the final common pathway is bone ischemia due to any combination of factors that include obliterative arteritis, thrombophilia, hyperlipidemia and fat embolism, repeated microfractures of weight-bearing bone, and increased intramedullary pressure that is possibly secondary to increased intramedullary fat (reviewed (Fink et al. 1998)). Glucocorticoid therapy increases intramedullary fat content and was the factor most associated with increased risk for developing AVN among adult long-term survivors of HCT at Fred Hutchinson Cancer Research Center, but increased duration of steroid use did not provide additional risk (Koc et al. 2002). Alternate-day prednisone therapy combined with cyclosporine for chronic GVHD was less likely to result in AVN than alternate-day prednisone alone suggesting that steroid-sparing approaches may be helpful (Pritchett 2001). Other factors include age older than 16 years and a diagnosis of aplastic anemia or acute leukemia (Tofferi and Gilliland 2006).

Treatment for AVN includes a variety of interventions and tends to follow a graduated approach calibrated to the severity of symptoms and radiological staging. Pain relief is sometimes difficult to achieve, often prompting referral to experts in pain management. Unfortunately, at least 50 % of patients need surgery within 3 years of diagnosis (Tofferi and Gilliland 2006; Fink et al. 1998), and this has prompted interest in the use of bisphosphonates and statins for prevention and treatment of early AVN (Pritchett 2001; Lai et al. 2005; Ramachandran et al. 2007; Agarwala et al. 2005; Castro and Barrack 2000). Early referral to an orthopedic surgeon with experience in allograft-related AVN is recommended so that the timing and outcome of the various surgeries is optimized.

In children and young adults, a major goal is to avoid early replacement with artificial joints that have a finite life span. An initial temporizing procedure is core decompression (CD), which attempts to relieve the intramedullary compartment syndrome by opening the area of the dead bone, restoring blood circulation and relieving pain. CD is a well-tolerated, short-stay procedure that provides excellent and immediate pain relief in 50 %–80 % with Stage I and 20 %–35 % with Stage II AVN (Mont et al. 1996; Stulberg et al. 1991). Two small randomized studies confirmed that CD provided better pain relief than nonoperative therapy for early stage AVN (Koo et al. 1995; Palmas et al. 1998; Stulberg et al. 1991). CD does not alter the progression of AVN in Stage II hips and is not appropriate for advanced stage AVN.

Most patients with advanced AVN eventually require total joint arthroplasty that can provide excellent pain relief for many years. A less invasive procedure for patients with superficial damage to joint surfaces is partial or total hip resurfacing, which caps the head of the femur with a metal shell and lines the acetabulum, if necessary, with a congruent metal cup (total resurfacing). Hip resurfacing preserves the femoral head and neck, which is especially attractive for young, active patients who are likely to require more than one total joint arthroplasty during their lifetime.

7.2.5.7 Neurocognitive Issues

Treatment-related long-term neurocognitive complications occur frequently after chemotherapy and/or irradiation in non-transplant patients. The intensive conditioning regimen, frequently including TBI, and immunosuppression contribute to an increase in the HCT patient's risk for neurological complications. Declines in neurocognitive function are often seen in the pediatric HCT recipient (Campbell and Moravec 2008), although the incidence of neurocognitive disabilities varies and is dependent on previous chemotherapy (systemic and intrathecal), cranial radiation, and age at the time of HCT (Shah et al. 2008). Shah and colleagues studied neurocognitive function in pediatric patients with hematologic malignancies before HCT and at 1, 3, and 5 years after HCT. All patients received therapy to the central nervous system (CNS). Patients were compared with healthy sibling donors who showed no significant decreases in cognitive function before HCT except in academic accomplishments. Those most affected were patients who received cranial irradiation prior to HCT or when included in the HCT conditioning regimens (Shah et al. 2008).

Cognitive impairment is an area of significant concern to survivors, and the ability to learn and perform at the previous level of cognitive functioning is an important objective after HCT. Many studies identify memory and attention disorders as the most prevalent and lingering impairments affecting adult survivors as determined by neuropsychological testing. However, the cognitive impairments described in both allogeneic and autologous survivors can show improvement over time (Syrjala et al. 2004; Jacobs et al. 2007). TBI, female sex, prolonged immunosuppressive therapy, HCT under the age of 3 years, and pre-transplant cranial irradiation are factors associated with highest risk of cognitive deficit. Better global health scores and profiles documenting fewer physical symptoms are associated with fewer deficits in neuropsychological performance (Harder et al. 2007).

Children are vulnerable to the effects of radiation and chemotherapy, and following HCT, age appears to be the most significant factor determining cognitive outcomes (Phipps et al. 2000). Although Phipps and colleagues concluded that most children undergoing HCT did not have significant cognitive deficit, children under the age of 3 were at risk and displayed deficits, as were children who had received prior cranial irradiation, particularly when they later received additional CNS radiation dose from TBI (Rourke and Kazak 2005). Kramer and colleagues reported a major decline in cognitive function 1 year post-HCT, but then no significant decline at 3-year follow-up. Pre-HCT IQ was the most significant predictor of post-BMT functioning. There was no impact detected based on the difference in age, TBI- or Bu-containing regimens, or other treatment- or diagnosis-related factors (Kramer et al. 1997). Barrera found no decline in cognitive functioning, but that children evaluated 1 and 2 years post-HCT had problems with academic functioning, especially in math (Barrera et al. 2008). In several studies, socioeconomic status and pre-HCT full-scale intelligence quotient (IQ) measures correlated strongly with post-HCT outcomes.

Patients should be counseled that cognitive impairment may be noted during and in the few months following treatment but that the majority of patients can also show improvement by about one year after HCT. Children should undergo careful assessment of cognitive functioning, and the school should be alerted to other confounding issues, such as hearing loss, that might further compromise the child's function. Neuropsychological testing, individual educational plans (IEP) and a program of training to assist in development of cognitive strategies, and behavior adjustments to lessen the impact of lingering deficits may contribute to improved performance and the individual's awareness of improvement (Poppelreuter et al. 2008).

7.3 Quality of Life

Quality of life (QOL) has emerged as an important outcome variable in evaluating the benefits and hurdles of cancer treatment. The increasing body of QOL literature supports the view that this is a critical and valuable outcome measure following aggressive therapy where the potential for long-term complications is high. Despite the short- and long-term physical toxicities of HCT on the patient, overall their QOL has generally been reported to be very good. Childhood cancer survivors have been compared with their close-in-age siblings in cognitive, educational, psychosocial, and QOL outcomes with variable results. In one study, 46 patients after HCT were compared to 33 siblings and found that, except for some deficits in educational outcomes and physical QOL, survivors' cognitive and psychological outcomes 2 years after HCT were similar to those of their siblings (Barrera and Atenafu 2008). Many patients may already have impaired QOL when then begin the HCT process, become further impaired during the early transplant phase and then show improvement thereafter, typically back to population normative values (Clarke et al. 2008). Although there is very limited long-term follow-up data, at least one study found that adult survivors of HCT in childhood reported their QOL to be inferior to that of age-matched norms (Lof et al. 2009). Additionally, many long-term survivors report functional limitations that can prevent them from being able to work or attend school, and these issues may have an ongoing negative impact on QOL (Ness et al. 2005).

Health-related QOL issues involving physical and neurocognitive function were recently reviewed by Parsons et al. as a result of the National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI)/Pediatric Blood and Marrow Transplant Consortium (PBMTC) First International Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation in 2011. The pediatric QOL data lags behind the adult data primarily due to limited validated tools for assessment, small numbers of affected patients, and reluctance for assessing QOL in this population over traditional transplant endpoints such as transplant-related toxicity and mortality (Parsons et al. 2012). An additional group of patients that require investigation are children who undergo HCT for non-malignant diseases as there is minimal data on them. Depending on the disorder, many of these children may have substantial limitations secondary to their underlying disease that have impacted their QOL prior to, as well as after, HCT.

Although survivors of pediatric HCT may have a complex array of late effects compared to non-transplant childhood cancer survivors, overall they experience a good quality of life. Unfortunately, there are limited data extending beyond the initial few years post-HCT; thus the full impact on QOL as the child HCT survivor becomes an adult is yet unknown.

7.4 Secondary Malignant Neoplasms

Certainly one of the most devastating long-term complications after HCT is that of developing a second malignancy. Although the risk of secondary malignancy for those undergoing HCT during childhood is certainly increased compared to age-matched controls, it may also be increased compared to individuals undergoing transplantation at older ages (Baker et al. 2003). In a study of over 19,000 HCT patients, 3,200 of whom had survived more than 5 years, Curtis et al. documented a cumulative incidence rate of secondary malignancy of 2.2 % five years after HCT, increasing to 6.7 % in those who survived 15 years or longer (Faraci et al. 2008). Survivors undergoing HCT at less than 10 years of age had a risk of new malignant neoplasms 36.6 times the general population; this risk decreased to 4.6-fold for those transplanted between the ages of 10 and 29 years and reached parity for those transplanted above the age of 29. The most common secondary cancers were brain tumors (9/13 patients), significantly associated with craniospinal irradiation, and thyroid carcinoma; when these two tumors were excluded, there was no difference in incidence of secondary malignancy between younger and older patients in this study. Cohen et al. also identified an increased risk of

secondary thyroid carcinoma following HCT, with the strongest relative risk in children undergoing HCT at less than 10 years of age. Additional risk factors included female gender, chronic GVHD, and the use of ionizing radiation (Cohen et al. 2007). An additional study evaluating children transplanted for leukemia showed a cumulative risk of secondary solid tumors of 11 % 15 years following HSCT (Kolb et al. 1999). Again, the risk was highest among the youngest children and those who had received high-dose TBI; in this study, chronic GVHD was not associated with an increased risk of a second malignancy, although others studies have reported an increased risk with chronic GVHD.

The risk of secondary malignancy may increase with prolonged survival post-HCT. Although no pediatric-specific data were reported, Kolb et al. reported a 3.5 % actuarial incidence of secondary malignancy at 10 years post-HCT, increasing to 12.8 % at 15 years (Kolb et al. 1999). Of 3,182 children receiving allogeneic HCTs for leukemia reported to the International Bone Marrow Transplant Registry (IBMTR), 45 developed secondary malignancies, 25 with invasive solid tumors, and 20 with posttransplant lymphoproliferative disorders (PTLD). Most common reported solid tumors were thyroid carcinoma, malignant melanoma, osteosarcoma, carcinomas of the tongue and salivary gland, and malignant fibrous histiocytoma. Again, younger age at time of transplant and use of high-dose TBI conferred a higher relative risk of invasive solid tumors. Patients at increased risk of PTLD had a significantly higher incidence of chronic GVHD, unrelated donor stem cell source, or related donor mismatched at greater than 2 human leukocyte antigen (HLA) antigens, T-cell-depleted grafts, and use of antithymocyte globulin as prophylaxis or treatment for acute GVHD (Geenen et al. 2007). Given the heterogeneity in the type of second malignancies that are seen after HCT, there is no specific screening program that will be useful for early detection other than those already recommended as screening for cervical (pap smears), breast (mammography), colon (colonoscopy), and prostate (PSA) cancers in the general population. HCT survivors, however, should pay careful attention to their skin, and any suspicious appearing moles or skin lesions should be evaluated and biopsied or removed. Cancer prevention is also very important for HCT survivors, and they should be provided with counseling and education regarding actionable items for reducing cancer risk such as appropriate diet, exercise, avoidance of smoking, limiting alcohol intake, and use of sunscreen.

Conclusion

While survivors after HCT during childhood face many potential risks and challenges as they age, the majority actually do quite well leading healthy and productive lives. As we learn more about long-term risks that may either be preventable with appropriate monitoring and screening or manageable with appropriate interventions, it is important that our long-term survivors be educated regarding their potential long-term risks and that they continue to receive periodic evaluations by providers who are knowledgeable regarding these issues. However, given the complexities of the healthcare system and mobility of the population, it is also important that primary care providers be educated about the potential long-term complications HCT survivors may face and that we provide survivors and these providers with specific long-term follow-up guidelines—a survivorship care plan—that can serve as a guide for maintaining the survivors' long-term health. Fortunately, there are guidelines available that can facilitate this process, including the Children's Oncology Group Long-Term Follow-up Guidelines (www.survivorshipguidelines.org) as well as recently published guidelines from the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation, and the American Society for Blood and Marrow Transplantation. These guidelines are specific to HCT survivors and provide recommendations for periodic long-term follow-up and screening (Majhail et al. 2012a) (see Table 7.1). Efforts such as these will provide guidance for providing appropriate long-term follow-up care.

Table 7.1 Selected Screening Recommendations for Late Effects After HCT in Pediatric Patients

	Children's Oncology Group (COG) recommendations[a]	Joint Transplant Society[b] recommendations (Majhail et al. 2012)	Expert panel recommendations (Pulsipher et al. 2012)	
			Screening	Management
Iron overload	HCT section 95 AST, ALT, bilirubin, ferritin screening at entry into f/u and prn. Biopsy, chelation, phlebotomy as indicated	Serum ferritin at 1 year after HCT in patients who have received RBC transfusions; consider liver biopsy or imaging study for abnormal results based on magnitude of elevation and clinical context; subsequent monitoring is suggested for patients with elevated LFTs, continued RBC transfusions, or presence of HCV infection	Annual serum ferritin; if elevated, consider T2* MRI	Phlebotomy or chelation
GI	HCT section 95 AST, ALT, bilirubin, ferritin screening at entry into f/u and prn. Hepatology consultation for persistent abnormal LFTs Hep B, C viral testing as indicated	LFTs every 3–6 months in the first year, then individualized, but at least yearly thereafter Monitor viral load by PCR for patients with known hepatitis B or C, with liver and infectious disease specialist consultation Consider liver biopsy at 8–10 years after HCT to assess cirrhosis in patients with chronic HCV infection	Annual screening for chronic GVHD Hepatitis virus infection screening Annual hepatocellular carcinoma screening for high risk patients: HCV or HBV infection Obesity, diabetes Low platelet count	
Renal	Chemotherapy, alkylating agents section 13 Risks—therapy with ifosfamide, cisplatin, carboplatin, amino-glycosides, amphotericin, immunosuppressants, XRT of kidney. Screen with lytes/BUN/Cr urinalysis at entry into f/u and prn. Rx electrolyte supplementation, nephrology for hypertension, proteinuria, progressive renal insufficiency	Blood pressure assessment at every clinic visit, with aggressive hypertension management Assess renal function with BUN, creatinine, and urine protein at 6 months, 1 year and at least yearly thereafter Consider further workup (kidney biopsy or renal ultrasound) for further workup of renal dysfunction as clinically indicated	Monitor urine for albumin:creatinine ratio at day 80 and then annually If ratio ≥30 and <300 mg/g, confirm with two positive tests in 3–6 months and monitor every 3–6 months If ratio >300 mg/g, monitor every 3–6 months	Treat with ACE inhibitor or ARB if albumin:creatinine ratio is >300 mg/g on one occasion or if patient has persistent ratio above 30 g/kg on three occasions in a 6-month period and has hypertension
Pulmonary	HCT section 101 Risks—chest XRT/TBI, bleomycin, busulfan, BCNU, CCNU, cGVHD; screen with CXR and PFTs at entry into f/u and prn. Avoid smoking, caution with SCUBA, anesthesia. Give influenza and pneumococcal vaccines	Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter Assessment of tobacco use and couselling against smoking PFTs and focused radiologic assessment for allogeneic HCT recipients	Pulmonary function testing for allogeneic recipients twice per year for two years with consideration for more frequent screening in recipients of mismatched or unrelated donors grafts, or patients with active chronic GVHD After 2 years, consider yearly f/u PFTs based upon symptoms and past measurements	If patients experience a decrease in PFTs >15 % or a new pulmonary infiltrate, evaluate for infection/GVHD. Refer to pulmonology for disease-specific care as needed

(continued)

Table 7.1 (continued)

	Children's Oncology Group (COG) recommendations[a]	Joint Transplant Society[b] recommendations (Majhail et al. 2012)	Expert panel recommendations (Pulsipher et al. 2012)	
			Screening	Management
Cardiac	XRT Section 71—multiple cardiac effects (CHF, cardiomyopathy, etc.) Risks higher with previous anthracyclines or combined with cyclo phosphamide as conditioning for HCT. Screen with baseline echo/EKG, fasting glucose/lipid profile q 2 yrs. Recommendations regarding screening and treatment based upon condition and total anthracycline dose	Routine clinical assessment of cardiovascular risk factors as per general health maintenance at 1 year and at least yearly thereafter Education and counseling on "heart" healthy lifestyle (regular exercise, healthy weight, no smoking, dietary counseling) Early treatment of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	Annual CV risk assessment Blood pressure each visit and at least annually; ECG/ECHO at least every 5 years, more frequently if anthracyclines, TBI or chest irradiation was given	Referral to cardiology for abnormal or declining cardiac function
Metabolic	XRT Section 49—Metabolic syndrome as a possible late effect of TBI. Screen with ht/wt/bp/BMI yearly plus fasting glucose/lipid profile every two years. Rx with diet, counseling, physical activity	Screening for cardiovascular risk factors as outlined under "cardiac"	Lipid profile and fasting glucose at least every 5 years; if abnormal, screen annually	No transplant-specific recommendations available
Thyroid dysfunction	XRT Section 64/65—hypo/hyperthyroidism Risks—XRT ≥10Gy, thyroid in field. Yearly screening, more frequently during rapid growth	Thyroid function testing yearly post-HCT, or if relevant symptoms develop	TSH and FT4 annually: (1) for 10 years after busulfan (2) for at least 30 years after TBI. PE of thyroid yearly to screen for tumors after TBI	If TSH is high and FT4 normal, either treat or repeat in 2 months Replace thyroid as indicated for low levels Rare secondary thyroid tumors post-TBI can be cured with surgery
Growth impairment	XRT Section 50—Growth Hormone Deficiency Risks—young age, TBI≥10Gy single fx, ≥12 Gy fractionated. Screen with dietary assessment, ht/wt/BMI every 6 m until growth completed. Refer to endocrine for ht<3rd %, drop≥2 % rankings, growth velocity<4–5 cm/year, lack of growth spurt.	Monitor growth velocity in children annually; assessment of thyroid, and growth hormone function if clinically indicated	Accurate measure of growth yearly through full growth (age 17 girls, 19 boys). Bone age as needed	Bone age and referral to endocrine for patients not growing appropriately. GH therapy may unmask hypothyroidism

Low bone mineral density	HCT section 97 Risks—young age, Caucasian, low BMI, steroids, calcineurins, cranial XRT/TBI, GH deficiency, delayed puberty, hyperthyroidism, poor exercise, poor nutrition, smoking, alcohol use, carbonated beverages. Dexa at entry into long-term f/u and prn. Rx with Vit D, Ca, exercise. Endocrine consultation for osteoporosis/history of fractures	Dual photon densitometry at 1 year for adult women, all allogeneic HCT recipients and patients who are at high risk for bone loss; subsequent testing determined by defects or to assess response to therapy Physical activity, vitamin D, and calcium supplementation to prevent loss of bone density -Patients with cGVHD: Consider dual photon densitometry at an earlier date in patients with prolonged corticosteroid or calcineurin inhibitor exposure	Dexa-scan pre-HCT, 1 year post-HCT, yearly if Z-score < -1	Patients with Z-score < -2, history of fractures refer to endocrine. Supplement Ca & Vit. D, weight-bearing exercise, avoid smoking, alcohol, caffeine
Osteonecrosis	HCT section 96 Risks—age ≥ 10 at HCT, steroids, TBI, focal XRT, allogeneic > autologous, cGVHD. Screen yearly with exam, MRI as clinically indicated	MRI to evaluate patients with joint symptoms	Consider MRI screening of asymptomatic patients on high-dose steroids. Early MRI screening of any patients with symptoms of joint pain, pain in groin or anterior thigh, limping.	Minimize steroids and alcohol consumption, offer analgesics, non-weight-bearing exercise, PT. Refer to Orthopedics
Reproductive risks	Chemotherapy, Alkylating agents section 7 Risks—combined doses of alkylators/heavy metals/DTIC/temazolamide with XRT to cranium or gonads. Screen FSH/LH/testosterone, Tanner staging ages 13–14 and as clinically indicated for delayed puberty, irregular menses. Semen analysis, repeat as indicated as resumption can occur 10 years after Rx	Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving Counsel sexually active patients in the reproductive age group about birth control post-HCT	Women: monitor of ovarian failure (FSH, assess cycling) Men: semen analysis	Women: Anti-Mullerian hormone (AMH) may assess ovarian reserve. Treat ovarian failure with hormone replacement therapy Men: If oligospermia noted, could offer intracytoplasmic sperm injection

[a] www.survivorshipguidelines.org

[b] Recommendations from the Center for International Blood and Marrow Transplant Research (CIBMTR), the American Society of Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplantation (EBMT), Asia-Pacific Blood and Marrow Transplantation Group (APBMT), Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), East Mediterranean Blood and Marrow Transplantation Group (EMBMT) and Sociedade Brasileira de Transplante de Medula Ossea (SBTMO)

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8 Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia: Biology, Indications, and Outcomes

Michael A. Pulsipher, Elizabeth Raetz, and Christina Peters

Contents

M.A. Pulsipher, MD (✉)
Division of Hematology/BMT, Primary Children's Medical Center/Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA
e-mail: michael.pulsipher@hsc.utah.edu

E. Raetz, MD
Division of Pediatric Hematology/Oncology, Department of Pediatrics, New York University Langone Medical Center and Cancer Institute, New York, NY, USA

C. Peters, MD
Department of Hematology and Oncology, St. Anna Children's Hospital, Vienna, Austria

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8.1 Introduction

Survival of children treated for acute lymphoblastic leukemia (ALL) has improved dramatically over the past decades in developed countries. In a recent analysis of the outcomes of more than 21,000 children, adolescents and young adults age 0–22 years treated on Children's Oncology Group (COG) protocols from 1990 to 2005, the 5-year overall survival (OS) rate reached 90.4 % for the 2000–2005 treatment era (Hunger et al. 2012). With these remarkable improvements, recent efforts have focused on refining current measures to define high-risk groups using emerging data from genome-wide analyses and serial measurements of minimal residual disease (MRD) response. The goal is to define those at highest risk for relapse and tailor their therapy to overcome disease resistance, improving their chances for cure.

Historically, risk in childhood ALL has been allocated on the basis of established clinical features, blast characteristics including specific cytogenetic abnormalities, and early initial response to therapy (Schultz et al. 2007). Children, adolescents, and young adults with high-risk disease features and response characteristics are assigned to more intensive chemotherapy regimens. Hematopoietic cell transplantation (HCT) has been a part of several cooperative group studies for patients in first complete remission (CR1) generally only for specifically defined very high-risk groups (i.e. predicted event-free survival (EFS) with chemotherapy alone <40–50 %). With a greater and evolving understanding of underlying disease biology, coupled with examples of the benefits of combining targeted agents with chemotherapy (e.g., tyrosine kinase inhibitor + chemotherapy in Philadelphia chromosome-positive [Ph+] ALL), efforts are underway to redefine the subsets of patients at diagnosis who will derive the greatest benefit from HCT (Hunger et al. 2011; Mullighan 2011; Schultz et al. 2009). Genome-wide studies of genetic alterations in ALL have identified new high-risk groups, and there has been a growing understanding of the prognostic impact of MRD measurements at early time points in therapy; both of these factors are likely to reshape traditional risk classification.

As opposed to newly diagnosed patients, outcomes for children with relapsed ALL have changed little over time, despite efforts by many groups to intensify therapy with approaches that often include HCT. While studies have reported OS rates in the 35–40 % range when all types of relapse are included (Einsiedel et al. 2005; Freyer et al. 2011; Reismuller et al. 2009; Saarinen-Pihkala et al. 2006; Tallen et al. 2010), inferior outcomes have been observed for bone marrow relapses, especially when they occur early, with long-term OS rates of around 25 % (Table 8.1) (Freyer et al. 2011; Ko et al. 2010; Nguyen et al. 2008; Reismuller et al. 2009; Saarinen-Pihkala et al. 2006). Reported outcomes of children with relapsed ALL have remained remarkably similar internationally, in spite of differences in components of salvage regimens, allocation to HCT, frontline therapy, and supportive care.

Excessive rates of relapse in subsets of high-risk CR1 patients and the persistence of poor outcomes of patients after relapse highlight the need for understanding when to optimally include intensive therapies such as HCT in the treatment of ALL. This chapter will attempt to define the role of HCT in the treatment of ALL by (1) describing how to assess studies in order to determine when HCT is indicated, (2) reviewing high-risk subgroups of ALL at diagnosis and relapse, (3) outlining current indications for HCT in all phases of ALL therapy, (4) detailing optimal approaches to ALL HCT (i.e., preparative regimens, stem cell sources, MRD status pre-HCT), and (5) providing a brief overview of immunological and cell-based therapies that are beginning to be tested in high-risk ALL patients and will likely have a larger role in the near future.

Table 8.1 Survival after first relapse of ALL

Trial	Treatment era	Risk status	% Achieving 2nd CR	Outcome
SJCRH (Rivera et al. 2005)	1984–1994	Intermediate risk (BM) only High risk	81 % 66 %	42.6 ± 7.8 % 12.5 ± 3.9 %
ALL-REZ90 (Tallen et al. 2010)	1990–1995	Group A early BM + CNS Group B late Group C IEM any time PPG very early BM/T	83 % 94 % 100 % 65 %	10 yrs EFS 17 ± 3 10 yrs EFS 43 ± 4 10 yrs EFS 54 ± 6 10 yrs EFS 15 ± 3
NOPHO (Saarinen-Pihkala et al. 2006)	1981–2001	Group 1 early BM Group 2 all others	84 % 95 %	10 yrs OS 17.5 % 10 yrs OS 42.6 %
COG (CCG) (Nguyen et al. 2008)	1988–2002	Late BM Early BM Very early BM	NR	5 yrs OS 43.5 % 5 yrs OS 18.4 % 5 yrs OS 11.5 %
UKALL R2 (Roy et al. 2005)	1995–2002	Standard risk Intermediate risk High risk	92 % 96 % 81 %	5 yrs OS/EFS 92/92 % 5 yrs OS/EFS 64/51 % 5 yrs OS/EFS 14/15 %
TACL (Ko et al. 2010)	1995–2004	Very early BM Early BM Late BM IEM excluded	83 % very early and early 93 %	5 yrs DFS 19 ± 6 % 5 yrs DFS 35 ± 7 % 5 yrs DFS 35 ± 8 %
COG AALL01P2 (Raetz et al. 2008a)	2003–2005	Relapse <18 m from dx Relapse 18–36 m from dx Relapse ≥36 m from dx	45 ± 11 % 79 ± 6 % 96 ± 3 %	5 yrs EFS 11 ± 7 % 5 yrs EFS 24 ± 9 % 5 yrs EFS 40 ± 7 %

8.2 Rationale Behind the Use of Allogeneic HCT for High-Risk ALL (Graft vs. Leukemia (GVL) Effects)

Progress in chemotherapy approaches to curing ALL over the past few decades has occurred through better definition of disease risk, which has allowed dose intensification and refined schedules of established and occasionally new chemotherapy agents. Approaches to HCT for ALL through the years have focused on taking high-risk children with poor prognoses with chemotherapy alone and offering them high-dose treatment approaches in the hope of overcoming chemotherapy resistance. While chemotherapy approaches continue to have room for dose intensification or addition of new agents, HCT approaches quickly reached a limit in dose intensity due to increased transplant related mortality (TRM) when already very intensive myeloablative preparative regimens were further dose escalated (Clift et al. 1990). Approaches to refinement of HCT for ALL, therefore, have focused on eliminating or modifying preparative regimens that lead to excess toxicity, defining ideal stem cell sources, and improving supportive care to minimize toxic complications.

The current rationale for and benefit derived from allogeneic HCT is a decrease in relapse rate due to allogenicity against leukemic blasts, often termed the graft-versus-leukemia (GVL) effect. There has been debate about whether allogeneic HCT for ALL is associated with a significant GVL effect. This debate has largely been a reflection of the relatively poor response of early relapse after HCT to donor lymphocyte infusions (DLI, see Sect. 7.11). A number of key studies, however, support a GVL effect as shown by (1) decreased relapse in patients who develop acute and/or chronic graft-versus-host disease (GVHD) compared to those who do not (Dini et al. 2011; Locatelli et al. 2002; Horowitz et al. 1990; Cornelissen et al. 2001; Passweg et al. 1998; Esperou et al. 2003; Lee et al. 2007; Nordlander et al. 2004; Gustafsson Jernberg et al. 2003;

Zikos et al. 1998; Remberger et al. 2002) (Table 8.2 reviews representative pediatric studies), (2) increased relapse in patients undergoing T-cell depleted HCT (Marmont et al. 1991; Horowitz et al. 1990), (3) significant improvements in survival using allogeneic HCT compared to autologous HCT (see Sect. 7.7) or syngeneic HCT (Gale et al. 1994; Horowitz et al. 1990), and (4) reasonable levels of disease-free survival (DFS) in studies (mainly in adults) using reduced-intensity conditioning regimens, approaches that do not involve therapy at dose levels that would result in cure without an accompanying immunologic effect (Pulsipher et al. 2009a; Mohty et al. 2008; Verneris et al. 2010; Bachanova et al. 2009; Stein et al. 2009; Cho et al. 2009) (see Sect. 7.8).

8.3 Methodological Approaches to Comparing Allogeneic Transplant with Chemotherapy for Specific High-Risk ALL Indications: Understanding Risk Categories and Minimizing Bias

In the 1990s, as HCT techniques and outcomes were undergoing rapid development and application in pediatrics, several groups attempted randomized (actual or biological based on presence of a matched sibling) studies of HCT versus chemotherapy for high-risk ALL. In the United Kingdom, the UKALLR1 study randomized children with a first relapse of ALL to chemotherapy

Table 8.2 Pediatric HCT studies defining effects of GVHD on relapse and survival

Study	*N*	GVHD effect on relapse		*P*-value	GVHD effect on survival		*P*-value
Gustafsson-Jernberg Swedish (2003)	112	Status	Relapse rate	0.01	Status	Overall survival (5 yrs)	0.01
		cGVHD	30 %		cGVHD	77 %	
		No cGVHD	53 %		No cGVHD	50 %	
Locatelli Italian (2002)	63	Prophylaxis		0.0002	Grade of aGVHD	EFS	0.04
		CSP + MTX	Relapse rate 0 %		Grade 0–I	36 %	
					Grade II	64 %	
		CSP + MTX + Campath	relapse rate 72 %		Grades III–IV	29 %	
Dini AIEOP-HCT Group (2011)	395	aGvHD	RR of relapse (95 % CI)	0.008	Grade of aGvHD	RR of death (95 % CI)	0.0001
		Grade I vs. 0	0.48 (0.28–0.82)	0.008	Grade I vs. 0	0.31 (0.17–0.56)	0.0001
		Grade II vs. 0	0.45 (0.25–0.81)	0.019	Grade II vs. 0	0.27 (0.15–0.50)	0.047
		Grade III vs. 0	0.32 (0.12–0.83)	0.008	Grade III vs. 0	0.46 (0.22–0.99)	N.S.
		Grade IV vs. 0	0.06 (0.01–0.47)	0.026	Grade IV vs. 0	1.24 (0.64–2.41)	
		cGvHD		N.S.			
		Limited vs. absent	0.44 (0.21–0.91)				
		Extensive vs. absent	0.74 (0.33–1.64)				

aGVHD acute GVHD, *cGVHD* chronic GVHD, *RR* relative risk

versus autologous HCT, with a nonrandom assignment of those with matching siblings to allogeneic HCT. During the trial, emerging data from other studies showed (1) differences in risk between early and late marrow relapses as well as isolated extramedullary relapses, (2) no advantage of autologous HCT over chemotherapy approaches, and (3) improving outcomes with unrelated donor HCT approaches. The result was that an astonishing number of investigators and patients failed to follow protocol therapy (only 9 % of eligible patients accepted randomization) (Lawson et al. 2000). Patients receiving chemotherapy, autologous HCT, and allogeneic HCT had similar rates of survival; however, the risk factor profiles of patients receiving each therapy were dramatically different, and assessment of the comparative efficacy of the three approaches for patients of a given risk group was not feasible.

A second study by investigators in the Children's Cancer Group (CCG-1941) attempted another randomized comparison, but refined the approach by testing only high-risk complete remission 2 (CR2) patients (i.e., early bone marrow (BM) relapse), nonrandomly assigning patients with sibling donors to allogeneic HCT and randomizing the remainder of patients to chemotherapy versus unrelated donor HCT (Gaynon et al. 2006). Although this reasonable design could have definitively compared related and unrelated allogeneic HCT with chemotherapy for this high-risk cohort, the protocol again had significant problems with compliance. The study enrolled slowly, closing with just over half of the projected enrolment of 400 patients. Of those qualifying for randomization, 36 % were not randomized by patient or physician choice. Of those randomized to chemotherapy, 34 % received HCT; of those randomized to HCT, 49 % received chemotherapy.

These two studies illustrated that trials attempting to randomize HCT with chemotherapy for high-risk relapsed ALL were not feasible for many reasons, including perceived lack of therapeutic equipoise and institution/physician preference. Because HCT has become an accepted modality for treating patients with high-risk ALL, the approach currently taken by most institutions and cooperative groups is to define risk groups with a decreased chance of cure with chemotherapy and assign or allow patients the option of proceeding with HCT at defined points in their therapy as long as an appropriate donor has been arranged and there is evidence to support a survival benefit with HCT. Analysis to support the assignment is then done by comparison of similar patients who received or did not receive HCT, and risk groups are then redefined. Over time, some indications remain fairly consistent (e.g. primary induction failure) and others change (e.g. Ph+ ALL).

Deciding when HCT is an appropriate therapy for a given patient in the midst of the frequent redefinitions of clinical, molecular, and MRD-based risk classifications for children with ALL that occur through the years is a challenge that is best met by ongoing evidence-based comparisons of current transplant and chemotherapy outcomes, as survival with both approaches tends to improve over time. In the past decade, significant improvements in HCT have led to less TRM and better survival after unrelated donor transplantation (MacMillan et al. 2008), less GVHD in pediatric recipients (Davies et al. 2009), decreases in TRM and better survival in unrelated cord blood transplantation (Eapen et al. 2007b), a possibility of decreased relapse using killer immunoglobulin receptor (KIR) mismatching (Brunstein et al. 2010; Cooley et al. 2009), and early data from a series of both targeted and nontargeted cellular therapies (Jena et al. 2010; Pulsipher et al. 2008). Equally compelling advances have occurred in chemotherapy approaches with the introduction of novel and targeted agents (Schultz et al. 2009), better definition of high-risk groups (Hunger et al. 2011; Pui et al. 2011), and intensification of therapy in these groups in order to prevent relapse (Matloub et al. 2011). The rapid pace of advancement in both HCT approaches and chemotherapy for ALL will likely continue.

8.3.1 Considerations in Comparing HCT and Chemotherapy Studies

In general, HCT approaches tend to offer benefit to children at high risk for relapse with standard

chemotherapy approaches, but do not offer an advantage when the chance for survival with chemotherapy alone is moderate or good. Thus, as mentioned above, most centers and cooperative groups have adopted approaches that identify high-risk patients and offer HCT if the patients achieve remission and have an appropriately HLA-matched donor. Some groups take this approach one step further by defining a *very* high-risk group and allowing such patients HCT using either conventional approaches or higher-risk approaches to HCT if the patients do not have appropriate donors available (e.g., HLA haploidentical or significantly mismatched donors) (Schrauder et al. 2008). For study designs that assign patients to HCT based upon risk and availability of a donor, intent-to-treat analysis should be performed.

Because nonrandomized study approaches are by necessity used so frequently to decide ALL HCT indications, several issues need to be addressed in order to make chemotherapy and HCT comparisons as unbiased as possible (Pulsipher et al. 2010, 2011):

1. *Remission status:* Patients failing to obtain remission do very poorly with any therapy; therefore, comparisons between HCT and chemotherapy approaches can avoid bias by including only those who obtain remission, preferably after similar approaches to salvage therapy. Patients obtaining remission prior to a planned HCT, who then relapse before that HCT, are at extremely high risk compared to those who maintain remission, even if they go back into remission prior to HCT. A well-established method of correcting for this issue is to include only those who maintain remission to the point of HCT, and then in order to account for time-to-transplant bias, the chemotherapy comparator arm should only include patients who maintain remission until the median time to HCT. Patients who fail to obtain remission or who relapse prior to the median time to HCT can be analyzed for outcome, but they have a different risk profile and should be analyzed separately.
2. *Past or current therapy approaches used:* Disease and era-appropriate chemotherapy and HCT approaches should be compared.
3. *HCT approach:* HCT approaches that are very high risk or have documented lower rates of survival (i.e., haploidentical approaches) should not be combined for analysis with standard-risk HCT approaches (matched sibling and well-matched unrelated donors treated with total body irradiation (TBI)-based regimens). Autologous HCT has very different outcomes compared to allogeneic HCT for high-risk ALL patients, and patients receiving the two approaches should never be combined into a single "transplant" group.
4. *Analysis by risk groups:* ALL disease biology-based risk factors for relapse should be carefully defined and comparative analysis based upon the most current knowledge of risk should be performed. One should not combine patient groups at different risk because a benefit for HCT in a high-risk group can be masked in an analysis that pools high- and standard-risk groups (Mann et al. 2010; Pulsipher et al. 2011).
5. *Selection Bias:* Attempts should be made to understand and eliminate or correct for selection bias. Examples include the following:
   - *Higher*-risk patients preferentially undergoing HCT
   - *Sicker* patients deferred from HCT because of comorbidities
   - Patient/parent refusal
   - Lack of insurance or inability to obtain insurance approval for HCT
   - Lack of access to HCT due to distance/inability to travel

One source of bias difficult to control for or detect is physician bias for or against HCT. The effect of access to HCT and therapeutic bias on outcomes of pediatric malignancies where HCT may be indicated has been poorly studied to date.

8.4 High-Risk ALL Subsets at Diagnosis

There are several subgroups of ALL in children, adolescents, and young adults for which HCT is considered in CR1 due to poor historical outcomes with chemotherapy alone. These include

hypodiploid ALL (<44 chromosomes) and primary induction failures. HCT has also been considered for other subgroups, although the indications have been more controversial or have changed with the advent of targeted treatment strategies. These groups include Ph+ ALL, infants with ALL, adolescents and young adults (AYAs) with ALL, and those with persistent MRD at later time points in treatment.

In contrast to relapsed ALL, for which HCT indications have changed only slightly in the last two decades, definitions of risk and advances in therapy over the past decade have significantly altered recommendations and practice for transplantation in CR1. We will discuss current recommendations for the treatment of high-risk ALL of the Children's Oncology Group (COG) in North America/Australia and the International Berlin, Frankfurt, Münster (iBFM) Study Group, but it is important to recognize that definitions of risk of relapse and recommendations for HCT in CR1 are highly dependent upon initial approaches to chemotherapy. Many other cooperative groups and individual institutions (e.g., St. Jude Children's Research Hospital and the Dana-Farber Cancer Center in the United States, the Medical Research Council (MRC) in the United Kingdom, the Nordic cooperative group, the Japanese cooperative group) have developed HCT recommendations that are similarly adapted to their initial chemotherapy approaches. While some definitions of risk resulting in recommendations for HCT in CR1 seem to apply to all settings (i.e., an M3 marrow (>25 % blasts) primary induction failure where subsequent remission is obtained), other definitions are highly dependent upon the initial chemotherapy approach and specific technologies (i.e., late persistent MRD as shown by polymerase chain reaction (PCR) in the iBFM group) and should not be assumed to be valid across groups using different initial induction chemotherapy, unless prospectively validated. Specific high-risk groups and the role of HCT in CR1 are discussed below.

8.4.1 Primary Induction Failure (PIF)

Slow or incomplete response to a prednisone pre-induction prophase or to induction chemotherapy itself has been shown to be one of the most significant risk factors for relapse and treatment failure in ALL (Conter et al. 2010; Borowitz et al. 2008). Patients have been shown to be at increased risk by several approaches including early morphological disease assessments as well as the persistence of MRD.

Well before the establishment of MRD measurement techniques, failure to achieve remission after an induction course of chemotherapy was noted to have a very poor outcome (Silverman et al. 1999). Although the vast majority (>95 %) of children achieve an initial remission (<5 % of blasts by morphology on BM), those with a T-cell phenotype (especially without a mediastinal mass) and those with B-precursor ALL with very high presenting leukocyte counts and/or the Philadelphia chromosome are at increased risk of induction failure (Oudot et al. 2008; Silverman et al. 1999). Survival with either HCT or chemotherapy is very unlikely unless patients achieve remission with subsequent courses of salvage chemotherapy, and currently only about 30 % of these children are alive at 5 years.

Silverman reported the outcomes of 23 patients failing remission with M2 or M3 bone marrows after induction out of 774 enrolled on two consecutive Dana-Farber Consortium protocols between 1987 and 1995. In spite of the fact that 91 % of those with persistent leukemia eventually achieved remission, 5-year EFS was only 16 % (95 % CI 0–31 %). Only 3 of the 23 patients received a bone marrow transplant (BMT) in CR1 with one long-term survivor, so the role of HCT in CR1 was not assessed (Silverman et al. 1999). A study from the French ALL 93 study (conducted between 1993 and 1999) tracked the outcome of 53/1,395 children (3.8 %) with either >5 % blasts on post-induction bone marrow (BM) assessment ($n=50$) or relapse within 4 weeks of the post-induction BM assessment ($n=3$) (Oudot et al. 2008). Among the 43 children who achieved remission with subsequent therapy, 23 underwent allogeneic HCT (10 matched sibling, 9 matched unrelated donors (URD), 2 mismatched family, and 2 mismatched cord blood donors). Eight underwent autologous HCT and 12 received chemotherapy. The protocol

did not define a preferred therapy; therefore, the rationale for treatment allocation is unknown. In addition, MRD was not measured routinely, so the depth of remission eventually achieved was not documented. Five-year OS for the PIF group was 30 ± 6 % compared to 85 ± 2 % in the cohort that achieved CR after a single induction. If PIF patients entered remission, 5-year OS was 37 % compared to 0 % for those who did not achieve remission. Of those undergoing HCT, 5 of 10 matched sibling recipients survived compared to 2 of 13 of unrelated or mismatched donors. Three of 12 patients treated with chemotherapy alone survived and one more initially treated with chemotherapy was salvaged with unrelated donor HCT. The study suggests that matched sibling donor allogeneic HCT may be beneficial, but numbers are small. Suzuki et al. reported a Japanese experience during a later time frame (1997–2005) that showed similar outcomes: 2.2 % failed induction; 74 % of those achieved remission, with 82 % ($n = 14$) staying in remission until time of planned HCT. Twelve of 14 planned HCT procedures occurred and 5-year OS after HCT was 50 %. The 5-year OS of 16 patients with non-Ph+ and 7 patients with Ph+ ALL were 43.8 ± 12.4 % and 14.3 ± 13.2 %, respectively ($p = 0.012$) (Suzuki et al. 2010).

A larger study comparing chemotherapy with transplant outcomes was conducted by Balduzzi and colleagues from Europe (2008). Based on intent-to-treat analysis (no donor vs. donor) of patients with PIF who eventually achieved remission, those with no donor ($n = 58$) had a 5-year DFS of 26.5 % (standard error [SE] 5.9) versus 56 % (SE 9.9) for those with a donor ($n = 25$, $p = 0.03$). Survival was also better by treatment received (5-year DFS 30.7 % for chemotherapy vs. 50 % for HCT). Three other European studies comparing chemotherapy to HCT for patients with various risk factors including induction failure showed an advantage with HCT, but due to low numbers, they were unable to specifically compare PIF patients (Balduzzi et al. 2005; Arico et al. 2002; Moricke et al. 2008). A number of HCT studies in the more modern era have shown promising outcomes with patients who have PIF and who eventually attain remission and undergo HCT using any donor, with survival exceeding 70 % (Pulsipher et al. 2009b; Satwani et al. 2007). Due to poor outcomes with chemotherapy alone, most pediatric ALL groups recommend HCT for patients who experience PIF, eventually obtain a remission, and have a reasonable HCT donor (Oliansky et al. 2012; Schrauder et al. 2008; Pulsipher et al. 2011).

A large retrospective study from 14 cooperative groups has provided insight regarding possible subsets of children with PIF who may not need HCT in CR1. The analysis examined outcomes of 1,041 children with induction failure (2.4 % of 44,017 enrolled on trials) treated between 1985 and 2000 (Schrappe et al. 2012). Although some groups considered M1 marrows with hypocellularity to have induction failure, and times of measuring remission varied, the study authors had enough information about the levels of remission to define key differences in risk. High-risk features included older age, high leukocyte count at diagnosis, >25 % blasts after induction (M3 marrow), T-cell phenotype, Ph+, and mixed-lineage leukemia (*MLL*) rearrangements. Certain patients with B-lineage ALL fared better with chemotherapy alone, especially children with high hyperdiploidy between the ages of 1 and 5 years. The authors compared outcome of chemotherapy to HCT by analyzing a subset of patients alive 6 months after diagnosis (to correct for time-to-HCT bias). In this subanalysis, children with B-cell ALL without *MLL* rearrangements who were younger than 6 years of age at diagnosis had a 10-year survival rate of 72.5 ± 5 % with chemotherapy, compared to 59 ± 12 % with matched related donor HCT and 57 ± 14 % with other allogeneic donor HCT (Fig. 8.1a, $p = 0.007$). An advantage for HCT was observed in an analysis of patients with PIF who had T-cell disease, although the numbers were smaller and therefore the statistical power was lower (Fig. 8.1b, chemotherapy 26 ± 4 % vs. matched related HCT 40 ± 9 % and other allogeneic HCT 45 ± 8 %, $p = 0.06$). One other comparison of HCT versus chemotherapy performed by the authors showed an advantage for HCT using matched sibling HCT for children 6 years of age and older with B-cell disease, but no advantage using unrelated

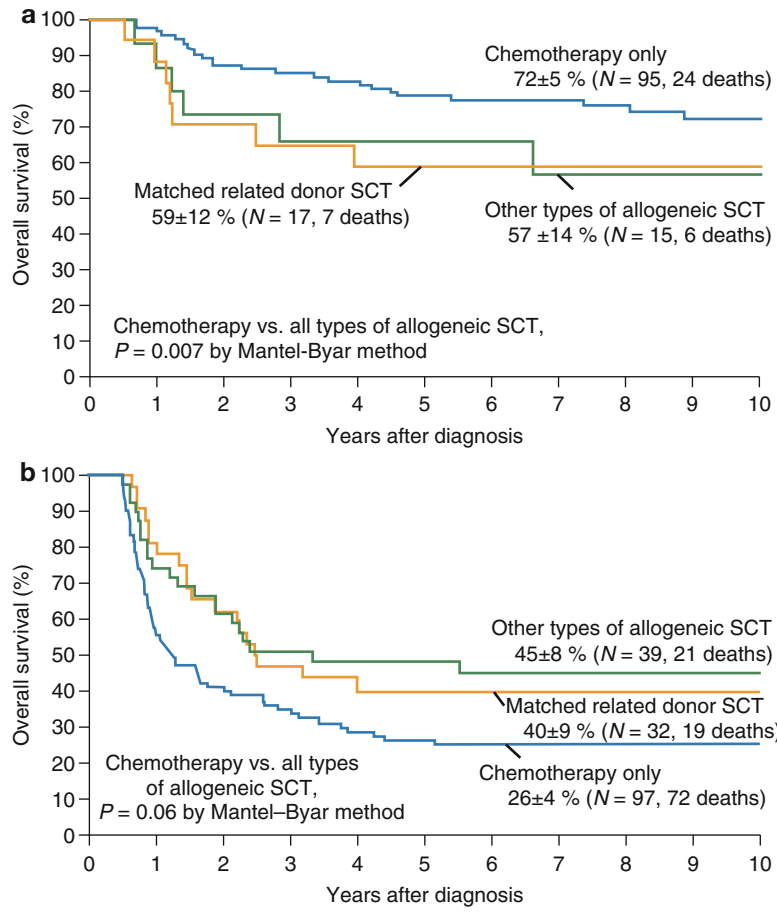


Fig. 8.1 Analysis of subsets of patients with PIF comparing HCT to chemotherapy. (**a**) Survival of patients with PIF who achieved remission with consolidation chemotherapy. Patients in this subset are < age 6 with B-cell disease. Patients with MLL rearrangements are excluded. (**b**) This analysis includes patients with T-cell ALL (Schrappe et al. 2012)

donor HCT. The study was performed during an era when TRM with URD approaches was high and may not reflect modern outcomes. Comparisons of HCT versus chemotherapy for other risk subsets did not have enough power to draw firm conclusions. This study suggests that in younger children with PIF who have B-lineage ALL without adverse cytogenetics and who eventually achieve a remission, especially an MRD-negative remission, HCT in CR1 may not provide an advantage.

8.4.2 Hypodiploidy

Patients with hypodiploid blasts have been noted to have increased risk of treatment failure, but this risk was clarified by a joint US-European study published by Nachman et al. (2007). The investigators studied 139 ALL patients with <45 chromosomes on diagnostic cytogenetic examinations and analyzed survival outcomes stratified by number of chromosomes. When a small number of patients who had Ph+ disease along with hypodiploidy were removed, patients with 44 chromosomes were noted to do significantly better than those with <44 (8-year EFS 52.2 % vs. 30.1 % $p=0.01$; OS 69 % vs. 37.5 % $p=0.017$). Only 6 % of this cohort underwent HCT in CR1, so the role of HCT in this setting could not be addressed by this study. Unpublished data from the Center for International Blood and Marrow Transplant Research (CIBMTR) has shown 2-year survival of 68 % for children with ALL

and hypodiploidy undergoing HCT (Mary Eapen, personal communication). Based upon these data, CR1 transplantation is offered on COG clinical trials to patients with <44 chromosomes and a DNA index <0.81 (Pulsipher et al. 2011).

8.4.3 Philadelphia Chromosome-Positive (Ph+) ALL

The presence of cytogenetics showing t(9;22), or Ph+ ALL, in children had been a well-established indication for CR1 HCT in the pre-tyrosine kinase inhibitor (TKI) era, with a survival benefit shown by large, well-performed retrospective comparative studies (Arico et al. 2000, 2010). The incorporation of TKIs into intensive multiagent chemotherapy, however, has resulted in significantly higher rates of initial remission, deeper remissions with lower MRD, better survival after CR1 HCT, and promising survival rates using chemotherapy without HCT. Investigators from the COG published a study that escalated imatinib from intermittent to continuous dosing in the context of an intensive chemotherapy backbone. The highest dose cohort (i.e., daily imatinib) achieved a 3-year EFS of 87.7 % ($n=25$, 95 % CI, 66.4–95.8 %). Unrelated and related donor HCT recipients enrolled on the trial had statistically similar rates of 3-year EFS (56.6 % for matched siblings [$n=21$, 95 % CI, 30.4–76.1 %] and 71.6 % [$n=11$, 95 % CI, 35.0–89.9 %]) for unrelated donor HCT. With follow-up exceeding 4 years and small numbers, this study suggests that chemotherapy using this approach offers at least as good of an outcome as allogeneic HCT; however, the results have not been confirmed, and trials from the European Intergroup and others are ongoing.

A follow-up study, COG AALL0622, using the same chemotherapy backbone and a similar approach of escalating exposure, with dasatinib (a second-generation tyrosine kinase inhibitor) instead of imatinib, has been performed by investigators at COG. Rates of CR after induction increased from 89 to 98 % with imatinib-versus dasatinib-containing regimens, respectively ($p=0.01$). In addition, 59 and 89 % of patients on the dasatinib protocol compared to 25 and 71 % of patients using imatinib had MRD <0.01 % at the end of induction and end of consolidation, respectively ($p<0.001$ and 0.04) (Slayton et al. 2012). These early results suggest that dasatinib in combination with chemotherapy may be advantageous. A major challenge with the COG chemotherapy/TKI approach is that the chemotherapy backbone is rigorous and requires meticulous supportive care.

A joint protocol for Ph+ ALL between COG and the European Intergroup testing an approach that incorporates dasatinib with the well-tolerated European EsPhALL chemotherapy platform is presently underway (COG AALL1122). HCT in CR1 is reserved only for those patients who are defined as very high risk by persistent MRD. Depending upon the results of these and other studies, it is likely that the role of HCT in CR1 for children with Ph+ ALL will be limited to a very select group of high-risk patients or only performed after relapse.

8.4.4 Persistent Minimal Residual Disease (MRD)

Early treatment response is a well-established prognostic marker that takes into account the elements of therapy as well as individual features of the patient and their disease (Schultz et al. 2007). While traditionally measured by morphological responses in the blood or bone marrow early in induction, study groups worldwide have now adapted measurements of MRD routinely in disease response assessments. MRD can be measured using multiparameter flow cytometry or molecular techniques analyzing immunoglobulin and T-cell receptor (*TCR*) gene rearrangements and has been shown to be a robust prognostic marker. In an analysis of MRD in the recently completed COG 9900 series of studies, end of induction MRD was shown to be the most significant predictor of long-term outcome in a multivariate analysis (Borowitz et al. 2008). In addition to demonstrating the prognostic importance of MRD at the end of induction, recent studies have now examined the importance of MRD at earlier

and later time points and have defined the optimal cutoffs. Given its strength as a prognostic marker, MRD response is a key element of risk classification algorithms and late time point MRD positivity at the end of consolidation therapy, or an equivalent time point, portends a particularly poor outcome in some subsets of patients, and may be used to define candidates for HCT in CR1 (Schrappe et al. 2011).

The AIEOP-BFM ALL 2000 study stratified patients into risk categories based upon PCR-based measurement of immunoglobulin and T-cell receptor gene rearrangements. Standard-risk patients were negative for MRD after induction (day 33) with at least two markers demonstrating sensitivities of $<10^{-4}$ for disease detection. Intermediate-risk patients had one detectable event at day +33 or +78, but MRD was $<10^{-3}$ at time point 2 with at least two markers. MRD high-risk patients were positive at day +78 at $>10^{-3}$ (Flohr et al. 2008). Five-year EFS was 92.3 % (SE 0.9) for standard, 77.6 % (SE 1.3) for intermediate, and 50.1 % (SE 4.1) for high-risk patients ($p < 0.001$) (Conter et al. 2010). Using a different technique (multichannel flow cytometry, MFC), COG investigators demonstrated that measurement of peripheral blood MRD at day +8 and BM MRD post-induction and post-consolidation were major determinants of relapse risk. Although some markers (presence of *TEL-AML1* [now, *ETV6- RUNX1*], trisomies of chromosomes 4 and 10) modified the effect of persistent MRD, in most patient populations persistence of MRD at these time points was the strongest factor determining risk of relapse (Borowitz et al. 2008). Children with flow MRD >0.01 % after completion of consolidation were noted to be at especially high risk (5-year EFS 43 ± 7 % vs. 83 ± 1 %, Fig. 8.2).

The ability to identify very high-risk cohorts has led some groups and centers to recommend HCT for patients with persistent MRD. At St. Jude Children's Research Hospital, persistent MRD of 1 % at the end of induction as well as persistent MRD at 16 weeks were indications for HCT in CR1 on their Total Therapy XV Study. Of 33 very high-risk patients (6 with Ph+ ALL, 21 with early high and 5 with persistent MRD, and 1 with hypodiploidy), 24 achieved long-term survival (73 %) (Pui et al. 2009). All of these patients were treated with intensification aimed at achieving MRD negativity prior to HCT. BFM studies have recommended HCT in CR1 for any patient with persistent MRD as measured by PCR of $\geq 10^{-3}$ after 12 weeks of therapy (Schrauder et al. 2008).

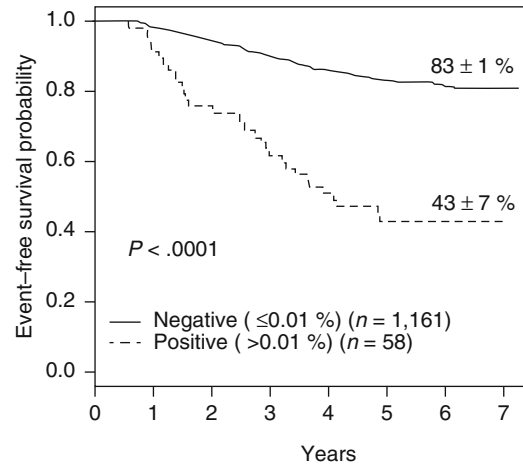


Fig. 8.2 Effect of MRD detected by flow cytometry after consolidation on survival with ALL chemotherapy (Borowitz et al. 2008)

A study by a German adult cooperative group demonstrated a better outcome in patients who had persistent PCR-based MRD at 16 weeks after induction and underwent HCT in comparison to those who continued with chemotherapy alone. The probability of continuous complete remission (CCR) after 5 years was significantly higher for patients with persistent MRD who underwent HCT in CR1 compared to those who received chemotherapy alone (66 ± 7 % vs. 12 ± 5 %; $p < 0.0001$). A landmark analysis was performed to exclude those with remission duration shorter than 232 days (median time to HCT plus 1 month). HCT continued to show an advantage for patients who underwent HCT in CR1 ($n = 29$) versus those who did not ($n = 40$) (EFS 74 ± 9 % vs. 15 ± 6 %; $p < 0.0001$). This also led to better survival in patients receiving HCT in CR1 compared to those receiving chemotherapy (OS 54 ± 8 % vs. 33 ± 7 %; $p = 0.06$) (Gokbuget et al. 2012).

8.4.5 Infants with ALL

Infants with ALL have long been noted to have a poor outcome. Most of the increase in risk has been attributed to a unique leukemia biology. With known poor survival using chemotherapy alone, Japanese investigators designed a study that offered HCT in CR1 to infants whose leukemia had rearrangement of *MLL* (those possessing one of many common translocations involving the *MLL* gene located on chromosome band 11q23). Of 44 *MLL* rearranged infants, 38 underwent HCT and 29 received HCT during CR1 (64 % 3-year EFS). Infants undergoing HCT in CR2 or relapse had a very poor outcome (22 % 3 years EFS) (Kosaka et al. 2004). Using an intensified chemotherapy approach, COG investigators showed that infants without *MLL* rearrangements did significantly better, with the majority of them surviving without HCT (60.3 % vs. 33.6 % 5-year EFS in *MLL* non-rearranged vs. rearranged patients) (Hilden et al. 2006). Multivariate analyses of infant ALL by this COG group showed higher risk associated with absence of the surface marker CD10, age <6 months, the presence of an *MLL* (11q23) rearrangement, and WBC >200,000/μL at presentation (Hilden et al. 2006).

With improved chemotherapy outcomes noted, the COG attempted to assess whether HCT improved survival in *MLL* rearranged infants undergoing HCT in CR1. They combined two studies (one which recommended HCT and one for which HCT was optional) and retrospectively gathered data from many patients who received off-protocol HCT. Combining both high-risk (younger children with high WBC) and low-risk populations, outcomes were identical (49 % for both HCT and chemotherapy; $p = 0.6$) (Dreyer et al. 2011), and the authors concluded that routine HCT in CR1 for infants may not be needed. The HCT preparative regimen specified in the research protocol was noted to be nonoptimal, and just over half of the patients did not receive it. Subanalysis focused on high-risk infants (*MLL* rearranged with high WBC and age <6 months or <3 months) was not performed.

The Interfant-99 study group, a large international consortium, performed a similar analysis of outcomes of infants undergoing intensive chemotherapy with or without HCT for consolidation in CR1. With much larger numbers, this group was able to identify an improved survival using HCT for their high-risk group of patients (*MLL* rearranged, age <6 months, and either poor response to steroids at day 8 or presenting WBC ≥300,000/μL). DFS at 5 years was 61 % versus 54 % for HCT and chemotherapy, respectively, in their medium-risk patients ($p = 0.09$), while outcomes were markedly better with HCT in their high-risk group (DFS 59 % vs. 22 %, $p = 0.01$, Fig. 8.3) (Mann et al. 2010). While the numbers of high-risk infants transplanted in these studies were small, there may be a role for HCT in CR1 for selected high-risk infants. This case is an important illustration that a benefit from HCT versus chemotherapy in a high-risk population can be hidden when high-risk patients are combined for analysis with intermediate- or low-risk patients.

8.4.6 Conclusions: HCT in CR1

As outlined, the decision regarding which patients should receive HCT in CR1 varies as new initial therapies targeted at risk groups affect their outcome. In addition, specific groups based their recommendations on risk factors that may be specific to their approach to therapy and detection of MRD. Fig. 8.4 shows indications for HCT in CR1 on the AIEOP-BFM ALL 2009 trial. This approach is based upon risk factors (PIF, t(4:11), hypodiploidy, prednisone poor response in T-ALL) all in the context of MRD measured at two time points. Highest-risk patients are allowed transplantation with any donor (matched or mismatched), while intermediate-risk patients are allowed matched related or unrelated HCT. The COG approach to CR1 allows HCT with any donor for patients with PIF and hypodiploidy (guidelines for very high-risk T-cell disease are under development).

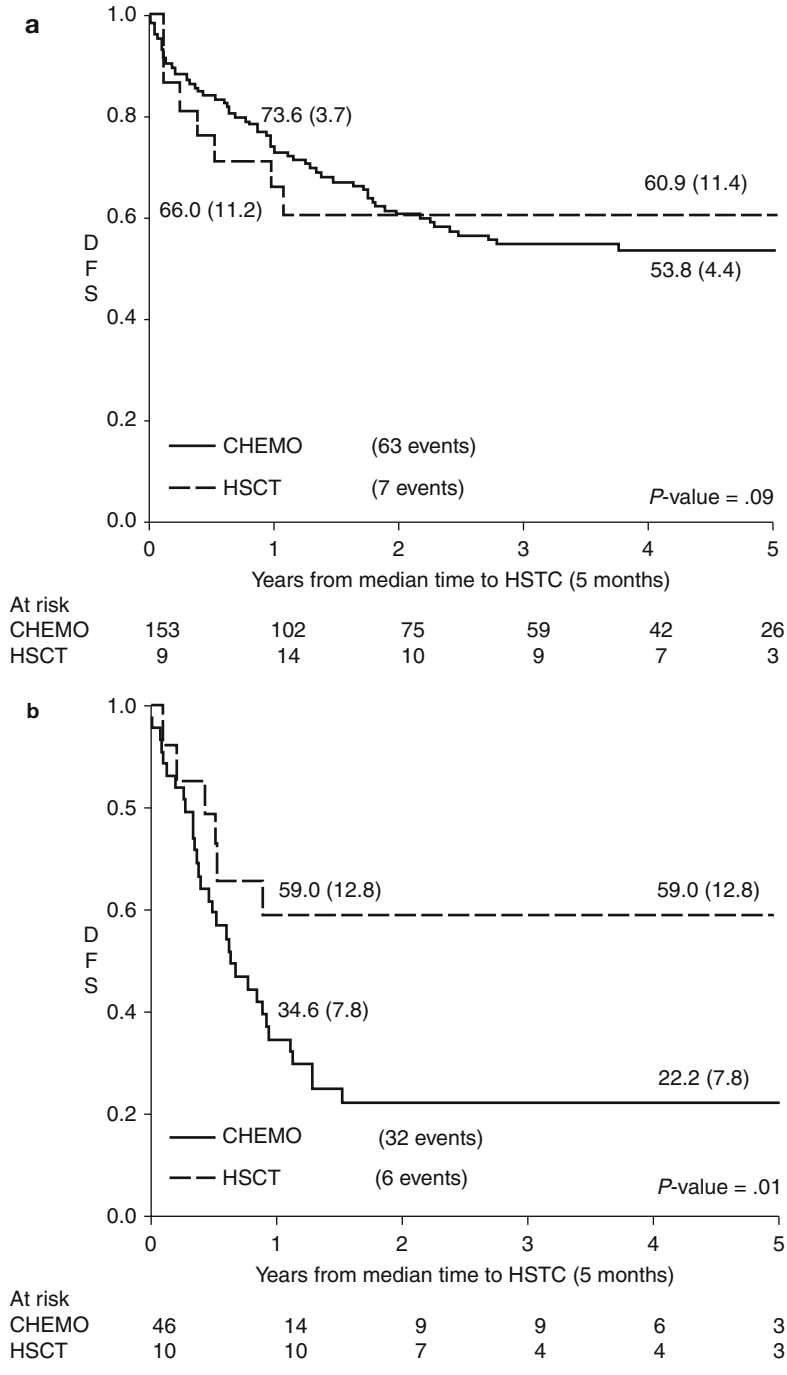


Fig. 8.3 DFS of (**a**) medium-risk and (**b**) high-risk infants treated with HCT versus chemotherapy on Interfant-99

Because of the promise of TKIs for Ph+ ALL, a joint protocol between the two groups defines a subset of patients who have persistent MRD after consolidation as eligible for HCT. These recommendations will continue to be modified as new high-risk populations are defined and new therapies improve outcomes in subsets of patients.

Indications for allogeneic stem cell transplantation CR1

		PCR-MRD results[a]				
		MRD-SR	MRD-MR[b]	MRD-HR		no MRD result
				MRD TP2 ≥ 10^{-3}– <10^{-2}	MRD TP2 ≥ 10^{-2}	
Criteria hierarchical	no CR d33	no[f]	MMD	MMD	MMD	MMD
	t(4;11)[c]	no	MD	MD	MMD	MD
	Hypodiploidy <44 chromosomes[d]	no	MD	MD	MMD	MD
	PPR + T-ALL	no	no	MD	MMD	MD
	None of the above features[e]	no	no	MD	MMD	no

no listed in a box means that HSCT is not indicated.
MD permitted donor: HLA-matched sibling or non-sibling donor
MMD permitted donor: HLA-matched or HLA-mismatched donor
[a] FCM-MRD results have no impact on the alloHSCT indication
[b] including MRD-MR SER (MRD TP1 ≥ 10-3 and TP2 10-4/-5)
[c] independent of prednisone response
[d] the finding of exactly 44 chromosomes qualifies for HR treatment but has no impact on alloHSTC indication
[e] including patients with 44 chromosomes
[f] non-remission in patients with this rare constellation should be due to extramedullary disease.
AlloHSCT indication in these cases should be discussed with the national study coordinator.

Fig. 8.4 Indications for CR1 HCT on the AIEOP-BFM 2009 Trial

8.5 Transplantation for ALL After Relapse

8.5.1 Risk Classification and Overview of Indications for HCT in CR2

Although there has been continued incremental improvement in outcomes of patients with ALL in CR1 over the past several decades (Pui et al. 2009; Gaynon et al. 2010; Moricke et al. 2010), survival of patients after relapse has remained poor (Rivera et al. 2005; Saarinen-Pihkala et al. 2006; Nguyen et al. 2008; Tallen et al. 2010; Ko et al. 2010; Roy et al. 2005). Table 8.1 illustrates that survival in high-risk patients has remained in the 10–20 % range, while about half of the children whose relapse can be classified as intermediate- or lower-risk categories will go on to survive. One of the reasons for poor survival is also illustrated in Table 8.1: up to one-third of high-risk children and up to 10 % of lower-risk children have refractory disease, never achieving a remission even after multiple attempts. Although a small percentage of these children may survive with HCT (Duval et al. 2010) (see Sect. 7.5.6), the outcome of patients who have relapsed but not achieved at least a morphological CR following relapse is dismal with any therapy, including HCT.

Figure 8.5a–c shows long-term survival probabilities of 1961 children (out of 9,585 enrolled) with ALL who relapsed on CCG studies between 1988 and 2002 (Nguyen et al. 2008). The figure clearly illustrates the major impact on risk of time from first remission to relapse and location of relapse. Figure 8.5a shows an improvement from 18 to 44 % in children with isolated marrow relapses occurring <18 months after initial remission versus those relapsing after >36 months. The same pattern but better OS is shown for those with combined BM and central nervous system (CNS) relapse (Fig. 8.5b) and isolated CNS relapse (Fig. 8.5c). These observations have been

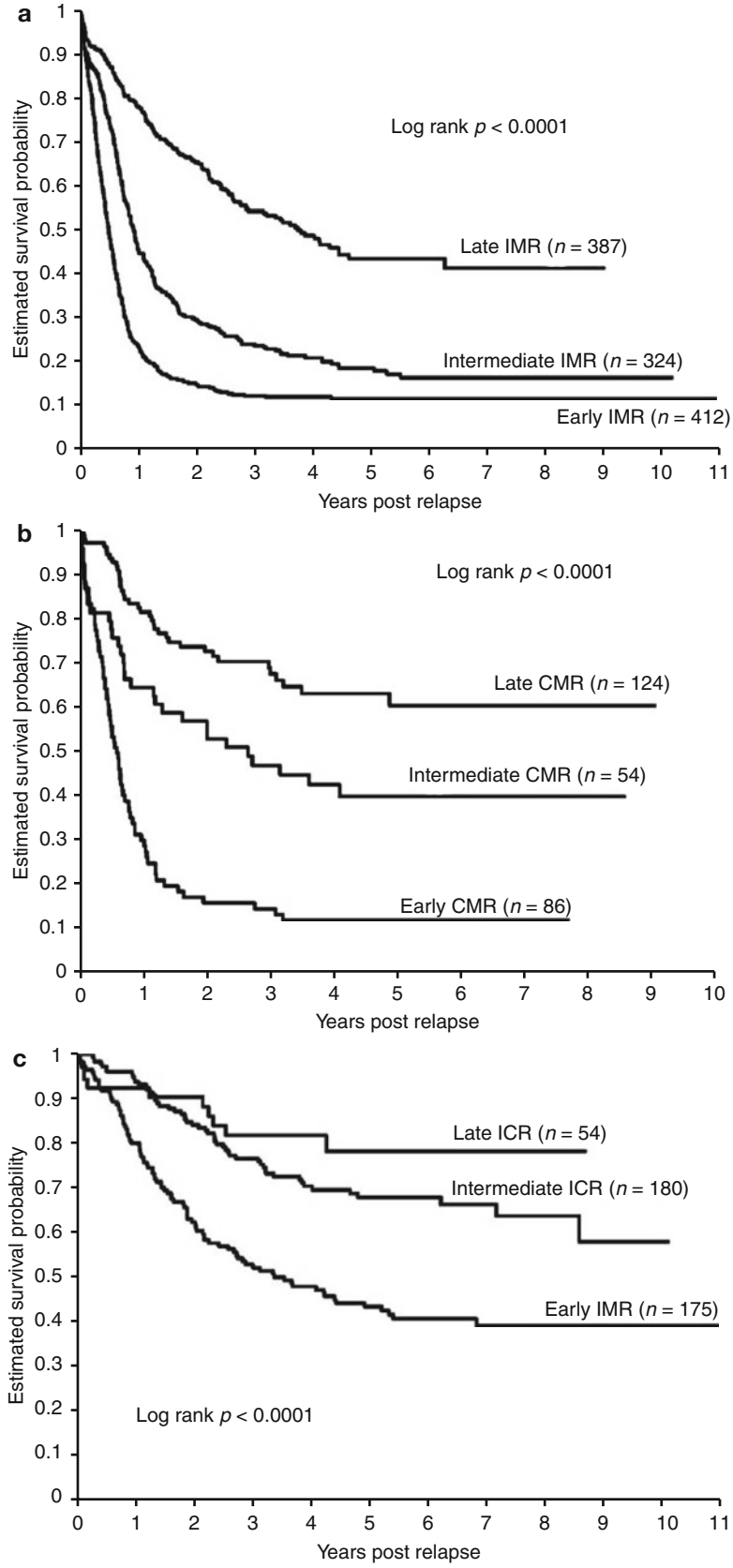
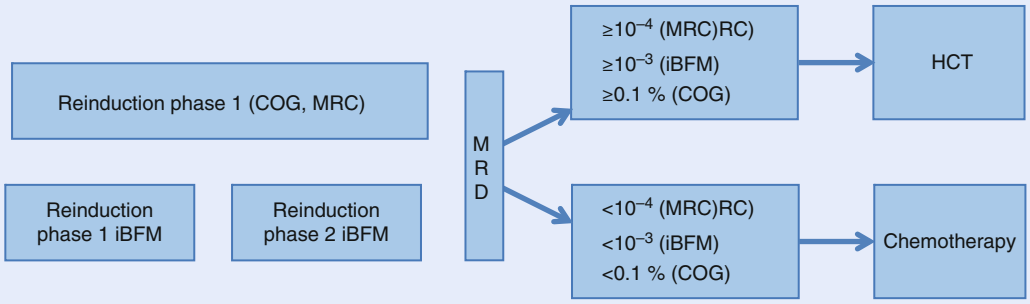


Fig. 8.5 Survival at 5 years from first relapse of 1961 ALL patients treated on COG protocols between 1988 and 2002. (**a**) Patients with isolated marrow relapse (*IMR*) based upon time to relapse (early <18 m, intermediate 18–36 m, late >36 m). (**b**) Patients with combined marrow and extramedullary relapse (*CMR*) based upon time to relapse. (**c**) Patients with isolated CNS relapse (*ICR*) based upon time to relapse

Table 8.3 Risk classification schemas of COG, MRC, and iBFM[a] for relapsed ALL (Parker et al. 2010; Schrauder et al. 2008)

Immunophenotype	Site of relapse	Very early	Early[b]	Late[b]
B cell	Isolated extramedullary	High risk	Intermediate risk	Standard risk
	Isolated marrow	High risk	High risk	Intermediate risk
	Combined[c]	High risk	Intermediate risk	Intermediate risk
T cell	Isolated Extramedullary	High risk	Intermediate risk	Standard risk
	Isolated marrow	High risk	High risk	High risk
	Combined[c]	High risk	High risk	High risk

Response-based determination of HCT for intermediate-risk/standard-risk groups



[a]iBFM also uses circulating peripheral blasts at diagnosis and has a hierarchical approach to HCT based upon donor availability

[b]MRC and iBFM consider early relapse as ≥18 m to <6 m after completion of therapy. COG defines ≥18 m to <36 m as early. Late relapse is any relapse after early

[c]COG treats combined marrow/EM relapses the same as isolated marrow relapses

noted by many groups through the years and have been used to divide patients into standard-, intermediate-, and high-risk groups. Table 8.3 overviews risk classification schemas used by COG, iBFM, and the MRC; all patients at high risk for relapse are recommended to go to HCT with the best available donor. The illustration below Table 8.3 also outlines how risk classification is further refined by determination of MRD after 1 or 2 rounds of induction therapy, thus clarifying when intermediate-risk patients may benefit from HCT (Borgmann et al. 2003; Schrauder et al. 2008; Parker et al. 2010; Pulsipher et al. 2011). High-risk groups are those with BM relapse of any kind <18 months from diagnosis or isolated BM relapse of any kind occurring either within 36 months of diagnosis or within 6 months of completing maintenance chemotherapy. In addition, all patients with T-cell or Ph+ BM relapses occurring at any time are considered high risk. Some groups consider B-cell combined BM and CNS relapse occurring after 18 months to be intermediate risk, while others consider these patients high risk. Some groups consider B-cell very early isolated extramedullary (IEM) relapses to be high risk, while others classify these as intermediate risk and just consider very early T-cell disease as high risk. Most groups consider BM or combined BM/CNS relapse occurring at or after 36 months to be intermediate risk, and late IEM relapses are considered standard risk.

Independent of these general risk classifications, other factors associated with worse outcome after first relapse by multivariate analysis include age (>10 years), the presence of CNS disease at initial diagnosis, male sex, and T-cell disease (Nguyen et al. 2008).

Once risk is assigned, different groups have recommended HCT based not only upon level of risk but also upon the presence or absence of certain types of donors. For example, iBFM protocols have allowed HCT with matched siblings for some types of intermediate-risk disease while allowing matched related or unrelated donors for higher-risk patients. The highest-risk patients are allowed HCT using any donor, including

mismatched umbilical cord blood (UCB) and haploidentical donors (Schrauder et al. 2008). COG investigators have allowed best matched donor HCT including single-antigen mismatched URD and double-antigen mismatched cord blood for unrelated donors while restricting HCT for intermediate-risk patients to matched related donors (Pulsipher et al. 2011).

8.5.2 HCT in CR2 for High-Risk Relapse

Table 8.4 shows a number of studies performed between the late 1980s through 2001 that show a clear survival advantage for children in high-risk CR2 who obtain a remission and undergo allogeneic HCT versus chemotherapy (Barrett et al. 1994; Henze et al. 1991; Locatelli et al. 2002; Feig et al. 1997; Bleakley et al. 2002b; Torres et al. 1999; Boulad et al. 1999; Eapen et al. 2006a). The studies are retrospective and thus subject to treatment bias, but most of these comparisons between HCT and chemotherapy have been appropriately analyzed to avoid time-to-HCT bias. The studies point to a survival advantage with HCT that varies between 20 and 40 % and is statistically significant in spite of small numbers. The main reason for improved success in this high-risk group after HCT is a dramatic decrease in risk of relapse that is not offset by TRM (Eapen et al. 2006a).

Although studies comparing the role of matched sibling donor (MSD) BMT in the literature are abundant for high-risk CR2 ALL, very few studies show direct comparisons of URD HCT outcomes with chemotherapy for this patient population. Such studies were more difficult to perform with the MSD comparisons that occurred during the 1990s because URD HCT was in the process of development and was generally performed off study, making comparisons difficult. To address this challenge, investigators with the BFM published a matched-pair analysis of URD HCT in 2003 that showed a clear advantage for HCT for high-risk CR2 patients (Table 8.4, pEFS 44 ± 7 % for URD HCT vs. 0 % for chemotherapy, $p < 0.001$) (Borgmann et al. 2003). A similar outcome was seen in high-risk patients in the UK ALLR2 study (Roy et al. 2005), but a study from the CCG that attempted to randomize high-risk patients between chemotherapy and HCT showed no advantage (Gaynon et al. 2006). This trial was reviewed in the section above and had many challenges with both patients and investigators refusing randomization and not following through with allotted therapy. The trial conclusion, that by intent-to-treat analysis unrelated HCT recipients had a 3-year DFS of 21 ± 7 % compared to 27 ± 8 % with chemotherapy, must be seen in the context of these challenges.

A marked improvement in outcomes of children undergoing URD HCT was noted after 1998 compared with earlier studies (Locatelli et al. 2002), and further improvement has been noted since 2003, mostly due to dramatic decreases in TRM that were likely due to better HLA typing, standardized HCT regimens, and improvements in supportive care (MacMillan et al. 2008). In addition, survival after URD HCT has been shown to be essentially equivalent to MSD HCT (Shaw et al. 2010; Pulsipher et al. 2011) (although the GVHD and complication profiles differ); therefore, in spite of an increased risk of GVHD, URD HCT has been widely adopted for use in high-risk CR2 ALL. With the increased ability to offer HCT to patients with rare HLA types by using unrelated UCB or haploidentical approaches, there is good evidence to offer HCT to children with high-risk relapsed ALL who have an acceptable donor.

8.5.3 HCT in CR2 for Intermediate- and Standard-Risk Relapse

8.5.3.1 Late BM Relapse in B-lineage Patients

The statistically significant survival advantage from HCT using any donor for high-risk relapse noted above is not present for many categories of patients with intermediate- and standard-risk relapse. The largest of the groups of intermediate-risk disease includes patients with B-lineage ALL with late BM relapses (i.e., relapse greater than

Table 8.4 Comparative studies of chemotherapy versus HCT in CR2 for high-risk relapse

Study (era)	Population	*N* (chemo/BMT)	Chemotherapy outcome	Allogeneic transplant outcome	*P*-value
Related donor studies					
IBMTR/POG (Barrett et al. 1994) HCT registry vs. patients on POG trials (1983–1991)	First relapse after remission <36 m, MSD	179/179	10 ± 3 % (5 yrs LFS)	35 ± 4 % (5 yrs LFS)	<0.001
BFM (Henze et al. 1991) (1985–1987)	First relapse <6 m off therapy	115/51	22 ± 4 % (7 yrs EFS)	52 ± 8 % (7 yrs EFS)	<0.01
GITMO/AIEOP (Locatelli et al. 2002) (1992–2000)	First relapse after remission <30 m, MSD	142/29	16.1 ± 4.5 % (3 yrs DFS)	33.4 ± 8.6 % (3 yrs DFS)	0.002
CCG 1884 (Feig et al. 1997)	Early relapse, mostly MSD	33/19	18 ± 13 % (2 yrs EFS)	37 ± 22 % (2 yrs EFS)	0.017
CHW (Bleakley et al. 2002a) Single center, Australia (1990–1997)	First relapse after remission <36 m, MSD	26/13	10 % (8 yrs EFS)	54 % (8 yrs EFS)	<0.02
Spanish (Torres et al. 1999) (1980–1988)	First relapse after remission <30 m, MSD	30/14	6.9 ± 4.7 % (>10 yrs DFS)	36 ± 12.8 % (>10 yrs DFS)	0.01
Nordic (Schroeder et al. 1999) (1981–1991)	First BM relapse after remission <6 m after finishing chemotherapy	126/63 (2:1 chemo:HCT case control)	15 ± 3 % (EFS)	35 ± 6 % (EFS)	<0.01
MSKCC (Boulad et al. 1999) Single center, United States (1979–1992)	First relapse after remission <24 m, MSD	21/11	9 ± 9 % (5 yrs DFS)	48 ± 11 % (5 yrs DFS)	<0.01
CIBMTR (Eapen et al. 2006a) HCT registry vs. patients on POG trials (1991–1997)	First relapse after remission <36 m, MSD	110/92 (TBI) + 19 (non-TBI)	23 % (8 yrs LFS)	41 % TBI, 8 % non-TBI (8 yrs LFS)	<0.001
Unrelated donor studies					
BFM (Borgmann et al. 2003) (1983–2001)	First BM relapse after remission <6 m after finishing chemotherapy	53/53 (matched-pair analysis)	0 ± 0 % (pEFS)	44 ± 7 % (pEFS)	<0.001
CCG-1941 (Gaynon et al. 2006) (1995–1998)	First BM relapse <51 m from dx (boys) and <39 m from dx (girls)	35/37 intent to treat	20 ± 7 % (5 yrs DFS ITT, only 66 % received intended therapy)	21 ± 7 % (5 yrs DFS ITT, 51 % received intended therapy)	NS
Combined URD and MSD studies					
ALLR2 (Roy et al. 2005) (1995–2002)	First BM relapse after remission <6 m after finishing chemotherapy	15/11 (mix of related and URD)	7 % (all relapsed, 1/15 alive in CR3)	45 % (5/11 alive)	Not reported
ALLBFM REZ 90 (Tallen et al. 2010) (1990–1995)	First BM relapse <6 m off therapy, All T-BM relapses	76/84 (all HCT) 76/53 (HLA matched)	20 ± 5 % (10 yrs EFS)	33 ± 5 % 40 ± 7 % (10 yrs EFS)	$p < 0.005$ $p < 0.001$

Table 8.5 Comparative studies of chemotherapy versus HCT in CR2 for late-relapsing B-lineage ALL (intermediate-risk relapse)

Study	Population	*N* (Chemo/BMT)	Chemotherapy outcome	Allogeneic transplant outcome	*P*-value
IBMTR/POG (Barrett et al. 1994) HCT registry vs. patients on POG Trials (1983–1991)	Relapse >36 m from diagnosis, MSD	76/76	32 ± 6 % (5 yrs LFS)	53 ± 7 % (5 yrs LFS)	<0.001
BFM (Henze et al. 1991) (1985–1987)	Relapse >6 m off therapy	165/51	41 ± 6 % (7 yrs EFS)	52 ± 8 % (7 yrs EFS)	NS
GITMO/AIEOP (Locatelli et al. (2002) (1992–2000)	Relapse >30 m from diagnosis, MSD	88/28	39.6 ± 5.9 % (3 yrs DFS)	54.7 ± 9.2 % (3 yrs DFS)	NS
CHW (Bleakley et al. 2002a) Single center, Australia (1990–1997)	Relapse >36 m from diagnosis, MSD	8/7	0 % (8 yrs EFS)	57 % (8 yrs EFS)	0.14
Spanish (Torres et al. 1999) (1980–1988)	Relapse >30 m from diagnosis, MSD	10/7	20 ± 12.6 % (>10 yrs DFS)	57 ± 18.7 % (>10 yrs DFS)	0.07
MSKCC (Boulad et al. 1999) Single center, United States (1979–1992)	Relapse >24 m from diagnosis, MSD	18/26	37 ± 3 % (5 yrs DFS)	81 ± 10 % (5 yrs DFS)	<0.01
CIBMTR (Eapen et al. 2006a) HCT registry vs. patients on POG Trials (1991–1997)	Relapse >36 m from diagnosis, MSD	78/61 (TBI) + 14 (non-TBI)	66 % (8 yrs OS)	63 % TBI 32 % non-TBI (8 yrs OS)	NS (chemo vs. TBI)
ALLBFM REZ 90 (Tallen et al. 2010) (1990–1995)	Relapse >6 m off therapy and IEM, matched donor	33/25	46 ± 9 % (10 yrs EFS)	52 ± 10 % (10 yrs EFS)	NS

36 months from diagnosis). These patients have a better chance of reentering remission (>90 %), becoming MRD negative after induction (49 %), and achieving long-term survival (Raetz et al. 2008a). Chemotherapy approaches alone can cure approximately 40–50 % of patients (Gaynon et al. 1998; Lawson et al. 2000; Kolb and Steinherz 2003). Survival using MSD HCT for this group has been shown to offer an advantage or a trend toward a superior outcome in some studies (Barrett et al. 1994; Locatelli et al. 2002; Bleakley et al. 2002a, b; Boulad et al. 1999; Torres et al. 1999), but outcomes similar to chemotherapy in others (Table 8.5) (Eapen et al. 2006a; Tallen et al. 2010; Henze et al. 1991). HCT for these patients has been offered on many studies when an MSD is present, but deferred to a second relapse if an alternative donor (i.e., a donor other than an MSD) is necessary or the family prefers a non-transplant approach.

Recent data has shown that patients with late BM relapsing B-lineage ALL who have persistent MRD detected after reinduction fare significantly worse than those achieving a negative MRD status after reinduction (Fig. 8.6) (Raetz et al. 2008a). With this observation in mind, most groups are choosing to offer HCT, with any donor to those with measurable MRD after reinduction and chemotherapy to those who are MRD low/negative after reinduction (Table 8.3) (Parker et al. 2010). The increase in risk based on levels of MRD detected after reinduction of late BM relapsing B-lineage patients seems to hold even if they eventually achieve remission. Further

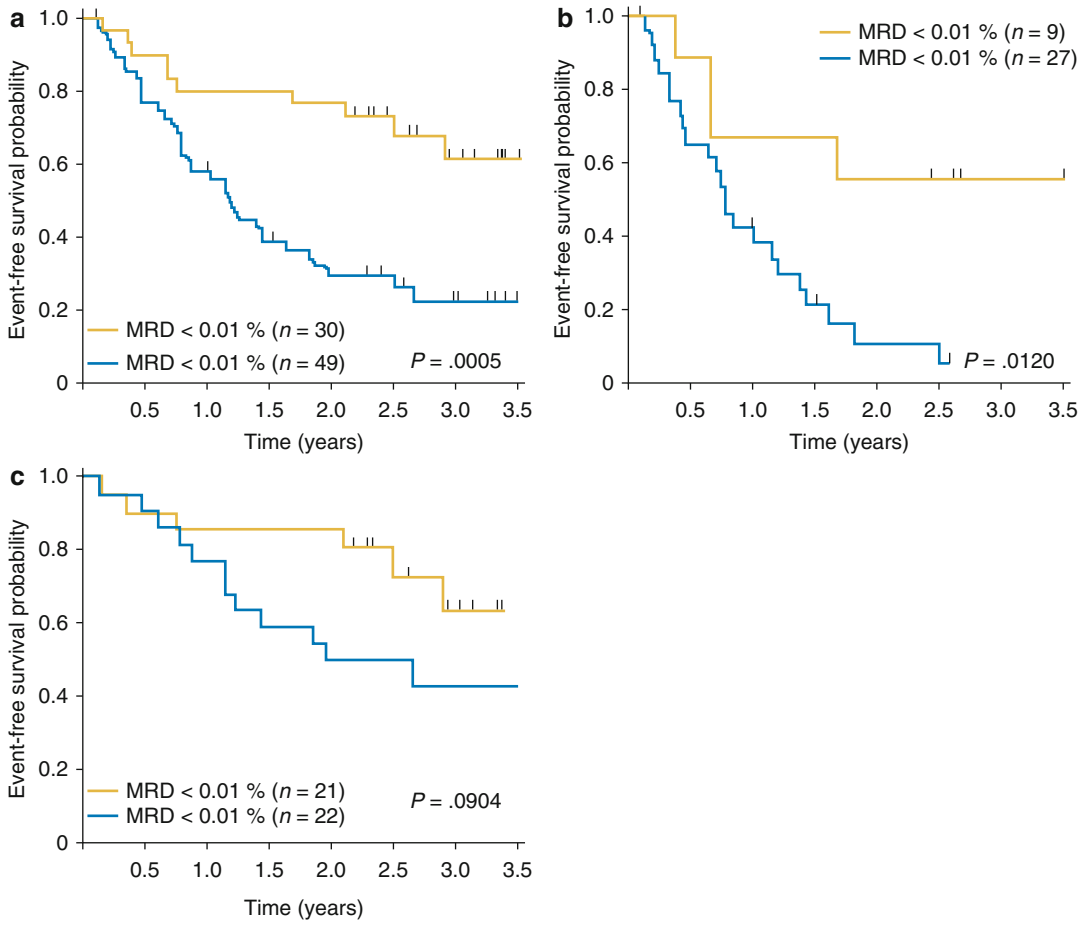


Fig. 8.6 Effect of persistent MRD after reinduction on survival. (**a**) Patients with BM relapse (entire cohort), (**b**) patients with early relapse (<36 m), and (**c**) patients with late relapse (Raetz et al. 2008a)

studies may clarify if other markers can assist in delineating better risk relapsed ALL patients who may not need HCT.

8.5.3.2 Isolated Extramedullary (IEM) Relapses

Central Nervous System: Over the past few decades, approaches to prevention of ALL relapse in the CNS have focused on intensification of CNS-penetrating chemotherapeutic agents and intrathecal therapy, allowing dramatic reductions in the use of prophylactic CNS radiation (Krishnan et al. 2010; Pui et al. 2009). This has, in turn, affected rates of isolated CNS relapse and subsequent treatment approaches. In spite of these fundamental changes in approach, several general principles in treating relapsed isolated CNS disease have been noted. As with BM relapse, time to isolated CNS relapse is critically important, with B-ALL patients relapsing prior to 18 or 24 months surviving 40–45 % of the time and those relapsing after 18 or 24 months surviving 70–80 % of the time using chemotherapy approaches (Ritchey et al. 1999; Barredo et al. 2006; Domenech et al. 2008; Krishnan et al. 2010). With favorable chemotherapy outcomes for patients with B-lineage disease relapsing after 18 months from diagnosis, most groups do not recommend HCT for these patients unless they experience a second relapse. The role of HCT in very early relapsed isolated CNS B-lineage ALL (i.e., <18 months from diagnosis) or isolated

CNS T-lineage ALL occurring at any time, where survival with chemotherapy is approximately 40 %, is more controversial.

A CIBMTR retrospective registry study comparing all patients undergoing HCT for isolated CNS relapse between 1990 and 2000 with patients enrolled on Pediatric Oncology Group (POG) 9061 and 9412 chemotherapy clinical trials showed similar outcomes for chemotherapy versus MSD transplantation. Limitations to this study included (1) the cohorts were small; therefore, subanalysis of the high-risk and low-risk cohorts could not be performed (potentially diluting an affect in the high-risk cohort); (2) the cohorts were not directly comparable, with those receiving HCT more likely to be older, have earlier relapse, or have T-lineage disease; and (3) the registry cohort included all patients undergoing HCT, while the chemotherapy cohort included only patients eligible for and registered on clinical trials (introducing a possible study enrollment bias) (Eapen et al. 2008). In addition, investigators from the iBFM showed that the presence of PCR-detectable BM disease equal to or greater than 10^{-4} in patients thought to have no BM disease was associated with an EFS of 11 ± 9 % compared to 63 ± 17 % in those with $<10^{-4}$ as detected by PCR (Hagedorn et al. 2007). Several studies have shown very low rates of relapse and good survival with allogeneic transplantation after very early IEM relapse (Harker-Murray et al. 2008; Pulsipher et al. 2009c; Yoshihara et al. 2006). With these issues in mind, although further comparative studies are warranted, several groups are allowing HCT for selected high-risk groups with isolated CNS relapse, including those with very early relapse and T-cell ALL at other times.

Testicular: Defining a role for HCT in isolated testicular relapse is challenging due to low numbers. Similar to isolated CNS relapse, chemotherapy approaches for early relapse (i.e., relapse while on therapy) result in survival in about 40 % of patients, while patients with late relapse survive more than 80 % of the time (Wofford et al. 1992). Due to low numbers, these patients have often been grouped with isolated CNS disease in investigational protocols (Domenech et al. 2008). Similar to isolated CNS, detection of submicroscopic disease in BM is prognostically significant (Hagedorn et al. 2007). HCT is not needed for patients with late isolated testicular relapse. Specific comparative studies of chemotherapy versus HCT for patients with isolated testicular relapse at higher risk have not been performed. Similar to isolated CNS, patients with early relapse or detectable disease in the BM by MRD techniques may benefit from HCT. Further study in this area is needed.

8.5.4 Treating Relapse in Adolescents and Young Adults

With the growing recognition of the unique biological features of ALL in AYA (Schafer and Hunger 2011), the prognostic importance of age has also been analyzed and there is evidence to suggest this may portend a poor outcome in relapsed ALL as well. Three-year post-relapse survival rates for children, adolescents, and young adults following treatment on the COG CCG-1961 trial for National Cancer Institute (NCI)-defined high-risk ALL were recently analyzed according to age at diagnosis (Schafer and Hunger 2011). OS rates following marrow relapse were 48.6 ± 5.3 %, 35.4 ± 5 %, and 14.7 ± 6.8 % ($p = 0.001$) for 1–9-, 10–15-, and 16–20-year-olds, respectively. Although the details of salvage therapy were not reported, these outcomes suggest that age at diagnosis is a prognostic factor in relapsed ALL, just as it is for newly diagnosed disease, and greater age at diagnosis may be a consideration for HCT at the time of relapse.

8.5.5 HCT for Patients in CR3+

Although there are no studies directly comparing chemotherapy with HCT for patients in CR3+, because cure with chemotherapy alone is rare, transplant is generally considered a reasonable approach for those achieving another state of remission. Outcome of all patients after a

second relapse is particularly poor, in the 10–20 % or less range (Saarinen-Pihkala et al. 2006). One of the principal reasons for this is failure to obtain a third remission. As reviewed by Gaynon, only about 40 % of children with second relapse achieve remission, in spite of numerous attempts at novel combination approaches (Gaynon 2005). There is some indication that novel immunologic agents may improve CR3+ rates (see Sect. 7.12), and offering such approaches or other promising targeted agents to these patients in order to achieve CR should be encouraged. Once such patients achieve CR, HCT has been shown to cure 20–35 %, with failures occurring due to high rates of relapse and TRM (Woolfrey et al. 2002; Afify et al. 2005; Gassas et al. 2008).

8.5.6 HCT for Refractory ALL

Children undergoing HCT after failing to obtain remission (defined by morphologic CR, <5 % blasts) have a poor outcome. Data from the 1990s showed survival rates of approximately 20 % if patients were early in their therapy (after a primary induction failure) and <10 % if later in their treatment course (refractory after subsequent relapses) (Biggs et al. 1992). A more recent CIBMTR study including 582 patients with ALL undergoing HCT with refractory disease showed that patients with PIF or first untreated relapse had the best chance of success, while those with refractory disease after first or subsequent relapses fared poorly (Duval et al. 2010). Favorable characteristics included age <10, BM blasts <25 %, and donor CMV status (negative). Patients with all three favorable characteristics had 3-year survival rates just over 40 %, but this was a small subset of patients. Patients with 2 and 3 unfavorable characteristics had 3-year survival rates of 22 and 10 %, respectively. Although this study clearly demonstrates that the majority of patients going to HCT with refractory ALL do very poorly, there are some subsets of more favorable-risk patients for whom HCT may offer some chance of success.

8.6 Stem Cell Sources for ALL HCT: Bone Marrow, Peripheral Blood Stem Cells, and Cord Blood

Three stem cell sources are currently available to provide an allogeneic hematopoietic stem cell product: bone marrow, peripheral blood after stimulation with granulocyte colony-stimulating factor (G-CSF), and umbilical cord blood. The graft sources vary substantially with respect to cell numbers, cytokine profile, and immunological features (Deliliers et al. 2001; Arcese et al. 1998).

8.6.1 Clinical Outcomes After Allogeneic HCT For Pediatric ALL by Stem Cell and Donor Source

The advantages and disadvantages of using a given stem cell source are in part related to its T-cell content. PBSCs contain high doses of T cells and lead to rapid engraftment and less early morbidity, but this benefit is tempered by an increase in chronic GVHD and late morbidity. UCB recipients receive a much lower T-cell dose, and engraftment and immune reconstitution are generally delayed, resulting in more early infectious morbidity and less chronic GVHD. Moderate or intense T-cell depletion of either PBSCs or BM can lead to much less GVHD but has been associated with slow immune reconstitution, increased relapse, and an increase in post-transplantation Epstein-Barr virus (EBV) lymphoproliferative disorder (EBV-LPD), a potentially fatal complication.

8.6.1.1 Bone Marrow Versus PBSC from HLA-Identical Siblings

Trials randomizing adult HCT recipients between MSD BM and PBSC have generally favored PBSC for high-risk disease while showing equivalent outcomes for lower-risk indications (Champlin et al. 2000; Bensinger et al. 2001). Early outcome data on the use of PBSC transplantation in pediatric patients

suggested rapid engraftment with comparable relapse risk, but an increased incidence of chronic GVHD (Diaz et al. 2004, 2005; Levine et al. 2000; Watanabe et al. 2002). A small pediatric comparison between BM and PBSC in children was published by a single institution and described outcomes in 16 patients. Faster engraftment and a higher incidence of acute GVHD was noted in the PBSC group, but no difference in OS was observed (Meisel et al. 2005). The only available multicenter, retrospective analysis comparing PBSC to BM transplants in patients (age: 8–20 years) with ALL or acute myeloid leukemia (AML) was conducted by the CIBMTR. The study showed a higher mortality rate in PBSC recipients due to GVHD. This study included 143 PBSC recipients and 630 BM recipients. The patient cohorts were not completely comparable as PBSC recipients were more likely to have advanced leukemia, more likely to receive growth factors and higher cell doses, and more likely to have undergone HCT more recently. The PBSC donors also tended to be older than BM donors. Donor age was highly correlated with recipient age in both groups: median 18 years (4–36) for PBSC donors and median 14 years (2–37) for BM donors. Hematopoietic recovery was faster after PBSC transplantation. Risks of grade II–IV acute GVHD were similar, but chronic GVHD risk was higher after PBSC transplantation. While the risk of relapse was similar between the two groups, overall mortality was higher resulting in a 10 % decrease in OS in the group receiving PBSCs (Eapen et al. 2004).

Donation of PBSC from sometimes very small pediatric sibling donors has been problematic due to theoretical concerns about long-term effects of G-CSF along with risks of central line placement and exposure to blood products for priming of the apheresis machine in young, small children (Pulsipher et al. 2005, 2006). Because of these obstacles, and because of the possibly inferior outcome with PBSC in the CIBMTR retrospective trial, a large majority of pediatric centers prefer BM for sibling transplants for ALL, although many centers will use PBSC from siblings for special circumstances such as second transplants (especially if the first graft is rejected), reduced-intensity procedures, and haploidentical procedures where cell selection is required.

8.6.1.2 Matched Sibling Versus Mismatched Family Versus Matched Unrelated Donors

The distance between HLA antigens on chromosome 6 is such that crossovers involving HLA genes occur in approximately 1 % of siblings who would otherwise be matched, most frequently resulting in a single-antigen mismatch (5/6 antigen match or 7/8 allele level matching). In addition, family members who are not genotypically matched can share one haplotype and have a second haplotype that is matched at several antigens. This leads to a low percentage of non-sibling family members (parents, other first-degree relatives) that type as either fully matched or single-antigen/allele mismatches. Early studies in HCT for pediatric leukemia often treated single-antigen mismatched or non-sibling matched family members as matched sibling donors for decisions regarding when to move forward with HCT; however, a recent large study from the CIBMTR demonstrated that outcomes with non-sibling matched or single-antigen mismatched family members are much closer to fully matched unrelated donors than they are to sibling donors. In an analysis of 1,485 patients with acute leukemia undergoing HCT, children receiving matched or mismatched related donors (mmRD) had more acute and chronic GVHD and higher TRM than matched siblings, but identical rates compared to 8/8 matched URDs. The OS was best when patients received HCT from MSDs; survival of those receiving 8/8 matched URDs and mmRDs was similar and inferior to MSDs (Shaw et al. 2010). Other studies have shown equivalent outcomes of matched URD to MSDs for children with high-risk ALL (Schrauder et al. 2006), but this study illustrates well that GVHD and TRM are higher. Therefore, although an appropriate non-sibling family member is a reasonable alternative to a matched unrelated donor, the current donor of choice remains an MSD if available.

8.6.1.3 Cord Blood Transplantation from HLA-Identical Siblings

UCB from matched sibling donors has been performed since 1988, demonstrating acceptable outcomes when sufficient cell dose is infused (Gluckman et al. 1989). Wagner and colleagues reported 44 patients undergoing sibling donor UCB transplant (UCBT). Indication for transplant was acute leukemia in 18 of these patients. The majority of patients received an UCB unit that was fully matched or had a single-antigen mismatch. The probability of event-free survival was 46 % (Wagner et al. 2007). Smythe and colleagues reported three children with ALL who underwent HCT using cryopreserved sibling UCB (Smythe et al. 2007). Two patients died from relapse, and one was alive 4 years after the procedure. Outcome data comparing HLA-identical sibling UCB with sibling BM is scant. Rocha and colleagues reviewed 113 children who received UCB from an HLA-identical sibling transplanted between 1990 and 1997 and compared them to 2,052 children who were transplanted using BM from HLA-identical siblings during the same period. The recipients of UCB were younger than the recipients of BM (median age, 5 years vs. 8 years; $p < 0.001$), weighed less, and were less likely to have received methotrexate for GVHD prophylaxis. Multivariate analysis demonstrated a lower risk of acute GVHD (relative risk, 0.41; $p < 0.001$) and chronic GVHD (relative risk, 0.35; $p < 0.02$) among recipients of matched sibling UCB transplants. Although overall engraftment rates were similar, the likelihood of neutrophil and platelet recovery was significantly lower in the first month after UCB transplantation compared to sibling BM. Mortality was similar in both groups. Deaths related to infection from any cause and hemorrhage were more common in the UCB group, whereas deaths related to GVHD, interstitial pneumonitis, and organ failure were more common in the BM group. The number of relapse-related deaths was similar in the two groups. OS was not statistically different between the two groups (Rocha et al. 2000).

8.6.1.4 Unrelated Donors: BM, PBSC, and UCB

Since only 20–25 % of children with an indication for allogeneic HCT have an MSD, the availability of volunteer HLA-matched URDs has widened the donor pool over the past decade. The chance of finding a suitable donor mainly depends on ethnic group (ranging from 60–70 % for Caucasians to 20–40 % for patients belonging to some ethnic minorities) and the frequency of the HLA phenotype of the patient. High-resolution DNA matching of HLA class I and II of unrelated donors and recipients has impacted outcome with reduced morbidity and mortality over the last decade (Afify et al. 2005; Cornish 2005; Green et al. 1999). Consequently, the use of matched URDs has now become standard in children lacking an HLA-identical sibling. Retrospective studies over the past years have shown reduced early toxicity, especially acute and chronic GVHD, lower TRM, and similar relapse rates compared with the early reported matched URD-BMT experience (Dini et al. 2003; Eapen et al. 2006b; Locatelli et al. 2002). It is likely that improved outcomes have resulted not only from better HLA matching but also from the use of intensified GVHD prophylaxis by in vivo or in vitro T-cell depletion (MacMillan et al. 2008).

Unrelated BM Versus PBSC

Although a transplant physician may request BM or PBSC from an URD, whether donors are willing to give the requested source is ultimately up to them. Donors are counseled about both BM and PBSC harvest procedures and are able to choose which product they wish to donate. Currently, approximately 80 % of unrelated donations to adult patients are PBSC, while donations to children are mostly BM (Ballen et al. 2008). Data to substantiate a choice of PBSC or BM from a URD for a given patient have been retrospective and contradictory (Eapen et al. 2007a; Remberger et al. 2001). A phase III study of pediatric and adult patients with leukemia randomized to receive unrelated BM or PBSC from URDs was completed by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

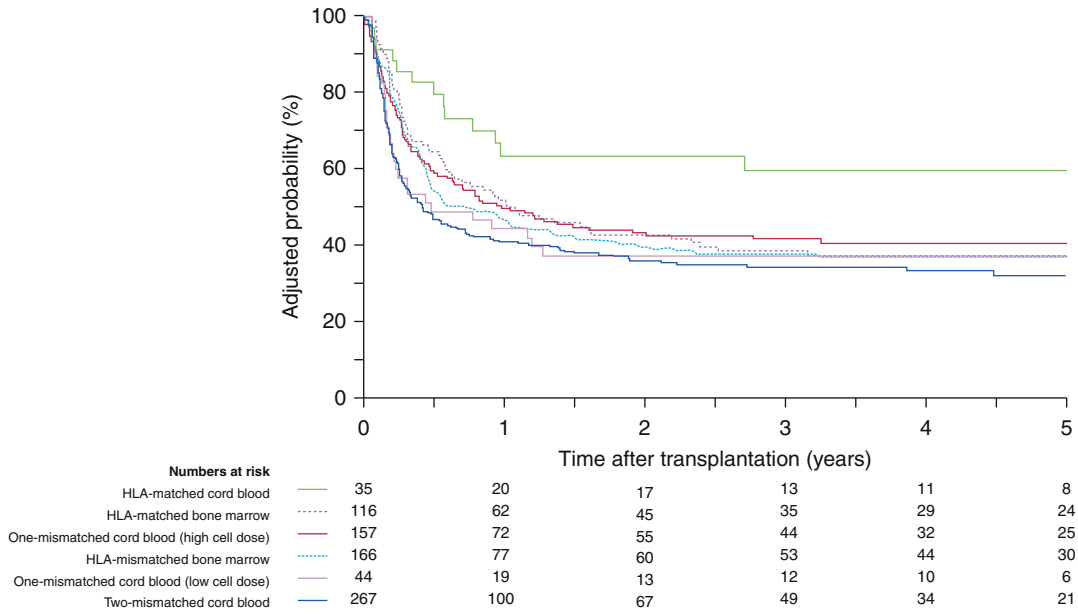


Fig. 8.7 Survival of ALL patients after HCT using matched and mismatched UCB and BM (Eapen et al. 2007b)

The trial showed that TRM, relapse, DFS, and OS were identical between the two graft sources; however, chronic extensive GVHD occurred in 48 % versus 32 % ($p<0.001$) of recipients of PBSC and BM, respectively (Anasetti et al. 2012). With this data in mind, many pediatric HCT physicians prefer BM. Further studies assessing the role of antithymocyte globulin (ATG) in preventing chronic GVHD in recipients of URD PBSC are ongoing.

Unrelated BM Versus UCB

Reporting on data from the CIBMTR, Eapen and colleagues compared outcomes of 503 children (<16 years) with acute leukemia undergoing unrelated UCBT with outcomes of 282 HCT recipients. Five-year leukemia-free survival (LFS) was similar in recipients of 8/8 allele-matched BM compared to UCB mismatched for either one or two antigens. TRM rates were higher after transplants of two-antigen HLA-mismatched UCB and possibly after one-antigen HLA-mismatched low-cell-dose UCB transplants. Relapse rates were lower after two-antigen HLA-mismatched UCB transplants. In this report, cell dose and HLA match affected the risk of TRM; recipients of two-antigen and one-antigen mismatched UCB with low cell dose had worse outcomes (Fig. 8.7) (Eapen et al. 2007b).

Unrelated UCB Versus Related Haplo-T Depleted PBSC

Comparing UCBT with haploidentical T-cell depleted PBSC transplants in children with ALL showed that failure of engraftment was significantly higher following UCBT than after haplo-HCT (23 % vs. 11 %, $p<0.007$). Acute II–IV GVHD was higher in the UCBT group. Relapse incidence was higher in haploidentical HCT recipients compared with UCBT. TRM and LFS were, however, not significantly different (Hough et al. 2009).

Taken together, these studies show that UCB transplant outcomes are comparable with those of matched URD transplants, but a decreased incidence of engraftment or delayed engraftment is one of the drawbacks. Newer strategies to enhance engraftment, such as combining two cord blood units, supplementing cord blood with haploidentical donor cells,

Table 8.6 Comparison of stem cell sources for ALL HCT

		Alternative donors		
	MRD	MUD	Unrelated UCB	Haploidentical PBSC with TCD
Availability	+	++	+++	++++
Donor risk	+	++	0	++
Time to procurement	+	+++	+	+
Cost	+	+++	+++	+++
Time to engraftment	+	+	+++	+
GVHD risk	+	+++	++	+
GVL effect	++	++	++	+
Infections	+	++	+++	+++
Relapse	+	+	+	+++

MRD matched related donor, *MUD* matched unrelated donor, *UCB* umbilical cord blood

third-party mesenchymal cells, ex vivo expansion, and better HLA matching, may mitigate these issues and decrease the incidence of graft failure and GVHD incidence for children with acute leukemias (Barker et al. 2009; Fernandes et al. 2007; Gonzalez-Vicent et al. 2010; Kelly et al. 2009).

8.6.1.5 Haploidentical Family Donors

When pediatric patients with very high-risk features of acute leukemia lack a suitable HLA-compatible related or unrelated donor, another option available is allogeneic PBSC transplantation from a T-cell depleted haploidentical parental donor (Handgretinger et al. 2003). Like UCB, almost immediate access to an allogeneic stem cell product is assured in nearly all patients (Lang and Handgretinger 2008). Outcomes of adult patients who have undergone PBSC transplant from G-CSF mobilized haploidentical donors are widely published (Ruggeri et al. 2002). As described in adults, with the modern techniques of either "positive" CD34+ selection using immunomagnetic columns or more recently with "negative" CD34+ selection by CD3/CD19 depletion approaches, a megadose of CD34+ cells can overcome the increased tendency to graft rejection. This leads to enough CD3+ T-cell depletion that the risk of GVHD can be decreased substantially (Handgretinger et al. 2008). While T-cell depletion has been necessary to decrease GVHD, the consequent delay in immune reconstitution is responsible for the two major challenges with this approach: (1) a very high risk of posttransplant infections and (2) increased relapse rates. Limited data are available on the results of haploidentical transplantation in pediatric patients with acute leukemias. Children and adolescents with acute leukemias who have not responded adequately to chemotherapy are, by definition, a high-risk population with comorbidities that increase the risk of infectious and toxic complications after transplant. In a recent analysis, 118 children with high-risk ALL who received haploidentical HCT after a myeloablative regimen had a 3-year LFS of 32 % for patients in CR1, 28 % forpatients in CR2 or CR3, and 0 % for children who were not in remission. This data confirms the importance of remission status before the transplant procedure. Furthermore, relapse incidence and TRM tended to be different, though not statistically different, between centers that performed greater than 10 haploidentical transplants in the observation period compared with centers with less than 10 transplants. In the more experienced centers, TRM was 27 % and relapse incidence 24 %, compared with 41 % TRM and 41 % relapse incidence in the less experienced centers ($p = 0.10$) (Klingebiel et al. 2010). This data suggests that it may be necessary for centers to focus on this approach and gain appropriate experience in order to achieve the best outcomes. To overcome the period of profound immune deficiency after haploidentical HCT, several strategies have been developed, including the adoptive transfer

of pathogen-specific cytotoxic T cells and disease-directed cell therapies (Feuchtinger et al. 2010; Serangeli et al. 2010; Montagnoli et al. 2008; Comoli et al. 2008; Locatelli et al. 2009).

Despite promising results in experienced single centers, to date, no specific studies have prospectively compared UCB and haploidentical family donor procedures. Table 8.6 provides a comparison of key clinical outcomes associated with different graft sources.

8.7 Autologous HCT for Children with ALL

A number of institutions pursued autologous HCT approaches in the 1980s and 1990s. Concern about potential contamination of leukemic blasts in harvested marrow was often addressed by varying approaches to purging of ALL blasts. While many of these procedures successfully cured patients, a consistent pattern of a high probability of relapse in high-risk patients emerged (Sallan et al. 1989; Messina et al. 1998; Colleselli et al. 1994). Many studies (Maldonado et al. 1998; Billett et al. 1993; Canals et al. 1997; Lonnerholm et al. 1992; Houtenbos et al. 2001; Pico et al. 1986; Ramsay et al. 1985; Schmid et al. 1993; Rossetti et al. 1993; Granena et al. 1999; Badell et al. 2005; Sallan et al. 1989; Messina et al. 1998; Colleselli et al. 1994) demonstrated survival rates comparable with intensive chemotherapy salvage regimens given during the same eras.

As outlined in prior sections, allogeneic HCT has been shown to offer a survival advantage over chemotherapy for many categories of high-risk ALL patients, and an allogeneic GVL effect has been clearly documented. In addition, salvage chemotherapy protocols have been developed that offer reasonable survival rates for selected patients with standard-risk relapses. These developments have dampened enthusiasm for autologous HCT in favor of chemotherapy for lower-risk relapses and allogeneic HCT for higher-risk patients. A few centers continue to use purged autologous approaches. An Italian group recently published a study favorably comparing survival of children with late BM relapse treated with purged autologous HCT compared to similar patients treated with BFM relapse protocols (Balduzzi et al. 2011). Although autologous HCT appeared to be better in this retrospective comparison, children treated with this approach were from a single center and highly selected, having achieved MRD-negative status early, whereas MRD status was not known for the comparator group. At best, it can be concluded that autologous HCT for lower-risk relapsed ALL may yield similar outcomes to era-appropriate chemotherapy and therefore is generally not recommended outside of the context of a clinical trial.

8.8 Preparative Regimens for Children with ALL

8.8.1 Myeloablative Approaches for ALL

The choice of conditioning regimen has a significant impact on survival after HCT. The standard for many years was a combination of TBI and cyclophosphamide (CY) (Wingard et al. 1990; Brochstein et al. 1987). Because single dose TBI was noted to lead to more acute and late side effects, it was replaced by fractionated TBI (Deeg et al. 1984). Irradiation, particularly TBI, increases the risk of late effects in children and adolescents, as the risk for secondary malignancies is higher compared to pharmacological conditioning (Friedman et al. 2008; Ferry et al. 2007; Loren et al. 2011). Only a few studies have investigated alternative options to TBI. In a retrospective analysis, Davies showed superior survival after HLA-identical sibling bone marrow transplants for ALL using the CY/TBI regimen compared to busulfan (Bu) plus Cy (Davies et al. 2000). Eapen further demonstrated better OS for high-risk patients undergoing TBI-based MSD HCT for ALL compared to non-TBI approaches, mostly due to decrease in relapse risk after TBI (overall relapse rate 27 % lower with TBI, $p < 0.001$) (Eapen et al. 2006a). The only randomized trial for children with ALL was undertaken

by Bunin through the Pediatric Blood and Marrow Transplant Consortium (PBMTC). The primary aim of this study was to evaluate the outcome for children with ALL undergoing allogeneic HCT with either oral Bu or TBI regimens. Patients <21 years with ALL undergoing allogeneic HCT were eligible. Conditioning included either Bu or TBI, with etoposide 40 mg/kg and CY 120 mg/kg. At a median follow-up of 43 months, EFS was 45 % at 3 years, with 29 % EFS in the Bu arm and 58 % in the TBI arm ($p=0.03$). There was not a significant difference between Bu and TBI for patients who received stem cells from related donors (36 % vs. 58 %, $p=0.3$), likely because of low numbers. Even with low numbers, for URD recipients the EFS was 20 % for Bu and 57 % for TBI ($p=0.04$). Relapses were similar in both arms (Bunin et al. 2003). Other irradiation-free conditioning (e.g., Bu/CY/melphalan) proved to be inferior in a comparison because of a higher incidence of relapse and high TRM (Carpenter et al. 1996).

A retrospective European study showed that conditioning with TBI plus etoposide was superior to TBI/CY (Dopfer et al. 1991). In addition, Marks et al compared TBI/Cy versus TBI/Cy/etoposide as conditioning for ALL patients in CR2 undergoing sibling allografting. They concluded that best outcomes occurred when etoposide was used or when the TBI doses used with CY were ≥13 Gy. Similarly promising outcomes have been shown when adding thiotepa to TBI (12Gy) and CY, though direct comparisons have not been performed (Bunin et al. 2005; Zecca et al. 1999). With these studies in mind, the current standard backbone for the biggest European prospective trials consists of fractionated TBI (12Gy) and etoposide (Spitzer et al. 1994), and studies conducted in North America have allowed TBI (12Gy)/CY with either thiotepa or etoposide with a third option of slightly higher dosed TBI (13-14Gy) with CY alone.

There is controversy about the use of TBI-based regimens in children under age 3–4 years due to worries about late effects during this period of rapid neurological development. Some centers use TBI on patients of all ages, due to concern that Bu-based approaches may have a similar toxicity profile (Sanders et al. 2005). Others have attempted non-TBI regimens for children under age 2–4 years, with variations by center preference. A retrospective study of infants with leukemia showed similar long-term developmental outcomes with TBI versus non-TBI regimens (Eapen et al. 2006b), but a large portion of infants in the study had either AML or an *MLL* gene rearrangement, which have been shown to do well with Bu-based regimens. In iBFM trials, children judged to be ineligible to receive TBI because of young age or previous radiation doses have received Bu/CY or in selected patients (t(4;11) needing HCT) Bu/CY/melphalan (Peters et al. 2005; Locatelli et al. 1994).

8.8.2 Reduced-Intensity and Nonmyeloablative Regimens for ALL

With the recognition that donor T cells can facilitate engraftment and tumor kill through GVL, reduced-intensity or minimal-intensity HCT approaches designed to establish donor chimerism and foster GVL have been developed. The lower toxicity associated with these regimens has led to reduced rates of TRM and an expanded ability to offer allogeneic HCT to patients who have organ damage or infections that would have traditionally precluded them from myeloablative approaches (Deeg and Sandmaier 2010). Several preparative regimen approaches have been developed that include varying degrees of myelosuppression and immune suppression. They have been categorized clinically into three major categories (Bacigalupo et al. 2009):

- Myeloablative (MA): Intense approaches that cause irreversible pancytopenia requiring stem cell rescue for restoration of hematopoiesis
- Nonmyeloablative (NMA): Regimens that cause minimal cytopenias and do not require stem cell support
- Reduced-intensity conditioning (RIC): Regimens that are of intermediate intensity and do not meet the definitions of NMA or MA regimens

There is a well-established role for RIC approaches in the treatment of older adults with ALL. In patients achieving CR1, many of whom are older and have comorbidities, several studies, using a variety of approaches and stem cell sources (including cord blood), report survival in the 50–60 % range (Stein et al. 2009; Cho et al. 2009; Bachanova et al. 2009). Survival for these patients with current chemotherapy would be expected to be less than 40 %. Outcomes with more advanced stages are worse (CR2, OS 27 %, DFS 20 %) (Mohty et al. 2008).

High rates of initial cure in pediatric ALL mean that those patients considered for HCT are very high risk and the large majority of transplants for children with ALL occur in CR2 and thus would have an expected survival less than 30 % with RIC. For this reason, RIC approaches have been reserved for children with comorbidities or infections that would make them otherwise ineligible for myeloablative HCT. Survival rates are varied, but have been in the 40–60 % range (Del Toro et al. 2004; Gomez-Almaguer et al. 2003; Strullu et al. 2012). Verneris reviewed the CIBMTR experience using RIC approaches to treat ALL, describing 38 patients undergoing the procedure as a first allogeneic HCT. Approaches varied, but all met CIBMTR definitions of RIC or nonmyeloablative procedures. Most patients (60 %) were in ≥CR2, 22 % had active disease, and 13 % were in CR1. Although the reasons for choice of a RIC approach were not known, 47 % of the patients had performance scores <90 %. DFS was 30 %, less than what would be expected with TBI-based regimens, but difficult to compare as most patients were likely not eligible for TBI (Verneris et al. 2010).

The one published prospective trial of RIC approaches for ALL in children, conducted by the PBMTC, used a modified Bu/CY/ATG approach for pediatric patients at high risk for TRM with myeloablative regimens (e.g., history of previous myeloablative transplant, severe organ system dysfunction, or active invasive infection). Seventeen children with ALL were enrolled. TRM with this approach was low (11 %) and 2-year EFS was 40 %, with no difference between ALL and AML patients. The most important factor in determining outcome was the presence of measurable disease at the time of RIC HCT. Patient with no detectable MRD at HCT had 2-year OS of 63 %, while there were no survivors when MRD was present at the time of the RIC HCT procedure (Pulsipher et al. 2009a).

In summary, RIC approaches offer a chance of cure for a portion of pediatric patients with ALL who are ineligible for MA regimens and are in a complete remission. If future development of these approaches results in improved relapse prevention, these methods could potentially result in lower TRM and decreased late effects.

8.9 Therapeutic Implications of Persistent MRD Pre-HCT

Several studies have demonstrated that patients with measurable MRD at the time of HCT have an increased risk of relapse. Using a PCR-based MRD approach, Bader and colleagues from the ALL-REZ BFM group demonstrated a progressive increase in relapse risk as MRD levels increased. The key cutoff point in this study was detection of disease at or above 10^{-4} by quantitative PCR (MRD $\geq 10^{-4}$ relapse rate 57 ± 8 %, 5-year EFS 27 ± 7 %; MRD $< 10^{-4}$ relapse 13 ± 6 %, EFS 60 ± 8 %) (Bader et al. 2009). This observation was further confirmed in a phase III COG trial using a sensitive multiparametric flow cytometry (MFC) detection method. Patients with any detectable MRD pre-HCT had an estimated 2-year cumulative incidence of relapse (CIR) of 70.8 % (50.4–99.4), while those with no detectable MRD had a CIR of 27.4 % (17.4–43.1) ($p = 0.003$, Fig. 8.8) (Pulsipher, personal communication).

A third study investigated the significance of MRD using either PCR or flow-based detection in childhood ALL transplanted with UCB. With a median follow-up time of 4 years on 170 patients, the presence of MRD before UCB transplant was shown to be a strong predictive factor for increased risk of relapse and lower LFS. The probability of LFS at 4 years was 44 % (56, 44, and 14 % for patients transplanted in CR1, CR2, and CR3, respectively ($p = 0.0001$)). LFS was improved in patients with MRD status before

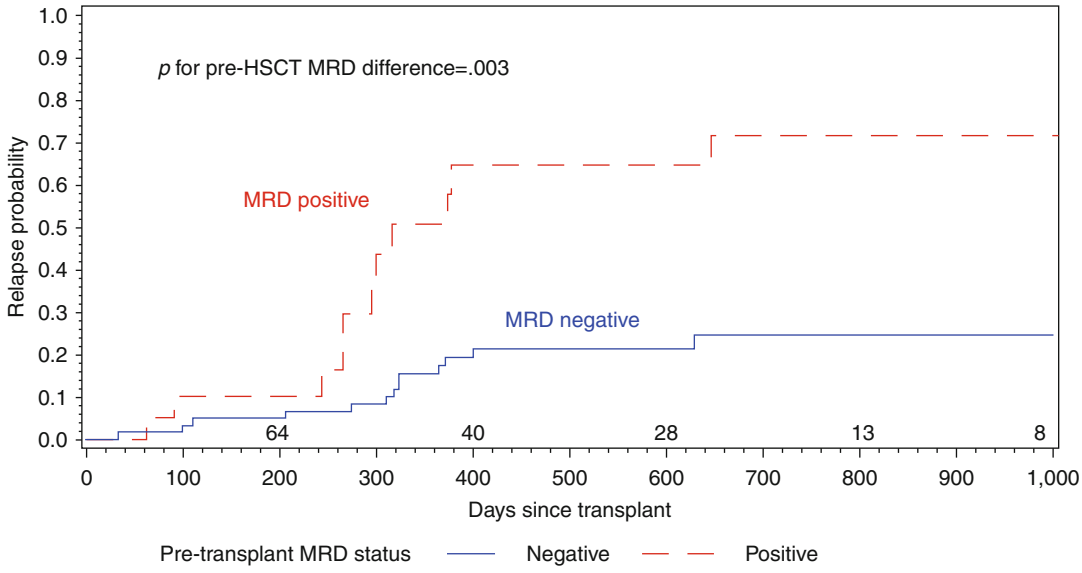


Fig. 8.8 Relapse risk after allogeneic HCT for patients with and without detectable MRD by flow cytometry (Data from COG study ASCT0431)

UCBT (54 % vs. 29 %; hazard ratio = 2, $p = 0.003$). This analysis confirmed that the presence of detectable MRD assessed by PCR ($n = 119$) or by MFC ($n = 51$) was statistically associated with decreased LFS (PCR: $p = 0.02$, MFC: $p = 0.05$) and increased relapse (PCR: $p = 0.04$, MFC: $p = 0.01$). A multivariate model for relapse and LFS suggested that MRD positivity before UCB is an adverse risk factor independent of other factors, including cytogenetics (Ruggeri et al. 2012).

Two single-center studies add further insight to this area. A Spanish center assessed the effect of MRD detected by MFC pre-HCT on outcomes of 31 children with high-risk ALL. Estimated EFS rates at 2 years for the minimal MRD-negative and MRD-positive subgroups were 74 and 20 %, respectively ($p = 0.004$), and OS rates were 80 and 20 %, respectively ($p = 0.005$). Bivariate analysis identified pre-transplant MRD as the only significant factor for relapse and also for death ($p < 0.01$). The presence of MRD measured by MFC identified a group of patients with a 9.5-fold higher risk of relapse and a 3.2-fold higher risk of death than those without MRD (Elorza et al. 2010). Investigators at St. Jude Children's Research Hospital showed that level of MRD detected by MFC was highly associated with survival and relapse. In an ALL cohort of 33 patients, survival in patients with MRD <0.01 %, 0.01- <5 %, and ≥5 % was 87.5 % (95 % CI 58.6–96.7 %), 48.5 % (17.9–73.7 %), and 0 %, respectively, with relapse progressively worse according to MRD level (Leung et al. 2012).

These studies show that MRD pre-HCT detected either by MFC or PCR is associated with increased risk of relapse and poor survival. The technologies for testing MRD vary somewhat, and standardization of approaches will help clarify risk of relapse as interventions are developed to address this risk. What has yet to be determined is (1) whether modification of MRD with further intensive therapy beyond two or three induction/consolidation regimens can be done without causing morbidity that would prevent patients from going to HCT, (2) whether and how often intense therapies can actually convert these patients to an MRD-negative status, and (3) whether conversion of patients who are still MRD positive after 2–3 intense inductions to an MRD-negative status will actually improve survival or whether persistent MRD-positive status after first reinduction is a biomarker for poor outcome that cannot be modified. Trials over the next few years are attempting to answer these questions using targeted immunological therapies (see Sect. 7.12).

8.10 Prevention of Relapse After HCT

8.10.1 Modulation of Immunosuppression in MSD HCT to Decrease Relapse

Pharmacological immunosuppression is the gold standard for preventing acute and chronic GVHD. In addition to the widely used combination of cyclosporine (CSA) and methotrexate (MTX), other drugs have been evaluated and are frequently used to prevent GVHD, including corticosteroids, mycophenolate mofetil (MMF), tacrolimus, sirolimus, and – especially in the setting of HCT from unrelated donors – poly- and monoclonal antibodies (e.g., different ATG preparations, alemtuzumab, IL2-receptor-Ab) (Peters et al. 2000).

Locatelli evaluated whether a reduction of the dosage of CSA used for GVHD prophylaxis could reduce relapse rate (RR) in children with acute leukemia undergoing HCT. Fifty-nine children who underwent HCT using MSD were randomized to receive CSA intravenously at a dose of 1 mg/kg/day (CSA1) or 3 mg/kg/day (CSA3) until patients were able to tolerate oral intake. Subsequently, both groups received CSA orally at a dose of 6 mg/kg/day, with discontinuation 5 months after BMT. The probability of developing grade II–IV acute GVHD was 57 % for the CSA1 group versus 38 % for the CSA3 group ($p = 0.06$); the probability of developing chronic GVHD was 30 % for the CSA1 group and 26 % for the CSA3 group ($p = $NS). Three patients died of grade IV acute GVHD: 2 were in the CSA1 and the third in the CSA3 group. The RR was 15 % for the CSA1 group and 41 % for the CSA3 group ($p = 0.034$); 1-year TRM estimates were 17 and 7 %, respectively ($p = $NS). With a median observation time of 44 months from BMT, the 5-year EFS for children belonging to CSA1 and CSA3 groups was 70 and 51 %, respectively ($p = 0.15$) (Locatelli et al. 2000).

The BFM study group tried to confirm this observation in a pilot study; however, all patients developed acute GVHD and 70 % developed extensive chronic GVHD. In a follow-up study, 3 mg/kg of CSA was given, but continued for only 60 days for MSD transplants. This resulted in a very low TRM (5 % at 2 years) and an acceptable cumulative relapse incidence of 18 % at 2 years (Pulsipher et al. 2011). This approach is now standard in iBFM trials. Although most North American centers still use CSA or tacrolimus in combination with MTX for sibling donors, based upon data about early tapering of CSA from an Australian study (Shaw and Afify 1999) and further data showing promising outcomes with half-dose MTX in combination with tacrolimus (Uberti et al. 2004), COG/PBMTC investigators have used a combination tacrolimus/mini MTX with early tapering (starting on day +42). Although these moderate decreases in immune prophylaxis for MSD HCT appear to have lowered relapse with tolerable TRM, specific studies comparing these approaches with more standard CSA/MTX approaches have not been performed. Studies attempting to decrease immune prophylaxis with unrelated donors have not been fruitful due to increased GVHD rates.

8.10.2 Monitoring Chimerism After HCT to Predict Relapse

Molecular surveillance of hematopoietic chimerism has become part of the routine follow-up of patients early after allogeneic HCT at many centers. Chimerism testing permits early prediction and documentation of successful engraftment, as well as facilitates early detection of impending graft failure (Breuer et al. 2012). In patients transplanted for malignant hematological disorders, monitoring of chimerism can provide an early indication of incipient disease relapse (Bader et al. 2002). Although detection of single-nucleotide and insertion/deletion polymorphisms by real-time PCR is a sensitive, competing approach, the most widely used technique in clinical chimerism testing is PCR comparisons of microsatellite (short-tandem repeats, STR) polymorphisms (Lion et al. 2012; Hancock et al. 2003). The investigation of chimerism within specific leukocyte subsets isolated from peripheral blood or bone marrow samples by

flow-sorting or magnetic beads-based techniques provides more specific information on processes underlying the dynamics of donor/recipient chimerism. Moreover, cell subset-specific analysis permits the assessment of impending complications at a significantly higher sensitivity, thus providing a basis for earlier treatment decisions (Lion et al. 2001; Thiede 2004).

8.10.3 Withdrawal of Immunosuppression/DLI to Prevent Relapse

Despite the fact that increasing recipient chimerism levels are associated with risk of relapse, the intervention repertoire to reverse this finding and decrease relapse risk is limited. One approach used to treat persistent or increasing recipient chimerism is early tapering or cessation of immunosuppression followed by DLI, if necessary. The BFM study group investigated this approach in a prospective multicenter study of 163 children with ALL following allogeneic HCT. Hematopoietic chimerism was analyzed serially and quantitatively using a fluorescent-based short-tandem repeat PCR. In all, 101 patients revealed complete chimerism (CC) or low-level mixed chimerism (MC) (CC/low-level MC); increasing MC was found in 46 patients and decreasing MC in 16 patients. Relapse was significantly more frequent in patients with increasing MC (26/46) than in patients with CC/low-level MC (8/101) or in patients with decreasing MC (0/16; $p \leq 0.0001$). The probability of 3-year EFS was 54 % for all patients, 66 % for patients with CC/low-level MC ($n = 101$), 66 % for patients with decreasing MC ($n = 16$), and 23 % for patients with increasing MC ($n = 46$; $p \leq 0.0001$).

Of the 46 patients with increasing MC, 31 received immunotherapy. This group had a significantly higher 3-year EFS estimate (37 %) than the 15 patients who did not receive immunotherapy (0 %; $p \leq 0.001$). Immunotherapy for patients receiving CSA consisted of immediate discontinuation of the immunosuppressive agent. Chimerism was then assayed weekly until CC status was restored. If MC continued to increase after cessation of CSA, a DLI was given. Immunotherapy for patients not receiving CSA consisted of DLI as frontline treatment. The cell dose administered was based on the number and potential severity of HLA mismatches between the donor and recipient and ranged from 2.5×10^4 to 1×10^6/kg CD3+ cells/kg of recipient body weight. After DLI, chimerism status was assayed weekly until CC status was restored. Patients who showed a further increase in MC were given an additional DLI after at least 3 weeks had elapsed (Bader et al. 2004).

The Dutch Childhood Oncology Group conducted a prospective MRD-guided alloimmune intervention study in which 48 patients were stratified according to pre-HCT MRD level. Eighteen children with MRD level $\geq 1 \times 10^{-4}$ were eligible for intervention, consisting of early CSA tapering followed by consecutive, incremental DLI. The intervention was associated with GVHD > grade II in only 23 % of patients. EFS in the intervention group was 19 %. In contrast with the usual early recurrence of leukemia expected in these high-risk children, relapses were delayed up to 3 years after HCT. In addition, several relapses presented at unusual extramedullary sites, suggesting that the immune intervention may have altered the pattern of leukemia recurrence (Lankester et al. 2010).

8.10.4 Administration of Targeted Therapies Post-HCT to Prevent Relapse

Early efforts to prevent relapse after HCT by administration of interleukin-2 in order to enhance a GVL effect have not gone far after the approach was shown to be largely ineffective in AML patients and excessive GVHD was noted in some studies (Lange et al. 2011; Robinson et al. 1996). It is challenging to give intensive therapies such as IL-2 in the first few months after HCT due to risks of GVHD, toxicity, and drug interactions. With the emergence of a number of small molecule inhibitors with reasonable toxicity profiles, studies are underway to assess the efficacy of use

of these agents early after HCT to prevent relapse. The best studied of these agents post-HCT are TKIs, used for treatment of Ph+ ALL or chronic myelogenous leukemia (CML). Carpenter demonstrated that imatinib can be given relatively early after HCT with moderate effects on counts and liver function tests (Carpenter et al. 2007). Schultz and COG investigators also showed that post-HCT imatinib could be given safely for an extended period in a multi-institutional setting (Schultz et al. 2009). Because this is a relatively uncommon disease, studies randomizing use of TKIs after HCT have not been undertaken. Data are conflicting about whether imatinib or other TKIs increase or decrease GVHD (Pulsipher et al. 2008), and the effect of TKIs on GVL is unknown (Seggewiss et al. 2008), but responses have occurred post-HCT for molecular relapse (Czyz et al. 2010; Merante et al. 2009), and survival in older adults undergoing reduced-intensity HCT in CR1 appears to be better when post-HCT prophylactic TKIs are used (Ram et al. 2011). It is currently not clear whether the use of TKIs after myeloablative HCT improves survival in children with Ph+ ALL (Pulsipher et al. 2008; Burke et al. 2009), but many HCT physicians are routinely using these agents, especially if patients have PCR-detectable disease after HCT.

Another class of agents, mTOR inhibitors, has been investigated as a means of preventing relapse after HCT for ALL. Based on promising data showing synergy after HCT with sirolimus and MTX in killing human ALL cells in an animal model (Brown et al. 2003), better outcomes when sirolimus was used as GVHD prophylaxis for lymphoma patients receiving RIC allogeneic HCT (Armand et al. 2008), and promising pilot data (Pulsipher et al. 2009b), COG/PBMTC investigators performed a phase III trial randomizing sirolimus plus tacrolimus/MTX versus tacrolimus/MTX alone for GVHD prophylaxis in children with ALL undergoing HCT. The study was closed early when it became clear that survival would not be improved in the experimental arm. Although acute GVHD was significantly decreased in the sirolimus arm, EFS was not improved, and the presence of GVHD was associated with less relapse and better survival. A key lesson learned from this study is that in order for post-HCT interventions to be successful, they must either not significantly interfere with GVL or have a potent antitumor effect that is stronger than GVL.

8.11 Treatment of Relapse After HCT

8.11.1 Second HCT

If ALL patients relapse after HCT, a portion of them may benefit from a second allogeneic HCT. However, many patients will be unable to undergo a second HCT procedure due to failure to achieve remission, early toxic death, or severe organ toxicity related to salvage chemotherapy (Mehta et al. 1997). Among the highly selected group of patients able to undergo a second ablative allogeneic HCT, approximately 10–30 % may achieve long-term EFS (Eapen et al. 2004; Mehta et al. 1997; Bosi et al. 2001; Michallet et al. 2000; Radich et al. 1993). Prognosis is more favorable in patients with longer duration of remission after the first HCT and in patients with complete remission at the time of the second HCT. Reduced-intensity approaches can also cure a portion of patients when used as a second allogeneic transplant approach, increasing cure rates in adult patients undergoing this procedure (Shaw et al. 2008; Baron et al. 2006). Survival rates for children with ALL undergoing a second HCT using RIC approaches have exceeded 40 %, but patients with measurable disease by MRD at the time of HCT have done poorly (Pulsipher et al. 2009a). There is no data directly comparing MA with RIC approaches for second HCT, but rates of TRM are much lower with RIC approaches, and this method may be preferable when patients are in an MRD remission.

8.11.2 Donor Lymphocyte Infusions

Although DLI induces long-term DFS in patients relapsing after HCT for CML and can cure a portion of patients with acute leukemia (Porter et al. 1999), relatively poor results have occurred

when used as therapy for relapsed ALL. The EBMT reported on 21 patients with ALL who received DLI for relapse after HCT. Among four patients who received DLI alone and 8 patients who received induction therapy but did not achieve a CR, there were no patients who achieved remission. Six of nine patients maintained remission when DLI was given after achieving remission with reinduction therapy, but these patients relapsed at a median of 15 months (Kolb et al. 1995). Collins collected data from 27 US centers and reported outcomes of 44 patients who received DLI from both related and unrelated donors. Fifteen patients received DLI with no chemotherapy and two went into remissions that were prolonged (1,112 and 764+ days). Twenty-five patients received DLI at the nadir of their chemotherapy; 5 entered remissions that lasted 42, 68, 83, 90, and 193 days. Four patients received DLI after achieving remission with chemotherapy with remissions that continued for 65, 99, 195, and 672+ days. In spite of 49 and 25 % of evaluable patients developing acute or chronic GVHD, respectively, overall actuarial survival was only 13 % at 3 years (Collins et al. 2000). Levine described 18 pediatric patients, 14 of whom died without achieving CR. Of the 4 who achieved CR with chemotherapy prior to DLI, two died of relapse (4 months and 3 years), one died of an infection complicating chronic GVHD, and one was alive at 6 years after DLI (Levine et al. 2008). It is clear from these data that nontargeted infusion of donor T cells does treat and cure a small portion of patients with ALL, but response without chemotherapy is rare and remissions obtained may be short. Given the poor efficacy of DLI for patients relapsed after HCT, experimental approaches or second HCT for selected late-relapsing patients in CR should be considered in preference to DLI.

8.12 Emerging Cellular/ Immunological Approaches for High-Risk ALL

The major advances in cure of children with ALL over the past 4 decades have largely been attributable to delivering standard cytotoxic chemotherapies in improved combinations with timing and intensity determined by risk factors. For very high-risk ALL such as early BM recurrence, however, increasing intensity of therapy has not improved outcomes. Several new immunological and cellular approaches are emerging that show promise over the next decade of both increasing rates of cure (especially with high-risk patients) and decreasing late effects. These therapies are currently being developed both in the context of and independent of allogeneic HCT approaches. A brief review of how these therapies can be used in the context of HCT is reviewed below.

8.12.1 Targeted Antibody Therapies

Antibodies directed at molecules on the surface of tumors have significantly improved survival in many tumor types. Such antibodies can be either "naked" (enhances the patient's own immune system), conjugated to a toxin that causes direct tumor kill by contact and endocytosis, or conjugated to radioactive molecules and thus used to deliver local radiotherapy. The two most common targets that are being investigated in ALL therapy are CD19 and CD22, both of which are expressed on most B-cell ALL blasts. COG investigators have studied a naked CD22 antibody, epratuzumab, as part of reinduction chemotherapy (Raetz et al. 2008b), but utility of this antibody in increasing remission rates or when given peri-HCT is unknown. Two antibodies to CD22 conjugated to toxins (inotuzumab ozogamicin and moxetumomab pasudotox) have shown significant single-agent activity in ALL (Kantarjian et al. 2012). Moxetumomab is currently being tested just prior to initiation of an HCT preparative regimen with a hypothesis that the agent can successfully reduce MRD and improve survival when given to patients who have achieved remission but have persistent MRD. Because antibodies conjugated to toxins are not dependent upon highly active immune systems, these molecules may be useful when given prophylactically post-HCT to prevent relapse, and trials to assess post-HCT efficacy of these agents are being planned.

8.12.2 T-Cell Engager Molecules

A class of antibody-like molecules called bi-specific T-cell engagers (BiTE) increase activation and specificity of T-cell cytotoxicity by binding simultaneously to the CD3 protein on T cells and a tumor target. The first of many molecules in this class that has been tested in ALL is blinatumomab, which binds CD3 and CD19. An early study of single-agent blinatumomab given as a 4-week continuous infusion to B-cell ALL patients with refractory MRD-positive disease showed response with MRD negativity in 76 % and prolonged survival (Topp et al. 2011). Targeting of the T cells to CD19 is not specific to ALL cells, as profound B-cell depletion occurs in these patients (Klinger et al. 2012). Blinatumomab has been successfully used in pediatric patients relapsing post-HCT and has allowed them to obtain remission, going on to second transplants (Handgretinger et al. 2011). Phase II studies in pediatrics are underway and a study using the agent pre-HCT to obtain deeper remission or eliminate MRD with a goal of improving survival after HCT is in the planning stages. Use of the agent post-HCT to prevent relapse may be beneficial, although success is dependent upon functional T-cell populations; just when a given individual has enough T-cell immunity post-HCT to allow the agent to be efficacious is unknown.

8.12.3 Chimeric Antigen Receptor T Cells

Another approach to enhancing T-cell-mediated tumor kill is the use of chimeric antigen receptor T cells (CART cells). The approach involves transduction of T cells with genes for a molecule that is then expressed on the cell surface. The portion of the peptide on the cell surface has an antigen recognition region that can bind specific tumor antigens. The portion of the protein inside the cell is designed to activate the cells and also assist in survival and proliferation of the targeted T cell. Improvements made on this concept through the years have resulted in efficient transduction and proliferation methods and now finally creation of long-lasting T cells. Treating adults with CLL with CD19-CART cells, investigators at the University of Pennsylvania showed significant responses with long-lived, functional T cells (Porter et al. 2011; Kalos et al. 2011). Studies in pediatric ALL are underway, and complete remissions in refractory patients have been documented (personal communication, Stephen Grupp). Use of these cells either pre-HCT or instead of HCT is being explored. In addition, because some patients may not have adequate T cells to create functional CART cells, use of allogeneic T cells may be possible, but this would require establishment of an allogeneic graft using the same donor.

8.12.4 Natural Killer Cell Therapy/ KIR-Ligand Donor-Recipient Mismatching

Natural killer (NK) cells are important in the immune response and promising results using NK cells to prevent relapse have been published for children with AML (Rubnitz et al. 2010). Killer cell immunoglobulin-like receptors (KIR) on the surface of NK cells interact with HLA class I molecules on target cells. A number of centers have reported that haploidentical HCT using donors with specific combinations of KIR-Ligand (KIR-L) donor/recipient HLA class I mismatches have resulted in decreased relapse and improved survival in patients with AML, but not ALL (Giebel et al. 2003; Ruggeri et al. 2007). Data showing a possible effect of KIR-L mismatching in children with ALL has been put forward by two groups (Leung 2011; Leung et al. 2011; Feuchtinger et al. 2009; Pfeiffer et al. 2010), but methods vary and the best way to define appropriate KIR-L/HLA class I mismatches is being refined. Further study is needed to demonstrate what role NK-cell infusions or KIR-L mismatched haploidentical approaches should play in the treatment of high-risk ALL. Because NK-cell-based approaches do not worsen and

may possibly decrease GVHD, several approaches aimed at expanding NK cells and targeting tumor with them are being explored. For example, BiTE-like molecules that link NK cells to tumor targets such as CD19 are being developed.

8.12.5 Other Immunologic Approaches

Although ALL seems to have less immunogenicity than other tumors, attempts to create tumor vaccines with stronger immunological effect are underway (Rousseau et al. 2006). Such an approach will likely only be successful in the context of minimal disease, such as after allogeneic HCT. Nonspecific enhancement of post-HCT immunity is being tested in the form of cytosine-phosphate-guanine oligodeoxynucleotides (CpG-ODNs). These molecules stimulate toll-like receptors (TLR), enhancing immune response. Enhanced allogeneic T helper 1 (Th1) responses against ALL have been demonstrated after treatment with CpG-ODNs (Reid et al. 2005), and a phase I trial using this approach for children with refractory ALL is underway. With the abundance of highly efficacious immune-mediated approaches to treatment of ALL reviewed above, it is highly probable that ALL therapy in the future will have immune approaches as a key component.

Conclusion

HCT is an effective therapy for high-risk ALL, but its use should be reserved for patients at high risk for recurrence. As therapies targeting specific biological pathways are successfully integrated into ALL treatment, indications for HCT will likely be modified. ALL that is refractory to chemotherapy approaches will continue to occur in a subset of patients, however. New immunological approaches, either associated with HCT or in place of it, may in the coming years prove efficacious in treating children with this challenging disease.

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Acute Myeloid Leukemia

9

John Horan, Henrik Hasle, and Soheil Meshinchi

Contents

9.1 Introduction

Acute myeloid leukemia (AML) continues to be one of the most common indications for allogeneic HCT in children, surpassed only slightly by acute lymphoblastic leukemia (ALL), the leading indication (Pasquini and Wang 2012). Trials of matched related bone marrow transplantation involving children and young adults with leukemia performed in the 1970s and early 1980s at the Fred Hutchinson Cancer Research Center, the University of Minnesota, Johns Hopkins University and Memorial Sloan Kettering Cancer

J. Horan (✉)
Aflac Cancer and Blood Disorders Center, Emory University, Children's Healthcare of Atlanta, Atlanta, GA, USA
e-mail: john.horan@choa.org

H. Hasle
Department of Pediatrics, Aarhus University Hospital, Skejby, Denmark

S. Meshinchi
Clinical Research Division, Fred Hutchinson Cancer Research Center, Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA

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Center established HCT as an effective therapy for pediatric AML (Brochstein et al. 1987; Kersey et al. 1982; Santos et al. 1983; Thomas et al. 1977). These studies yielded seminal findings, which continue to guide our approach to HCT for children with AML today. The numerous advances that have been made in the field of HCT since then, including the introduction of unrelated donor transplants, of more effective forms of graft versus host disease (GVHD) prophylaxis and of more effective forms of supportive care, have not only expanded the role of HCT in pediatric AML, they have also improved outcomes (Horan et al. 2011).

9.2 Epidemiology

9.2.1 Incidence

The annual incidence of AML in children up to 15 years of age is estimated to be between 5–7 cases per million children at risk, accounting for 15–20 % of all childhood leukemias (Hjalgrim et al. 2003; Hasle et al. 1999b). The peak incidence of childhood AML occurs in the first year of life with 30 % of childhood AML patients being younger than 2 years at diagnosis. The incidence remains relatively constant from 3 years of age throughout childhood and early adulthood (Hjalgrim et al. 2003; Gurney et al. 1995). There is a slight female predominance in infants followed by a higher incidence in males, but no strong gender-specific difference in incidence (Gurney et al. 1995).

The frequency of some subtypes of AML varies according to ethnicity. For example, acute promyelocytic leukemia (APL) occurs at a much higher incidence in the Hispanic and Southern European populations (Douer et al. 1996).

9.2.2 Environmental Exposures

Relatively few studies have focused on the etiology of AML (Puumala et al. 2013). Environmental factors may involve direct damage to DNA or repair mechanisms and show similarities with the leukemogenic potential of predisposing inherited bone marrow failure syndromes. Prenatal exposure to ionizing radiation results in an increase in the incidence of AML; however, the association between exposure to diagnostic x-ray and the risk of AML remains unclear (Shu et al. 1994).

Prenatal exposures to maternal cigarette use, drug use, and alcohol consumption may increase the risk of AML (Severson et al. 1993). Maternal ingestion during pregnancy of foods and vegetables with high contents of topoisomerase II inhibitors (e.g., flavonoids) has been associated with a higher risk of infant AML with mixed lineage leukemia (*MLL*) gene rearrangements (Ross 2000).

In general, the known etiological association between external factors and pediatric AML is very low.

9.3 Inherited and Acquired Predisposition to AML

Secondary myeloid neoplasia in patients with predisposing conditions often shares the biologic characteristics of myelodysplastic syndrome (MDS), including relative resistance to chemotherapy, regardless of the presenting blast count, and the prognosis appears to depend primarily on the cytogenetic profile.

9.3.1 Constitutional Genetic Abnormalities

Down syndrome (DS) is the most common predisposition to myeloid leukemia. It is often stated that children with DS have a 500-fold increased risk of acute megakaryoblastic leukemia (AMKL) compared to the general pediatric population; however, myeloid leukemia of Down syndrome (ML-DS) is very distinct from AMKL occurring in non-DS children. Only a few children with DS above 4 years of age have classical AML (Hasle et al. 2008). Children with DS below 5 years of age have a 40-fold increased risk of ALL and a 150-fold increased risk of myeloid leukemia (Hasle et al. 2000).

Myeloid leukemia has been reported in association with a number of constitutional cytogenetic abnormalities other than trisomy 21, but there is only solid evidence for an increased risk in trisomy 8 mosaicism (Maserati et al. 2002). AML has occasionally been reported in patients

with Klinefelter and Turner syndromes, but no increased risk has been documented in cohort studies (Hasle et al. 1995, 1996).

9.3.2 Inherited Bone Marrow Failure Syndromes

Most inherited bone marrow failure syndromes are associated with an increased risk of myeloid leukemias (Alter et al. 2010). The highest risk is found in Fanconi anemia (FA) with myeloid leukemia in up to 50 % of patients with FA before 40 years of age. The risk varies according to genetic subtype (Rosenberg et al. 2008). The constitutional abnormalities associated with Fanconi anemia may be subtle, and the diagnosis should always be considered in patients with myeloid leukemia.

The survival of patients with severe congenital neutropenia (SCN) improved significantly after the introduction of granulocyte colony-stimulating factor (G-CSF) (Donadieu et al. 2005). The increased survival has revealed a 10-year cumulative risk of myeloid leukemia (often with monosomy 7) of 21 % (Rosenberg et al. 2006). There is no direct relationship between myeloid neoplasm and G-CSF therapy, but the risk of leukemia is highest in those with an inferior response to G-CSF (40 % at 10 years) (Rosenberg et al. 2006).

Myeloid neoplasms develop in approximately 30 % of children with Shwachman-Diamond syndrome (SDS) (Smith 2002) and is also associated with chromosome 7 abnormalities. MDS/AML have occasionally been described in patients with Diamond-Blackfan anemia (Hasle et al. 1999a, b; Vlachos et al. 2008), dyskeratosis congenita (Dokal 2000), and congenital amegakaryocytic thrombocytopenia (Maserati et al. 2008), but no reliable risk estimates are available.

9.3.3 Familial AML/MDS

There is an almost 100 % concordance rate of AML in identical twins during infancy attributed to the shared circulation of the monochorionic placenta as evidenced by the common clonal origin (Greaves et al. 2003; Kadan-Lottick et al. 2006).

Several families affected by MDS/AML, often associated with monosomy 7, have been reported (Hasle et al. 1999b; Owen et al. 2008). Familial MDS/AML has a poor prognosis and HCT is indicated in most cases. Families with germ line mutations of the transcription factors CEBPA or RUNX1 (associated with chronic thrombocytopenia) represent an exception, carrying an increased risk of AML with the clinical features and prognosis of de novo AML (Pabst et al. 2008; Shinawi et al. 2008). The development of AML is hypothesized to follow additional somatic mutations (Nanri et al. 2010).

9.3.4 Therapy-Related Myeloid Neoplasms

Therapy-related myeloid neoplasms (t-AML, t-MDS) often share the biologic characteristics of MDS and are included as a separate disease entity in the World Health Organization (WHO) classification (Vardiman et al. 2009). Exposure to radiotherapy, epipodophyllotoxins, anthracyclines, or alkylating agents may all lead to t-AML. Most children with therapy-related myeloid neoplasms have received a combination of genotoxic agents; therefore, a classification according to the type of therapy is not applicable (Vardiman et al. 2009). The peak incidence of therapy-related MDS and AML occurs 3–5 years after initial treatment, but some cases still occur 10–12 years later (Barnard et al. 2002; Schmiegelow et al. 2009). Individual variation in genes involved in drug metabolism, cellular protection, and DNA repair may determine the risk of t-AML. An example is the genetic polymorphism in thiopurine methyltransferase (TPMT) catalyzing the methylation of 6-mercaptopurine and 6-thioguanine. The risk of therapy-related myeloid neoplasms is significantly higher in ALL patients heterozygous for TPMT low activity (Schmiegelow et al. 2009).

9.4 Biology of AML in Children

AML is a complex and extremely heterogeneous hematopoietic malignancy that is the culmination of interaction between genetic and epigenetic alterations in the hematopoietic stem/progenitor cells, leading to dysregulation of multiple critical signal transduction pathways, and resulting in hematopoietic insufficiency. As no individual has

recapitulated AML phenotype, it has been suggested and experimentally confirmed that AML evolves as a result of cooperation between different classes of genetic alterations that are sequentially acquired and cooperate to lead to leukemic phenotype. In a classic two-hit model suggested by Gilliland et al., an initial transforming event is thought to arise in the hematopoietic stem/progenitor cells, which would lead to differentiation arrest and self-renewal properties (Levine and Gilliland 2008; Kelly et al. 2002a). As these "arrested" clones lack proliferating capability, they may persist as minor clones for extended periods. Acquisition of secondary, proliferative "hits" may lead to the expansion of the differentially arrested clone and leukemic phenotype. Recent technologic advances have allowed more complete interrogation of the AML transcriptome, genome, and epigenome, leading to the identification of an increasing number of disease associated alterations, suggesting that AML pathogenesis may be more complex than this "two hit" hypothesis. Data suggest that AML is a continually evolving and molecularly heterogeneous disease, and further selection pressure by exposure to chemotherapeutic agents may lead to significant clonal selection and emergence of resistant clones that may not be present at diagnosis (Arceci and Meshinchi 2011; Meshinchi et al. 2012).

9.4.1 Structural Alterations

Structural genomic alterations that contribute to AML pathogenesis can be grouped into several broad categories, including large structural alterations, such as duplications, deletions, and translocations identified by standard karyotype analysis or sub-karyotypic (cryptic) alterations that are detectable by more targeted approaches (reverse transcription-polymerase chain reaction (RT-PCR), single nucleotide polymorphism (SNP)/comparative genome hybridization (CGH) arrays, RNA sequencing, whole genome sequencing). Karyotypic abnormalities remain the cornerstone of diagnosis in AML and have provided valuable tools for appropriate diagnosis as well as clinically meaningful prognostic tools for risk-based therapy allocation. Although a large number of chromosomal alterations are identified in AML, the majority of pediatric AML cases fall into a few specific cytogenetic categories (Fig. 9.1), where 20 % have core binding factor (CBF) AML (t(8;21) or Inv(16)), 12 % have t(15;17), 20 % have rearrangements involving the *MLL* gene, and 20 % do not have identifiable karyotypic abnormalities (normal karyotype, NK). Abnormalities in CBF have been shown to be highly associated with AML and as a result of this association, its presence is considered

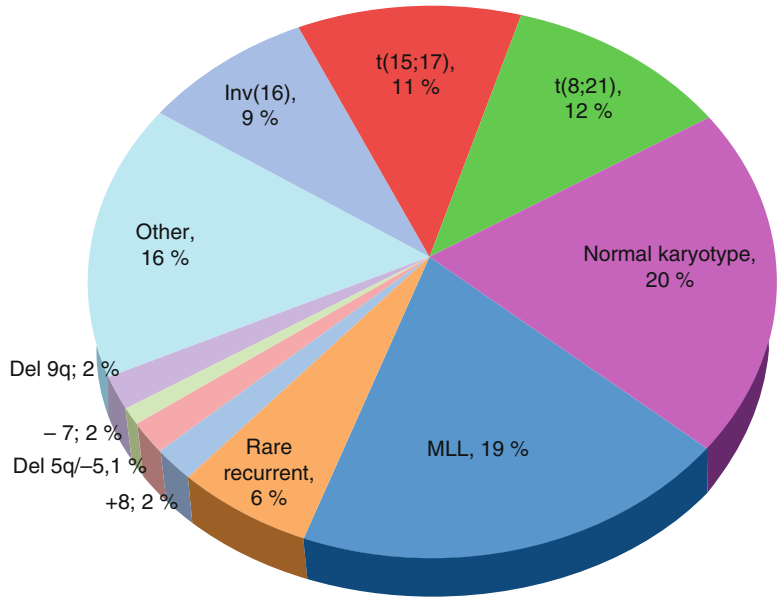


Fig. 9.1 Prevalence of karyotypic alterations in childhood AML

sufficient for the definitive diagnosis of AML, regardless of marrow blast percentage (Swerdlow et al. 2008). Patients with CBF-associated AML are highly responsive to induction chemotherapy and have better outcomes and as a result are considered a favorable risk group (Gibson et al. 2005; Gibson et al. 2011). In contrast, the presence of either monosomy 7 (–7) or monosomy 5/deletion 5q (–5/del5q), although rare in childhood AML, portends a poor outcome (Wheatley et al. 1999). Patients with alterations of *MLL* gene constitute nearly 20 % of all cases of childhood AML and its presence appears to be associated with outcome based on the specific translocation partners (Balgobind et al. 2011). *MLL* is highly promiscuous and has been shown to form fusion products with a large number of translocation partners. Although overall *MLL*-associated AML has been considered to be a standard-risk group, specific subsets have been shown to be associated with poor outcome (e.g., t(10;11)) or better outcome (t(1;11)) (Balgobind et al. 2011).

9.4.2 Somatic Mutations and Their Contribution to Survival in Childhood AML

Somatic mutations in genes known to contribute to hematopoiesis have been identified in a significant proportion of AML, and presence of these mutations has been shown to be associated with clinical outcome. Currently, numerous mutations have been implicated in AML pathogenesis with the number rising with new discovery phase initiatives (The Cancer Genome Atlas Research Network 2013). Currently, mutations in three genes (*FLT3*, *NPM1*, and *CEBPA*) have been shown to have clinical implications in childhood AML and have been incorporated in clinical trials as either prognostic markers, therapeutic targets, or both. Although larger numbers of mutations have been identified in adult AML, such mutations, including recently identified *IDH1* and *DNMT3A* mutations, have been shown to be extremely rare (not present) in pediatric AML (Fig. 9.2) (Ho et al. 2011).

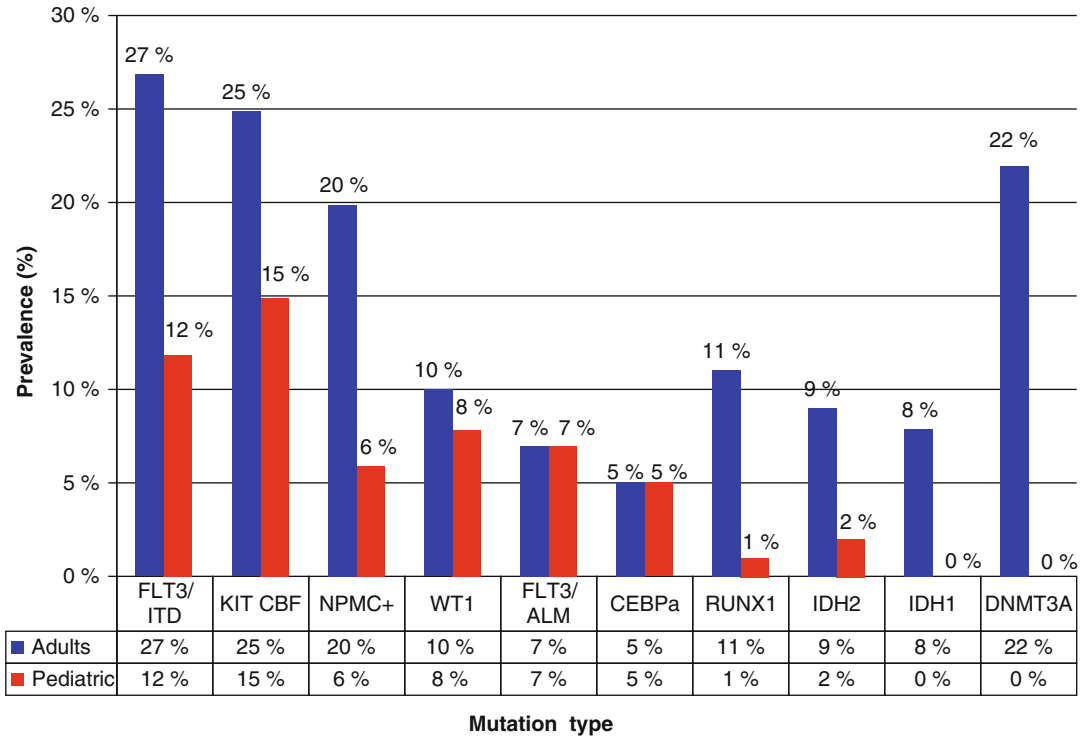


Fig. 9.2 Prevalence of somatic mutations in pediatric versus adult AML studies

9.4.2.1 FLT3 Mutations

The most commonly mutated gene in childhood AML is FMS-like tyrosine kinase 3 (*FLT3*) which leads to constitutive activation of the receptor kinase activity and can be due to the internal tandem duplication (FLT3/ITD) of the juxtamembrane domain coding sequence or a missense mutation in the activation loop domain (FLT3/ALM) (Nakao et al. 1996; Yamamoto et al. 2001). Internal tandem duplication (FLT3/ITD) is detected in 15 % of all children with AML and has been shown to be highly associated with poor response to induction chemotherapy and high relapse rate (Meshinchi et al. 2001, 2006a). Despite biologic similarity to FLT3/ITD, those with FLT3/ALM do not have increased failure rate (Meshinchi et al. 2006a). Several studies have shown that patients with FLT3/ITD who receive allogeneic stem cell transplantation in complete remission (CR) have an improved outcome, thus providing a target-based therapy allocation for this high-risk cohort of patients (Meshinchi et al. 2006a, b; Bornhauser et al. 2007). Further, novel kinase inhibitors have shown efficacy in inducing a high rate of remission in patients with FLT3/ITD, although long-term benefits of such interventions are yet to be determined (Ravandi et al. 2010). Again, in contrast to FLT3/ITD, FLT3/ALM does not seem to be similarly amenable to inhibition by kinase inhibitors (Kelly et al. 2002b; Weisberg et al. 2002; Spiekermann et al. 2003).

9.4.2.2 Nucleophosmin (NPM1) Mutations

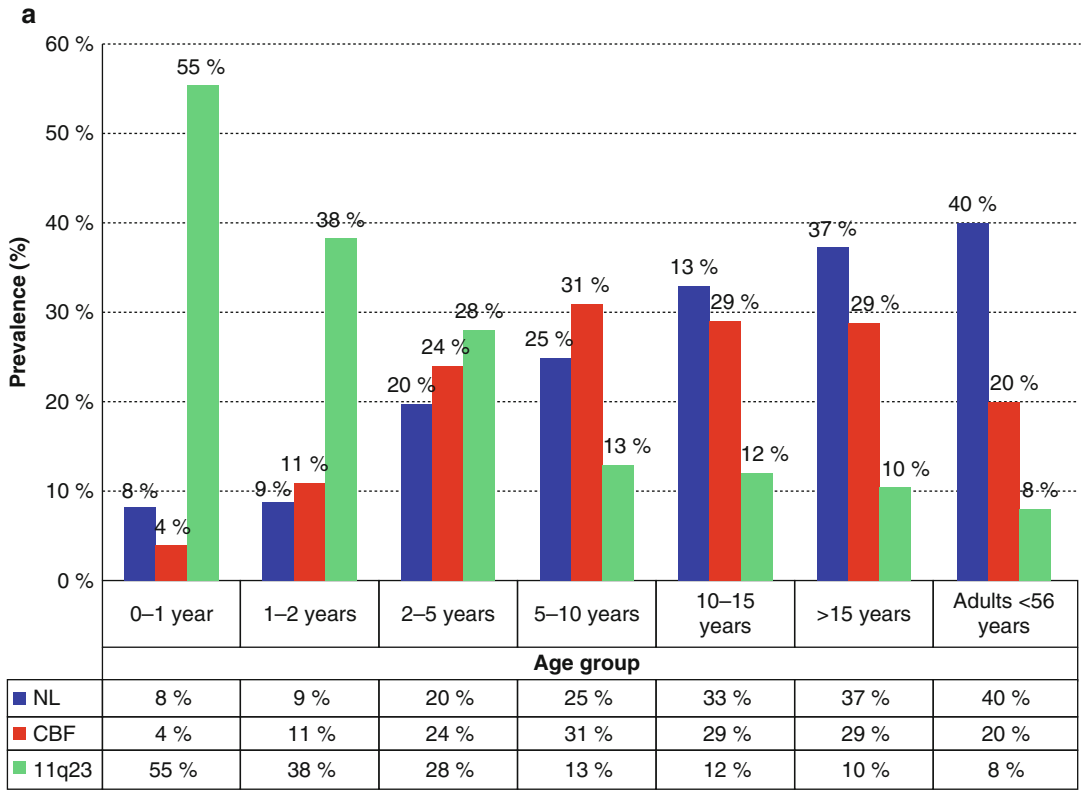
NPM1 encodes a ubiquitously expressed molecular chaperone that shuttles rapidly between the nucleus and cytoplasm. Mutations in *NPM1* are common in AML, with a prevalence of 30 % in adult and 8–10 % in pediatric AML (Dohner et al. 2005; Gale et al. 2007; Hollink et al. 2007; Brown et al. 2007). *NPM1* mutations appear to be more prevalent in AML with normal karyotype, with a prevalence of nearly 40–50 % in adults and 20 % in pediatric AML. Disease associated mutations, characterized by four base insertions in exon 12 of the *NPM* gene, lead to impaired nuclear localization of the nucleophosmin protein. Presence of *NPM* mutations portends favorable outcome with reduced relapse risk and improved survival; those with *NPM* mutations have a similar outcome as those with CBF AML. In pediatric AML, the presence of *NPM1* mutations appears to overlap in a subset of patients with FLT3/ITD and its co-expression appears to partially ameliorate the poor prognosis conferred by FLT3/ITD alone (Hollink et al. 2007).

9.4.2.3 CEBPA Mutations

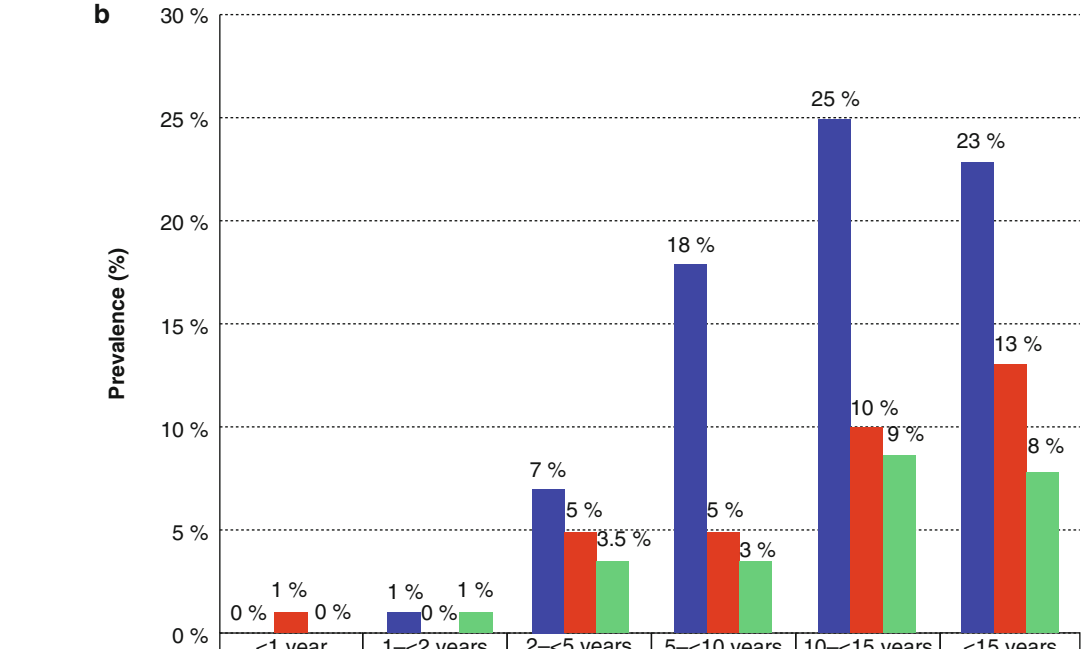
CEBPA gene encodes CCAAT/enhancer binding protein-alpha (C/EBPa), which functions as a transcription factor that regulates proliferation and terminal granulocytic differentiation. Mutations in the *CEBPA* occur in ~5 % of childhood AML cases and the overwhelming majority of cases with these mutations occur in a bi-allelic manner, in which two distinct mutations occur, one in the N-terminal domain (NTD) and the second in the opposite allele affecting the bZip domain (Ho et al. 2008). Such a bi-allelic mutation results in the expression of a truncated protein, which has been shown to be sufficient for development of AML (Kirstetter et al. 2008). Children's Oncology Group (COG) studies have demonstrated that *CEBPA* mutations tend to occur in patients with normal cytogenetics and are associated with decreased relapse risk as well as improved survival compared to patients without a mutation (Ho et al. 2009).

9.4.3 Age-Related Genomic Variation in Childhood AML

Because the disease biology may differ significantly from a newborn to adolescents and young adults, the prevalence and significance of genomic alterations in childhood AML should be considered based on the age of the patient. There is significant age-based variation in the type and the prevalence of structural and sequence alterations in childhood AML (Fig. 9.3). MLL translocations that are present in 20 % of all AML in the pediatric age range are significantly more prevalent in younger patients, where a majority of infants <1 year of age (~60 %) harbor chromosome band 11q23 alterations. The prevalence declines over the following decade of life to <10 %, similar to what is observed in young



	0–1 year	1–2 years	2–5 years	5–10 years	10–15 years	>15 years	Adults <56 years
NL	8 %	9 %	20 %	25 %	33 %	37 %	40 %
CBF	4 %	11 %	24 %	31 %	29 %	29 %	20 %
11q23	55 %	38 %	28 %	13 %	12 %	10 %	8 %



	<1 year	1–<2 years	2–<5 years	5–<10 years	10–<15 years	<15 years
ITD prevalence	0 %	1 %	7 %	18 %	25 %	23 %
NPMc+ prevalence	1 %	0 %	5 %	5 %	10 %	13 %
CEBPA prevalence	0 %	1 %	3.5 %	3 %	9 %	8 %

Fig. 9.3 Association of age and karyotypic alterations (**a**) or somatic mutations (**b**) in pediatric AML

adults (Fig. 9.3a). In addition, CBF-associated AML is quite rare in infants, but increases in prevalence with age to nearly 30 % by the second decade of life. Similarly, AML without karyotypic alterations (NK) is rare in younger patients, but its prevalence increases to nearly adult prevalence in adolescents and young adults. Sequence variations similarly vary by age; the prevalence of commonly mutated genes is extremely low (<1 %) in the early years of life and rapidly increases in the first decade of life (Fig. 9.3b).

9.4.4 Summary of AML Biology

Acute myeloid leukemia is an enormously complex disease characterized by a myriad of genomic and epigenomic alterations that interact to create a wide variety of different AML subtypes having significantly different outcomes. Knowledge of the genomic alterations, whether karyotypic abnormalities or specific disease associated mutations, provides a great deal of information for clinical decision making. Patients with specific favorable markers (e.g., CBF AML, *NPM1*, *CEBPA* mutations) can be spared more intensive post-induction therapy such as HCT. In contrast, patients with high-risk genotypes (e.g., −7, 05/del5q, FLT3/ITD) can be allocated to more intensive or experimental therapies. A more complete understanding of the biology of childhood AML is needed. Despite the increasing breadth of information about the genetic and epigenetic alterations in AML, a specific risk status can be identified for only 30–40 % of the patients and the ability to assign risk status or specific therapy for the remaining cohort, with a survival rate of near 50 %, is lacking. New discovery phase initiatives including the National Cancer Institute (NCI) sponsored TARGET AML initiative are aimed at discovering novel biomarkers to be used for more precise risk identification as well as the identification of potential therapeutic targets. With the increase in the number of tools for interrogation of the AML genome and epigenome, the ability to allocate patients to individualized therapy directed by the underlying biology of their disease is anticipated.

9.5 Role of Allogeneic HCT in the First Complete Remission

Historically, the extent to which cooperative groups have employed allogeneic HCT for children with AML in the first CR has varied considerably. In trials launched in the 1980s and 1990s by the two North American groups, the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG, now merged to form the COG), for instance, nearly all patients with an human leukocyte antigen (HLA)-matched related donor received HCT as consolidation (Ravindranath et al. 1996; Woods et al. 2001; Becton et al. 2006; Lange et al. 2008). On the other hand, in contemporaneous trials conducted by the British Medical Research Council (MRC) and the German Berlin-Frankfurt-Münster Group (BFM), few patients received transplant (Stevens et al. 1998; Creutzig et al. 2001). As the rate of survival improves with chemotherapy alone, however, the pattern of utilization of HCT in cooperative group trials is converging. Most trials opened since 2000 have not employed HCT for patients with low-risk disease. Also, in most trials, donor selection criteria have been relaxed to permit the use of unrelated donors for high-risk patients lacking related donors. In the Nordic Society for Pediatric Hematology and Oncology (NOPHO) AML 2004 trial, for example, patients were classified as having standard- or high-risk disease, and HCT was recommended for those with high-risk disease using a related or unrelated donor (Abrahamsson et al. 2011). The Associazone Italiana Ematologia Oncologia Pediatrica also employed a dichotomous risk system in its AML 2002/2001 trial and recommended HCT for all patients with high-risk disease, though limiting the use of alternative donors to infants and patients with French-American-British (FAB) M7 disease (Pession et al. 2009). In its AML99 trial, the Japanese Childhood AML Cooperative Study Group classified patients as having low-, intermediate- or high-risk disease. Transplant was recommended for intermediate-risk disease for patients with a matched related donor and for high-risk disease using a related or unrelated donor (Tsukimoto et al. 2009).

The St. Jude AML02 trial also employed a tripartite system, but only assigned patients with high-risk disease to HCT, again using a related or unrelated donor (Rubnitz et al. 2010). The COG AAML03P1 differed from these trials in that it continued to recommend transplant for all patients, but only if they had a matched related donor (Cooper et al. 2012). In the succeeding trials, however, the COG has altered its approach. In the AAML0531 trial, using a tripartite system, HCT using a matched related donor was recommended for patients with intermediate-risk disease and HCT using a related or unrelated donor was recommended for patients with high-risk disease. In the currently open COG Phase III study, AAML1031, adopting a dichotomous system, HCT using a related or unrelated donor is only considered for patients with high-risk disease.

It is unclear whether the now common practice of basing the decision whether to proceed to transplant in the first CR based on relapse risk is justified. The results of a meta-analysis (Horan et al. 2008) of four Phase III trials that compared HLA-matched related HCT to chemotherapy alone, CCG 2891 (Woods et al. 2001), POG 8821 (Ravindranath et al. 1996), CCG 2961 (Lange et al. 2008), and MRC 10 (Stevens et al. 1998), suggest that the impact of risk on the benefit of transplant may be complex. Using cytogenetics and the percentage of marrow blasts after the first course of chemotherapy, 1,373 patients were stratified into favorable-, intermediate- and high-risk disease groups. Patients who could not be risk classified were analyzed separately. Patients with acute promyelocytic leukemia (APML), Down syndrome, or therapy-related leukemia were excluded. In the intermediate-risk group, the estimated disease-free survival at 8 years for non-transplant patients was 39 %, while it was 58 % for HCT patients. The estimated overall survival for non-transplant patients was 51 %, while it was 62 % for HCT patients. Both differences were significant ($p<0.01$). There were no significant differences in survival in the other two risk groups or in the non-risk stratified patients (Fig. 9.4). These results provide support for treating children with low-risk disease with chemotherapy alone, a practice that has now been adopted internationally. The pediatric analysis included a very small number of high-risk patients. A more recent study performed by COG and the Center for International Blood and Marrow Transplant Research (CIBMTR)

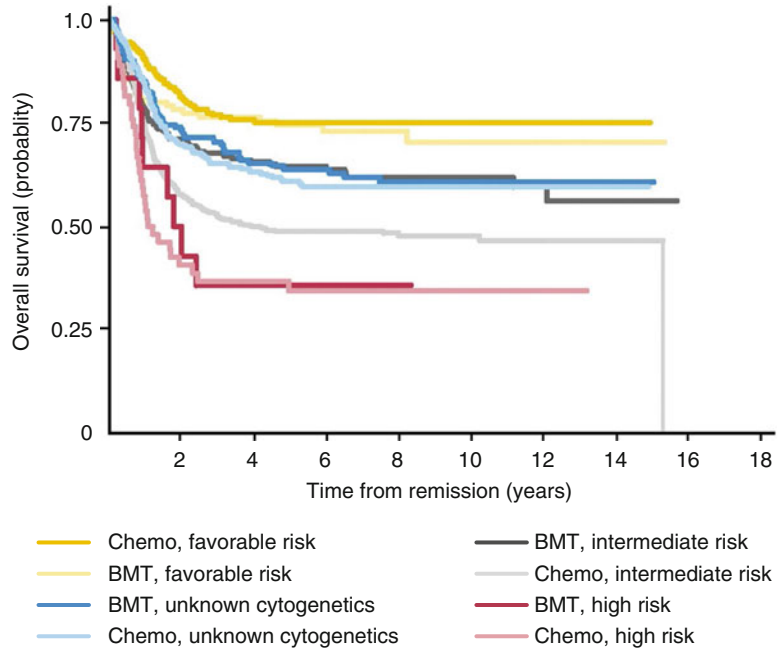


Fig. 9.4 Estimated overall survival stratified by risk group and post-remission treatment. *Chemo* chemotherapy, *BMT* bone marrow transplantation (From Horan et al. 2008)

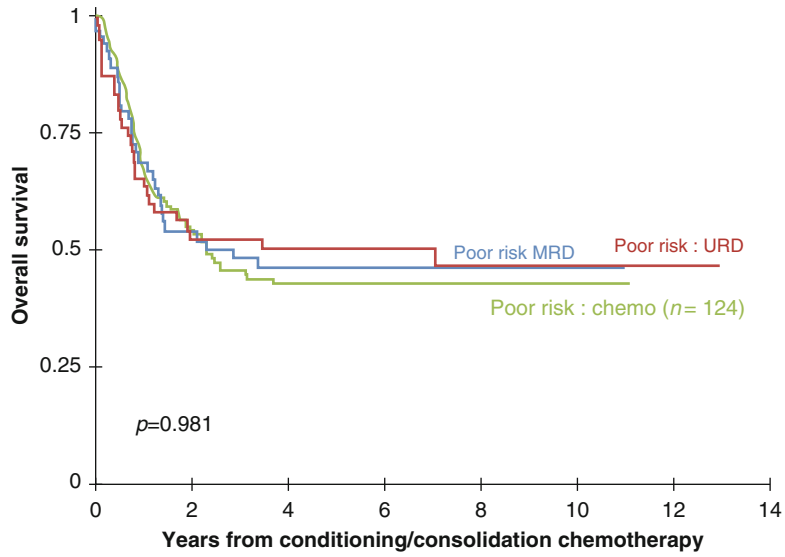


Fig. 9.5 Estimated overall survival in patients with poor-risk disease in the first complete remission stratified by post-remission treatment. *Chemo* chemotherapy, *MRD* matched related donor, *URD* unrelated donor (From Kelly et al. 2012)

examined the benefit of HCT in the first CR in a larger series of children with poor-risk disease (Fig. 9.5) (Kelly et al. 2012). This study of 234 patients, which used cytogenetic testing results to define high-risk disease, compared patients who received chemotherapy alone, those who received HLA-matched related sibling donor transplants, and those who received unrelated donor transplants (marrow, peripheral blood or cord blood). Survival did not differ between the three groups, suggesting that these patients do not benefit from HCT in the first CR.

More recently identified risk factors may help clarify, which, if any, patients should receive HCT in the first CR. Investigators from St. Jude Research Hospital and from COG have both demonstrated that end of induction minimal residual disease (EOI-MRD) detected by flow cytometry strongly predicts relapse and death from leukemia (Loken et al. 2012; Rubnitz et al. 2010). As noted previously, FLT3/ITD has also been shown to be a poor prognostic factor (Meshinchi et al. 2006a). While there is some evidence to suggest that HCT in the first CR may be appropriate for patients with FLT3/ITD (Meshinchi et al. 2006b), the impact of HCT relative to treatment with chemotherapy alone for patients with EOI-MRD and FLT3/ITD needs to be more accurately defined.

While the optimal role of HCT for children with poor-risk disease remains ill-defined, there is now international consensus that there is little role for HCT for children with good-risk disease, which now (as noted previously) can be more broadly defined by the presence of inv(16), t(8;21), *NPM1* mutations, or *CEBPA* mutations (Ho et al. 2009; Brown et al. 2007).

Down syndrome-associated AML and APML are highly distinctive forms of AML, both biologically and clinically. Highly effective, less intensive strategies have been developed for treating both and, as a result, the use of HCT in the first CR has been abandoned (Dvorak et al. 2008; Sorrell et al. 2012).

9.6 Role of HCT in Advanced Disease

Relapse remains the major cause of treatment failure in patients with AML in the first CR. A second CR is achieved in approximately 65–70 % of patients treated with aggressive re-induction therapy (Abrahamsson et al. 2007; Sander et al. 2010). Although drug resistance likely mediates the mechanisms of relapse, the most important predictors of achieving a second CR are favorable cytogenetics and a first remission duration of

at least 12 months (Abrahamsson et al. 2007; Sander et al. 2010; Kaspers et al. 2013). While occasional children in the second CR may be cured by chemotherapy alone, in general, these children fare poorly (Goemans et al. 2008; Stahnke et al. 1998; Webb et al. 1999). According to CIBMTR data, allogeneic marrow transplantation, whether matched related or unrelated, produces long-term survival in approximately 50 % of pediatric patients in the second CR (Bunin et al. 2008; Pasquini and Wang 2012).

The prognosis of patients for whom remission is not achieved, either after diagnosis (i.e., primary induction failure) or relapse (i.e., refractory), is very poor. The efficacy of transplantation for these children, on the whole, is only marginally better than that of chemotherapy. In a CIBMTR study of unrelated marrow transplantation for pediatric AML, children transplanted in primary induction failure and those transplanted in relapse had an estimated long-term survivals of 12 and 20 %, respectively (Bunin et al. 2008). Although the general outlook for these children is poor, another CIBMTR study, this one of allogeneic transplantation for children and adults with acute leukemia not in remission, demonstrated that subgroups of patients who are more likely to benefit from transplant can be identified. Prognostic factors, such as performance status and the presence of circulating blasts, were identified and used to create a risk classification system comprised of four subgroups. Long-term survival in the subgroups ranged from 6 to 42 % (Duval et al. 2010). While the results of these studies indicate that transplant for patients with AML with primary induction failure and relapse is not futile, they also highlight the desperate need for more effective approaches (transplant or non-transplant) for treating patients with chemotherapy resistant disease.

9.6.1 Minimal Residual Disease

The effects of pre-transplant MRD on outcome have been extensively studied in pediatric ALL (Bader et al. 2002; Knechtli et al. 1998; Leung et al. 2012). In pediatric AML, on the other hand, the results of research in this area are just beginning to emerge with the results of the first large-scale study, performed by St. Jude Research Hospital, just published in 2012 (Leung et al. 2012). This study, which included patients in the first, second, and third CR, suggests that MRD (detected by flow cytometry on marrow samples) just prior to allogeneic transplant has much less impact on outcome in pediatric AML than pediatric ALL. In fact, the survival of patients transplanted after 2001 for AML all exceeded 50 % regardless of whether they had no MRD, low-level MRD (0.1 to <1 %), or high-level MRD (≥1.0 %). While further research is needed in this area, these preliminary findings suggest that pre-transplant MRD should not be a deterrent to HCT in pediatric AML.

9.7 Autologous HCT

The use of autologous transplantation, once thought to hold great potential as an alternative to allogeneic HCT for children with AML, has largely been abandoned in this setting (www.cibmtr.org). The results of two multicenter trials conducted in the 1990s, the POG 8821 and CCG 2891 trials (Ravindranath et al. 1996; Woods et al. 2001), were largely responsible for the move away from autologous transplantation. In both trials, patients with AML in the first CR who lacked an HLA-matched related donor were randomly assigned to receive high-dose busulfan and cyclophosphamide followed by autologous marrow or consolidation chemotherapy; the marrow was treated with 4-hydroperoxycyclophosphamide to purge leukemia cells prior to infusion in both trials (Ravindranath et al. 1996; Woods et al. 2001). Neither trial showed benefit (in terms of survival) for autologous transplantation versus consolidation chemotherapy. At this time, there does not appear to be a role for autologous transplantation in the treatment of children with AML and this approach has been abandoned by the pediatric cooperative cancer groups.

9.8 Approach to Allogeneic HCT

9.8.1 Grafts for Allogeneic Transplants: Hematopoietic Stem Cell Sources and Donors

As noted in the introduction, the Fred Hutchinson Cancer Research Center, the University of Minnesota, and Memorial Sloan Kettering Cancer Center all employed bone marrow harvested from HLA-matched siblings as grafts in their seminal trials for children with acute leukemia conducted in the 1970s and early 1980s (Brochstein et al. 1987; Kersey et al. 1982; Sanders et al. 1985; Thomas et al. 1977). HLA-matched family donor (MFD) bone marrow remains an oft-used graft. This has been especially true when HCT is used for children in a first CR, a setting in which many children can be cured with chemotherapy alone and, thus, a setting in which the use of alternative donor grafts, because of the higher risk for transplant related mortality that they carry, is often considered inappropriate (Horan et al. 2008). The advent of cytokine-mobilized peripheral blood stem cell (PBSC) grafts and umbilical cord blood (UCB) grafts in the 1990s presented new options for children with AML. With their superior capacity for engraftment, PBSC grafts are frequently used for children, as for adults, needing reduced intensity conditioning (RIC) (Pulsipher et al. 2009). Despite initial enthusiasm for using PBSC after myeloablative conditioning, the use of PBSC grafts for children with AML, as for children with ALL, was largely abandoned following the publication of a comparative study by the CIBMTR demonstrating that the PBSC grafts were associated with excessive chronic GVHD and, as a result, inferior survival (Eapen et al. 2004). Although children in need of transplant often lack a MFD cord blood graft, a study conducted by Eurocord demonstrated UCB grafts are associated with a very low risk for GVHD and yield survival rates similar to marrow grafts (Rocha et al. 2000). As such, MFD UCB has become a suitable alternative to marrow for children with AML.

The creation of volunteer adult donor marrow registries in the 1980s provided children with AML lacking a MFD, access to unrelated donors. A registry study completed by the US National Donor Program in the early 1990s established HLA-matched unrelated donor marrow transplantation as an appropriate treatment for children as well as adults with advanced hematologic malignancies, including AML (Kernan et al. 1993). Advances in HLA typing, an improved understanding of the influence of HLA matching and a tremendous growth in the number volunteer donors worldwide, now accessible through an international network of registries, have made unrelated marrow a readily available alternative for most children with AML in developed nations (Flomenberg et al. 2004; Lee et al. 2007; Morishima et al. 2002; Petersdorf et al. 2001). Because not all racial and ethnic groups are well represented in registries, however, access for selected groups, including black children, remains limited (Beatty et al. 1995; Confer 2001). Although the role of unrelated marrow transplantation for children with AML in the first CR continues to be defined, its appropriateness in the second CR, where its safety and efficacy have been well characterized, has been firmly established (Bunin et al. 2008).

Since their introduction in the 1990s, unrelated cord blood units have been established as an appropriate alternative to unrelated marrow. With the steady growth of banked cord blood units, the comparative ease of obtaining these units and the less stringent need for HLA matching has spurred dramatic growth in the use of UCB units for children with AML and other diseases (Pasquini and Wang 2012). For many children now, particularly younger ones in whom the limited cell dose provided by UCB grafts is likely not to be an issue, UCB and unrelated bone marrow grafts are both readily available options. An important consideration for children with AML, then, is the comparable effectiveness of these two sources. There have been two registry studies comparing UCB and unrelated bone marrow for children with acute leukemia, one by Eurocord, published in 2001 and one by the CIBMTR, published in 2007 (Eapen et al. 2007; Rocha et al. 2001). The Eurocord study, the smaller of the two, compared three broadly defined groups: T-cell-replete unrelated marrow transplants, T-cell-depleted marrow

transplants, and cord blood transplants. There was considerable intragroup heterogeneity. The cord blood transplant group, for instance, included patients who had received fully matched grafts, single mismatched grafts, and double mismatched grafts. A multivariate analysis demonstrated that, in general, cord blood and T-cell-replete marrow grafts are associated with similar probabilities of survival and were superior to T-cell-depleted grafts. The much larger CIBMTR study was able to build on the foundation laid by the Eurocord study, by accounting for the impact of HLA matching on outcome in unrelated bone marrow transplant (Flomenberg et al. 2004; Lee et al. 2007; Morishima et al. 2002) and HLA matching and cell dose on outcome in UCB transplantation (Rubinstein et al. 1998) in its comparison. All unrelated bone marrow grafts were T-cell replete. Patients were grouped according to whether they received an HLA-matched unrelated marrow graft (defined as an allele level match at the A, B, C and DRB1 loci), a mismatched unrelated marrow graft (defined as mismatching at one or two of eight loci), an HLA matched unrelated cord blood unit (defined as antigen level matching at the A and B loci and allele level matching at the DRB1 loci), a single mismatched cord blood unit with high cell dose (defined as total nucleated cell dose/kg $>3\times10^7$), a single mismatched cord blood unit with low cell dose (defined as total nucleated cell dose/kg $\leq3\times10^7$), and a double-mismatched cord blood unit. Although the study included both children with ALL and AML, about two-thirds had ALL. Most patients were transplanted in a second or later CR. While there were statistically significant differences in the multivariate analysis between groups for some of the secondary outcomes like relapse and treatment-related mortality, there were no statistical differences for the primary endpoint of treatment failure (relapse or death), using a p-value cut-off of 0.008. A strong trend (HR 0.54, 95 % CI, 0.30–0.97, $p=0.0406$) toward decreased treatment failure, however, was observed for matched UCB transplants even though there were only 35 patients receiving 6/6 matched units. The relative lack of differences between groups is apparent from the univariate analysis, displayed as a Kaplan-Meier plot (Fig. 9.6).

Until recently, the high risk for delayed and failed engraftment stemming from the small cell

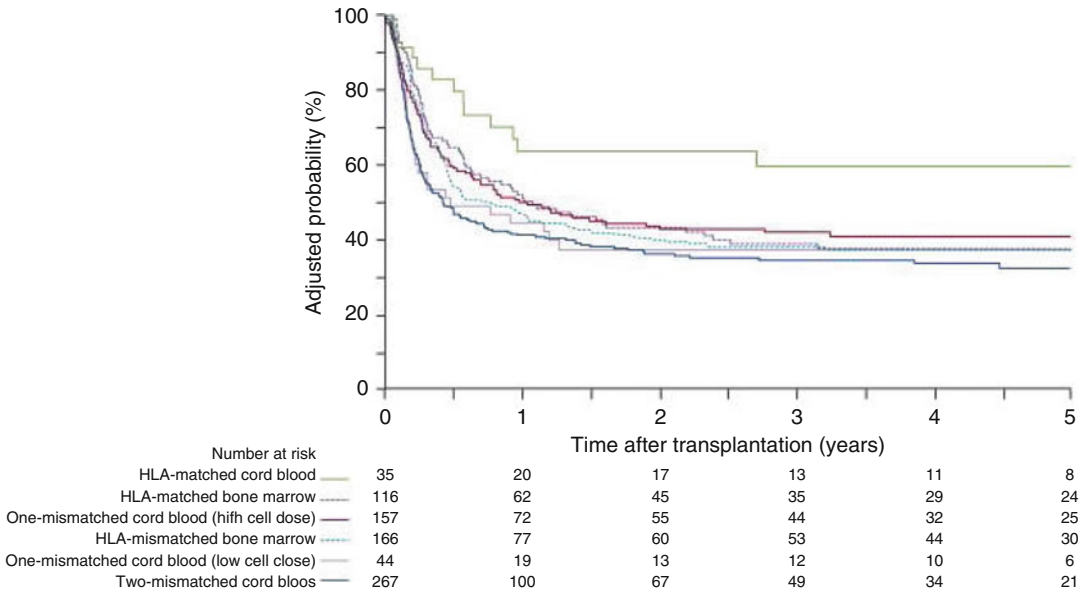


Fig. 9.6 Probability of leukemia-free survival after bone marrow and cord blood transplantation adjusted for disease status at transplantation (From Eapen et al. 2007)

dose of most cord blood units had limited the use of these grafts in older children and adolescents as well as adults (Rubinstein et al. 1998). This limitation has been overcome with the recent advent of double unit transplants; single center experience suggests that this approach more frequently causes GVHD but has a potent graft versus leukemia (GVL) effect (Barker et al. 2005). This experience raised the possibility that even for children with access to large single units, the use of double unit transplants might improve survival by reducing leukemic relapse. This possibility was explored in a randomized controlled Phase III trial comparing one and two unit transplants in pediatric patients with acute leukemia or myelodysplasia. This trial conducted by the US Blood and Marrow Transplant Clinical Trials Network closed in 2012 after completing accrual. The preliminary results, however, indicate that there appears to be little benefit to double unit transplants. Estimated overall survival at 1 year was 71 and 65 % ($p=0.13$) in patients assigned to one and two unit transplants, respectively. Estimated relapse at 1 year was 12 and 14 % ($p=0.37$) (Wagner et al. 2012).

While the relative effectiveness of unrelated bone marrow and UCB is an important matter, an equally important consideration is the relative effectiveness of MFD grafts and unrelated donor (URD) grafts. Several recent studies have suggested that in adults and children with AML and other hematological malignancies, leukemia-free survival rivaling that is seen with MFD transplantation can be achieved with well-matched URD transplants. Three such studies deserve mention because they were multicenter efforts (Eapen et al. 2006; Gupta et al. 2010; Yakoub-Agha et al. 2006). The first, a French multicenter trial, in which adult patients with hematologic malignancies (primarily acute leukemia) who had either an HLA-matched related donor ($n=181$) or a 10/10 (A, B, C, DRB1 and DQB1) allele-matched unrelated donor ($n=55$) were eligible, was conducted from 2000 to 2003. All participants received unmanipulated bone marrow grafts, myeloablative conditioning with cyclophosphamide and total body irradiation (TBI), and cyclosporine and methotrexate for GVHD prophylaxis. While there was a difference in the incidence of GVHD, there were no differences in estimated 2-year overall survival or event-free survival (Yakoub-Agha et al. 2006). The second study, conducted by the CIBMTR, included children less than 18 months with acute leukemia transplanted with matched related bone marrow, unrelated cord blood (with up to a single mismatch at 6 loci), or unrelated bone marrow (with up to a single mismatch at 6 loci), between 1990 and 2001. All patients received myeloablative conditioning. While treatment-related mortality was higher in patients receiving unrelated grafts, relapse was more common in the patients receiving matched related grafts. As a result, leukemia-free survival and overall survival were comparable even after adjustment for potentially confounding variables in multivariate analyses. The similarity in survival is illustrated by Fig. 9.7, a Kaplan-Meier plot of leukemia-free survival, stratified according to

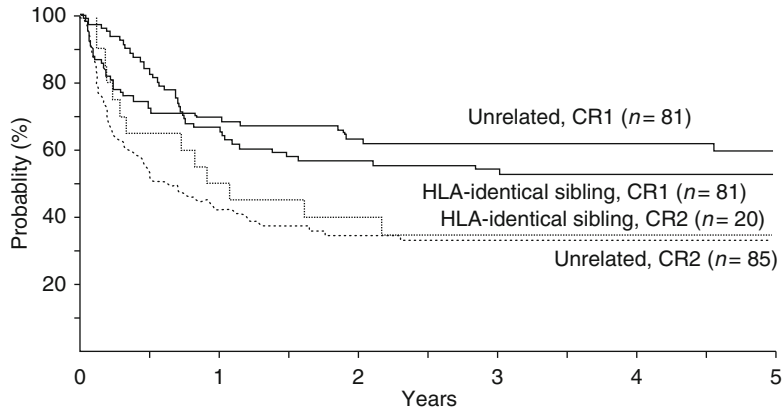


Fig. 9.7 Adjusted probabilities of overall survival in children younger than 18 months. *CR* complete remission, *HLA* human leukocyte antigen (From Eapen et al. 2006)

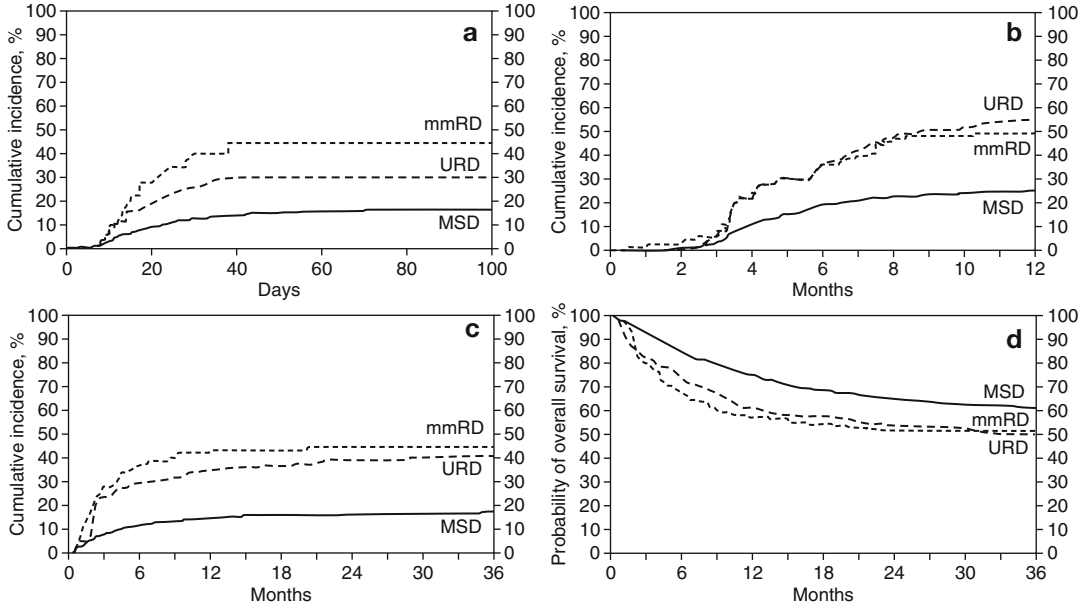


Fig. 9.8 Unadjusted curves of acute graft versus host disease (GVHD) grades 3–4, chronic GVHD, treatment-related mortality (TRM), and overall survival (OS) by donor types. (**a**) Cumulative incidence of acute GVHD grades 3–4. (**b**) Cumulative incidence of chronic GVHD. (**c**) Cumulative incidence of TRM. (**d**) Probability of OS. *MRD* matched related donor, *mmRD* mismatched related donor, and *URD* unrelated donor (From Shaw et al. 2010)

disease status (Eapen et al. 2006). The third study, also conducted by the CIBMTR, included children and adults transplanted for cytogenetically defined high-risk AML in the first CR transplanted between 1995 and 2006. The sample included patients that received reduced intensity conditioning as well as well as myeloablative conditioning and peripheral blood stem cell grafts as well as marrow grafts. The multivariate analysis demonstrated that, after adjustment for differences in baseline characteristics, patients who received well-matched URD transplants (matched at A, B, C and DRB1 loci) faired the same as those who received MFD transplants (Gupta et al. 2010).

In contradistinction to these studies, a large study conducted by the CIBMTR that included over 1,500 children with AML, ALL, MDS, or chronic myelogenous leukemia (CML) indicated that even well-matched URD transplants are inferior to MFD transplants (Shaw et al. 2010). The sample included children transplanted between 1993 and 2006 who received myeloablative conditioning and marrow transplants from minimally mismatched relatives (siblings or parents with a single antigen mismatch at the A, B, and DRB1 loci or parents that were antigen matched at these loci), HLA-matched siblings, or unrelated donors allele matched at the A, B, C, and DRB1 loci. In the univariate and the multivariate analyses comparing unrelated and matched related transplants, there was a significantly higher risk for treatment-related mortality with unrelated donor transplantation, which translated into poorer disease-free and overall survival. Figure 9.8 compares the unadjusted curves for acute GVHD grades 3–4, chronic GVHD, treatment-related mortality, and overall survival. The figure also shows the similarity in outcomes with matched unrelated and the minimally mismatched related groups. While it is not easy to fully reconcile the results of this study with those mentioned above, it should be noted that the magnitude of the difference in survival between unrelated donor and matched related donor recipients in this study is not large. Considered together, then, the results of these four studies suggest that, in many circumstances, it may be appropriate to use a well-matched unrelated marrow donor for children with AML lacking a matched related donor.

9.8.2 Haploidentical Grafts

In recent years there has been a renewed interest in using haploidentical grafts for treatment of children and adults with AML and other hematologic malignancies, and strategies that effectively prevent both GVHD and graft rejection have emerged (Reisner et al. 2011). Encouraging results have been achieved in patients with AML receiving myeloablative conditioning, using *ex-vivo* T-cell-depleted (Aversa et al. 2005) as well as T-cell-replete grafts (Huang et al. 2009). While haploidentical grafts continue to be used primarily for the small group of children who lack well-matched related or unrelated grafts, it seems likely that, given the ready availability of partially matched related donors, the ease of obtaining grafts from them, and the recent improvement in outcomes, the use of haploidentical donors will increase.

9.8.3 Preparative Regimens

Myeloablative regimens are most commonly used for children with AML. In cooperative group trials for newly diagnosed AML, the combination of TBI and cyclophosphamide, the combination of high-dose busulfan and cyclophosphamide, and the combination of TBI and etoposide have been used prior to HLA-matched related HCT (Becton et al. 2006; Lange et al. 2008; Ravindranath et al. 1996; Stevens et al. 1998; Woods et al. 2001). The comparative efficacy of these regimens in this setting has not been well studied. A small case series from the Société Française de Greffe de Moelle demonstrated similar outcomes in children with AML who received busulfan and four 50 mg/kg doses of cyclophosphamide (BuCy4) and TBI-based conditioning. Busulfan and two 60 mg/kg doses of cyclophosphamide (BuCy2), however, was associated with inferior survival (Michel et al. 1994). A much larger study of adults from the CIBMTR, in contrast, demonstrated comparable outcomes with TBICy, BuCy4, and BuCy2 (Litzow et al. 2002). Importantly, both of these studies utilized experience that largely predates the widespread adoption of pharmacokinetic testing-based busulfan dosing and the introduction of the intravenous formulation of busulfan (Yeager et al. 1992; Kletzel et al. 2006). While the effectiveness of TBI-based conditioning and BuCy appear to be similar, BuCy may be more appropriate for children, as it has been associated with fewer late effects (Michel et al. 1997).

In recent years, there has been a move toward the use of less toxic myeloablative conditioning regimens for patients with AML. In adults, fludarabine has been coupled with myeloablative doses of busulfan. While this regimen produces less toxicity than BuCy, its anti-leukemic effect appears to be comparable (Bornhauser et al. 2003; de Lima et al. 2004; Russell et al. 2002). This regimen is now being investigated in children as part of the COG AAML1031 trial. Emerging experience in children and adults using high-dose treosulfan, an alkylating agent that may be less toxic than busulfan, in combination with fludarabine, suggests that treosulfan and fludarabine may also be a safe and effective regimen for pediatric AML (Nemecek et al. 2011).

RIC is often used for adults with AML, particularly for older adults and those with comorbid conditions. A study performed by the CIBMTR comparing RIC and myeloablative conditioning showed that the two approaches yielded comparable survival, although, as might be expected, the patterns of treatment failure differed. Relative to myeloablative conditioning, failure with RIC was less likely to be treatment related and more likely to be disease related (Aoudjhane et al. 2005). Experience with RIC for pediatric AML remains limited. The results of a recent multicenter trial of RIC that included children and adolescents with a variety of hematological malignancies, a small number of whom who had AML, have provided a foundation for further work in this area (Pulsipher et al. 2009). At present, then, there is little justification for the use of RIC in children with AML other than in those who are not candidates for myeloablative conditioning because of comorbidities.

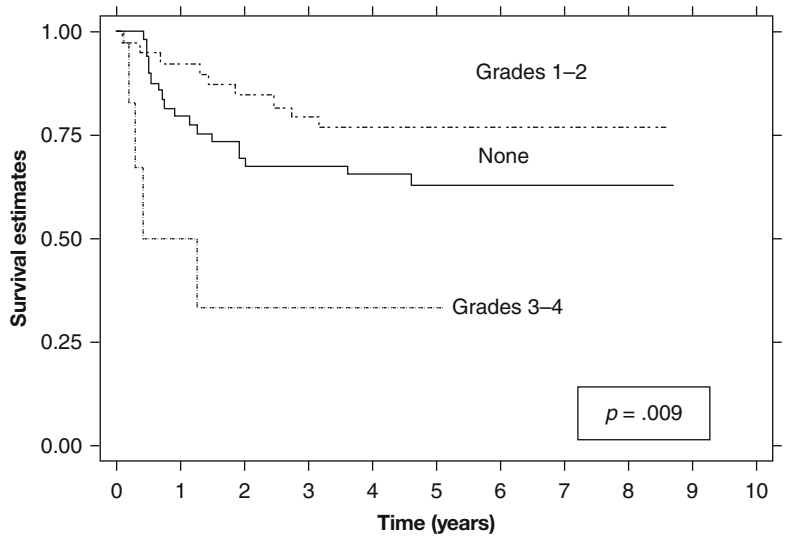


Fig. 9.9 Effect of grades 1 or 2 acute GVHD on DFS in CCG 2891 Trial. None ($n=49$), grades 1–2 ($n=39$), and grades 3–4 ($n=6$). Estimates at 6 years are 63 and 79 %; at 3 years, 33 % (From Neudorf et al. 2004)

9.8.4 Graft Versus Host Disease Prophylaxis

In transplants for AML, as with other types of leukemia, a delicate balance exists between the beneficial GVL and the harmful GVH reactions (Horowitz et al. 1990; Neudorf et al. 2004). A seminal study performed by the CIBMTR of over 2,000 children and adults receiving HLA-matched related HCT for leukemia demonstrated that in patients with AML in the first CR, the occurrence of acute or chronic GVHD strongly reduced the risk of relapse. Because of the deleterious effects of GVHD, though, only mild GVHD was associated with improved survival (Horowitz et al. 1990). A smaller study performed by the COG of children with AML in the first CR who received matched related HCT as part of the CCG 2981 trial yielded similar findings (Neudorf et al. 2004). In this study, patients who developed mild to moderate acute GVHD had the best disease-free survival rate, followed by patients who did not develop acute GVHD, followed by patients who developed severe acute GVHD (Fig. 9.9). In the multivariate analysis, the relative risk of relapse or death associated with mild to moderate acute GVHD was 0.66, although this result did not achieve statistical significance in this relatively small study ($p=0.165$). A more recent study performed by the CIBMTR in children undergoing unrelated bone marrow transplantation for acute leukemia, however, did not show that GVHD had a significant influence on the probability of relapse (Davies et al. 2009).

In HCT for pediatric AML, regardless of whether a related or an unrelated donor is used, as in many other settings, the combination of cyclosporine (or tacrolimus) and four doses of methotrexate are typically employed for GVHD prophylaxis (Storb et al. 1989; Ratanatharathorn et al. 1998; Nash et al. 2000). A CIBMTR study, however, suggests that in matched related HCT for pediatric leukemia, where the risk for severe GVHD is low, this combination is no better, as measured in terms of survival, than the less potent regimens of cyclosporine alone or methotrexate alone (Ringden et al. 1993). A more recent Italian multicenter randomized controlled trial in pediatric patients with leukemia that compared low-dose cyclosporine to standard-dose cyclosporine demonstrated, in fact, a strong trend toward improved disease-free survival, largely attributable to a lower rate of relapse, in the group

that received the less potent regimen (Locatelli et al. 2000). In unrelated cord blood transplantation, in which the pace of engraftment is slow, the myelosuppressive effects of methotrexate are usually avoided and, instead, cyclosporine is used either alone or in combination with methylprednisolone or mycophenolate mofetil (Barker et al. 2005; Kurtzberg et al. 2008; MacMillan et al. 2009; Rocha et al. 2000). *Ex vivo* T-cell depletion, once a commonly employed means of preventing GVHD from unrelated bone marrow transplants, has been abandoned by many centers after a multicenter randomized controlled trial in unrelated donor transplantation demonstrated that while T-cell depletion greatly reduces the risk for acute GVHD, this benefit is outweighed by an increased risk for infection and leukemic relapse (Wagner et al. 2005). Further research is needed to identify optimal strategies for preventing GVHD in children with AML and other forms of leukemia.

9.9 Relapse After HCT

Children with AML or leukemias who relapse after HCT have a dismal prognosis; according to data from the CIBMTR, only about 1 in 5 survive long term (Levine et al. 2008). Many patients and families opt against aggressive therapy (Lee et al. 2013). For patients who do go on to receive salvage therapy, the factor that is most predictive of survival is time to relapse with patients relapsing less than 6 months from transplantation being extremely unlikely to benefit from salvage therapy (Lee et al. 2013; Levine et al. 2002, 2008; Meshinchi et al. 2003; Munoz et al. 2002). For children with AML who relapse after 6 months, donor leukocyte infusions (administered after re-induction chemotherapy) and second transplants (using the original donor or a different donor) appear to be similarly effective, producing cure in about 1 in 3 cases (Levine et al. 2002, 2008; Meshinchi et al. 2003; Munoz et al. 2002). Recent data from Korea suggests that even chemotherapy alone can achieve cure in these children (Lee et al. 2013).

9.10 Survivorship

9.10.1 Quality of Health

Heath-Related Quality of Life (HRQoL) is in varying degrees impaired in individuals who have undergone HCT during childhood. Satisfaction with physical health, general health, partner relations, and sexual function are the areas most affected (Lof et al. 2009; Redaelli et al. 2004). The reduced HRQoL is also prominent in adult AML, where HCT has a significantly worse long-term impact on quality of life compared to conventional chemotherapy (Messerer et al. 2008).

HRQoL values consistently demonstrate lower values when reported by the parents compared with reports from the patients. Parents generally view their child as having greater difficulties in adjustment, while self-reports tend to correlate more with objective measures of disease severity (Parsons et al. 1999; Brice et al. 2011). This difference may be a reflection of the physical and emotional burdens placed on parents caring for a seriously ill child. The psychological well-being of parents correlates with improvements in the HRQoL of their child. The majority of patients and their parents report linear improvements in HRQoL in the first year post-transplant. Older age at transplant significantly predicts lower HRQoL at baseline for self- and parent-reports, whereas female gender significantly impacts lower self-reported physical HRQoL over time. African-American children report the highest HRQoL in contrast to a low HRQoL in children of Asian descent (Brice et al. 2011), indicating that the premorbid experiences and expectations influence the parent and child's perceptions of the HCT process.

Late effects scoring of organ system function does not always have any direct relationship to HRQoL. Despite a high burden of chronic disease, unrelated HCT recipients may rate their overall health as equivalent to non-transplanted survivors; yet, when asked specifically about functional impairment or activity limitations, the former transplant patients are more vulnerable (Armenian et al. 2011).

9.10.2 Late Adverse Effects of HCT in Children

The late adverse effects after allogeneic HCT are primarily due to the conditioning chemotherapy and/or radiotherapy. These effects include organ toxicities like cataract, nephrotoxicity, neurotoxicity, myocardial toxicity, endocrinopathy, and dental problems. The adverse effects are particularly prominent in children transplanted during the first years of life. Endocrine late consequences constitute the most frequent adverse effects among transplanted children of all age groups. The overall burden of late morbidity has a major impact on the quality of survival, although the association is not linear. The long-term results of HCT may result from the combined effects of pre-HCT treatment exposures, HCT-related conditioning regimen, and post-HCT complications such as GVHD. A more general discussion of late effects following HCT is presented in Chap. 7.

9.10.3 Late Adverse Effects After Childhood AML

A questionnaire-based study from the North American Childhood Cancer Survivor Study (CCSS) of 272 non-transplanted 5-year AML survivors showed a 20-year cumulative incidence of second malignant neoplasms (SMN) of 2 and a 5 % cumulative incidence of cardiac events. Half of the survivors reported a chronic medical condition and, compared with siblings, were at increased risk for severe or life-threatening chronic medical conditions (16 % vs. 5.8 %). Marriage rates were similar among survivors and the general population. Employment rates were similar between survivors, siblings, and the general population (Mulrooney et al. 2008).

The Scandinavian NOPHO population-based study evaluated quality of health in 138 childhood AML survivors treated without HCT. The self-reported health of the survivors was good, and their use of health care services was limited. Reported health and social outcomes were comparable to those of their siblings (Molgaard-Hansen et al. 2011). Many studies combine data on different HCT indications and only sparse data are available on the toxicity profile of long-term effects in individuals who have been transplanted for AML during childhood.

The primary, pre-HCT, therapy of AML is very intensive with a high risk of acute complications. AML therapy includes a high cumulative dose of anthracycline that together with the conditioning regimen may be a major risk factor for long-term cardiac health.

TBI is an important risk factor for long-term toxicity when applied in young children (Mulcahy Levy et al. 2013; Bajwa et al. 2012). AML, in contrast to ALL, may be managed without TBI and thereby have a more favorable toxicity profile. The use of busulfan-cyclophosphamide represents an alternative conditioning regimen for children with AML associated with reduced risk of post-transplant growth impairment, thyroid dysfunction, Leydig cell damage, and cataracts (Michel et al. 1997).

Only few studies have compared chemotherapy alone versus HCT in children with AML (Liesner et al. 1994; Leahey et al. 1999; Leung et al. 2000; Klusmann et al. 2012). The results of the studies are summarized in Table 9.1. Most of the studies are small and from a period when more patients received TBI than what is practiced today. However, the four studies give a similar impression of significantly more endocrine late-effects in HCT survivors, whereas the risk of cardiac failure seems comparable with and without HCT.

The Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survival Study (CCSS) compared self-reported chronic health conditions in 145 HCT survivors with survivors treated with chemotherapy only as well as with sibling controls (Armenian et al. 2011). The study included 75 AML patients but the results were not specified by disease group. More than two chronic health conditions were reported in 95 % and severe/life-threatening conditions in 26 % of the HCT survivors. HCT survivors were

Table 9.1 Comparative studies of late-effects following chemotherapy alone versus HCT in children with AML

Study	*N*	Therapy	Main findings
Liesner et al. (1994)	33	25 CT, 8 HCT, 7 TBI Cy, 1 BuCy	CT: endocrine function normal, four hearing deficits and two impaired renal function TBI: six growth failure, three thyroid dysfunction, four gonadal failure, two renal impairment, and six cataracts Reduced ventricular function in 8 CT and 2 TBI
Leahey et al. (1999)	52	26 CT, 26 HCT, 17 BuCy, 9 TBI Cy	Decreased height and increased weight in both groups but hypothyroidism and hypogonadism only in the HCT group 6/9 HCT females >12 years needed estrogen supplementation 3/18 (17 %) in the CT group and 1/25 (4 %) in the HCT group had reduced left ventricular function
Leung et al. (2000)	77	44 CT, 18 CT+CI, 15 HCT, 15 TBI Cy	Growth abnormalities in 51 %, cataract 12 %, neurocognitive abnormalities 30 %, endocrine abnormalities 16 %, cardiac abnormalities 8 % HCT risk factor for growth hormone deficiency, hypothyroidism, hypogonadism, infertility, cataract, and restrictive pulmonary disease. The risk of cardiac dysfunction was similar in the three groups
Klusmann et al. (2012)	171	131 CT, 40 HCT, 40 BuCy	Higher rate of skeletal anomalies and need for hormone replacement among the HCT patients. One or more late sequelae occurred in 73 % of HCT versus 32 % of chemotherapy only

CT chemotherapy only without HCT, *CI* cranial irradiation, *Bu* busulfan, *Cy* cyclophosphamide, *TBI* total body irradiation

more likely than sibling controls to have severe/life-threatening (relative risk [RR] =8.1) and two or more chronic health conditions (RR = 5.7), as well as functional impairment (RR = 7.7) and activity limitation (RR = 6.3). Compared with CCSS survivors, BMTSS survivors demonstrated significantly more health problems (severe/life-threatening conditions: RR = 3.9; functional impairment: RR = 3.5; activity limitation: RR = 5.8). Unrelated donor HCT recipients were at greatest risk but there were no differences in the prevalence and severity of chronic health conditions among BMTSS participants who underwent HCT in CR1 compared with more advanced disease (Armenian et al. 2011).

HCT exposes the patients to a higher risk of late toxicity, which should be considered when indications for HCT in AML are discussed. We need to ensure long-lasting support and relevant intervention for pediatric survivors of HCT, including regarding issues affecting quality of life (Pulsipher et al. 2012; Parsons et al. 2012). Pediatric HCT survivors have decades of life to live following transplant, thus making lasting support critical for ensuring survivors live with a minimum of chronic health problems. Continued research of the health status of adult survivors who received HCT as children will improve our understanding of the needs of this unique population.

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Lymphomas

10

Maureen M. O'Brien, Michael J. Absalon,
Thomas G. Gross, and Kara M. Kelly

Contents

10.1 Malignant Lymphomas in Children and Adolescents

Lymphomas are the third most common malignancy in children and adolescents, after acute leukemias and brain tumors; they account for approximately 15 % of all pediatric cancers (Howlader et al. 2012). Among children <15 years of age, non-Hodgkin lymphomas (NHL) predominate, accounting for approximately 6 % of childhood cancers, while Hodgkin lymphoma (HL) is more rare (3.6 %). In older adolescents, Hodgkin lymphoma incidence increases significantly, such that it represents 17 % of new cancer diagnoses compared to 8.3 % for NHL (Howlader et al. 2012). Fortunately, lymphomas are among the most curable of childhood cancers, with 5-year survival rates improving substantially from 1975 (44 % for NHL, 82 % for HL) to 2006 (80 % for NHL, 95 % for HL) (Smith et al. 2010). In NHL, improved understanding of the biology of different subtypes (lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma) has led to refined treatment strategies. In HL, advances in risk- and response-adapted chemotherapy and radiation therapy have contributed to high cure rates for newly diagnosed patients. As a result, there is

M.M. O'Brien, MD, MS (✉) • M.J. Absalon, MD, PhD
Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: maureen.obrien@cchmc.org

T.G. Gross, MD, PhD
Department of Pediatrics, Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA

K.M. Kelly, MD
Division of Pediatric Oncology, Columbia University Medical Center, New York, NY, USA

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currently no pediatric lymphoma diagnosis for which hematopoietic stem cell transplantation (HCT) is standard of care for frontline therapy. HCT does play an important role for subsets of children and adolescents who have disease that is either refractory to primary therapy or who relapse following an initial response. However, clinical trials to define optimal salvage chemotherapy regimens and transplant strategies are few, and as a result, treatment approaches for children and adolescents with relapsed or refractory lymphomas are often extrapolated from studies in adults.

10.2 Hodgkin Lymphoma

10.2.1 Approach to the Newly Diagnosed Patient

Hodgkin lymphoma arises from a malignant crippled germinal center B-cell (Hodgkin Reed-Sternberg cell), which elaborates cytokines that recruit normal immune effectors and create the inflammatory lymph node infiltrate (Steidl et al. 2011). At initial diagnosis, patients are risk stratified based on Ann Arbor staging of disease, presence of bulky adenopathy, and presence of B symptoms (persistent fevers, weight loss, drenching night sweats). While risk grouping is not uniform across pediatric cooperative groups, children with non-bulky localized disease are generally considered low risk, and patients with advanced stage disease and B symptoms are high risk (Freed and Kelly 2010). For patients with low-risk disease, outcomes are excellent with event-free survival (EFS) and overall survival (OS) approaching 90 and 95 %, respectively. For these patients, clinical trials are focused on an optimal balance between cure rate and late effects of treatment, with attempts to decrease or eliminate the use of radiation therapy and chemotherapy agents with significant risks of infertility and second malignancy (Keller et al. 2009).

For intermediate-risk patients, combined modality therapy with multi-agent chemotherapy and low-dose involved-field radiation therapy (IFRT) results in 5-year EFS and OS rates of 85 and 95 % (Freed and Kelly 2010). The Children's Oncology Group (COG) AHOD0031 study evaluated whether radiation therapy could be omitted after 4 cycles of ABVE-PC chemotherapy (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) in the subgroup of patients defined as rapid responders to two cycles of chemotherapy and complete responders to four cycles of chemotherapy. They found no significant benefit to the addition of IFRT as 3-year EFS rates were 87.9 % (95 % CI 83.3–91.4 %) for patients randomized to receive IFRT compared to 85.4 % (95 % CI 80.8–89.0 %) for those randomized to no IFRT ($p=0.07$) (Friedman et al. 2010). For high-risk patients, COG studies have focused on chemotherapy intensification, such as the use of dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine) for all patients (Kelly et al. 2011), and the incorporation of vinorelbine and ifosfamide, agents with demonstrated activity in the relapse setting, for newly diagnosed patients with slow early response to initial therapy (Kelly 2011).

For intermediate and high-risk patients, other cooperative groups have evaluated the Stanford V combined modality regimen (Stanford/St. Jude/Dana-Farber consortium), which has 3-year EFS rate of 79 % and 3-year OS rate of 90 %, and the OEPPA (vincristine, etoposide, prednisone, procarbazine, doxorubicin)-based regimens (German/EuroNet GPOH group) with 5-year EFS rate of 87.7 % and 5-year OS rate of 96.2 % (Mauz-Korholz et al. 2010; Metzger et al. 2012). Thus, even for high-risk patients, outcomes are generally favorable with 5-year EFS rates of 80–85 % and OS approaching 95 %, although certain subgroups (e.g., stage IVB patients) continue to have EFS estimates <80 % in most studies (Freed and Kelly 2010). While research is ongoing to improve frontline regimens for the highest-risk subgroups, given the overall success with combined modality therapy, there is currently no role for HCT in newly diagnosed patients with HL regardless of initial risk stratification.

10.2.2 Refractory/Relapsed Hodgkin Lymphoma

Despite improvements in risk stratification and treatment strategies for newly diagnosed patients with HL, approximately 15 % will be refractory to

or relapse following initial therapy (Daw et al. 2011). For these patients, cure may still be achieved. In the prospective ST-HD-86 salvage trial for patients with first relapse, 10-year disease-free survival (DFS) and OS rates were 62 % and 75 %, respectively (Schellong et al. 2005). Salvage strategies include second-line chemotherapy, radiation therapy, and high-dose chemotherapy (HDCT) with autologous HCT. In certain circumstances, use of allogeneic HCT with either myeloablative or reduced-intensity conditioning (RIC) may be considered. Unfortunately, there are no randomized trials in children that define the best salvage chemotherapy and optimal transplant conditioning regimens or that compare standard chemotherapy to HDCT followed by autologous HCT. Standard of care treatment practices in pediatric oncology has been derived from retrospective pediatric series as well as extrapolation from adult studies. Currently, cooperative group trials for relapsed HL with treatment allocation based on potential prognostic factors are in progress (EuroNet-PHL-C1, NCT00433459) or in development in the Children's Oncology Group.

10.2.3 Prognostic Factors at Relapse

Retrospective studies in adults have identified risk factors for adverse prognosis at the time of relapse including advanced stage at relapse, relapse within a previously irradiated site, short duration of first remission, B symptoms, anemia, extranodal disease, and poor response to salvage chemotherapy (Brice et al. 1996; Josting et al. 2002a; Brice 2008; Majhail et al. 2006; Horning et al. 1997; Moskowitz 2004) (Table 10.1). Of these factors, one of the most powerful predictors of outcome after relapse is duration of first remission, with significantly inferior outcomes for patients who relapse within 12 months of completion of frontline therapy (Brice et al. 1997; Josting et al. 2000, 2002a). Outcomes are particularly dismal for those who have disease refractory to primary therapy (Josting et al. 2000; Tarella et al. 2003). One prospective adult study of salvage chemotherapy followed by HDCT with autologous HCT identified three factors at the time of relapse that predicted outcome (B symptoms, extranodal disease, and first remission duration < 12 months) and documented EFS of 83 % for patients with zero or one risk factor and EFS of 10 % for those with three risk factors (Moskowitz et al. 2001). An additional powerful predictor of outcome in adults is response to salvage chemotherapy, with favorable prognosis for those with chemosensitive disease, even if refractory to primary therapy, but dismal outcomes for those with chemoresistant disease (Greaves et al. 2012; Moskowitz et al. 2004; Schmitz et al. 1993). With the advent of functional imaging with ^{18}F-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET), response to salvage therapy as defined by negative FDG-PET imaging has emerged as a critical prognostic factor with lack of normalization of functional imaging prior to autologous HCT predicting poor outcome after retrieval therapy (Cocorocchio et al. 2012; Moskowitz et al. 2010a, b, 2012; Devillier et al. 2012; Jabbour et al. 2007; Spaepen et al. 2003).

For children and adolescents, additional prognostic factors have been identified, including

Table 10.1 Adverse prognostic factors in relapsed Hodgkin lymphoma

Primary refractory/progressive disease (Schellong et al. 2005; Baker et al. 1999; Claviez et al. 2004a; James et al. 1992)[a]
Short duration of first remission (<12 months) (Schellong et al. 2005; Josting et al. 2002a; Brice et al. 1996)[a]
Chemoresistant disease to salvage chemotherapy (Baker et al. 1999; Claviez et al. 2004a; Metzger et al. 2010)[a]
Relapse within a previously irradiated site (Crump et al. 1993)
Residual disease at time of HCT (B symptoms, elevated LDH, mediastinal mass) (Baker et al. 1999; Lieskovsky et al. 2004)
Advanced stage at relapse (Claviez et al. 2004a; Josting et al. 2002a; Lieskovsky et al. 2004)
Extranodal disease at relapse (Lieskovsky et al. 2004; Reece et al. 1995)
B symptoms, anemia, elevated ESR at relapse (Metzger et al. 2010; Moskowitz et al. 2001; Akhtar et al. 2010)
Residual disease at time of HCT as measured by FDG-PET uptake (Moskowitz et al. 2010a, 2012)[b]

[a]Highly prognostic in multivariate analysis
[b]FDG-PET under investigation in pediatric cohorts but prognostic in adults

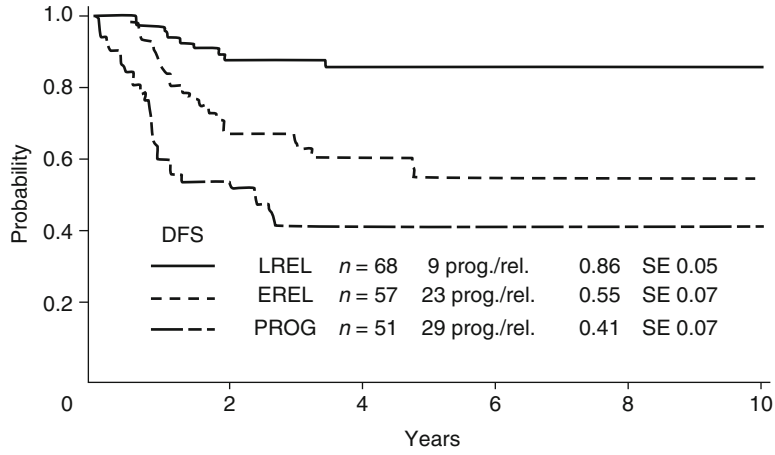

Fig. 10.1 Probabilities of disease-free survival for patients treated on ST-HD-86 trial for first relapse of HL, stratified by timing of relapse. *EREL* early relapse (3–12 months), *LREL* late relapse (>12 months), *PROG* progressive disease or relapse within 3 months of completing primary therapy (Copyright 2005 *Journal of Clinical Oncology*. Reproduced with permission from Schellong et al. (2005))

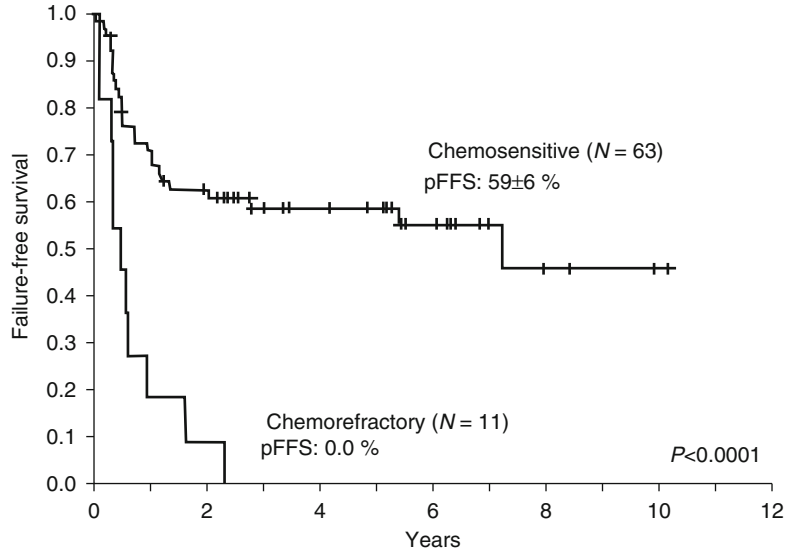

Fig. 10.2 Failure-free survival in 74 pediatric and adolescent patients with recurring Hodgkin lymphoma according to disease status at auto-HCT (Copyright 2008 Nature Publishing Group. Reproduced with permission from Claviez et al. (2008))

stage at the time of original diagnosis, local versus distant site relapse, and amount and type of primary therapy (Claviez et al. 2004a; James et al. 1992; Lieskovsky et al. 2004; Schellong et al. 2005). However, like adults, time to disease recurrence and response to salvage chemotherapy remain the most critical prognostic factors in children (Baker et al. 1999; Lieskovsky et al. 2004; Claviez et al. 2004a, 2008). In the largest published series of salvage therapy in pediatric HL, time to disease recurrence was the most important prognostic factor; patients who had progressive disease or relapsed within 3 months of completing primary therapy had 10-year DFS of 41 % compared to 55 % for those with early relapse within 3–12 months and 86 % for those who relapsed more than 12 months from the completion of primary therapy (Fig. 10.1) (Schellong et al. 2005).

In addition to duration of first remission, chemosensitive disease at relapse and disease status at the time of autologous HCT are important prognostic factors for pediatric patients with 5-year DFS of 44–59 % for those with disease sensitive to salvage chemotherapy compared to 0–9 % for those with refractory disease, even with the use of autologous HCT (Fig. 10.2) (Baker et al. 1999; Claviez et al. 2008). At the time of HCT, residual active disease as measured by elevated lactate dehydrogenase (LDH) level, B symptoms, or mediastinal adenopathy is

associated with dismal outcome (Baker et al. 1999; Lieskovsky et al. 2004; Akhtar et al. 2010). In a St. Jude Children's Research Hospital cohort of 50 pediatric patients, 15 had primary refractory HL, 14 had early relapse (within 12 months), and 21 had late relapses (Metzger et al. 2010). Overall, 5-year freedom from treatment failure (FFTF) and OS were 57.8 % and 74.2 %, respectively. However, of the 15 with refractory disease, seven did not have adequate response to first salvage chemotherapy attempt, and five never responded to any regimen. While 5-year OS was 53.3 % for primary refractory patients and 83.2 % for patients with relapse, it was only 17.9 % for those who did not respond to primary salvage therapy. Prognostic risk factors in univariate analysis included primary refractory disease, anemia at treatment failure, erythrocyte sedimentation rate (ESR) > 50 at treatment failure, and inadequate response to initial salvage therapy; in the multivariate analysis, only response to the first two cycles of salvage therapy remained prognostic (Metzger et al. 2010).

Historically, chemosensitive disease has been defined by computed tomography (CT). There are no published prospective pediatric studies specifically evaluating the role of functioning imaging with FDG-PET in predicting outcome in the setting of relapse, although one small retrospective pediatric study has been reported. Children's Oncology Group protocol AHOD0321 was a phase 2 study to evaluate the safety and efficacy of weekly gemcitabine and vinorelbine (GV) for patients with relapsed or refractory HL, and response was defined by reduction in size of target lesions on CT (Cole et al. 2009). Subsequently, responses were retrospectively reevaluated based on International Harmonization Project (IHP) criteria including FDG-PET, where complete response (CR) for patients whose pretreatment disease was FDG-avid is defined as PET negativity after treatment, regardless of the size of residual masses seen on conventional imaging modalities such as CT (Cheson 2008; Juweid et al. 2007). The authors observed considerable variability in response assessment between FDG-PET and CT-based criteria; 6 of 13 had CR by IHP criteria, while only 1 of these 13 met CT-based protocol criteria for CR. With median follow-up of 20.9 months, there was no significant difference in EFS or OS among the six patients with negative PET scans after two cycles of GV and the seven who were still positive. The study was limited by small numbers and heterogeneous subsequent therapy, indicating that larger, prospective studies of the prognostic role of FDG-PET versus CT imaging in pediatric patients with relapsed Hodgkin lymphoma are necessary. In the EuroNet-PHL-CL1 trial for pediatric patients with relapsed HL, early response assessment to IEP-ABVD (ifosfamide, etoposide, prednisolone, adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy including FDG-PET is a critical component, and FDG-PET results will be used to select salvage therapy pathways (Daw et al. 2011).

Currently, robust biomarkers predictive of response to salvage therapy are lacking. Most promising has been the association between infiltrating tumor-associated macrophages, identified by expression of CD68, and prognosis in adult HL patients at both initial diagnosis and at relapse (Steidl et al. 2010). At relapse, second-line therapy failed in 12.5, 51.7, and 62.5 % of patients with <5, 5–25, and >25 % CD68-positive cells detected by immunohistochemistry, respectively. Other biomarkers of interest include CD20 expression, MMP11 (matrix metallopeptidase expressed by tumor-associated macrophages), soluble CD30, IL-10, TARC (thymus and activation regulated chemokine), bcl-2 expression, and the presence of inflammatory T-cells. To date, none have demonstrated sufficient prognostic power to be incorporated into algorithms for frontline or relapse therapy (Blum 2010).

The goal of refining prognostic factors in the setting of refractory or relapsed HL is to use these factors prospectively to allocate patients to risk-adapted salvage therapy such that patients with low-risk relapses who may be cured with second-line chemotherapy and radiation are treated appropriately, while those who are most likely to derive benefit from HCT and autologous HCT receive treatment with this modality and patients with disease refractory to salvage chemotherapy are referred for novel therapeutic trials. Patients with late relapse (greater than 12 months from

primary treatment) with disease that is sensitive to salvage chemotherapy generally have favorable outcomes with standard chemotherapy plus radiation therapy, and often are not considered candidates for autologous HCT. For adults with favorable risk relapse (nodal relapse outside prior irradiated field at least 12 months from the end of primary ABVD therapy), therapy recommendations currently include four cycles of BEACOPP or MOPP/ABV (mechlorethamine, vincristine, prednisone, procarbazine, doxorubicin, bleomycin, vinblastine) followed by IFRT to 30–36 Gy if CR is achieved with chemotherapy, with autologous HCT reserved for those low-risk patients who do not have a CR with second-line chemotherapy (Brice 2008).

In the pediatric ST-HD-96 trial, 68 patients with late relapses were treated with IEP-ABVD salvage chemotherapy followed by radiation to sites involved at relapse and original sites if primary therapy had not included radiation to 25Gy; outcomes for these patients were excellent with 10-year DFS 86 ± 5 % and 10-year OS 90 ± 4 % (Schellong et al. 2005). Small retrospective reports in children support the finding that certain patients with late relapses may be salvaged without HDCT and HCT. For adults, patients with low-stage disease who relapsed after primary therapy with two cycles of ABVD plus radiation therapy had similar freedom from second treatment failure and OS regardless of whether they received salvage chemotherapy with escalated BEACOPP or with HDCT and autologous HCT (James et al. 1992; Shankar et al. 1997; Sieniawski et al. 2007). However, some patients with late relapses may be considered for intensification of salvage therapy including HDCT and autologous HCT depending on features of their initial diagnosis and therapy; for example, a child with initial high-risk features such as advanced stage and B symptoms who was treated with an intensive chemotherapy regimen such as BEACOPP plus radiation therapy would be considered for autologous HCT even with a long duration of first remission. On the pediatric EuroNet-PHL-C1 trial (Fig. 10.3), low-risk patients are defined as those with late relapse (>12 months complete remission) following two cycles of primary chemotherapy for early stage disease; these patients are treated with salvage chemotherapy and IFRT without autologous HCT. Patients with late relapses but with a history of more advanced stage disease and more intensive primary therapy are included in the intermediate-risk group. These patients are allocated to chemotherapy + IFRT or HDCT with autologous HCT based on early interim response assessment including FDG-PET scanning, with those responding favorably proceeding with chemotherapy without autologous HCT (Daw et al. 2011).

10.2.4 General Approach to Salvage Chemotherapy

The goals of salvage chemotherapy are reduction of disease burden, demonstration of chemosensitive disease prior to HDCT and autologous HCT, and facilitation of peripheral blood stem cell (PBSC) collection. Effective regimens combine agents to which patients are unlikely to have been exposed in primary therapy in order to minimize cross-resistance and avoid cumulative drug toxicities. Numerous salvage chemotherapy regimens have been evaluated in single-arm studies with reported overall response rates [ORR = complete response (CR) + partial response (PR)] of 65–85 % (Kuruvilla et al. 2011). However, no single salvage regimen has been demonstrated to have superior activity or disease control, and there are no randomized trials comparing these regimens. Ultimately the choice of salvage regimen for an individual patient is based on such factors as the patient's prior therapy and associated comorbidities, potential long-term toxicities of each regimen, ease of administration, and ability to mobilize sufficient PBSC in combination with granulocyte colony-stimulating factor (G-CSF) stimulation (i.e., minimum 2×10^6 CD34+ cells/kg with optimal dose at least 5×10^6 CD34+ cells/kg). The most common cause of mobilization failure is stem cell damage due to prior chemotherapy, particularly after exposure to DNA cross-linking agents and purine analogs; as a result, PBSC collection should be performed early during salvage therapy in any patient for whom HDCT with autologous SCT is being considered, provided they

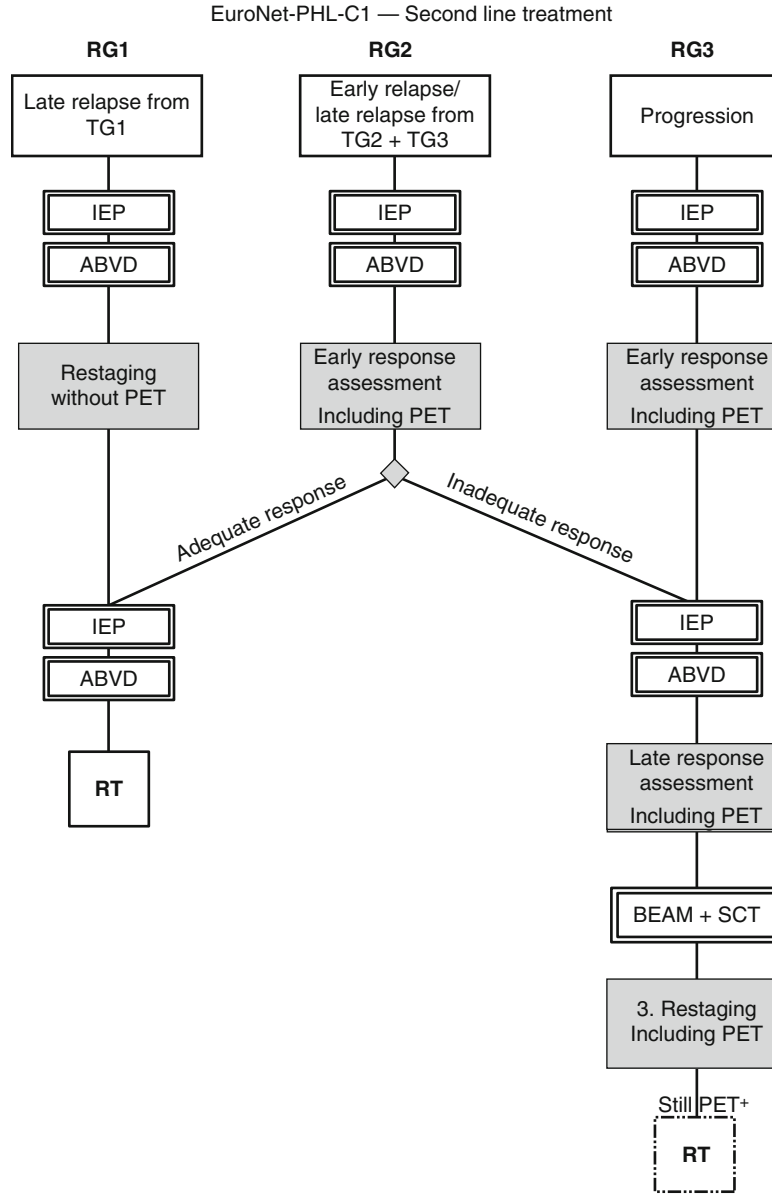

Fig. 10.3 Risk-adapted treatment plan for relapsed and refractory Hodgkin lymphoma according to the EuroNet-PHL-C1 trial. *RG1* low-risk group, *RG2* intermediate-risk group, *RG3* high-risk group, *TG1* treatment group 1, *TG2* treatment group 2, *TG3* treatment group 3, *IEP* ifosfamide, etoposide, prednisolone, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *PET* positron emission tomography, *RT* radiotherapy, *BEAM* BCNU, etoposide, cytarabine, melphalan, *ASCT* autologous stem cell transplantation, *HDCT* high-dose chemotherapy (Copyright 2011 Wiley. Reproduced with permission from Daw et al. (2011))

demonstrate chemosensitive disease and clearance of any bone marrow involvement with lymphoma (Motabi and Dipersio 2012). Thus, patients receiving salvage chemotherapy should be evaluated early (e.g., following two cycles) to identify those who should proceed with PBSC collection as well as those with inadequate response who might be candidates for an alternative salvage regimen or clinical trials of novel agents.

10.2.5 Salvage Chemotherapy Regimens

A variety of salvage regimens have been used in relapsed HL, which are summarized in Table 10.2. Mini-BEAM was first developed as a salvage chemotherapy regimen for comparison to autologous HCT regimens, but has been supplanted by other regimens given significant

Table 10.2 Salvage chemotherapy regimens with activity in relapsed Hodgkin lymphoma

Regimen	Chemotherapy drugs	References
IEP-ABVD	Ifosfamide, etoposide, prednisolone, adriamycin, bleomycin, vinblastine, dacarbazine	Daw et al. (2011)
Mini-BEAM	BCNU, etoposide, cytarabine, melphalan	Kuruvilla et al. (2006), Martin et al. (2001), Moore et al. (2012), Villa et al. (2011)
Dexa-BEAM	Dexamethasone, BCNU, etoposide, cytarabine, melphalan	Schmitz et al. (2002), Pfreundschuh et al. (1994)
DECAL	Dexamethasone, etoposide, cisplatin, cytarabine, L-asparaginase	Kobrinsky et al. (2001)
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin	Akhtar et al. (2010), Aparicio et al. (1999)
DHAP	Dexamethasone, cytarabine, cisplatin	Abali et al. (2008), Josting et al. (2005)
APE	Cytarabine, cisplatin, etoposide	(Josting et al. (2002b), Wimmer et al. (2006)
ICE	Ifosfamide, carboplatin, etoposide	Abali et al. (2008), Moskowitz et al. (1999, 2010b)
MIED	Methotrexate, ifosfamide, etoposide, dexamethasone	Sandlund et al. (2011)
IV	Ifosfamide, vinorelbine	Horton et al. (2010), Trippett et al. (2004), Bonfante et al. (2001, 1998)
GDP	Gemcitabine, dexamethasone, cisplatin	Kuruvilla et al. (2006), Baetz et al. (2003)
IGEV	Ifosfamide, gemcitabine, prednisone, vinorelbine	Magagnoli et al. (2007), Santoro et al. (2007)
GV	Gemcitabine, vinorelbine	Suyani et al. (2011), Cole et al. (2009)

hematologic toxicity and rates of febrile neutropenia as well as potential compromise of stem cell mobilization. Currently, mini-BEAM is considered for patients who are refractory to other salvage regimens (Linch et al. 1993; Martin et al. 2001; Moore et al. 2012; Villa et al. 2011). Platinum-based regimens, such as ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), DHAP (dexamethasone, cytarabine, cisplatin), or APE (cytarabine, cisplatin, etoposide), have demonstrated efficacy in relapsed HL with ORR of 68–88 % (Aparicio et al. 1999; Wimmer et al. 2006; Josting et al. 2002b, 2005; Akhtar et al. 2010). More recently, ifosfamide-based regimens have come to the forefront, and numerous salvage combinations have been reported. Alternating IEP-ABVD is the standard of care for children in Europe and demonstrated an ORR of 85 % in the ST-HD-86 trial in a cohort of 176 pediatric patients whose primary therapy was COPP/OPPA or COPP/OEPA (cyclophosphamide, vincristine, prednisone, procarbazine, doxorubicin, ± etoposide) (Daw et al. 2011; Schellong et al. 2005). ICE (ifosfamide, carboplatin, etoposide) has significant activity in adults with relapsed HL (ORR 88 %) (Moskowitz et al. 1999, 2010b) and better outcomes compared to DHAP in one trial (Abali et al. 2008). In pediatric patients, the ICE regimen has been used extensively in a variety of solid tumors and lymphomas (Cairo et al. 2001; Van Winkle et al. 2005; Griffin et al. 2009). Indeed, ICE is so well studied and frequently utilized that it is a common backbone for the addition of novel active agents, such as bortezomib, a proteasome inhibitor with activity in HL (Fanale et al. 2011). Alternative ifosfamide-based regimens with demonstrated efficacy and adequate stem cell mobilization in children include MIED (methotrexate, ifosfamide, etoposide, dexamethasone, ORR 84 %) and IV (ifosfamide/vinorelbine, ORR 72–83 %) (Bonfante et al. 1998; Magagnoli et al. 2001; Bonfante et al. 2001; Sandlund et al. 2011; Trippett et al. 2004). Most recently, the COG AHOD0521 study evaluated the combination of IV plus bortezomib in 23 pediatric patients with relapsed or refractory HL and found the regimen to be well tolerated with 61 % ORR by CT criteria and 91 % ORR by PET/CT after 4 cycles (Horton et al. 2010).

Gemcitabine, a pyrimidine antimetabolite, demonstrated activity as a single agent in HL (Santoro et al. 2000; Venkatesh et al. 2004; Zinzani et al. 2000) and has subsequently been incorporated into multi-agent salvage regimens. The GDP (gemcitabine, dexamethasone, cisplatin) regimen achieved ORR of 69 % in a cohort of 23 adult patients, all of whom had successful stem cell collection and underwent autologous HCT (Baetz et al. 2003). Despite similar response rates, the GDP regimen performed favorably compared to mini-BEAM in terms of both progression-free survival (PFS; 74 % vs. 35 %) and PBSC mobilization with 97 % of GDP patients mobilizing $\geq 5 \times 10^6$ CD34+ cells/kg compared to 57 % with mini-BEAM (Kuruvilla et al. 2006). Santoro and colleagues reported excellent results with IGEV (ifosfamide, gemcitabine, prednisone, vinorelbine) with an ORR of 81 %, minimal toxicity, and excellent mobilization of peripheral blood stem cells with 98 % of patients achieving at least 3×10^6 CD34+ cells/kg (median 10.5×10^6 CD34+ cells/kg) (Magagnoli et al. 2007; Santoro et al. 2007). GV (gemcitabine and vinorelbine) has been evaluated in both adult and pediatric populations (Suyani et al. 2011; Cole et al. 2009). In the pediatric cohort of 25 patients, the GV regimen was well tolerated with an ORR of 76 % including 25 % CR and 44 % VGPR (very good partial response), which compares favorably with other regimens (Cole et al. 2009). The GV regimen has the additional advantages of less acute toxicity and minimal risk for late toxicity compared with other retrieval regimens, as well as ability to be administered as an outpatient.

10.2.6 Autologous HCT in Relapsed Adult Hodgkin Lymphoma

The use of autologous HCT in relapsed pediatric HL is based on the adult experience in which HDCT and autologous HCT is considered the standard of care for most patients with relapsed disease (Kuruvilla et al. 2011). The use of autologous HCT in adults evolved from early studies that demonstrated poor outcomes with salvage chemotherapy (Bonfante et al. 1997; Longo et al. 1992), as well as two randomized trials demonstrating improved DFS with autologous HCT compared to conventional salvage chemotherapy (Schmitz et al. 2002; Linch et al. 1993). In the first trial, 40 patients were randomized to BEAM followed by autologous HCT or to mini-BEAM chemotherapy. Interim results demonstrated significant EFS benefit (53 % vs. 10 %) for the autologous HCT arm, although no OS advantage was found; the trial was closed early as patients refused randomization and requested autologous HCT (Linch et al. 1993).

In the German HD-1 trial, all patients were treated with two cycles of Dexa-BEAM, after which those with chemosensitive disease (n = 117 of 161 patients initially enrolled) were randomized to either two additional Dexa-BEAM cycles or BEAM with autologous HCT. FFTF at 3 years was 55 % for the patients who received BEAM and autologous HCT compared to 34 % for those treated with Dexa-BEAM (Fig. 10.4) (Schmitz et al. 2002). With updated follow-up, 7-year FFTF showed a benefit to HCT for patients with early first relapse (Dexa-BEAM 12 % vs. autologous HCT 42 %, $p < 0.01$) and patients with late first relapse (Dexa-BEAM 44 % vs. autologous HCT 63 %, $p = 0.07$), but not for patients with multiple relapses. Despite the improvement in relapse-free survival with HCT, OS at 7 years was similar with 56 % (CI 42–69 %) for Dexa-BEAM compared with 57 % (CI 43–71 %) for autologous HCT, and neither patients who relapsed early nor late had improved OS with HCT (Fig. 10.5) (Schmitz et al. 2005). The lack of difference in OS may be due to subsequent salvage therapy for those relapsing after Dexa-BEAM, as treatment-related toxicity did not appear to be higher in the autologous HCT group. Complementing these early randomized trials, a retrospective comparison of 60 patients treated with autologous HCT compared to a matched group treated with conventional salvage chemotherapy also favored autologous HCT in terms of EFS (53 % vs. 27 %, $p < 0.01$) but not OS (54 % vs. 47 %, $p = 0.25$) (Yuen et al. 1997). Additional non-randomized adult studies have reported 5-year EFS rates with autologous HCT

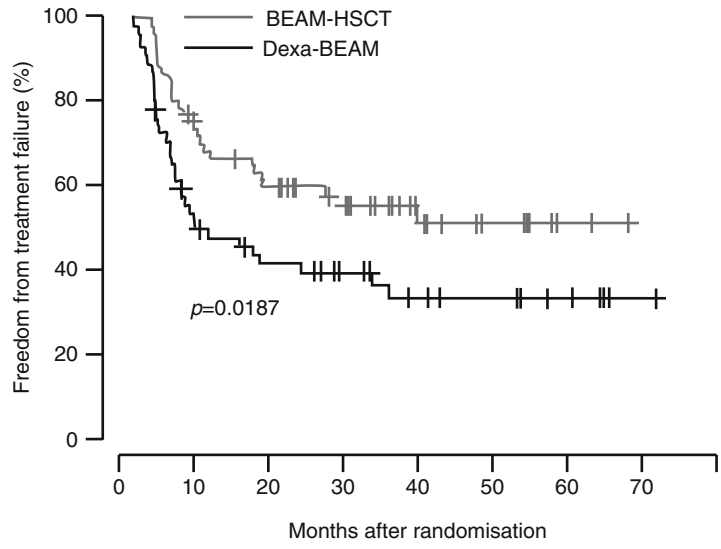

Fig. 10.4 Freedom from treatment failure for patients with relapsed chemosensitive HL treated with Dexa-BEAM or autologous HCT (Copyright 2002 Elsevier. Reproduced with permission from Schmitz et al. (2002))

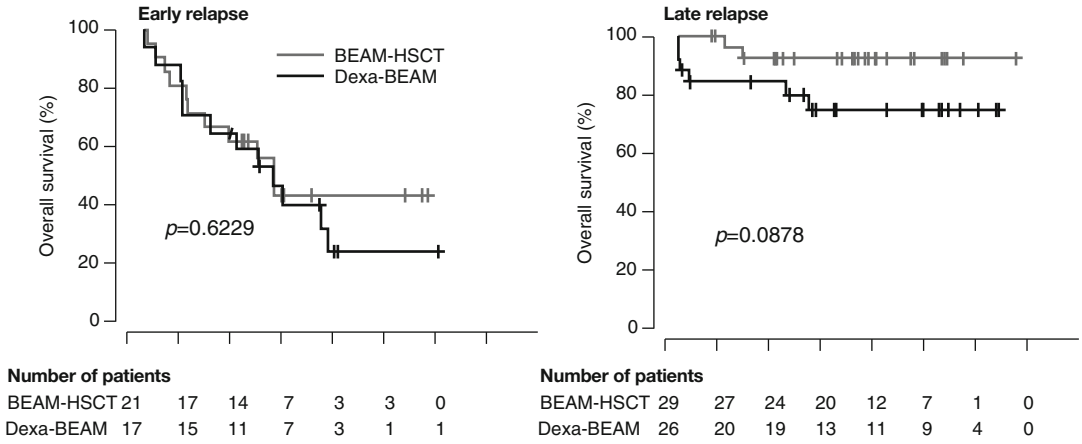

Fig. 10.5 Overall survival for early and late relapse of HL treated with Dexa-BEAM or autologous HCT (Copyright 2002 Elsevier. Reproduced with permission from Schmitz et al. (2002))

ranging from 25 to 60 % and OS ranging from 35 to 66 % with inferior outcomes for patients who experienced induction failure with initial therapy and those with residual disease or chemoresistant disease at the time of HCT (Andre et al. 1999; Moskowitz et al. 2004; Sweetenham et al. 1999; Bierman et al. 1993; Sureda et al. 2001; Popat et al. 2004; Chopra et al. 1993; Reece et al. 1994; Anselmo et al. 2000; Viviani et al. 2010). Of note, neither of the randomized trials included patients with disease refractory to chemotherapy.

For adults with high-risk relapse, retrospective studies favor the use of autologous HCT. In a report of 86 patients with progressive disease or early relapse within 3 months who were treated with HDCT and autologous HCT, 5-year EFS and OS were 25 and 35 %, respectively. Compared to a matched cohort treated with chemotherapy alone, autologous HCT was a superior option for

patients with primary induction failure, with response to second-line treatment the only factor that correlated with survival (Andre et al. 1999). Ferme and colleagues reported the outcome of 157 patients with advanced stage (IIIB–IV) disease enrolled on the H89 trial who had either induction failure (IF), partial response (PR) of less than 75 %, or relapse (Ferme et al. 2002). Patients received salvage chemotherapy (mitoguazone, ifosfamide, vinorelbine, and etoposide) followed by high-dose BEAM (BCNU, etoposide, cytarabine, and melphalan) with autologous HCT. With a median follow-up of 50 months, the 5-year survival estimates were 30, 72, and 76 % for the IF, PR, and relapse groups, respectively (p =0.0001), 71 % for the 101 patients given HDCT, and 32 % for the 48 patients treated without HDCT ($p=0.0001$). Multivariate analysis demonstrated that B symptoms at the time of relapse, salvage chemotherapy without autologous HCT, and chemoresistant disease before HDCT were significantly associated with shorter overall survival (Ferme et al. 2002).

10.2.7 Autologous HCT in Relapsed Pediatric Hodgkin Lymphoma

There have been no randomized trials in relapsed pediatric HL comparing conventional salvage chemotherapy with autologous HCT, but multiple retrospective and prospective series of HDCT with autologous HCT have been reported and are summarized in Table 10.3. Williams and colleagues reported a case–control study comparing 81 pediatric patients who had undergone autologous HCT with 81 matched adult patients and found a 3-year progression-free survival (PFS) rate of 39 % and OS of 64 % for children, which was comparable to the adults suggesting that adult data may be extrapolated to children (Williams et al. 1993). Subsequently, Baker and colleagues reported 53 pediatric patients treated with autologous HCT with 5-year failure-free survival (FFS) of 31 % and OS of 43 % with superior outcomes for patients with normal LDH levels and chemosensitive disease. Similar to adults, children with chemoresistant disease had dismal outcomes with 5-year FFS of 9 % (Baker et al. 1999). Claviez and colleagues echoed these results with 5-year OS approaching 60 %, but with all 11 patients who entered HCT with chemoresistant disease experiencing progression (Claviez et al. 2004a).

In COG study A5962, 39 pediatric patients with HL received salvage chemotherapy, most with ifosfamide-based regimens, and the 28 patients with PR or CR after no more than four cycles of chemotherapy and adequate PBSC collection proceeded to HDCT with autologous HCT (Harris et al. 2011). The 3-year EFS and OS for the HL group as a whole were 45 and 63 %, respectively, with significantly better outcomes for those with chemosensitive disease who received autologous HCT (3-year EFS and OS ~ 65 %). In contrast, Stoneham and colleagues compared 51 pediatric patients treated with HDCT and autologous HCT to 78 patients treated with conventional salvage chemotherapy and found no difference in OS (hazard ratio = 1.5; 95 % confidence interval = 0.9-8.2; $p=0.40$) even when patients were stratified by duration of first remission (Stoneham et al. 2004). However, of the 11 patients who received autologous HCT for refractory disease, nine remain alive with follow-up ranging from 2 to 18 years, leading the authors to conclude that HCT does not offer any significant survival advantage over conventional salvage therapy in children with relapsed HL, although it may be of benefit for patients with primary refractory disease.

In the pediatric ST-HD-86 trial, of 176 patients enrolled and treated with IEP-ABVD, 53 (30 %) underwent autologous HCT, all of whom had either progression during primary therapy or relapsed within 12 months (Schellong et al. 2005). 18 were transplanted in second remission following their first relapse, and 35 were transplanted after second or multiple relapses. For the subgroup transplanted in second remission, 6-year DFS and OS were 51 % and 66 %, respectively, with no significant difference from patients with similar risk factors treated without autologous HCT (6-year DFS 47 %, OS 65 %). For those transplanted after second or greater

Table 10.3 Pediatric series of autologous HCT in Hodgkin lymphoma

Reference	Year	N	Patients	Salvage chemotherapy	Conditioning regimen	DFS/EFS/PFS	Overall survival	Median follow-up
Williams et al. (1993)	1993	81	17 CR2, 5 CR1, 23 PR, 20 primary refractory, 8 untreated relapse, 6 resistant relapse	Variable	CBV (55 %), BCNU/ melphalan based (36 %)	39 % 3-year PFS (chemosensitive 55 %, chemoresistant 25 %)	64 % (3-year)	3 years
Baker et al. (1999)	1999	53	40 with ≤2 prior chemo regimens, 11 with resistant disease	Not reported	CBV (83 %)	31 % 5-year FFS (chemosensitive 35 %, chemoresistant 9 %)	43 % (5-year)	5.4 years
Verdeguer et al. (2000)	2000	20	12 CR2, 1 CR1, 1 PR1, 3 CR>2, 2 relapse	Not reported	CBV (55 %), BEAM, fTBI/Cy	62 % 5-year EFS	95 % (5-year)	3.3 years
Frankovich et al. (2001)	2001	34	All relapsed/refractory; 17 CR,	Variable (MOPP, DHAP, Stanford V)	Cy/VP-16 plus BCNU, CCNU, or fTBI	67 % 5-year DFS	76 % (5-year)	Not reported
Stoneham et al. (2004)	2004	51	20 1st relapse, 8 primary progressive disease; 76 % in CR at time of HCT	Variable (EPIC, ABVD, ChIVP)	86 % BEAM	66 % 5-year DFS	72 % (5-year)	4.5 years
Lieskovsky et al. (2004)	2004	41	5 primary refractory, 31 1st relapse, 5 2nd or greater relapse	Variable (MOPP, DHAP, ICE, Stanford V)	Cy/VP-16 plus BCNU, CCNU, or fTBI	53 % 5-year EFS,63 % 5-year PFS	68 % (5-year)	4.2 years
Claviez et al. (2004a)	2004	74	28 progressive disease, 34 early relapse, 12 late relapse; 63 CR2/PR2, 11 resistant	Not reported	64 % BEAM, 26 % CBV	50 % 5-year FFS (chemosensitive 59 %, chemoresistant 0 %)	59 % (5-year)	2.7 years
Prete et al. (2005)	2005	91	33 CR2, 35 PR2, 23 advanced disease	Not reported	BCNU based (42 %), thiotepa based (38 %)	64 % 5-year EFS 55 % 10-year EFS (83.5 % 5-year EFS for CR2 patients)	67 % (5-year) 59 % (10-year)	6.6 years
Schellong et al. (2005)	2005	53	18 2nd CR, 35≥2nd relapse	IEP-ABVD	Not reported	51 % 6-year DFS for CR2 patients	66 % for CR2; 52 % for≥2nd relapse (6-year)	Not reported

Akhtar et al. (2010)	2010	58	24 relapsed, 34 refractory; 88 % chemosensitive	Not reported	ESHAP	45 % 11-year EFS	55 % (11-year)	3.6 years
Metzger et al. (2010)	2010	50	15 progressive disease, 14 early relapse, 21 late relapse	Variable (MIED, Stanford V, MOPP and derivatives, ICE, GV)	Variable (BEAM, BuCy, BuMel)	58 % 5-year FFS [53 % for primary progressive disease; 83 % for early/late relapse]	74 % (5-year) [17.9 % for nonresponders to salvage therapy; 97 % for responders	4.9 years
Harris et al. (2011)	2011	39 total, 28 auto-HCT	All patients with PR/CR after 4 cycles of salvage	ICE, VI	CBV	All patients 45 % 3-year EFS; patients with auto-HCT 66 %	All patients 63 % (3-year); patients with auto-HCT 64 %	3.2 years

HCT hematopoietic stem cell transplant, *PR* partial response, *CR* complete response, *ICE* ifosfamide, carboplatin, etoposide, *VI* ifosfamide, vinorelbine, *CBV* cyclophosphamide, *BCNU*, etoposide, *EFS* event-free survival, *MIED* methotrexate, ifosfamide, etoposide, dexamethasone, *MOPP* mechlorethamine, vincristine, procarbazine, prednisone, *GV* gemcitabine, vinorelbine, *BEAM* BCNU, etoposide, cytarabine, melphalan, *BuCy* busulfan, cyclophosphamide, *BuMel* busulfan, melphalan, *FFS* failure-free survival, *PFS* progression-free survival, *ESHAP* etoposide, methylprednisolone, cytarabine, cisplatin, *IEP-ABVD* ifosfamide, etoposide, and prednisone; ABVD, doxorubicin, bleomycin, and vinblastine, dacarbazine, *VP-16* etoposide, *DHAP* dexamethasone, cytarabine, cisplatin, *fTBI* fractionated total body irradiation, *Cy* cyclophosphamide

relapse, 6-year OS was 52 %, compared to 29 % for those with multiple relapses who did not receive a transplant. The authors concluded that there is a survival advantage for autologous HCT for patients with second or greater relapse but not for first recurrence (Schellong et al. 2005).

Ultimately, the data is mixed as to the optimal role of autologous HCT for pediatric patients with relapsed HL and limited greatly by lack of randomized trials, variability in initial therapy received by patients as well as salvage chemotherapy, conditioning regimens, and use of adjunctive radiation therapy, lack of uniform response criteria (i.e., CT vs. FDG-PET), and changes in supportive care over time. In general, based on the adult literature, pediatric patients with primary progressive disease or early relapse within 12 months who demonstrate chemosensitive disease with salvage chemotherapy are recommended for HDCT and autologous HCT, as well as select patients with late relapses and high-risk features.

10.2.8 Conditioning Regimens for Autologous HCT

The most commonly used conditioning regimens are BEAM (BCNU, etoposide, cytarabine, melphalan) and CVB/CEB (cyclophosphamide, etoposide, BCNU), although no regimen has been demonstrated to have superior remission rates or long-term outcomes (Caballero et al. 1997; Argiris et al. 2000; Patti et al. 1993; Reece et al. 1991). Randomized trials are lacking. In adult studies, 5-year OS is reported at 40–55 % for both regimens, although BEAM has been reported to have a more favorable toxicity profile than CVB, including less hepatotoxicity, mucositis, and treatment-related mortality (Wang et al. 2004; Puig et al. 2006). Attempts to intensify CVB chemotherapy with infusional etoposide and dose escalation of BCNU were associated with improved response rates but a high rate of interstitial pneumonitis (Benekli et al. 2008). BEAM has been compared to BEAC, replacing melphalan with cyclophosphamide; BEAC was associated with less mucositis, diarrhea, and septicemia, although efficacy may not be comparable to BEAM (Jo et al. 2008; Jantunen et al. 2003).

Because BCNU-containing regimens are associated with a significant risk of pulmonary toxicity, which was particularly evident in pediatric patients with a history of atopy, there is significant interest in novel conditioning regimens without BCNU (Alessandrino et al. 2000; Frankovich et al. 2001). Data from the Bone Marrow Transplant Survivor Study demonstrated a significant rate of non-relapse mortality for patients treated with BCNU-based regimens compared to busulfan or total body irradiation (TBI)-based regimens (Bhatia et al. 2005). In pediatrics, TBI-based regimens are generally avoided due to risk of late effects, including second cancers, combined with lack of proven superior efficacy over HDCT regimens (Stiff et al. 2003; Nademanee et al. 1995). Regimens avoiding BCNU by using high-dose melphalan or melphalan with etoposide and cyclophosphamide have been reported (Puig et al. 2011; Guilcher et al. 2012; Schutt et al. 2007). Modified BEAM regimens have substituted alternative chloroethylnitrosureas for BCNU, including fotemustine and lomustine (Musso et al. 2010; Ramzi et al. 2012), although neither regimen has supplanted traditional BEAM.

More recently, the BeEAM regimen, with BCNU replaced by bendamustine, a drug with proven clinical activity in B-cell malignancies, demonstrated an excellent toxicity profile although efficacy in HL remains to be proven (Visani et al. 2011). The GN-BVC regimen added gemcitabine and vinorelbine, two agents with demonstrated efficacy in HL, and decreased the dose of BCNU with improvements in pulmonary toxicity and with encouraging FFP and OS (Arai et al. 2010). The novel non-BCNU regimen using high-dose gemcitabine combined with busulfan and melphalan (GemBuMel) demonstrated an acceptable toxicity profile and high activity as conditioning for adults with relapsed HL (Nieto et al. 2011). These regimens have yet to be studied in the pediatric setting and studies in adults are limited by small patient numbers. The vast majority of pediatric autologous HCT reports have used either CVB or BEAM, and these remain the standard of care in the absence of a clinical trial.

10.2.9 Radiation Therapy Following Autologous HCT

Following autologous HCT, the majority of relapses occur in sites of prior disease, which has led to the incorporation of radiation therapy in an attempt to improve relapse-free survival following HCT (Phillips et al. 1989; Yahalom et al. 1993). Radiation therapy is generally administered to prior disease sites after HCT when stable recovery of blood counts has occurred and acute transplant-related toxicities have resolved. Radiation dosing is individualized depending on cumulative doses delivered to specific organs and fields during primary therapy, ideally to total dose of 21–40 Gy. Optimal dosing, timing, and extent of post-HCT radiation therapy are unknown and the potential benefits of improved disease control must be balanced by increased risk of toxicity, depending on sites of disease requiring radiation, prior cumulative chemotherapy exposures and toxicities, and HCT conditioning regimen.

There have been no randomized trials evaluating the use of post-HCT radiation therapy. Support for this approach is limited to retrospective series that generally demonstrate improved local control and disease-free survival, particularly in the subset of patients with bulky disease, but without effect on overall survival (Mundt et al. 1995; Yahalom et al. 1991; Poen et al. 1996; Kahn et al. 2011; Lancet et al. 1998). Most recently, University of Rochester researchers reported improved 3-year EFS and OS with IFRT (median dose 30.6 Gy, range 6–44 Gy) administered within 6 months (median 2 months) following autologous HCT (Biswas et al. 2012). IFRT was administered only to those patients who had residual disease following salvage chemotherapy or with bulky disease at the time of relapse. Notably, with longer follow-up, the survival advantage for IFRT was lost.

Other investigators have found either no survival benefit for radiation therapy or increased treatment-related mortality, predominantly pulmonary and hematologic, which may increase when radiation is administered prior to HCT (Vose et al. 1992; Pezner et al. 1995; Tsang et al. 1999; Wendland et al. 2006). For example, in a case–control study of 92 adult patients with relapsed/refractory HL treated with HDCT and autologous HCT, there was a trend toward better disease control with relapse in 22 % of those receiving IFRT within 2 months of HCT and 37 % of those who did not receive IFRT (Kahn et al. 2011). However, toxicities were significantly higher in the IFRT group with 28 % of patients experiencing grade 4 or greater toxicity, including pulmonary fibrosis/pneumonitis or myelitis. All severe toxicities occurred in patients treated with busulfan-based conditioning regimens (Kahn et al. 2011).

Retrospective studies may underestimate the value of radiation therapy in disease control, as the studies often included patients with chemotherapy-resistant bulky disease present prior to HCT, which is now recognized as a subgroup of patients for whom alternative novel therapies should be considered because outcomes are dismal with HCT in this setting. In addition, more patients receiving autologous HCT in the current treatment era will have received lower-dose, smaller fields, or no radiation therapy during primary treatment due to improvement in frontline chemotherapy regimens and radiation techniques. In this patient population, radiation therapy following autologous HCT may be both more effective and less toxic. In addition, novel radiation modalities such as proton therapy may be able to decrease target volume and the dose administered to nontargeted normal tissues, with subsequent decrease in toxicity (Hoppe et al. 2012). Currently, if radiation therapy is included in a patient's treatment regimen for relapse, recommendations for patients with CR prior to HCT are to administer 20 Gy IFRT to sites of previously relapsed disease after at least 1 month has elapsed post-HCT to minimize risk of pulmonary toxicity (Wadhwa et al. 2002). There are no pediatric studies evaluating the role of radiation therapy as an adjunct to HDCT with autologous HCT, and clinical practice is extrapolated from the adult experience.

10.2.10 Allogeneic HCT in Relapsed Hodgkin Lymphoma

Patients who relapse or have disease progression after autologous HCT have a dismal prognosis

with median survival less than 12 months, and the optimal treatment strategy for such patients is unclear (Vose et al. 1992; Varterasian et al. 1995). Allogeneic HCT has generally been reserved for patients with disease recurrence following autologous HCT, in an attempt to harness alloreactive donor-derived T-cells for graft-versus-lymphoma (GVL) effect (Jones et al. 1991; Peggs et al. 2005). Studies of allogeneic HCT in relapsed HL are summarized in Table 10.4, including studies with myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC). No randomized trials comparing allogeneic and autologous HCT have been conducted, although retrospective studies have compared allogeneic HCT with historical controls treated with autologous HCT (Jones et al. 1991; Anderson et al. 1993a). Early adult studies did not support the use of allogeneic HCT with MAC (typically busulfan/cyclophosphamide or cyclophosphamide/TBI) over autologous HCT in relapsed and progressive HL due to high rate of non-relapse mortality from graft-versus-host-disease (GVHD), pulmonary toxicity, and infections, although the relapse rate was lower in patients receiving allografts compared to autografts, consistent with some GVL effect (Milpied et al. 1996; Anderson et al. 1993a; Jones et al. 1991; Peniket et al. 2003). Assessment of the true efficacy of allogeneic HCT is further complicated by the fact that patients in retrospective series often had poor performance status and highly refractory disease (Gajewski et al. 1996; Peniket et al. 2003; Akpek et al. 2001). One potential benefit of allogeneic HCT compared to autologous HCT is that secondary acute myeloid leukemia (AML) is very rare following allogeneic HCT, but is a significant late effect for patients who received autologous HCT (Sirohi et al. 2008). Factors associated with favorable outcome following allogeneic HCT in adults with lymphoma relapse following autologous HCT include disease remission at the time of HCT, matched-sibling donor, and use of TBI (Freytes et al. 2004).

Due to the toxicity of MAC regimens, regimens with RIC were developed to minimize non-relapse mortality while maintaining a GVL effect (Alvarez et al. 2006; Anderlini et al. 2000, 2005; Peggs et al. 2007; Robinson et al. 2002; Sarina et al. 2010; Sureda et al. 2008; Vose et al. 1992). The European Group for Blood and Marrow Transplantation (EBMT) study of 168 adults with relapsed HL treated with allogeneic HCT demonstrated nearly twice the relapse incidence for patients who received RIC (57 %) compared to MAC (30 %), but with 5-year OS significantly lower for the MAC group compared to the RIC group (22 % vs. 28 %, $p=0.003$) (Sureda et al. 2008). The lack of survival benefit for MAC was attributed to excess of non-relapse mortality (NRM) at 1 year [46 % for MAC group compared to 23 % for RIC ($p=0.05$)]. The development of chronic GVHD significantly decreased the incidence of relapse, which translated into a trend for a better PFS (Sureda et al. 2008). An analysis of 285 patients in the EMBT treated with allogeneic HCT with fludarabine-based RIC conditioning found that patients in complete remission or with chemosensitive disease, good performance status, and transplants in which both donor and recipient were negative for cytomegalovirus (CMV) had improved OS. With a median follow-up of 26 months, 3-year OS, PFS, NRM, and cumulative incidence of relapse were 29, 25, 21, and 53 %, respectively (Robinson et al. 2009). Ultimately, subsequent relapse remains the primary cause of failure following RIC-based allogeneic HCT.

Multiple prospective trials have reported results of allogeneic HCT with RIC using fludarabine and melphalan (Flu/Mel) (Anderlini et al. 2008; Alvarez et al. 2006; Peggs et al. 2007). In a study of 49 patients (90 % of whom had failed prior autologous HCT) treated with Flu/Mel plus alemtuzumab with donor lymphocyte infusions (DLI) starting 3 months post-HCT for those with residual disease or progression, 4-year PFS and OS were 39 % and 56 %, respectively, and patients with matched related donors fared best due to low non-relapse mortality (Peggs et al. 2007). Patients who had a remission of at least 12 months following autologous HCT fared best with PFS of 70 % following RIC with Flu/Mel (Alvarez et al. 2006). Anderlini and colleagues demonstrated the superiority of Flu/Mel over a RIC regimen using fludarabine, cyclophosphamide,

and anti-thymocyte globulin with 18-month OS of 73 % for patients with chemosensitive or stable relapsed HL (Anderlini et al. 2005). In a phase 2 study of 92 adults with relapsed HL and HLA-identical sibling treated with a Flu/Mel RIC regimen followed by allogeneic HCT, relapse remained the main challenge (Sureda et al. 2012). The non-relapse mortality rate was 8 % at 100 days and 15 % at 1 year, and the PFS rate was 47 % at 1 year and 18 % at 4 years from trial entry. Factors associated with lower risk of relapse included chronic GVHD and HCT in complete remission. Recently, RIC regimens have incorporated other drugs with known activity in HL such as gemcitabine into established Flu/Mel regimens with promising results (Anderlini et al. 2012). Retrospective studies comparing RIC allogeneic HCT to conventional chemotherapy and radiation therapy have demonstrated a survival benefit to allogeneic HCT for patients who relapse after autologous HCT (Castagna et al. 2009; Thomson et al. 2008; Sarina et al. 2010).

While children and adolescents have been included infrequently in adult studies (Table 10.4), pediatric reports have generally been limited to cases series (Claviez et al. 2004b). Claviez reported the EBMT data for 1395 HCTs for HL in patients younger than 18 years of age; fewer than 10 % were allogeneic, although the frequency has increased over the past 5 years with the advent of RIC regimens (Claviez et al. 2008). These RIC regimens accounted for 0 % of pediatric allogeneic HCT in 2000 and ~70 % of transplants in 2006–2007 (Claviez et al. 2008). In an EBMT retrospective report of 91 pediatric patients (median age 13.5 years, range 2.2–17.9 years) with relapsed HL treated with allogeneic HCT, 51 received RIC with mainly fludarabine-based regimens while 40 received MAC (Claviez et al. 2009). 44 % of patients had failed a prior autologous HCT. NRM was similar between the MAC and RIC groups (~23 % at 2 years) although NRM decreased significantly for children receiving MAC after 2002 (9 %). Relapse rate was significantly higher in the RIC group and became noticeable approximately 9 months post-HCT. For the group overall, PFS and OS at 5 years were 30 % and 41 %, respectively, with disease status at the time of HCT emerging as the most important prognostic factor. For the 26 patients with sensitive disease and good performance status (58 % of whom had failed prior autologous HCT) who underwent HCT between 2002 and 2005, 3-year PFS was 60 % and 3-year OS was 83 %. Based on these results, Claviez and colleagues suggested that children with relapsed HL with good performance status should be considered for MAC over RIC if they demonstrate chemosensitive disease, although others in the field warn against drawing this conclusion based on retrospective data in the face of numerous adult studies demonstrating benefit with RIC regimens (Claviez et al. 2009; Nachman 2009). Ultimately, data are lacking to make evidence-based recommendations, and further study is needed to determine the role of allogeneic HCT and the optimal conditioning regimens for pediatric patients with relapsed HL who are candidates for allogeneic HCT after failure of autologous HCT.

For patients who have relapsed following autologous HCT but for whom allogeneic HCT is not possible due to either lack of suitable donor or preexisting toxicities, second autologous HCT has been investigated. The Center for International Blood and Marrow Transplant Research (CIBMTR) retrospectively reported the outcomes of 40 patients with relapsed lymphomas (53 % HL) who received a second autologous HCT due to relapse after first autologous HCT (Smith et al. 2008). 85 % of patients successfully underwent a second stem cell collection despite prior high-dose chemotherapy, and 5-year PFS and OS were 30 % with 11 % treatment-related mortality at day +100. Similar to first relapse, the strongest predictors of outcome were time to relapse following first autologous HCT and demonstration of chemosensitive disease prior to second HCT.

10.2.11 Novel Agents in Relapsed Hodgkin Lymphoma

A recurring theme with regard to relapsed HL is that patients with chemosensitive disease and

Table 10.4 Allogeneic HCT in Hodgkin lymphoma

Reference	Year	Era	Number	Patients	Peds patients	Conditioning
Anderson et al. (1993a)	1993	1970–1991	59 allo, 68 auto	Median 29 years, range 10–55 23 primary refractory, 34 early first relapse or CR2, 70 refractory first relapse ≥ CR3 73 % advanced disease at HCT	Not reported	MAC 61 TBI based 66 chemotherapy
Gajewski et al. (1996)	1996	1982–1992	100	Median 28 years, range 12–44 89 not in remission at time of HCT 11 in ≥ CR2	6 pts 12–20 years	MAC (45 % with TBI)
Milpied et al. (1996)	1996	Before 1994	45 allo, 45 auto	Median 29 years, range 15–42 53 % progressive or resistant disease	Not reported	MAC (35 % with TBI)
Akpek et al. (2001)	2001	1985–1998	53 allo, 104 auto	Median 28 years, range 13–52 53 % resistant disease at allo-HCT vs. 37 % for auto	8 allo pts 13–20 years	MAC (28 % with TBI)
Robinson et al. (2002)	2002	1996–2000	52	Median 30 years, range 15–53 54 % sensitive relapse 69 % with prior auto-HCT	Not reported	RIC (84 % fludarabine based)
Peniket et al. (2003)	2003	1982–1998	167	Median 28 years, range 12–60 42 % resistant relapse 69 % with prior auto-HCT	Not reported	MAC
Freytes et al. (2004)	2004	1990–1999	114 total 35 HL	Median 34 years, range 15–65 79 % with disease at time of transplant 100 % with prior auto-HCT	Not reported	MAC
Claviez et al. (2004b)	2004	NR	6	Median 16 years, range: 11–19 All progressive disease or only partial response to prior therapy 4 refractory	100 %	RIC (fludarabine based)
Peggs et al. (2005)	2005	1997–2003	49	Median 32 years, range 18–51 90 % with progression after prior auto-HCT	None	RIC 100 % FluMel
Anderlini et al. (2005)	2005	1997–2003	40	Median 31 years, range 18–58 75 % prior auto-HCT 35 % refractory relapse	None	RIC 26 FluMel 14 Flu/Cy/ATG
Alvarez et al. (2006)	2006	1999–2004	40	Median 31 years, range 16–53 73 % prior auto-HCT 50 % resistant relapse	Not reported	RIC 100 % FluMel
Peggs et al. (2007)	2007	1997–2004	67	Median 35 years, range 19–56 75 % prior auto-HCT 41 % refractory relapse	None	RIC 100 % FluMel
Anderlini et al. (2008)	2008	2001–2005	58	Median 32 years, range 19–59 83 % prior auto-HCT 53 % refractory relapse	None	RIC 100 % FluMel
Sureda et al. (2008)	2008	1997–2001	168	Median 31 years, range 12–64 52 % prior auto-HCT ~55 % refractory relapse	9 pts age < 16 years	89 RIC 79 MAC

Donor	Non-relapse mortality	Cumulative incidence of relapse	EFS/PFS/ DFS	Overall survival	Median follow-up
50 MRD 6 single antigen mismatch related 3 MUD	5-year 46 % Allo 58 % Auto 41 %	5-year 65 % Allo 44 % Auto 77 %	5-year EFS 18 % Allo 22 % Auto 13 %	5-year 21 % Allo 22 % Auto not reported	4.5 years
100 % MRD	3-year 61 %	3-year 35 %	3-year DFS 15 %	3-year 21 %	4.2 years
100 % MRD	4-year Allo 48 % Auto 27 %	4-year Allo 61 % Auto 61 %	4-year PFS Allo 15 % Auto 24 %	4-year Allo 25 % Auto 37 %	2.6 years
100 % MRD; T-cell depleted	10-year Chemosensitive/resistant Allo 32/53 % Auto 24/28 %	10-year Allo 53 % Auto 60 %	10-year EFS Allo 27 % Auto 26 %	10-year Allo 30 % Auto 37 %	5.1 years
Majority MRD	2-year 17.3 %	2-year 46 %	2-year PFS 42 %	2-year 56 %	9.3 months
85 % MRD	4-year 51.7 %	Not reported	4-year PFS 15.5 %	4-year 25 %	Not reported
60 % MRD	5-year 25 % Note: all rates are reported for overall cohort including NHL patients	70 % at 5 years	5-year PFS 5 %	5-year 24 %	3.6 years
Variable donors	2 of 6	3 of 6	1 of 6 alive without disease	3 of 6	3.4 years
63 % MRD	2-year Overall 16·3 % MRD 7·2 % MUD 34·1 %	Not reported	4-year PFS 32.4 %	4-year 56 %	2.6 years
20 MRD 20 MUD	18-month 22 %	18-month 55 %	18-month PFS 32 %	18-month 61 % (73 % FluMel, 39 % Flu/Cy/ ATG)	1 year
93 % MRD	1-year 25 %	Not reported	2-year PFS 32 %	2-year OS 48 %	1 year
100 % MRD	2-year FluMel + ATG 7 % FluMel 29 %	3-year FluMel + ATG 54 % FluMel 44 %	4-year PFS FluMel + ATG 39 % FluMel 25 %	4-year FluMel + ATG 62 % FluMel 39 %	4.2 years
25 MRD; 33 MUD	2-year 15 %	55 % at 2 years	2-year PFS 32 %	2-year OS 64 %	2 years
88 % MRD	3-year MAC 48 % RIC 24 %	5-year MAC 32 % RIC 58 %	5-year PFS MAC 20 % RIC 18 %	5-year OS MAC 22 % RIC 28 %	6.3 years

(continued)

Table 10.4 (continued)

Reference	Year	Era	Number	Patients	Peds patients	Conditioning
Thomson et al. (2008)	2008	1998–2004	38	Median 31 years, range 20–51 100 % with prior auto-HCT 34 % refractory relapse	None	RIC 100 % FluMel
Burroughs et al. (2008)	2008	1998–2007	90	Median 32 years, range 14–64 92 % prior auto-HCT	Not reported	RIC
Robinson et al. (2009)	2009	1995–2005	285	Median 31 years, range 18–57 80 % with prior auto-HCT 25 % refractory relapse	None	RIC (88 % fludarabine based)
Castagna et al. (2009)	2009	1999–2006	24	Median 20 years, range 18–44 31 % received auto-allo for refractory disease 79 % with active disease at allo-HCT	None	RIC 100 % fludarabine based
Devetten et al. (2009)	2009	1999–2004	143	Median 30 years, range 13–53 89 % with prior auto-HCT 47 % resistant relapse	Not reported	66 % RIC 34 % non-myeloablative
Claviez et al. (2009)	2009	1997–2005	91	median 13.5 years, range 2–18 44 % prior auto-HCT 35 % resistant relapse 33 % sensitive relapse	100 %	51 RIC 40 MAC
Sarina et al. (2010)	2010	1999–2008	104	Mean 32 years 100 % relapse after auto-HCT 80 % with active disease at allo-HCT	Not reported	RIC
Anderlini et al. (2012)	2012	2007–2011	15	Median 33 years, range 20–46 46 % with prior auto-HCT 50 % with disease at allo-HCT but most chemosensitive, 50 % in CR	None	RIC (Gemcitabine plus FluMel)
Sureda et al. (2012)	2012	2000–2007	78	Median 28 years, range 13–54 86 % with prior auto-HCT 67 % with chemosensitive disease	Not reported	RIC 100 % FluMel

allo allogeneic, *auto* autologous, *CR* complete remission, *DFS* disease-free survival, *EFS* event-free survival, *FluMel* fludarabine/melphalan, *haplo* haploidentical donor, *HCT* hematopoietic stem cell transplantation, *MAC* myeloablative conditioning, *MRD* HLA-matched related donor, *MUD* HLA-matched unrelated donor, *OS* overall survival, *PFS* progression-free survival, *RIC* reduced-intensity conditioning, *TBI* total body irradiation

long duration of remission fare best, regardless of what treatment is applied. For patients with disease refractory to salvage therapy, outcomes are very poor even with the use of HCT, and novel therapies are needed for these patients. In addition, there are important long-term toxicities for patients who are able to receive autologous or allogeneic HCT and become long-term survivors. While the highest risk following salvage therapy with HCT remains death from HL recurrence, with extended follow-up there is an increasing incidence of secondary malignancies as well as significant chronic medical conditions such as cardiovascular disease, pulmonary fibrosis, hypothyroidism, and infertility (Goodman et al. 2008). Effective novel biologic agents might not only benefit those patients who do not respond to conventional chemotherapy but also decrease the intensity of salvage therapy prior to HCT or provide a survival benefit after HCT for

Donor	Non-relapse mortality	Cumulative incidence of relapse	EFS/PFS/ DFS	Overall survival	Median follow-up
63 % MRD	5-year 19 %	Not reported	5-year PFS 35 %	5-year OS RIC 51 % chemo 15 %	4.1 years
38 MRD; 24 MUD; 28 related haplo	2-year MRD 21 % MUD 8 % haplo 9 %	2-year MRD 56 % MUD 63 % haplo 40 %	2-year PFS MRD 23 % MUD 29 % haplo 51 %	2-year OS MRD 53 % MUD 58 % haplo 58 %	2.1 years
60 % MRD; 33 % MUD	3-year 21.2 %	3-year 53 %	3-year PFS 25 %	3-year OS 29 %	2.2 years
14 MRD; 10 other	1-year 8 %	NR	2-year PFS 41 %	2-year OS 71 %	2.5 years
77 % MUD, 23 % mismatched unrelated	2-year 33 %	2-year 47 %	2-year PFS 20 %	2-year 37 %	2.1 years
67 % MRD; 20 % MUD	5-year 26 %, no difference between MAC and RIC regimens	5-year Overall 44 % MAC ~54 % RIC ~34 %	5-year PFS Overall 30 % MAC ~40 % RIC ~20 %	5-year 41 % (similar for MAC and RIC)	1.8 years
55 % MRD, 32 % MUD, 13 % haplo sibling	2-year 12.7 %	Not reported	2-year PFS 31 %	2-year OS 57 %	4 years
10 MRD, 5 MUD	18-month 13 %	Not reported	18-month PFS 49 %	18-month 87 %	1.5 years
70 % MRD, 30 % MUD	4-year 19 %	4-year 59 %	4-year PFS 24 %	4-year 43 %	4 years

those patients who do respond. The targeted agents everolimus (mTOR inhibitor) and panobinostat (pan-histone deacetylase inhibitor) have demonstrated activity, and clinical trials are in development in combination with conventional cytotoxic chemotherapy (Panobinostat shows efficacy in Hodgkin lymphoma 2012; Lemoine et al. 2012; Dickinson et al. 2009; Guarini et al. 2012; Johnston et al. 2010; Oki et al. 2011; Younes et al. 2012b). Cellular therapies are under investigation, particularly in Epstein-Barr virus (EBV) positive HL, as it has been shown that EBV-specific T-cells can be expanded and administered to patients with relapsed disease (Bollard et al. 2004).

In 2011, brentuximab vedotin, a CD30-directed antibody-drug conjugate, was FDA approved for the treatment of patients with HL after failure of autologous HCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not HCT candidates (de Claro et al. 2012). A phase 2 study of brentuximab vedotin in relapsed/refractory classical HL showed an impressive overall response rate of

75 % with 34 % complete responses and median remission duration of 20 months in complete responders (Younes et al. 2012a). Brentuximab vedotin has significant activity in patients who have failed conventional therapy pre-HCT, as well as patients who have relapsed following allogeneic HCT, and does not appear to adversely affect engraftment, GVHD, or survival when given prior to reduced-intensity allogeneic HCT (Forero-Torres et al. 2012; Chen et al. 2012; Gopal et al. 2012). Brentuximab vedotin has very modest toxicity in heavily pretreated patients, with reversible peripheral neuropathy being the most common side effect, although emerging safety data has identified the rare occurrence of progressive multifocal leukoencephalopathy as well as pulmonary toxicity when co-administered with bleomycin (Wagner-Johnston et al. 2012; Haddley 2012). Ultimately, it remains to be determined how the use of brentuximab vedotin will impact the use of HCT in the management of patients with relapsed/refractory HL. For example, are patients who do not respond to cytotoxic chemotherapy but do respond to brentuximab vedotin considered to have "chemosensitive disease" for which high-dose chemotherapy and autologous HCT are indicated? Is there a role for brentuximab vedotin as maintenance therapy following autologous HCT in patients with high-risk relapse? Ongoing clinical trials such as the Seattle Genetics AETHERA trial of maintenance brentuximab vedotin (NCT01100502) will be critical to redefining the role of HCT in the era of novel biologic agents.

10.3 Non-Hodgkin Lymphoma

The non-Hodgkin lymphomas (NHL) are a diverse group of malignancies seen throughout childhood and adult life. The annual incidence in children and adolescents under 20 years of age is between 1 and 1.5 per 100,000: nearly 100 times less than that seen in the elderly (Howlader et al. 2012). As seen in older adults, there is a male predominance that exists throughout the childhood and young adult years (Howlader et al. 2012). The incidence of NHL increases with age, and the distribution of subtypes of NHL changes. Whereas low-grade processes predominate in the older adult population, NHL occurring in children is almost entirely high grade. The prevalent forms of NHL in children are Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (LBL), and anaplastic large cell lymphoma (ALCL). Natural killer (NK)-cell and non-ALCL peripheral T-cell neoplasms are rare forms of NHL in pediatrics as is follicular lymphoma (Lorsbach et al. 2002; Setty and Termuhlen 2010). BL predominates in younger children, making up nearly half of the NHL seen among those less than 15 years of age, but its absolute and relative incidence decreases significantly among the adolescents and young adults (AYA) in whom there is a higher incidence of DLBCL, LBL, and ALCL (Burkhardt et al. 2011; O'leary et al. 2006).

Histology-based conventional-dose chemotherapy treatment plans refined through collaborative research have resulted in greater than 80 % long-term event-free survival in children and adolescents with NHL (Howlader et al. 2012; Smith et al. 2010). Therefore, HCT is currently reserved for the few patients with relapsed or refractory disease.

10.3.1 Approach to the Newly Diagnosed Patient with NHL

10.3.1.1 Burkitt Lymphoma/Leukemia and Diffuse Large B-Cell Lymphoma

Burkitt lymphoma/leukemia (BL/B-ALL) and DLBCL are the primary mature B-cell malignancies encountered in pediatric oncology. Though usually distinguished by morphology, the distinction can be difficult at times. These entities can easily be distinguished from precursor B-cell lymphomas, in that they do not express TdT but do express similar B-cell antigens including CD20. BL is characterized by a translocation of the *MYC* gene on chromosome 8q24 to an immunoglobulin gene locus resulting in constitutive expression of *MYC* (Taub et al. 1982). Abnormalities involving MYC overexpression

are also seen in a majority of pediatric cases of DLBCL, but through different mechanisms from BL. MYC rearrangements are seen in about one-third of pediatric DLBCL, and gain or amplification is seen in another 50 % (Deffenbacher et al. 2012; Miles et al. 2008). DLBCL is itself a heterogeneous class of mature B-cell neoplasms. Immunohistochemistry and expression array studies show that most can be categorized into germinal center (GC) and activated B-cell (ABC) subtypes (Alizadeh et al. 2000; Hans et al. 2004). The GC subtype is by far the predominate form among pediatric patients, making up 75–83 % of the cases of DLBCL (Miles et al. 2008; Oschlies et al. 2006). In contrast, the GC subtype is only seen in 45–60 % of adults where it is associated with an improved outcome compared to the ABC subtype (Alizadeh et al. 2000; Hans et al. 2004; Lossos et al. 2001; Ohshima et al. 2001). Primary mediastinal B-cell lymphoma (PMBL) and T-cell/histiocyte-rich (TCHR) subtypes of DLBCL each make up 2–7 % of cases and occur primarily in adolescents with mature B-cell malignancies, with PMBL more common in females and TCHR more common in males (Burkhardt et al. 2005; Lones et al. 2000a, 2000b; Reiter and Klapper 2008). Mediastinal gray-zone lymphoma is a very rare entity in pediatrics with features of both classical HL and PMBL (Oschlies et al. 2011; Quintanilla-Martinez et al. 2009; Dunleavy et al. 2012).

The approach to therapy has largely been empirically derived with refinement through successive clinical trials. Early studies by the Children's Cancer Group demonstrated better outcomes when the mature B-cell lymphomas (non-lymphoblastic lymphoma) and BL/B-ALL were treated with short pulses of intensive therapy (COMP: cyclophosphamide, vincristine, methotrexate, and prednisone) compared with the protracted 10-drug LSA_2L_2 regimen then used for lymphoblastic leukemia (Anderson et al. 1993b). This realization led to further refinement so that DLBCL and BL/B-ALL in young patients are commonly treated with identical chemotherapy platforms. Whereas most adults with DLBCL are currently treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab (Habermann et al. 2006; Pfreundschuh et al. 2006), the regimens currently employed in pediatrics for DLBCL and BL/B-ALL use hyperfractionated cyclophosphamide dosing with lower cumulative doses of anthracyclines. Furthermore, the incorporation of high-dose cytarabine and/or methotrexate and intrathecal chemotherapy into pulse-chemotherapy regimens and prophylactic use of chemotherapy administered by intrathecal injection has allowed omission of cranial radiation in patients with BL and B-ALL (Cairo et al. 2007; Reiter et al. 1992, 1995; Patte et al. 2001).

Risk stratification used by both the Berlin-Frankfurt-Münster (BFM) and the French-American-British (FAB) collaborative groups is primarily based upon staging, surgical grouping, and response to a short cytoreductive phase containing cyclophosphamide (200–300 mg/m^2) (Cairo et al. 2007; Gerrard et al. 2008; Reiter et al. 1999; Woessmann et al. 2005; Patte et al. 1986, 1991, 2007). High-dose methotrexate (3–8 g/m^2) is typically used for all risk groups except those with completely resected localized disease. The French-American-British collaborative (FAB/LMB) incorporates etoposide and high-dose cytarabine for patients with CNS or extensive bone marrow disease and for those with a poor response to an initial cytoreductive phase (Cairo et al. 2007; Gerrard et al. 2008; Patte et al. 2007). The BFM regimens incorporate etoposide and ifosfamide for intermediate and high-risk patients and reserve high-dose cytarabine for high-risk patients (Reiter et al. 1999; Woessmann et al. 2005).

This risk-adapted approach to therapy has resulted in excellent outcomes (Cairo et al. 2012; Fujita et al. 2011; Burkhardt et al. 2011). The OS and EFS rates for the largest study of mature B-cell lymphoma in children and adolescents (FAB/LMB96, 1111 patients) are shown in Fig. 10.6 (Cairo et al. 2012). Those with completely resected disease (group A) were treated with two courses of chemotherapy and experienced a 98.3 % 4-year EFS and 99.2 % OS (Gerrard et al. 2008). Group B patients (no CNS involvement and less than 25 % blasts in the bone marrow) achieved an 89 % 3-year EFS

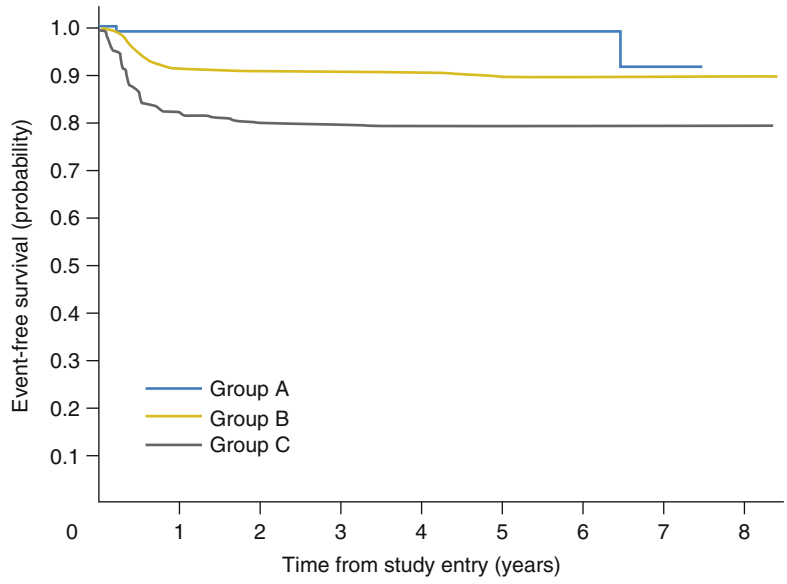

Fig. 10.6 Probability of event-free survival in pediatric patients treated on FAB LMB 96 with group A, group B, or group C therapy (Copyright 2012 *Journal of Clinical Oncology*. Reproduced with permission from Cairo et al. (2012))

Table 10.5 High-risk factors identified in the FAB/LMB studies for children with mature B-NHL

Risk factor	Relative risk of treatment failure or EFS	Reference
Poor response to reduction phase of therapy (<20 % reduction in lymphoma mass)	RR 12.3	Patte et al. (2001)
Lactate dehydrogenase ≥ 2 × upper limit of normal	RR 2.0, 3-year EFS 81 %	Cairo et al. (2012)
Mediastinal disease	RR 4.5, 3-year EFS 72%	Cairo et al. (2012)
Combined bone marrow and CNS disease	RR 4.9, 3-year EFS 61 %	Cairo et al. (2012)
Der (3q), del 13q, +7, aneuploidy, complexity	63–72 % EFS	Poirel et al. (2009)

with four courses of intensive multi-agent chemotherapy and intrathecal chemotherapy (Cairo et al. 2012). Those with CNS involvement or ≥25 % bone marrow blasts (group C) and those with a poor response to cytoreductive chemotherapy or residual disease following consolidation therapy achieved a 79 % 3-year EFS with four courses of intensive chemotherapy followed by one to four maintenance courses (Cairo et al. 2012).

While clearly yielding overall favorable results, the FAB/LMB studies did identify populations at high risk for treatment failure. Features associated with treatment failure are shown in Table 10.5. Elevated LDH ≥2 times the upper limit of normal, mediastinal disease, and combined bone marrow (≥25 % blasts) and CNS disease were also associated with treatment failure with relative risks of 2.0, 4.5, and 4.9, respectively) (Cairo et al. 2012). Poor response (<20 % size decrease) to the cytoreductive phase was perhaps the most powerful predictor of treatment failure (Patte et al. 1986, 2001) and was a particularly ominous sign among patients with CNS disease, with only about one-third of poor responders achieving long-term survival (Cairo et al. 2007). A cytogenetic evaluation of a cohort of patients participating on the study identified additional risk factors (Poirel et al. 2009). Among 182 patients with BL, deletion of chromosome 13q, additional chromosome 7q, and complex cytogenetic abnormalities or aneuploidy were associated with treatment failure. There were only five treatment failures among the 30 patients evaluated with DLBCL, which limited the interpretation of molecular risk factors in this subgroup.

The early identification of adverse risk factors during treatment could lead to further risk stratification and adjustment of chemotherapy intensity. Possible interventions include the

incorporation of immunotherapy or immune-conjugate therapy into standard chemotherapy approaches or consolidation with high-dose chemotherapy followed by autologous HCT. A recently completed pilot study by the COG clearly demonstrated the feasibility of incorporating the anti-CD20 antibody, rituximab, into intensive chemotherapy (Goldman et al. 2012). The effect upon outcome is being investigated in an international collaborative trial in which patients with high-risk disease are randomized to receive or not receive rituximab with FAB/LMB therapy (NCT01595048). High-dose chemotherapy with autologous HCT is used by some groups for patients with a poor response to reduction therapy (Sandlund et al. 2002), but there is currently a paucity of data to support or refute this approach. Whether rituximab or other therapeutic interventions, such as high-dose chemotherapy with autologous HCT or the incorporation of new agents into standard chemotherapy, benefits the patients at high risk for failure awaits further prospective study.

Successful therapy of PMBL in the pediatric and adolescent populations remains a challenge. With the incorporation of rituximab into chemotherapy regimens, PMBL is now regarded as a favorable form of DLBCL in adults with a nearly 70 % long-term PFS (Savage 2006; Savage et al. 2006). Although this rate is comparable to that achievable using FAB/LMB or BFM therapy, the successful eradication of PMBL lags significantly behind that seen with other mature B-cell lymphomas in children and adolescents (Seidemann et al. 2003; Gerrard et al. 2012). The addition of rituximab to the pediatric chemotherapy regimens may improve the outcome for PMBL, but large studies assessing this have not been conducted. Investigators at the National Cancer Institute (NCI) reported in a limited number of patients that the addition of rituximab to a continuous infusion chemotherapy regimen (dose-adjusted EPOCH-R) results in greater than 90 % EFS with 100 % overall survival in adults treated with PMBL (Dunleavy et al. 2009b; Dunleavy et al. 2006). This approach is currently being investigated in an international collaborative study for children and adolescents.

10.3.1.2 Lymphoblastic Lymphoma

Lymphoblastic lymphomas (LBL) make up 20–30 % of NHL among children and young adults (Sandlund et al. 1996; Burkhardt et al. 2011; O'leary et al. 2006). Greater than 75 % are derived from the T-cell lineage with the remainder from B-cell precursors. LBL and acute lymphoblastic leukemia (ALL) are often thought of as a spectrum disorder because they share morphological and immunohistochemical characteristics and many cytogenetic abnormalities, although differences in RNA expression have been described (Burkhardt 2009; Raetz et al. 2006). T-cell LBL typically presents with an anterior mediastinal mass or subdiaphragmatic lymphadenopathy, whereas B-cell LBL is frequently seen as localized disease in diverse sites such as bone, skin, and peripheral lymph nodes (Crist et al. 1988). CNS involvement (greater than 5 cells per microliter) occurs in about 3 % of cases, usually in T-cell disease (Salzburg et al. 2007).

The approach to therapy utilized by most groups for pediatric LBL is similar to that used for ALL. The use of protracted chemotherapy including a maintenance phase and CNS-directed therapy yields greater than 80 % long-term DFS (Neth et al. 2000; Goldberg et al. 2003; Uyttebroeck et al. 2008; Mora et al. 2003; Burkhardt et al. 2006b; Asselin et al. 2011; Termuhlen et al. 2012). Many regimens incorporate high-dose methotrexate therapy, although the benefit may be dependent upon the specific chemotherapy regimen. The use of prophylactic cranial radiation for LBL appears not to be needed. The BFM cooperative group concluded that minute differences in outcome between studies BFM86, 90, and 95 were due to the subtle changes in therapy, but not due to the exclusion of prophylactic cranial radiation (Burkhardt et al. 2006b). Additionally, prophylactic radiation is not advocated by the European Organization for Research and Treatment of Cancer (EORTC), COG, or St. Jude groups (Uyttebroeck et al. 2008; Sandlund et al. 2009; Termuhlen et al. 2012).

Neither high-dose chemotherapy with autologous HCT nor allogeneic HCT is routinely used in the initial therapy for LBL in children and adolescents, although with refinement of prognostic

features a role for HCT might well become defined. Initial response to therapy may be one indicator. The few patients in the recent EORTC study with less than 50 % disease reduction after a 7-day prednisolone pre-phase had a dismal 17 % EFS (Uyttebroeck et al. 2008). Molecular features may also be used to intensify therapy. Loss of heterozygosity at chromosome 6q14 occurs in about 19 % of pediatric T-cell LBL and is a potential poor prognostic feature, as indicated by a retrospective BFM study in which more than 60 % of patients with this abnormality relapsed (Burkhardt et al. 2006a, 2008). Whereas an early T-cell precursor (ETP) immunophenotype has been suggested as a poor prognostic feature in T-cell ALL (Coustan-Smith et al. 2009), immunophenotype has yet to be shown to correlate with outcome in T-cell LBL in the COG experience (Patel et al. 2012). It will be interesting to learn if further genetic interrogation of T-cell LBL eventually yields a footprint similar to ETP ALL (Zhang et al. 2012).

10.3.1.3 Anaplastic Large Cell Lymphoma and Peripheral T-Cell Lymphomas

The peripheral T-cell lymphomas (PTCLs) are a diverse group of post-thymic or mature T-cell neoplasms. The most common PTCL among children and adolescents is anaplastic large cell lymphoma (ALCL), which accounts for 10 % of all NHL in this age group (Burkhardt et al. 2011; O'leary et al. 2006). Patients with ALCL may have nodal or extranodal disease including skin and bone and may have systemic or "B" symptoms (Janik et al. 2004; Sandlund et al. 1994; Gross and Termuhlen 2008). The majority of ALCL has a T-cell immunophenotype, although null phenotype and a rare B phenotype have also been reported (Stein et al. 2000; Onciu et al. 2003).

ALCL was originally distinguished from other large cell lymphomas by its expression of CD30, a member of the tumor necrosis factor (TNF) ligand superfamily (Stein et al. 1985). This led to the identification of a recurrent cytogenetic abnormality, t(2;5)(p23;q35), in about 75 % of cases (Kaneko et al. 1989; Rimokh et al. 1989; Le Beau et al. 1989). Cloning of the gene revealed that the translocation results in fusion of the ALK tyrosine kinase to the amino terminus of nucleophosmin (NPM) leading to persistent expression of the NPM-ALK fusion product and constitutive activity of the ALK kinase (Morris et al. 1994). Several other translocations have since been described with the second most common being a translocation (1;2)(q25;p23) that results in the fusion of a non-muscle tropomyosin to ALK (Duyster et al. 2001).

Three entities of ALCL are generally described: ALK-positive and ALK-negative systemic ALCL and primary cutaneous ALCL. Nearly all (95 %) of systemic ALCL occurring in children is ALK-positive, whereas 40–50 % of adults with systemic ALCL are ALK-negative (Falini et al. 1999; Gascoyne et al. 1999; Liang et al. 2004). The distinction between ALK-negative and ALK-positive systemic ALCL has prognostic implications in adults with ALK-positive ALCL being more responsive to chemotherapy (Stein et al. 2000). Primary cutaneous ALCL does not harbor a translocation involving the ALK gene, does not express ALK, and typically has an indolent course, and spontaneous complete remissions have been reported (Kumar et al. 2005; Bekkenk et al. 2000).

Diverse therapeutic approaches to systemic ALCL in children and young adults have had amazingly similar outcomes. Protracted, leukemia-type therapy (modified LSA_2-L_2) administered over 24 months has been used by several groups with approximately two-thirds of patients surviving long term (Mora et al. 2000; Rosolen et al. 2005; Vecchi et al. 1993). The Pediatric Oncology Group (POG) used a modified APO regimen (doxorubicin, prednisone, vincristine, mercaptopurine) with and without methotrexate (1 g/m^2) and high-dose cytarabine after the induction phase (Laver et al. 2005). Courses of chemotherapy were administered every 21 days with 1-year total duration of therapy. The 4-year EFS for all patients was 67 % with no difference observed in the group receiving methotrexate and cytarabine. The French Society of Pediatric Oncology utilized a therapeutic approach similar to LMB therapy for

mature B-cell lymphomas that included high-dose methotrexate in two induction courses (COPADM) followed by combinations of high-dose methotrexate, etoposide, cyclophosphamide, vincristine or vinblastine, and doxorubicin in four consolidation courses over a total duration of 7–8 months (Brugieres et al. 1998). This approach yielded a 66 % 3-year EFS. The BFM also utilized short-pulse B-cell type therapy over a 2–5-month period tailored to stage and surgical resection status yielding 76 % 5-year EFS (Seidemann et al. 2001). The addition of vinblastine maintenance therapy to the BFM approach in a combined European trial, ALCL99, resulted in a slightly longer time to relapse but failed to improve the 2-year EFS (72 %) (Le Deley et al. 2010). Advantages of the BFM-based ALCL99 therapy without vinblastine included relatively low cumulative doses of anthracyclines and alkylator chemotherapy in addition to a brief therapy duration; however, the approach was associated with significant acute toxicity (e.g., neutropenia, stomatitis, infection, and weight gain) (Wrobel et al. 2011).

Several groups have identified prognostic features in an attempt to identify those children with systemic ALCL at high risk for treatment failure. Stage of disease has limited value in assessing risk in this group. The few patients with completely resected stage I disease appear to have excellent outcomes with the BFM approach, while those with unresected stage I disease fare the same as patients with advanced stage disease (Seidemann et al. 2001; Attarbaschi et al. 2011). The presence of "B" symptoms, skin involvement, mediastinal or visceral involvement, and elevated LDH (>2 times normal) have all been identified in univariate analysis as potential risk factors for relapse (Seidemann et al. 2001; Le Deley et al. 2008; Brugieres et al. 1998). Multivariate analysis, however, of data obtained from the treatment of 225 children in three European studies only identified visceral, mediastinal, and skin involvement as poor-risk factors (Le Deley et al. 2008). Additionally, the risk of treatment failure or relapse increased with the number of risk factors present. Those patients with all three risk factors had ten times the risk of treatment failure compared to those without visceral, mediastinal, or skin involvement.

Additional prognostic factors in ALCL can be identified by morphology or molecular characteristics. Prospective analysis by the European Intergroup for childhood non-Hodgkin lymphoma indicates that ALCL with small cell or lymphohistiocytic morphology, seen in nearly one-third of cases, increases the relative risk of treatment failure by 2.8 (Lamant et al. 2011). A similar adverse effect is described with perivascular histology (Lamant et al. 2011). Conversely, increased ALK gene copy number (primarily by having an extra chromosome 2) or ALK protein expression is reported by investigators in China to be associated with prolonged survival (Yu et al. 2012). The combination of clinical, morphological, and molecular characteristics may ultimately lead to a risk stratification approach to the therapy of children and adolescents with ALCL that incorporates new therapeutic approaches for those with high-risk disease.

The non-anaplastic PTCLs occur rarely in children. Among this boutique group of malignancies "PTCL-not otherwise specified" (PTCL-NOS) appears to be the most common subtype among children in North America and the United Kingdom (Hutchison et al. 2008; Windsor et al. 2008; Al Mahmoud et al. 2012). PTCL-NOS is an aggressive neoplasm. Patients often present with cervical or general lymphadenopathy or with extranodal disease involving liver, spleen, marrow, and skin. Systemic or "B" symptoms are common and a secondary hemophagocytic syndrome may be present (Jaffe 2006; Falini et al. 1990). Other forms of non-anaplastic PTCL reported in children include extranodal NK/T-cell nasal type, hepatosplenic, angioblastic, angiocentric, and subcutaneous panniculitis-like PTCL (Hutchison et al. 2008; Windsor et al. 2008; Kobayashi et al. 2010; Al Mahmoud et al. 2012). The most common non-anaplastic PTCL in East Asian children is extranodal NK/T-cell nasal type (Kobayashi et al. 2010; Hutchison et al. 2008). Patients with this lymphoma typically have local/regional disease involving the nasal cavity but may also have extensive disease and a secondary hemophagocytic syndrome.

The management for non-anaplastic PTCL in children is largely based upon the experience in adults. Initial therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like therapy is used most commonly in adults (Tang et al. 2010; Savage et al. 2004), although alternative multi-agent chemotherapy regimens are also used (Voss et al. 2012; Escalon et al. 2005). For patients with disease responsive to chemotherapy, consolidation with high-dose chemotherapy and autologous HCT is advocated by many groups (Blystad et al. 2001; Kyriakou et al. 2008; Numata et al. 2010; Voss et al. 2012; Reimer et al. 2009). In the largest prospective trial involving adults with PTCL, the 3-year OS for those receiving consolidation with high-dose chemotherapy with HCT was 71 % compared to 11 % for those who did not (Reimer et al. 2009). However, nearly one-third of the adults failed to undergo autologous HCT due to progressive disease yielding a 3-year OS rate of 48 % (Reimer et al. 2009). Other studies have failed to show a benefit of autologous HCT in the initial therapy for PTCL compared to conventional-dose chemotherapy (Mounier et al. 2004).

The outcomes in children with non-anaplastic PTCL appear to be equally as dismal as in adults. In a COG study, children were treated with a regimen of doxorubicin, vincristine, prednisone, mercaptopurine, and methotrexate (APO) with or without high-dose methotrexate and high-dose cytarabine (Hutchison et al. 2008). 6 of the 10 children with advanced disease relapsed. Those with localized disease fared better with only 2 of 10 relapsing. Results were similar among the 29 children treated in the United Kingdom, although there was a suggestion that better outcomes were obtained using therapy typically used for T-cell lymphoblastic leukemia rather than intensive pulses of therapy typically used for B-cell NHL (Windsor et al. 2008).

For those with PTCL refractory to chemotherapy, few options are available. The folate antagonist, pralatrexate, has a demonstrated 29 % response rate with 11 % complete response in a recent study of 111 adults with relapsed or refractory non-anaplastic PTCL and therefore may be of benefit to children with non-anaplastic PTCL (O'Connor et al. 2011). The retinoid, bexarotene, has activity in cutaneous T-cell lymphoma (Duvic et al. 2001) and has been used in children and adults with subcutaneous panniculitis-like T-cell lymphoma (Mehta et al. 2012). Allogeneic HCT with myeloablative or reduced-intensity conditioning is advocated by several groups for adults with relapsed disease affording approximately 45–60 % overall survival (Kyriakou et al. 2009; Wulf et al. 2005; Goldberg et al. 2012; Kim et al. 2006; Le Gouill et al. 2008; Zain et al. 2011; Jacobsen et al. 2011). Successful allogeneic HCT for a child with hepatosplenic PTCL conditioned with TBI has been reported (Domm et al. 2005), although large case series using this approach in children with non-anaplastic PTCL are lacking.

10.3.2 Relapsed/Refractory NHL

While initial therapy is successful in the vast majority of children and adolescents with NHL, the retrieval of those with refractory or relapsed disease remains a formidable challenge. Many patients with mature B-cell lymphoma or LBL who fail initial therapy do so either during therapy or soon afterward (Attarbaschi et al. 2005). Second complete remissions occur in less than half with conventional-dose chemotherapy, indicating the presence of multidrug-resistant disease. The reported OS rate among children with large cell lymphomas initially treated on CCG studies between 1977 and 1995 is only 31 % and is a more dismal 10 % for those with relapsed BL (Cairo et al. 2003a, b). The exception to the particularly poor outcomes among children and adolescents with relapsed NHL is ALCL. While relapse occurs in nearly one-third of the children with systemic ALCL, second complete remissions are achievable in up to nearly 90 % of cases (Attarbaschi et al. 2005; Brugieres et al. 2000; Woessmann et al. 2011; Mori et al. 2006). Second relapses occur in approximately 40 %, but prolonged third and greater complete remissions are not uncommonly achieved with continued chemotherapy including single agent vinblastine (Brugieres et al. 2000; Stockklausner et al. 2008).

10.3.2.1 Salvage Chemotherapy in Relapsed/Refractory NHL

The approach to relapsed or refractory NHL in children and adults has historically been to achieve a complete or partial remission with intensive salvage chemotherapy and then to consolidate with high-dose chemotherapy and autologous or allogeneic HCT. In adults with DLBCL, several chemotherapy retrieval regimens have been investigated although none has emerged as clearly superior. The international CORAL study randomized 396 adults with relapsed/refractory DLBCL to retrieval chemotherapy with either R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) prior to high-dose chemotherapy with BEAM and autologous HCT (Gisselbrecht et al. 2010). The response rate to both conventional-dose chemotherapy regimens was the same (62–63 %). Similarly, a 73 % response rate was seen in the GEL-TAMO study involving 163 adults with relapsed or refractory DLBCL using R-ESHAP (rituximab, etoposide, methylprednisolone, and high-dose cytarabine) as a retrieval regimen (Martin et al. 2008). Interestingly, both studies identified prior rituximab therapy as an independent adverse factor for response to chemotherapy, suggesting that highly resistant disease emerges from unsuccessful initial therapy with the current best known regimens. Other retrieval regimens yielding similar response rates include modified EPOCH regimens (Gutierrez et al. 2000; Jermann et al. 2004; Dunleavy et al. 2009a). Investigations using gemcitabine, oxaliplatin, and rituximab (GEMOX-R) have shown this regime to be a less intensive alternative though with a decreased response rate (~40 %) (Lopez et al. 2008; El Gnaoui et al. 2007).

Studies evaluating retrieval chemotherapy in children with relapsed or refractory NHL generally include all histologic subtypes except when the regimen is targeted to the unique biology of the disease. This is due in part to the success of frontline therapy for children with NHL and the resulting paucity of relapsed patients with a specific histology at single centers or even individual countries. A list of selected retrieval regimens and their reported efficacy is shown in Table 10.6. No retrieval regimen has clearly emerged as superior.

10.3.2.2 Autologous HCT in Relapsed/Refractory NHL

The Parma collaborative group provided the seminal justification for high-dose chemotherapy

Table 10.6 Selected retrieval therapies for relapsed/refractory NHL in children

Study group	Regimen	Therapy	# Evaluable patients	Response	Reference
POG	ICE	Ifosfamide 1.5 g/m^2 days 1–3 with mesna; carboplatin 635 mg/m^2 day 3; etoposide 100 mg/days 1–3	21 NHL, subtypes not specified	71 % response: 9 CR, 6 PR	Kung et al. (1999)
COG	R-ICE	Rituximab 375 mg/m^2 days 1 and 3; ifosfamide 3 g/m^2 and etoposide 100 mg/m2 days 3, 4, 5; carboplatin 635 mg/m^2 on day 3	20 with CD20+ NHL or Burkitt leukemia	60 % response: 3 CR among 6 with DLBCL; 4 CR and 5 PR among 14 with BL	Griffin et al. (2009)
St. Jude	MIED	Methotrexate 8 g/m^2 over 4 h on day 1; leucovorin beginning hour 24; ifosfamide 2 g/m^2 days 2–4 with mesna; etoposide 200 mg/m^2 days 3–4; dexamethasone 40 mg/m^2 days 1–3	24 NHL (8 ALCL, 6 DLBCL, 1 large T-cell, 3 unspecified, 3 LBL, 3 BL)	63 % response: 10 CR, 5 PR 7 responses among 8 patients with ALCL	Sandlund et al. (2011)
CCG	DECAL	Dexamethasone 10 mg/m^2, etoposide 100 mg/m^2, cytarabine 3 g/m^2 hour 0, 12, 24, 36; L-asparaginase 20,000 units/m^2 hour 36; cisplatin 90 mg/m^2 hour 42	68 NHL (26 LBL, 25 “large cell” ALCL or DLBCL, 13 BL, 4 other)	50 % response rate (23 CR, 6 PR)	Kobrinsky et al. (2001)

Table 10.7 High-dose chemotherapy with autologous HCT in children with relapsed/refractory NHL

Study group	Regimen	Number transplanted	Outcome after HCT	Comments	Reference
COG	Cy/BCNU/etoposide	13 [4 LBL, 2 DLBCL, 4 ALCL, 3 BL]	3-year EFS and OS 70 % (95 % CI: 33–89 %)	Only patients with CR/PR eligible for HCT (50 % of enrolled)	Harris et al. (2011)
KSPHO	Various, 6 patients with total body radiation	33 [14 LBL, 7 ALCL, 6 DLBCL, 6 BL]	2-year EFS 59 %, OS 63 %	28 patients in CR at time of transplant	Won et al. (2006)
St. Jude	Various, 13 patients with involved-field or total body radiation	22 [13 large cell, 5 BL, 4 LBL]	50 % alive (median f/u 57 months)	Includes 3 allogeneic HCT, 2 survivors required salvage therapy after transplant	Sandlund et al. (2002)
European Bone Marrow Lymphoma Registry	Various	89 BL	5-year EFS 54 % for those in CR, 37 % for those with PR at time of transplant	Only patients with sensitive disease survived	Ladenstein et al. (1997)
Institut Gustave Roussy	Bu/Cy, Bu/Mel	24 [16 B-cell, 8 T-cell]	8 alive	1 survivor among 7 with resistant disease	Loiseau et al. (1991)

with autologous HCT for relapsed NHL (Philip et al. 1995). This prospective study involved 215 adults with relapsed intermediate or high-grade lymphoma (predominately aggressive B-cell lymphomas) who received retrieval chemotherapy with DHAP. The 109 responders to chemotherapy were then randomized to radiation therapy followed by high-dose chemotherapy with carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC) with autologous HCT or to four additional courses of DHAP followed by radiation. The patients that underwent autologous HCT had improved 5-year EFS compared to those that were randomized to continued conventional-dose chemotherapy (44 % vs. 12 % 5-year EFS, respectively), thus setting the standard for autologous HCT in adults with relapsed NHL.

Pediatric oncologists have tended to apply the Parma lesson to all subtypes of relapsed NHL encountered among the pediatric and adolescent population. Selected studies primarily involving children are shown in Table 10.7. A prospective randomized study has not been reported in children and the advantage of autologous HCT for subtypes such as LBL and ALCL over conventional-dose retrieval therapies has not been unambiguously demonstrated. However, the experience with autologous HCT in children mirrors the experience in adults in that best results are obtained from autologous HCT when transplanting patients who have demonstrated chemotherapy-sensitive disease (Sandlund et al. 2002; Harris et al. 2011; Won et al. 2006; Ladenstein et al. 1997; Loiseau et al. 1991; Bureo et al. 1995; Fujita et al. 2008).

10.3.2.3 Allogeneic HCT in Relapsed/Refractory NHL

Myeloablative conditioning with allogeneic HCT is a consideration for children and adolescents with NHL that relapse following autologous HCT, and increasingly for children with LBL or ALCL *in lieu* of autologous HCT. The potential advantages of allogeneic HCT include the use of a tumor-free graft and potential graft-versus-lymphoma (GVL) effect. Retrospective clinical evidence for a GVL effect was first shown by Jones et al. in a review of 118 children and adults who underwent autologous or allogeneic HCT for relapsed Hodgkin and non-Hodgkin lymphomas (Jones et al. 1991). Preparative therapy consisted of busulfan and cyclophosphamide, or cyclophosphamide with TBI. Among those patients that demonstrated chemosensitive disease, the probability of relapse was lower in those

receiving an allogeneic graft (46 % vs. 18 %). There was no overall survival advantage, however, due to the higher rate of transplant-related mortality among those receiving an allogeneic graft.

Several reports indicate that the benefit of an allogeneic graft in reducing the relapse rate is specific to the subtype of NHL. A retrospective study of a mostly adult population of patients with LBL from the International Bone Marrow Transplant Registry and Autologous Bone and Marrow Registry demonstrated a decreased relapse rate with allogeneic HCT compared to autologous HCT (34 % vs. 56 %, respectively). The effect was primarily seen in those undergoing HCT in first complete remission, although a survival benefit was not observed due to transplant-related mortality (Levine et al. 2003). A recent review from the Center for International Blood and Marrow Transplant Research (CIBMTR) of 53 children with LBL undergoing HCT also supports a graft-versus-LBL effect with no significant difference in transplant-related mortality between allogeneic and autologous HCT (Gross et al. 2010). As a result, the approach to relapsed LBL mirrors that of relapsed all with similar retrieval regimens typically followed by allogeneic HCT for those achieving second remission. The BFM reported that 9 of 28 patients with relapsed T-LBL achieved a stable CR with intensive ALL-directed therapy and ultimately underwent allogeneic HCT (Burkhardt et al. 2009). Long-term survival was achieved in 4 patients. This approach is also supported by the Japanese Pediatric Leukemia Lymphoma Study Group's experience in 41 children with relapsed LBL (Mitsui et al. 2009). ALL or AML-type retrieval chemotherapy was used followed by autologous or allogeneic HCT. Allogeneic HCT was superior with 10 of 19 children treated with this modality achieving long-term survival compared to only 2 survivors among the 6 who underwent autologous HCT.

In contrast to results in LBL, the CIBMTR study found no significant improvement in EFS with allogeneic HCT compared to autologous HCT for children with BL, DLBCL, or ALCL (Gross et al. 2010). A subtle graft-versus-BL effect may not have been observed due to the early relapse rate seen after HCT. The failure to detect a significant difference among children with ALCL may be a result of the relatively small numbers of patients included in the registry. Benefit to allogeneic HCT for relapsed ALCL is suggested in several small series and for those that relapse following autologous HCT (Woessmann et al. 2006, 2011; Cesaro et al. 2005). Less convincing evidence exists for a graft-versus-DLBCL effect although responses to withdrawal of immunosuppression and infusion of donor lymphocytes are occasionally seen among those with persistent disease following allogeneic HCT (Lazarus et al. 2010; Bishop et al. 2008).

10.3.2.4 Novel Agents for Therapy for NHL

A number of new agents with relevance to pediatric/adolescent NHL have recently become available. In contrast to conventional chemotherapy, these agents tend to be specific to individual subtypes of lymphoma based upon molecular targets or cell surface proteins. While demonstrating significant activity as single agents, there is great excitement for their potential use in combination with other effective therapy.

Radioisotope conjugates of antibodies directed against CD20 have demonstrated activity as single agents and in combination with chemotherapy and HCT for adults with high-risk or recurrent B-cell NHL (Krishnan et al. 2008; Gordon et al. 2004; Wondergem et al. 2012; Vitolo et al. 2010; Gopal et al. 2007; Dosik et al. 2006). The reported experience with this class of agents in the pediatric population is limited to a COG phase1 study of Yttrium-90 labeled ibritumomab tiuxetan in five children (3 DLBCL, 1 BL, 1 posttransplant lymphoproliferative disease) (Cooney-Qualter et al. 2007). The agent was well tolerated with myelosuppression reported as the major toxicity. Future studies assessing its role as a preparative agent for HCT for children with refractory or relapsed BL or DLBCL are warranted.

Nelarabine is a nucleoside analog prodrug that is FDA approved for children and adults with

T-cell ALL and LBL refractory to two prior chemotherapy regimens. The phase 2 study in children by the COG showed a single-agent response rate of 14 % in those with LBL (Berg et al. 2005). As a single agent, nelarabine might be used to effect a chemotherapy response allowing subsequent HCT, but its greatest potential may be when used in combination with multi-agent chemotherapy. A COG pilot study has already demonstrated the safety of inserting nelarabine into BFM-type chemotherapy for T-cell ALL (Dunsmore et al. 2012). The efficacy of this approach in T-cell ALL and LBL is currently under investigation by the COG.

New agents for the therapy of systemic ALCL are particularly promising. Crizotinib is a small molecule that inhibits the kinase activity of ALK and is FDA approved for the treatment of non-small cell lung cancer. Successful treatment of patients with ALK-rearranged ALCL has been reported in small case series leading to further investigation of this agent in relapsed or refractory ALCL (Gambacorti-Passerini et al. 2011; Foyil and Bartlett 2012). Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to the tubulin inhibitor, monomethylauristatin E. It was recently FDA approved for adults with Hodgkin lymphoma after failure of autologous HCT or failure of at least two prior regimens in patients who are not autologous HCT candidates and for patients with refractory/relapsed systemic ALCL. The phase 2 study in 58 adolescent and adult patients with relapsed/refractory systemic ALCL yielded a 57 % CR rate and 86 % overall response rate with approximately 1-year duration of response (Pro et al. 2012). Clinical trials investigating this agent in combination with multidrug regimens for ALCL prior to HCT and as maintenance therapy are currently in progress by several groups. Additional trials addressing the efficacy of brentuximab vedotin in a significant subset of CD30-expressing DLBCL, including primary mediastinal B-cell lymphoma, may prove to be particularly interesting. Ultimately, the efficacy of these agents in both frontline and relapse therapy is likely to profoundly change the treatment approach to patients with NHL, including the role of HCT.

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Solid Tumors

11

Douglas S. Hawkins, Sarah Leary, Rochelle Bagatell, Melinda Merchant, and Isabelle Aerts

Contents

D.S. Hawkins (✉) • S. Leary
Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA
e-mail: doug.hawkins@seattlechildrens.org

R. Bagatell
The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA

M. Merchant
Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD , USA

I. Aerts
Département de pédiatrie, Institut Curie, Paris, France

11.1 Introduction

Non-hematopoietic solid tumors comprise approximately 60 % of all pediatric malignancies. Cooperative group clinical trials that evaluated the routine use of chemotherapy in combination with surgery and/or radiation therapy (RT) improved the overall survival for all pediatric cancers from 1975 to 1998 (Smith et al. 2010). Among the likely explanations for the dramatic improvements in outcome are the relative chemotherapy sensitivity of pediatric malignancies and the medical resilience of children in recovering from intensive treatment. From 1998 to 2006, however, further improvements in overall survival have been more modest, particularly for pediatric sarcomas (Smith et al. 2010). To improve overall survival rates, pediatric oncologists have attempted to exploit the inherent chemotherapy sensitivity of pediatric solid tumors and tolerance of children and adolescents for aggressive therapy. High-dose chemotherapy (HDCT) followed by autologous hematopoietic cell transplantation (HCT) to rescue from myeloablation is the ultimate dose intensification of treatment. Although based upon solid medical theory, the benefit of

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HDCT with autologous HCT has only been established by randomized clinical trials for neuroblastoma. Variable levels of non-randomized clinical trial evidence support the use of HDCT with autologous HCT in other pediatric solid tumors, including pediatric brain tumors, Ewing sarcoma, rhabdomyosarcoma, desmoplastic small-round-cell tumor, and retinoblastoma. This chapter reviews the rationale for HDCT with autologous HCT for each of these malignancies, the evidence supporting its use, and remaining controversies.

11.2 Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for 7 % of all childhood malignancies and approximately 10 % of childhood cancer mortality (Howlader 2011). Neuroblastoma arises from primordial neural crest cells, and the majority of primary tumors are adrenal in origin. However, neuroblastoma can arise in other tissues of neural crest origin in the neck, chest, abdomen, or pelvis. Some children with neuroblastoma are asymptomatic at the time of diagnosis, while others have impressive symptomatology related to the effects of the primary tumor or sites of metastatic disease. Just as the presentation of neuroblastoma can vary, so too can its clinical behavior. While a subset of tumors will regress without therapy, in some groups of patients, the disease progresses relentlessly despite intensive multimodality treatment regimens. Efforts to tailor therapy according to the predicted response and risk of relapse have been ongoing for more than four decades. Current risk stratification strategies take into account patient age and disease stage (based upon either surgical or imaging-based staging system) at diagnosis, as well as histologic subtype and genetic characteristics of the tumor.

For patients classified as having high-risk disease, 5-year event-free survival (EFS) rates remain less than 50 %. Current therapy for high-risk neuroblastoma includes three main phases: induction, consolidation, and post-consolidation. The induction phase consists of multi-agent chemotherapy and surgery. The consolidation phase is comprised of autologous HCT followed by local external beam radiotherapy. The post-consolidation phase employs both immunotherapy (chimeric 14.18 antibody directed against the disialoganglioside GD_2 augmented by granulocyte macrophage stimulating factor and interleukin-2) and a differentiating agent (isotretinoin) to treat minimal residual disease following dose-intensive therapy. Clinical trials designed to address issues pertinent to all three phases of therapy have resulted in improvements in survival over the past two decades (Howlader 2011; Kushner et al. 1994, 2004; Matthay 1999; Pearson et al. 2008; Yu et al. 2010), and results of current-era studies continue to inform the approach to the consolidation phase in particular.

11.2.1 Initial Trials of HDCT for Neuroblastoma

Studies of administration of marrow-ablative doses of chemotherapy with or without total body irradiation (TBI) have been conducted since the 1980s. By that time, neuroblastoma had been shown to be sensitive to both chemotherapy and radiation. In addition, improvements in supportive care and in the technology required for the harvesting, storage, and delivery of stem cells made HDCT feasible. Numerous retrospective studies and single-arm trials suggested that myeloablative therapy offered potential benefit to children with high-risk disease (August et al. 1984; Dini et al. 1989; Hartmann et al. 1986a, b; Kushner et al. 1991; Pearson et al. 2008; Philip et al. 1991; Pole et al. 1991). A large, retrospective analysis of the European experience between 1984 and 1996 also supported a role for myeloablative therapy in groups of patients with high-risk neuroblastoma. Among 1,070 patients with high-risk neuroblastoma who survived long enough to undergo HDCT with autologous HCT, overall survival was 49 % at 2 years and 33 % at 5 years post-autologous HCT, encouraging results compared with contemporaneous survival rates among patients who did not undergo HDCT (Philip et al. 1997).

Three large, prospective, randomized studies conducted in North America, Europe, and Germany subsequently confirmed the improved outcomes for patients with high-risk neuroblastoma following autologous HCT as consolidation therapy. In Children's Cancer Group (CCG) study 3891, patients randomized to the autologous HCT arm received TBI and received carboplatin, etoposide, and melphalan (CEM) prior to infusion of stem cells derived from autologous bone marrow. Patients randomized to receive continuation chemotherapy were treated with three cycles of cisplatin, etoposide, doxorubicin, and ifosfamide instead of HDCT with autologous HCT as consolidation. Among patients assigned to autologous HCT, the 3-year EFS starting from the time of randomization was 34 %, compared with 22 % for patients assigned to chemotherapy consolidation (Matthay et al. 1999). Overall survival did not differ among patients randomized to HDCT with autologous HCT compared to those assigned to continuation chemotherapy as consolidation. The improvement in EFS was confirmed with longer follow-up; at 5 years from randomization, EFS was 30 % for patients randomly assigned to the autologous HCT and 19 % for patients assigned to chemotherapy consolidation (Matthay et al. 2009). A total of 539 eligible patients were enrolled on the study overall; 379 patients underwent randomization to address the autologous HCT question, and 258 underwent a second randomization to evaluate post-consolidation treatment with isotretinoin compared to no additional therapy. As a result, a relatively small number of patients ($n=50$) underwent autologous HCT and subsequently received isotretinoin. However, the 50 % 5-year EFS rate observed in this group of patients was strikingly different from the 20 % EFS rate observed in those who received neither autologous HCT nor isotretinoin therapy. CCG3891 thus established transplant-based consolidation followed by differentiating agent therapy as the standard of care in North America.

The German NB97 study likewise supported the use of HDCT with autologous HCT as consolidation treatment for children with high-risk neuroblastoma. A total of 295 patients were randomized to undergo either myeloablative therapy with CEM or continuation therapy consisting of oral cyclophosphamide following an intensive induction regimen (Berthold et al. 2005). Similar to CCG 3891, a statistically significant difference in 3-year EFS was observed among patients randomized to autologous HCT compared to those receiving chemotherapy consolidation (47 % versus 31 %, respectively, $p=0.022$). Randomization was stopped early due to the improved outcome in the autologous HCT arm. Patients with therapy-responsive disease seemed to benefit most from intensification of consolidation therapy. Among those who experienced a complete response (CR) or very good partial response to initial therapy, 3-year EFS for those randomized to autologous HCT was 57 % compared to 35 % in those who received only oral cyclophosphamide. Importantly, the preparative regimen in this trial included chemotherapy only, indicating that the favorable results of intensified therapy could be achieved without TBI.

11.2.2 Conditioning Regimens

The results of the European ENSG-1 trial confirmed the finding that a non-TBI containing preparative regimen could be used successfully for conditioning in children with neuroblastoma (Pritchard et al. 2005). Sixty-five patients who had achieved CR or partial response (PR) to induction therapy were included in a randomization designed to evaluate autologous HCT with melphalan for myeloablation in children with high-risk neuroblastoma. Differences in survival between those who underwent autologous HCT and those who received no additional therapy were not statistically significant for the cohort as a whole; however, among children over 1 year of age with International Neuroblastoma Staging System (INSS) Stage 4 disease, 5-year EFS was improved when high-dose melphalan was delivered as myeloablative therapy (5-year EFS 33 % versus 17 %; $p=0.01$) (Pritchard et al. 2005). Although randomized data to definitively compare a TBI-containing preparative regimen to a

chemotherapy-only preparative regimen are lacking, results of a large ($n=4,098$) retrospective study indicate that there is no clear improvement in outcome attributable to inclusion of TBI in conditioning for children with neuroblastoma (Ladenstein et al. 2008). TBI has largely been abandoned in the hope that its elimination will mitigate some of the late toxicities observed in survivors, including growth abnormalities, cataracts, thyroid disease, and second malignancies (Flandin et al. 2006).

The chemotherapy-only preparative regimen most commonly used in North America, CEM, was initially evaluated in a limited institution study (91LA6) that included patients with stable disease or better at the end of induction. The 3-year EFS of 49 % achieved using CEM without TBI ($n=71$) led to further study of this preparative regimen in the context of the Children's Oncology Group (COG) trial, COG A3973, which included 368 patients treated with CEM. Although the toxic death rate (3 %) and the rate of renal failure requiring dialysis (<1 %) were low and the 2-year EFS was 48 %, CEM was associated with significant toxicity, including severe mucositis in nearly 75 % of patients (Kreissman et al. 2013).

In Europe, preparative regimens other than CEM have been explored. A multivariate analysis of retrospective data generated through the European Bone Marrow Transplant Registry suggested that busulfan-containing regimens were associated with improved outcomes compared with other regimens (Ladenstein et al. 2008). Based on these data, the European International Society of Paediatric Oncology (SIOP)-EN HR NBL-1 randomized phase III study was developed to directly compare busulfan-melphalan (BuMel) to CEM. Patients on this study were treated with an intensive induction regimen consisting of eight courses of alternating cycles of intensive chemotherapy including carboplatin, cisplatin, etoposide, vincristine, and cyclophosphamide given every 10 days. Those patients with a favorable response (>50 % improvement in the number of metaiodobenzylguanidine (MIBG) positive skeletal sites, with ≤3 sites of MIBG avid skeletal disease and no bone marrow disease by morphology) after induction were eligible for randomization to either CEM or BuMel. A total of 1,577 patients were enrolled; 598 went on to autologous HCT randomization. The 3-year EFS for those randomized to receive BuMel was 49 % compared to 33 % for those randomized to CEM ($p<0.001$). Relapse was less common among those randomized to BuMel rather than CEM, and overall survival at 3 years was higher among those randomized to the BuMel arm (61 % versus 48 %, $p=0.004$) (Ladenstein et al. 2011). The incidence of oral mucositis, gastrointestinal toxicity, ototoxicity, infection, and renal toxicity was lower among patients treated with BuMel compared with those treated with CEM. However, clinically relevant sinusoidal obstruction syndrome (SOS) occurred in 18 % of patients on the BuMel arm compared with 4 % on the CEM arm. Based on the results from the HR-NBL1 trial, BuMel has been identified as the standard transplant preparative regimen for SIOP-EN centers, and BuMel is currently being evaluated as a component of other cooperative group protocols.

Further intensification of consolidation therapy through use of rapid sequential tandem autologous HCT has also been studied. The LCME2 trial indicated that consecutive cycles of autologous HCT could be delivered (Philip et al. 1993), and additional pilot trials of tandem and even triple autologous HCT further demonstrated the feasibility of this approach (Granger et al. 2012; Grupp et al. 2000; Kletzel et al. 2002; Monnereau-Laborde et al. 2011; Qayed et al. 2012; Saarinen-Pihkala et al. 2012; Seif et al. 2013; Sung et al. 2013). The largest experience with tandem autologous HCT was a limited institution trial that included 97 patients, 82 of whom underwent two consecutive courses of myeloablative therapy (one TBI-containing preparative regimen and one chemotherapy-only preparative regimen) (George et al. 2006). The 7-year progression-free survival (PFS) and overall survival rates of 45 and 53 %, respectively, provided the impetus for a large randomized study of single versus tandem transplant through the COG, ANBL0532.

11.2.3 Stem Cell Sources and Processing

Although most early studies of autologous HCT in children with high-risk neuroblastoma were performed using autologous bone marrow as the stem cell source, studies of allogeneic hematopoietic stem cell transplants (allogeneic HCT) have also been performed. In a small study in which TBI was used during conditioning, there was no statistically significant difference in PFS when 20 patients who underwent matched sibling allogeneic HCT were compared to 36 patients who underwent autologous HCT. The differences in transplant related mortality (20 % in the allogeneic group and 8 % in the autologous HCT group) and frequency of ≥ grade 3 toxicity were not statistically significant when the two groups were compared (Matthay et al. 1994). However, another non-randomized, retrospective study suggested more severe toxicity with allogeneic HCT. Although transplant-related mortality decreased from 11 % prior to 1995 to 4 % after 1995 among autologous HCT patients, the incidence of transplant-related mortality in patients undergoing allogeneic HCT did not improve from 16 % (Ladenstein et al. 2008). Furthermore, 5-year PFS was significantly higher in patients who underwent autologous HCT compared to allogeneic HCT (Ladenstein et al. 2008). Studies of reduced intensity conditioning may permit reductions in transplant-related mortality with allogeneic HCT; additional data regarding this approach are needed before allogeneic HCT becomes more widely used in neuroblastoma.

While bone marrow was used most widely in early studies of autologous HCT for neuroblastoma, a transition to the use of PBSC was made after a series of studies demonstrated the feasibility of harvesting PBSC from small children (Fukuda et al. 1992; Lasky et al. 1991; Takaue et al. 1989). PBSC collection via apheresis was found to be efficient, and engraftment following PBSC rescue was rapid (Klingebiel et al. 1995; Takaue et al. 1995). In addition, PBSC collected following initiation of multi-agent chemotherapy were found to have relatively low rates of tumor cell contamination (Moss et al. 1990). PBSC have been mobilized successfully in children with neuroblastoma following administration of conventional doses of a number of different chemotherapeutic agents (Bensimhon et al. 2010), and harvest relatively early in induction therapy is recommended so that stem cells are less likely to have been affected by exposure to alkylators and epipodophyllotoxins (Grupp et al. 2006). Recent data indicate that collections are particularly robust when stem cells are harvested after administration of two cycles of topotecan/cyclophosphamide as initial therapy, followed by stimulation with filgrastim (Park et al. 2011). Published series describe only a limited number of patients to date; however, the CXCR4 inhibitor plerixafor has recently been successfully used for stem cell mobilization in heavily treated patients who did not undergo harvest with initial therapy (Modak et al. 2012; Worel et al. 2012).

Concerns regarding the potential tumorigenicity of small numbers of contaminating neuroblastoma cells among harvested PBSC products led to studies of *ex vivo* purging of stem cell products. Positive selection of CD34-expressing cells permits retention of hematopoietic progenitor cells and removal of neuroblastoma cells that do not express CD34 (Donovan 2000). CD34 selection can cause depletion of T-cells as well as tumor cells, however, and can potentially alter immune recovery in patients. An unexpectedly high incidence of Epstein-Barr virus lymphoproliferative disease was observed among 108 patients with high-risk neuroblastoma who received CD34-selected stem cell products. CD34 selection was discontinued during the COG ANBL00P1 trial of tandem autologous HCT due to a high rate of serious viral illness (Powell et al. 2004; Seif et al. 2013). Negative selection to diminish neuroblastoma cell contamination of stem cell products using monoclonal antibodies and immunomagnetic beads appeared to be a promising approach based upon preclinical data (Reynolds et al. 1986). However, when studied in a large, randomized cooperative group trial, immunomagnetic purging did not improve EFS. A total of 489 children with high-risk neuroblastoma were enrolled on the COG A3973 trial, and 244 patients received stem cell products

that had undergone carbonyl iron depletion of phagocytes followed by purging using five monoclonal antibodies. The 2-year EFS was 49 % in the unpurged group and 47 % in the purged group ($p = 0.788$) (Kreissman et al. 2013). In the absence of improved outcomes in patients receiving purged PBSCs, standard practice no longer includes purging as a component of stem cell processing.

11.2.4 Future Direction: Targeted Therapy in the Transplant Setting

Because neuroblastoma is a radiosensitive tumor and TBI is no longer widely used during conditioning for autologous HCT, there is interest in the use of the targeted radionuclide ^{131}I-MIBG as a component of consolidation therapy for patients with high-risk neuroblastoma. MIBG is a norepinephrine analog that is preferentially taken up by neuroblastoma cells. The myelosuppression associated with doses of ^{131}I-MIBG above 12 mCi/kg can be significant; for this reason higher doses of ^{131}I-MIBG are usually given with stem cell support. As a single agent, ^{131}I-MIBG at a dose of 18 mCi/kg results in an objective response rate of 37 % in patients with relapsed or refractory neuroblastoma (Matthay et al. 2007). One third of the patients treated at this dose level required stem cell support due to prolonged neutropenia or prolonged platelet transfusion dependence. Integration of this effective but myelosuppressive therapy into existing intensive upfront therapeutic regimens for children with high-risk neuroblastoma is under investigation. Forty-four children were enrolled on a Dutch study of ^{131}I-MIBG as the first intervention in newly diagnosed patients with high-risk disease; 39 received at least two infusions of ^{131}I-MIBG. The majority of these children (34/39) tolerated an interval of 4 weeks between infusions, and a 66 % response rate was observed after the two cycles of therapy (de Kraker 2008). A phase I study of ^{131}I-MIBG followed by CEM demonstrated that this therapy can be safely delivered to patients with refractory neuroblastoma with autologous HCT and aggressive supportive care (Matthay et al. 2006). A recent report described six patients with refractory neuroblastoma who were treated with ^{131}I-MIBG followed by BuMel autologous HCT at a single institution (French et al. 2013). Administration of ^{131}I-MIBG did not impair engraftment post-autologous HCT in this series of patients. ^{131}I-MIBG followed by CEM will be evaluated in the context of multimodality therapy in a multi-institution COG pilot study for newly diagnosed patients. If the feasibility of this approach is confirmed, COG will conduct a randomized trial comparing EFS in high-risk patients treated with or without ^{131}I-MIBG prior to BuMel HCT.

11.3 Brain Tumors

Primary brain tumors are a collection of pathologically and biologically distinct tumors (Louis et al. 2007; Pomeroy et al. 2002) that together constitute the most common solid tumor in the pediatric age group. Treatment of tumors within the central nervous system (CNS) is particularly challenging because the blood brain barrier reduces the exposure of tumor tissue to chemotherapeutics. Survival rates for patients diagnosed with a pediatric brain tumor have improved over the past several decades and approximately 70 % of children diagnosed with a malignant brain tumor are now expected to be cured using multimodality therapy including surgery, RT, and chemotherapy (Packer et al. 2006; Merchant 2009; McCarthy et al. 2012). Long-term brain tumor survivors often suffer from lasting toxicities with impaired neurocognitive, endocrine, and functional outcomes. Much of the long-term toxicity of therapy is associated with the use of RT (Mulhern et al. 1998; Fouladi et al. 2005; Kieffer-Renaux et al. 2000), and therefore strategies have been employed to increase the intensity of chemotherapy in order to reduce or delay RT, especially in the youngest patients (Geyer et al. 2005; Rutkowski et al. 2010). Unfortunately, certain tumors, such as high-grade gliomas and diffuse intrinsic pontine gliomas, still have a low chance of long-term control (Cohen et al. 2011a,

b). HDCT followed by autologous HCT is one mechanism of reducing dose-limiting hematologic toxicity of chemotherapy and allowing for increased dose and intensity of chemotherapy.

HDCT with autologous HCT has been employed in a variety of patient populations including newly diagnosed and recurrent patients, and for a variety of histologic types of brain tumors. Many initial studies included both pediatric and adult patients and used a variety of agents (Finlay et al. 1996; Papadakis et al. 2000; Gururangan et al. 2003a). Because of the nonuniformity of available study results, a great deal of controversy remains regarding the utility of HDCT in pediatric brain tumors as a whole, and appropriate patient selection remains a challenge, particularly in the relapsed setting. In patients who relapse after standard chemotherapy and RT, the benefit of HDCT with autologous HCT remains unclear, and physicians must carefully counsel patients with relapsed disease regarding the toxic risks involved with intensive therapy.

While further study is warranted to elucidate the benefit of transplant, if any, in many pediatric brain tumors, an exception to this controversy is emerging in young patients with embryonal brain tumors, for whom HDCT with autologous HCT appears to offer an effective strategy to avoid RT. In the following section, the experience and outcomes using HDCT with autologous HCT in pediatric brain tumor patients is organized by histological tumor type with a focus on the treatment of newly diagnosed patients. Studies of HDCT with autologous HCT in newly diagnosed pediatric brain tumor patients are summarized in Table 11.1.

11.3.1 Young Children with Embryonal Brain Tumors

Embryonal brain tumors are the most common primary brain tumors in children under the age of 4 and the most common malignant tumors in all children. In addition to medulloblastoma, embryonal tumors include the histological diagnoses of atypical teratoid/rhabdoid tumor (ATRT) and other primitive neuroectodermal tumors (PNET). Non-medulloblastoma PNET may originate from the pineal region (pineoblastoma), other supratentorial locations (sPNET), and rarely from the brainstem (bsPNET). ATRT may arise in any location within the CNS. About 30 % of embryonal tumors are metastatic at diagnosis (Dufour et al. 2012; Chi et al. 2009).

The youngest children with brain tumors are at particular risk for unacceptable neurocognitive toxicity from RT (Fouladi et al. 2005; Mulhern et al. 1998), but experience a high rate of disease-related mortality following surgery and conventional chemotherapy alone (Grill et al. 2005; Geyer et al. 2005; Lafay-Cousin et al. 2012b; Grundy et al. 2010), or with reduced-dose RT (Jakacki et al. 2004). Therefore, young children with embryonal tumors may derive the most benefit from HDCT regimens followed by autologous HCT as a strategy to delay RT. Table 11.1 summarizes published studies including HDCT regimens for pediatric patients with newly diagnosed embryonal brain tumors.

In 1991, the first Head Start (HS I) clinical trial opened for children under the age of 6 years with primary brain tumors. The Head Start treatment regimen included five 21-day cycles of induction chemotherapy with vincristine (0.05 mg/kg weekly), cisplatin (3.5 mg/kg on day 1), cyclophosphamide (65 mg/kg on day 2–3), and etoposide (4 mg/kg on day 2–3) followed by consolidation with myeloablative therapy including carboplatin (area under curve [AUC] = 7 × 3 days, days −8 to −6), etoposide (250 mg/m^2 or 8.3 mg/kg × 3 days, days −5 to −3), and thiotepa (300 mg/m^2 or 10 mg/kg × 3 days, days −5 to −3) with autologous HCT on day 0. The second Head Start trial (HS II) opened in 1997 with expanded enrollment to children under the age of 10 years and incorporated methotrexate in induction therapy (400 mg/kg on day 4). RT was reserved for patients who did not achieve a CR to induction therapy, those who were over the age of 6 years or those who relapsed (Dhall et al. 2008; Fangusaro et al. 2008a; Gardner et al. 2008a; Chi et al. 2004a).

Table 11.1 HDCT with autologous HCT for pediatric brain tumors

Study reference	Diagnosis (*n*)	Median age, months (range)	Years of study	Other therapy	HDCT regimen	Outcome	Comments	Toxic deaths
HS I and HS II (Dhall et al. 2008)	Localized MB (21)	21 (5–35)	1991–2002	5 cycles HS-IND	CTE	5-year EFS 52 %, 5-year OS 70 %	Desmoplastic histology and GTR predictive of survival, majority of survivors without RT	4 (19 %)
HS II (Chi et al. 2004b)	Metastatic MB (21)	38 (7–119)	1997–2003	5 cycles HS-IND, MTX	CTE	3-year EFS 49 %, OS 60 %	6 of 11 survivors without XRT	0
HS I and HS II (Fangusaro et al. 2008b)	sPNET (43)	37 (2–82)	1991–2002	5 cycles HS-IND	CTE	5-year EFS 39 % 5-yr OS 49 %	Non-pineal location predictive of survival	2 (5 %)
HS I and HS II (Fangusaro et al. 2008c)	bsPNET (6)	36 (2–54)	1991–2002	5 cycles HS-IND	CTE	2 survivors[a]	100 % of induction cycles with F&N	0
HIT 2000 (Friedrich et al. 2013)	sPNET (6)	34 (8–43)	2001–2005	3–4 cycles carboplatin/ etoposide	Tandem: carboplatin/ etoposide, thiotepa/ cyclophosphamide	3 survivors	All survivors received XRT	0
HS I and HS II (Zacharoulis et al. 2007b)	Ependymoma (29)	25 (8–106)	1991–2002	5 cycles HS-IND	CTE	5-year EFS 12 %, OS 38 %	Radiation-free survival 8 %	3 (10 %)
HS I and HS II (Gardner et al. 2008b; Gardner et al. 2008c)	ATRT (13)	36 (4–52)	1992–2002	5 cycles HS-IND (HS II with MTX)	CTE	3-year EFS and OS 23 %	Patients on HS II with improved survival compared to HS I	2 (15 %)
Canadian national retrospective cohort (Lafay-Cousin et al. 2012a)	ATRT (50 total, 40 treated, 18 treated with HDCT)	16.7 (1–187.9)	1995–2000	Mixed	CTE or CT3	2-year OS if HDCT 47.9 %[a] compared to 27.3 % if no HDCT	GTR predictive of survival, >50 % of survivors did not receive XRT	NR

Single-center cohort (Gururangan et al. 2003b)	Pineoblastoma (6)	48 (3–135)	1991–2000	Variable, cyclophosphamide +/− cisplatin, carboplatin, vincristine, etoposide	Cyclophosphamide/ melphalan	4 survivors	4 patients with bilateral retinoblastoma, 2/4 survivors received craniospinal XRT	0
Single-center cohort (Perez-Martinez et al. 2005a)	MB (5) sPNET (2)	34 (14–48)	1997–2002	SFOP	BuMel, BuToMe, or BuMelTt	2-year EFS 71 %[a]	100 % F&N	0
Single-center cohort (Perez-Martinez et al. 2005a)	MB (9), sPNET(5)	36 (12–168)	1995–2002	3 none, SIOP(5), SFOP(4) or CCG (1), 4 with chemo+ XRT	BuMel, BuToMe, or BuMelTt	2-year EFS 57 %	3 patients received thiotepa, 4 patients received topotecan,	2 (14 %)
Single-center cohort (Thorarinsdottir et al. 2007b)	Glial (5), MB (5), PNET (4) ependymoma (1)	18 (4–38)	1998–2005	3 cycles IND	CT3	2-year EFS 52.2 %, 2-year OS 72.1 %	GTR or NTR predictive of survival	0
BBSFOP salvage regimen (Ridola et al. 2007)	Local recurrent MB (39)	31 (8–58)	1988–2005	SFOP chemotherapy	Busulfan/thiotepa	5-year OS 68.8 %, EFS 61.5 %[a]	Posterior fossa XRT only, 33 % veno-occlusive disease rate	2 (5 %)
SJMB96 (Gajjar et al. 2006b)	MB (134 total, 86 average risk, 48 high risk)	91 (37–242)	1996–2003	XRT +/− topotecan window	Cisplatin/ cyclophosphamide/ vincristine	5-year EFS 83 % in average risk and 70 % in high risk, 5-year OS 85 % in average risk and 70 % in high risk	All patients >3 years at diagnosis, treated with craniospinal radiation	0

Abbreviations: *HDCT* high-dose chemotherapy, *HS* Head Start, *ATRT* atypical teratoid/rhabdoid tumor, *MB* medulloblastoma, *sPNET* supratentorial primitive neuroectodermal tumor, *bsPNET* brainstem primitive neuroectodermal tumor, *CTE* cisplatin, thiotepa, etoposide, *CT3* 3 cycles of cisplatin, thiotepa with stem cell rescue, *GTR* gross total resection, *NTR* near-total resection, *XRT*/*RT* radiation therapy, *EFS* event-free survival, *OS* overall survival, *HS-IND* induction chemotherapy with cisplatin, cyclophosphamide, etoposide, vincristine, *MTX* methotrexate, *ITMTX* intrathecal methotrexate, *F&N* fever and neutropenia, *BuMel* busulfan, melphalan, *BuMelTt* busulfan, melphalan thiotepa, *BuToMe* busulfan, topotecan, melphalan, *SIOP* International Society of Paediatric Oncology, *SFOP* French Society of Pediatric Oncology, *CCG* Children's Cancer Group, *BBSFOP* Baby Brain French Society of Pediatric Oncology, *SJMB* St. Jude Medulloblastoma

[a]Study only includes or reports survival of patients who received HDCT, while others report survival of entire cohort from the time of diagnosis

The results of HDCT for specific brain tumor diagnoses are discussed below.

11.3.1.1 Medulloblastoma

Twenty young patients with localized medulloblastoma enrolled in the Head Start I or Head Start II trials and experienced a 5-year survival of 70 % (Dhall et al. 2008). This approaches the 86 % survival rate of older patients treated with upfront RT (Packer et al. 2006; Gajjar et al. 2006a), and importantly, 52 % of the patients with nonmetastatic medulloblastoma treated on the Head Start trials did not receive RT. Twenty-one additional patients with metastatic medulloblastoma were treated uniformly on the Head Start II trial and experienced a 3-year survival of 60 % (Chi et al. 2004a), which also approaches the survival of older metastatic patients treated with craniospinal RT (Jakacki et al. 2012). Six of 11 survivors in the metastatic cohort did not receive any RT (Chi et al. 2004a). HDCT may be most beneficial to this group of metastatic patients, since the standard RT dose for metastatic medulloblastoma of 36 Gy would be expected to have a devastating detrimental effect on long-term neurocognitive ability (Fouladi et al. 2005). In patients who relapsed after HDCT, RT was the only successful salvage treatment (Dhall et al. 2008).

The French Society of Pediatric Oncology (SFOP) approached the treatment of young children with medulloblastoma with a strategy initially using conventional chemotherapy alone followed by a salvage regimen consisting of HDCT with autologous HCT and focal posterior fossa radiation after localized recurrence of medulloblastoma in the Baby Brain SFOP protocol (BBSFOP) (Ridola et al. 2007). In this group of patients pretreated with a prolonged course of conventional chemotherapy without prior RT, HDCT with busulfan (150 mg/m^2/day × 4 days) and thiotepa (300 mg/m^2/day × 3 days) followed by autologous HCT and focal RT was able to salvage the majority of patients with local recurrence. This regimen resulted in a 5-year EFS of 61.5 % and 5-year overall survival of 68.8 %. Despite supportive care including prophylaxis with ursodeoxycholic acid, the rate of reversible veno-occlusive disease of the liver was 33 % with this regimen, and there were two toxic deaths related to infection. Due to inferiority of conventional chemotherapy alone, the BBSFOP protocol was amended in 1996 to include HDCT for all patients on study (Ridola et al. 2007).

11.3.1.2 Atypical Teratoid/Rhabdoid Tumor (ATRT)

ATRT has been reported to have a lower survival since it was first described as a disease separate from medulloblastoma (Rorke et al. 1996). ATRT tends to occur in younger pediatric patients, and there have been few survivors reported with conventional chemotherapy alone (Blaney et al. 2005; Geyer et al. 2005; Grill et al. 2005; Rutkowski et al. 2010). Treatment on the Head Start regimen resulted in a 5-year survival of 23 %, with improving survival in the latter of the two regimens (Gardner et al. 2008a). Perhaps most encouraging is a population-based report from Canada (Lafay-Cousin et al. 2012b). In the Canadian experience, patients who received HDCT with autologous HCT had a significantly higher probability of survival (48 % at 2 years, $p = 0.04$) than patients who received conventional chemotherapy (27 %) or palliative care (0 %) after surgery. The majority of the survivors (6 of 9) who received HDCT with autologous HCT did not receive RT, while all three survivors treated with conventional chemotherapy also received radiation (Lafay-Cousin et al. 2012b). The most common regimen used in the Canadian cohort included three tandem cycles of carboplatin and thiotepa ($n = 14$), although the Head Start regimen was also used in four patients. The study was not designed to detect differences between these regimens. The use of intense chemotherapy including HDCT with autologous HCT continues to be studied for patients with ATRT within COG.

11.3.1.3 CNS Primitive Neuroectodermal Tumors (PNET)

Patients with sPNET are treated on regimens designed for medulloblastoma; however, this

approach has not been as effective as with medulloblastoma. Reddy and colleagues reported the outcome of children with sPNET over the age of 36 months treated with conventional therapy for medulloblastoma including maximal surgical resection, craniospinal radiation, and conventional maintenance chemotherapy with cisplatin, lomustine, and vincristine. The 5-year EFS was 37 %, compared to nearly 80 % for medulloblastoma patients treated with the same therapy during the same era (Reddy et al. 2000). The 5-year EFS of 43 sPNET patients treated on the Head Start regimen with HDCT was nearly identical at 39 %. Although tumor location was not associated with prognosis in the reported cohort of older patients treated with upfront RT (Reddy et al. 2000), patients with pineoblastoma fared worse in the younger cohort treated with the Head Start treatment (15 % versus 48 % 5-year EFS) (Fangusaro et al. 2008a). Although there are a few pineoblastoma survivors treated without RT reported in both the Head Start trials (Fangusaro et al. 2008a) as well as other institutional cohorts (Gururangan et al. 2003a), it appears that RT continues to provide a survival advantage over HDCT alone for pineoblastoma specifically. Non-pineoblastoma sPNET requires further study to determine an ideal treatment regimen.

Malignant tumors arising in the brainstem have a dismal prognosis. Brain tumors centered in the pontine region are often treated without tumor biopsy, and histology is presumed to be glial (Cohen et al. 2011a). However, with the advent of stereotactic techniques, the safety of biopsy has improved (Roujeau et al. 2007). As more patients with brainstem tumors undergo biopsy, PNET arising in the brainstem (bsPNET) have been observed, although the overall incidence of and appropriate treatment for this rare tumor remain unclear. Two of six patients with brainstem PNET treated on the Head Start regimen represent the only long-term bsPNET survivors described (Fangusaro et al. 2008d).

Further study is certainly warranted to evaluate the biologic differences between pineoblastoma and other CNS PNET. At this time, treatment with HDCT supported by autologous HCT should be considered optimal treatment for young patients with non-pineal sPNET. Because of the rarity of these tumors, international cooperative trials are absolutely required to evaluate CNS PNET separately from medulloblastoma.

11.3.1.4 Active Research

As noted previously, given the risk of devastating neurocognitive toxicity that can occur after craniospinal RT in young children (Fouladi et al. 2005), intensive chemotherapy including HDCT with autologous HCT should be considered the standard treatment option for young patients diagnosed with primary embryonal tumors of the CNS. There is little controversy surrounding the use of HDCT as the preferred option over craniospinal radiation for children under the age of 3 years at diagnosis. It may be reasonable to consider expanding such a treatment strategy to older children, and several ongoing studies include children up to the age of 4 (Pediatric Brain Tumor Consortium) or 10 years of age (Head Start). The neurocognitive toxicity of craniospinal radiation decreases with age. The age at which the risk of HDCT outweighs the risk of radiation remains unclear.

HDCT continues to have significant treatment-related morbidity and mortality. Toxicity may be improved with multiple cycles of therapy followed by stem cell support rather than a single autologous transplant (Panosyan et al. 2011). Preliminary reports of the use of a tandem transplant regimen consisting of three cycles of carboplatin and thiotepa within small cohorts have been promising (Thorarinsdottir et al. 2007a; Lafay-Cousin et al. 2012b). Several studies that incorporate three tandem cycles of high-dose carboplatin and thiotepa are ongoing. COG completed enrollment on an initial dose-finding study (A 99703) including three tandem cycles of carboplatin and thiotepa in children diagnosed with a brain tumor prior to 3 years of age, with final results pending. Ongoing COG and Pediatric Brain Tumor Consortium (PBTC) studies incorporating this backbone regimen include ACNS0334, a randomized trial evaluating methotrexate in newly diagnosed medulloblastoma

and sPNET patients; ACNS0333, a non-randomized trial incorporating methotrexate and focal RT for patients with newly diagnosed ATRT; and PBTC026, a non-randomized trial evaluating the addition of vorinostat and retinoic acid during induction and maintenance phases of therapy for medulloblastoma and sPNET patients. The results of these studies within the next several years will provide additional information to more precisely estimate survival in these specific subgroups of brain tumor patients.

Longer-term follow-up data is still needed, particularly regarding long-term neurocognitive outcomes (Grill et al. 2004). Without knowledge of long-term neurocognitive outcomes in brain tumor survivors treated with HDCT, it remains difficult to evaluate fully the benefit of HDCT in comparison to radiation. Two and even 5-year follow-up studies provide insufficient data, since many factors including events surrounding initial tumor presentation (Hardy et al. 2008) as well as surgery, chemotherapy, and RT may affect the ability to learn new skills. The measurement of many neurocognitive skills, such as intelligence quotient, is a ratio of performance over age appropriate normals. Therefore, it may take years to truly measure deficiencies that result from therapy during early childhood (Sands et al. 2010). Whether focal RT following HDCT may further decrease local recurrence and improve overall survival without substantial neurocognitive toxicity is another topic of interest and current study.

11.3.2 Older Pediatric Patients with Newly Diagnosed Medulloblastoma

HDCT with autologous HCT after craniospinal radiation is an alternative maintenance chemotherapy strategy in older patients with embryonal brain tumors. These patients are traditionally treated with craniospinal RT followed by maintenance chemotherapy lasting up to a year (Packer et al. 2006). Long-term audiologic and renal toxicity remains a significant limitation of cisplatin use (Gajjar et al. 2006a; Strother et al. 2001). One strategy to reduce the toxicity of prolonged cisplatin-based therapy is to administer a short but intense postradiation maintenance chemotherapy regimen with autologous HCT in older patients after completion of craniospinal radiation (Gajjar et al. 2006a).

The St. Jude protocol SJMB96 enrolled 134 medulloblastoma patients over the age of 36 months who were treated with risk-adapted craniospinal radiation followed by a shortened maintenance chemotherapy phase consisting of four 28-day cycles of chemotherapy with cisplatin, cyclophosphamide, and vincristine, each cycle followed by autologous HCT. The 5-year survival rate of 85 % for standard risk and 70 % for high-risk patients on the SJMB96 study suggests that HDCT with autologous HCT is a therapeutic option with equal outcomes to other options for maintenance therapy. The intensified St. Jude regimen was able to reduce cumulative vincristine dose by 75 % and cumulative cisplatin dose by 50 % while achieving equal survival to regimens using longer but less intense maintenance regimens (Gajjar et al. 2006a; Jakacki et al. 2012; Packer et al. 2006).

11.3.3 Recurrent Medulloblastoma

HDCT with autologous HCT remains a controversial issue for medulloblastoma patients who recur after standard therapy. The interpretation of study results is challenging due to variation in enrollment criteria, diagnoses, and additional treatments given before or after HDCT. It is important to recognize that survival is likely worse than reported given bias incurred by publications that report only patients who receive HDCT with autologous HCT rather than the entire population referred for potential HDCT with autologous HCT. Due to rapid disease progression and lack of response to salvage chemotherapy, only a minority of recurrent brain tumor patients who are referred undergo transplant even at major transplant centers (Butturini et al. 2009).

HDCT has been used as a strategy to achieve minimal residual disease status prior to RT. This

appears to be the most successful strategy in young patients who are radiation naïve (Butturini et al. 2009; Ridola et al. 2007), but long-term survival can be achieved in a minority of patients who relapse after craniospinal RT. The use of additional radiation, including repeat craniospinal irradiation, is associated with better outcome (Dunkel et al. 2010b). Because most series include RT administered either before or after HDCT, it is impossible to evaluate the benefit of HDCT separately from radiation or re-irradiation.

11.3.4 CNS Germ Cell Tumors

Germ cell tumors (GCT) are rare tumors that peak in incidence during adolescence and young adulthood. Approximately 20 % of GCT arise within the CNS, most commonly in pineal or suprasellar locations (McCarthy et al. 2012). Malignant GCT are classified as either pure germinoma or non-germinomatous GCT (NGGCT). Patients diagnosed with pure germinoma have an excellent survival potential >90 % with RT alone, and the addition of platinum-based chemotherapy has facilitated the reduction in dose and field of RT (Echevarria et al. 2008; O'Neil et al. 2011). NGGCT are relatively less sensitive to RT, and standard treatment includes a combination of chemotherapy and RT (Echevarria et al. 2008). Although a subset of patients with CNS GCT may be cured without RT, treatment with chemotherapy alone results in inferior EFS. The Third International CNS Germ Cell Tumor Study attempted treatment of CNS GCT without RT and reported a 6-year EFS of 45.6 %. However, there was an acceptable salvage rate with RT for those who relapsed, which brought overall survival to 75.3 % at 6 years (da Silva et al. 2010).

When CNS GCT patients relapse after standard therapy including radiation, HDCT with autologous HCT may be used as a salvage treatment strategy, either as initial therapy at the time of relapse or to consolidate response to standard chemotherapy. Similar to that seen in upfront therapy, the survival of patients with GCT after relapse is higher for patients with pure germinoma compared to NGGCT. A variety of high-dose treatment regimens have been evaluated in recurrent GCT, including carboplatin, etoposide, and cyclophosphamide; (Motzer et al. 1996) busulfan and thiotepa (Kalifa et al. 1992); melphalan, and cyclophosphamide (Mahoney et al. 1996); and cyclophosphamide and carboplatin (Foreman et al. 2005). One of the largest series reported the outcome of 21 patients (9 with germinoma and 12 with NGGCT) treated with a variety of thiotepa-based HDCT regimens; the 4-year survival was 57 %, with the majority (7/9) of germinoma patients and a minority (4/12) of NGGCT patients surviving (Modak et al. 2004). Although the optimal regimen remains unclear, HDCT with autologous HCT is a reasonable and perhaps optimal salvage strategy for pediatric patients with relapsed CNS GCT.

11.3.5 Ependymoma

Ependymoma represents the third most common pediatric brain tumor, and standard therapy consisting of surgical resection and focal RT results in approximately 75 % long-term survival (Merchant 2009). The focal distribution of RT used in patients with ependymoma results in lower neurocognitive toxicity compared to craniospinal RT (Fouladi et al. 2005), and this remains the treatment of choice even for very young children (Merchant et al. 2009). HDCT with autologous HCT has been evaluated in young patients with newly diagnosed ependymoma. Twenty-nine young patients with newly diagnosed ependymoma were treated with the Head Start chemotherapy regimen on either HS I or HS II trials (Zacharoulis et al. 2007a). Of these only 8 % remained radiation-free, which was not superior to previously reported chemotherapy regimens (Geyer et al. 2005; Grundy et al. 2007).

The use of HDCT for recurrent ependymoma has not proven to be more successful than repeat surgical resection and RT. In 1996, Grill and colleagues reported a French cohort of 16 patients with recurrent ependymoma treated with HDCT

consisting of busulfan and thiotepa followed by autologous HCT. There were few responses to chemotherapy observed, and all long-term survivors also received additional surgery and RT (Grill and Kalifa 1998). In 1998, the CCG reported the results of a cohort of pediatric patients with recurrent intracranial ependymoma treated with HDCT consisting of thiotepa, etoposide, and carboplatin followed by autologous HCT. The majority of patients (8/15) treated on this study died of disease, and five patients died of treatment-related toxicity. Only one long-term survivor was reported after additional disease recurrence, and no PR or CR were observed (Mason et al. 1998).

To date, there is no clear indication for HDCT in the treatment of ependymoma, either in the newly diagnosed or relapse setting. Conventional chemotherapy is currently indicated in patients with unresectable or recurrent disease to facilitate surgical resection (Garvin et al. 2012). The role of conventional chemotherapy in ependymoma after surgical gross total resection and radiation remains debatable and is the question of a randomized study open to enrollment within COG.

11.3.6 High-Grade Glioma

High-grade gliomas are the most common brain tumors in adults but represent less than 10 % of pediatric malignant brain tumors. Early pediatric studies demonstrated that treatment with combination chemotherapy resulted in improved survival over RT alone (Sposto et al. 1989), which has since been demonstrated in adult patients as well (Stupp et al. 2005). In 1999, CCG reported the results of a pilot phase II study on which patients with newly diagnosed glioblastoma multiforme (WHO grade IV) were treated with HDCT including carmustine, thiotepa, and etoposide followed by HCT and delayed radiotherapy. The study intended to enroll 30 patients but was discontinued after 11 patients were treated due to significant and intolerable toxicity, including pulmonary, neurologic, and gastrointestinal complications of therapy. The majority of patients died of disease, two died of toxicity, and one of three long-term survivors developed a secondary malignancy. The study concluded that the regimen was neither effective nor tolerable in this population (Grovas et al. 1999). Current studies attempting to improve outcomes for pediatric patients with high-grade glioma have abandoned HDCT and instead incorporated much less toxic chemotherapy given during and after standard focal RT (Cohen et al. 2011b). Ongoing studies are evaluating the incorporation of anti-vascular endothelial growth factor (VEGF) therapy as well as other targeted agents.

Diffuse intrinsic pontine glioma (DIPG) is not amenable to surgical resection due to their location within the pons and remains universally fatal (Cohen et al. 2011a). In 1998, CCG reported the results of a cooperative study of HDCT followed by autologous HCT in patients with DIPG. Six patients with newly diagnosed DIPG and 10 patients with refractory or recurrent tumors were treated with a single HDCT with autologous HCT with one of three regimens including thiotepa and etoposide alone, or in addition to either carmustine or carboplatin. Two toxic deaths occurred, and survival was not significantly improved over standard therapy (Dunkel et al. 1998). Ongoing studies of DIPG are focused on tumor biopsy and novel biologic targets for therapy.

11.3.7 Conclusions

The risk of toxic death remains a challenge in very young patients treated with HDCT; death is most commonly related to infection rather than direct organ toxicity in the most recent studies (Dhall et al. 2008; Fangusaro et al. 2008a; Gardner et al. 2008a), although cases of engraftment syndrome (Perez-Martinez et al. 2005b) and direct organ toxicity (Grovas et al. 1999; Ridola et al. 2007), specifically lung and liver, have been reported. Febrile neutropenic episodes occur in 100 % of cases in some series (Fangusaro et al. 2008a), and gram-positive bacteremia may be expected in the majority of patients (Thorarinsdottir et al. 2007a). Time trends suggest the rate of toxic death may be

decreasing (Dhall et al. 2008), likely as a result of aggressive supportive care. The importance of treatment at a major referral center with expertise in both transplant and neuro-oncology, close monitoring, and early intervention for fever or other signs of infection cannot be overemphasized.

The study of HDCT in the pediatric brain tumor population is challenging because of the myriad diagnoses which constitute this diverse population. Previous studies have employed a variety of agents at a variety of doses and are not directly comparable. There has been a recent shift towards study development for specific diagnoses within the brain tumor population. This will allow study results to be applied to appropriate populations but will exclude patients with rarer diseases such as bsPNET, who are no longer eligible for any cooperative trial within the United States at diagnosis. Further research is warranted to explore the role the immune system may play in the treatment of pediatric brain tumors. Clinical trials are currently underway that employ autologous T-cell therapy for adult patients with brain tumors, and pediatric trials are planned to begin shortly. Cellular therapy represents one novel strategy in the treatment of brain tumors.

HDCT with autologous HCT is a useful and beneficial treatment strategy for a subset of pediatric brain tumors, namely, young children with embryonal tumors and patients with recurrent GCT. This benefit appears to be due to the ability of HCT to facilitate increases in dose and dose intensity to overcome the blood brain barrier in chemosensitive tumors. HDCT has no proven role in ependymoma or DIPG and remains controversial in high-grade glioma and patients with medulloblastoma who relapse after RT.

11.4 Sarcomas

11.4.1 Ewing Sarcoma

Ewing sarcoma comprises a family of tumors unified by a common biology defined by specific recurring chromosomal translocations (Arndt et al. 2012). Historically, a variety of names have been used based upon the anatomic site of origin and degree of neuronal differentiation, including classical Ewing sarcoma of bone, extraskeletal Ewing sarcoma, Askin tumor of the thoracic wall, peripheral primitive neuroectodermal tumor, and Ewing sarcoma family of tumors. For simplicity, Ewing sarcoma will be used throughout this chapter. Less common than osteosarcoma, Ewing sarcoma is the second most common primary malignant bone cancer in children and young adults. The annual incidence of Ewing sarcoma in children younger than 20 years is approximately 2.9 per million, with a slight male predominance (Esiashvili et al. 2008; Gurney et al. 1999b). Cases continue to be diagnosed through the third decade and later, although with decreasing incidence. Although predominantly arising in bone, extra-osseous sites are also seen, particularly in patients younger than 5 years and older than 35 years (Applebaum et al. 2011). Nearly all Ewing sarcoma carry one of a family of recurring chromosomal translocations, most frequently t(11;22)(q24;q12) which joins *EWSR1* and *FLI1* (Delattre et al. 1994).

Treatment for Ewing sarcoma includes intensive chemotherapy and local treatment with surgery, RT, or a combination of surgery and radiation. In North America, the standard chemotherapy is interval compressed vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) (Womer et al. 2012), and in most of Europe, the standard chemotherapy is vincristine, ifosfamide, doxorubicin, and etoposide followed by vincristine, dactinomycin, and cyclophosphamide or ifosfamide (VIDE/VAC(I)) (Juergens et al. 2006; Strauss et al. 2003). The strongest prognostic factors are poor response (usually defined as >10 % viable tumor cells in a resected specimen after neoadjuvant chemotherapy) (Jurgens et al. 1988; Bacci et al. 2004; Oberlin et al. 2001; Paulussen et al. 2001) and the presence of distant metastases (Cotterill et al. 2000). Even for patients with localized disease at diagnosis, poor histologic response to chemotherapy is associated with an EFS of 20–38 % (Bacci et al. 2004; Oberlin et al. 2001; Paulussen et al. 2001). The overall EFS for

patients with initially metastatic Ewing sarcoma is approximately 20 % (Cangir et al. 1990; Cotterill et al. 2000), although somewhat more favorable for those with isolated pulmonary metastases (Paulussen et al. 1998) and worse for those with bone or marrow metastases (Ladenstein et al. 2010; Paulussen et al. 1998). Multiple cooperative group trials with intensified conventional chemotherapy have failed to improve the outcome for metastatic Ewing sarcoma. For example, the randomized addition of IE to VDC with dactinomycin did not improve the outcome for patients with metastatic disease, although it did improve outcome for those with localized disease (Grier et al. 2003; Miser et al. 2007). Similarly, the randomized addition of etoposide to VDC with dactinomycin in EICESS-92 did not improve the outcome for patients with metastatic disease, although there was a trend toward improved EFS for high-risk localized disease (Paulussen et al. 2008). Two additional non-randomized COG studies evaluating chemotherapy dose intensification or the addition of topotecan did not improve outcome (Bernstein et al. 2006; Miser et al. 2007). The prognosis is even worse for Ewing sarcoma patients who develop recurrent disease. Five-year post-relapse survival is 7 % for those who recurred early (defined as within 2 years of initial diagnosis, comprising 72–78 % of all recurrences) and only 29–30 % for late recurrence (Leavey et al. 2008; Stahl et al. 2011).

In contrast to neuroblastoma, no randomized trials for Ewing sarcoma comparing conventional therapy to HDCT with autologous HCT have been completed. The ongoing EuroEWING99 includes randomization between conventional chemotherapy and HDCT with autologous HCT for both high-risk localized patients (predominantly defined as poor histologic response to neoadjuvant chemotherapy), called R2loc, and patients with isolated pulmonary metastatic disease, called R2pulm (ClinicalTrials.gov NCT00020566). Until the results from EuroEWING99 are known, speculation regarding the benefit of HDCT with autologous HCT will be based upon institutional, cooperative group, and registry datasets with comparison to historic cohorts with similar disease features.

11.4.1.1 Retrospective Studies of HDCT with Autologous HCT for High-Risk Ewing Sarcoma

Two institutional retrospective series focused exclusively on recurrent Ewing sarcoma and included an accounting of all recurrent patients seen at the institution from the time of relapse regardless of whether or not HDCT with autologous HCT was used (Barker et al. 2005; McTiernan et al. 2006). Seattle Children's Hospital reported the outcome for 55 consecutive patients with recurrent Ewing sarcoma between 1985 and 2002 (Barker et al. 2005). Prior to 1992, most patients received conventional treatment at relapse. After 1992, HDCT with autologous HCT was encouraged for all patients who responded to second-line therapy. The timing (median 17 months after diagnosis) and pattern of relapse (71 % distant without concurrent local recurrence) was similar to other large series of recurrent Ewing sarcoma (Leavey et al. 2008; Stahl et al. 2011). Only 27/55 patients (49 %) responded to second-line therapy; 13 of the responding patients received HDCT with autologous HCT, with a preparative regimen of busulfan, melphalan, and thiotepa (BuMelTt) with or without total marrow irradiation (TMI) (Hawkins et al. 2000). Excluding patients who did not respond to second-line therapy (who all died at a median of 4 months after relapse), the 5-year overall survival was superior for those who received HDCT compared to those who did not (77 % versus 21 %, $p=0.018$). In multivariate analysis, response to second-line therapy, recurrence >2 years after initial diagnosis, and use of HDCT were all independently associated with outcome. The authors concluded that HDCT was a promising yet still unproven treatment of responsive relapsed Ewing sarcoma. London's University College Hospital reported a similar analysis of 114 patients with relapsed or progressive Ewing sarcoma between 1992 and 2002 (McTiernan et al. 2006). The timing (median 13 months after diagnosis) and pattern of relapse (57 % distant without concurrent local recurrence) was also similar to other large series of recurrent Ewing sarcoma (Leavey et al. 2008; Stahl et al. 2011). Only 29 out of 77 patients

treated with curative intent received HDCT with autologous HCT, with BuMel being the most common preparative regimen. Inadequate response to second-line therapy, rapid progression of disease after response, and poor organ function were the most common reasons for omitting HDCT. The 5-year overall survival was 50.6 % for those who received HDCT with autologous HCT and <5 % for all other patients. In multivariate analysis, recurrence >1.5 years after initial diagnosis, no extrapulmonary sites of metastasis at diagnosis or recurrence, local therapy to the site of recurrence, and use of HDCT were all independently associated with improved outcome. In contrast to the Seattle series, no comparison of outcome by use of HDCT among patients with responsive disease was reported. The authors concluded that HDCT with autologous HCT improved outcome for Ewing sarcoma with recurrent or progressive disease given the exceptionally poor outcome reported historically. Both of these series have the advantage of a concurrent comparison group, although selection bias for allocation to HDCT with autologous HCT could explain the difference in outcome.

11.4.1.2 Prospective HDCT with Autologous HCT Trials in Ewing Sarcoma

In contrast to small retrospective case series from single institutions, five larger prospective institutional studies and four prospective multi-institutional trials provide stronger levels of evidence regarding the role of HDCT with autologous HCT for Ewing sarcoma, with mixed results. Horowitz et al. reported the long-term results from three consecutive clinical trials conducted at the National Cancer Institute (NCI) from 1981 to 1986 for 91 patients, including 61 patients with high-risk Ewing sarcoma (Horowitz et al. 1993). The study design included induction chemotherapy and local RT, followed by consolidation with 8 Gy TBI, vincristine, doxorubicin, and high-dose cyclophosphamide, and autologous HCT. This series accounted for all patients from the time of diagnosis, including patients who did not undergo autologous HCT (failure to achieve a CR, $n=19$; elective decline, $n=7$). The 6-year EFS was 48 and 10 % for localized and metastatic classic Ewing sarcoma, respectively. Similar results were seen in patients classified with peripheral primitive neuroectodermal tumors. A similar institutional trial was conducted from 1990 to 1998 at the Memorial Sloan-Kettering Cancer Center (MSKCC), including 21 patients with Ewing sarcoma who had metastases to bone and/or marrow (Kushner and Meyers 2001). All patients received intensive induction chemotherapy with local therapy. Ten patients developed early disease progression prior to HDCT with autologous HCT. The remaining 11 patients received either melphalan with TBI or thiotepa/carboplatin as a preparative regimen. Only one patient survived relapse-free, yielding an EFS of 5 %. Both the NCI and MSKCC authors considered their outcome to be similar to historic results achieved with conventional treatment, suggesting little role for HDCT as consolidation for high-risk Ewing sarcoma, particularly for preparative regimens that included TBI.

Three other institutional series that combined both metastatic and recurrent patients reported more promising results than the NCI and MSKCC series. A two institution collaboration between Vienna St. Anna and Düsseldorf University Children's Hospitals included 17 patients with either metastatic ($n=7$) or recurrent ($n=10$) disease from 1987 to 1992 (Burdach et al. 1993). All patients received melphalan (with doses ranging from 120 to 180 mg/m^2), etoposide, and 12 Gy TBI; four patients also received carboplatin. Stem cell sources included PBSC ($n=9$), autologous bone marrow ($n=4$), and allogeneic bone marrow ($n=4$). A matched cohort of 41 Ewing sarcoma patients treated with conventional therapy served as a comparison group. Matching factors included gender, age, extent of disease, response to chemotherapy, and either interval from diagnosis event to transplant (cases) or relapse (controls). The 6-year relapse-free survival was 45 % for all patients who received HDCT, compared to 2 % for the matched control group who did not receive HDCT ($p=0.0002$). Within the context of a non-randomized trial, the authors concluded that HDCT improved the

outcome for metastatic or relapsed patients compared to conventional treatment. The Fred Hutchinson Cancer Research Center series included 16 patients with either metastatic ($n=2$) or recurrent ($n=14$) disease from 1993 to 1997 (Hawkins et al. 2000). All patients received BuMelTt as a preparative regimen, and nine also received 10.5–15 Gy TMI after recovery from BuMelTt, with a second autologous HCT. Most patients ($n=14$) received autologous PBSC, while two patients received allogeneic bone marrow or syngeneic PBSC. The most common reasons for not receiving TMI were insufficient cell dose of stored autologous PBSC ($n=4$) and extensive prior RT ($n=2$). The 3-year EFS for all patients was 36 %; all surviving patients received both BuMelTt and TMI. The University of Minnesota series included two consecutive prospective studies from 1995 to 2004 for 36 patients with high-risk solid tumors, including 16 with metastatic ($n=10$), recurrent ($n=5$), and large pelvic primary ($n=1$) Ewing sarcoma (Fraser et al. 2006). All patients received BuMelTt as a preparative regimen and two received post-autologous HCT whole lung RT. Eight of the 16 Ewing sarcoma patients survived at a median follow-up of 3.7 years (range 0.6–7.9 years). Neither the Fred Hutchinson nor the Minnesota series included a matched comparison group of patients treated with conventional therapy, and both had the potential for selection bias inherent in any study that only included patients allocated to HDCT.

Four prospective cooperative group trials of HDCT with autologous HCT have had mixed results. The North American CCG study 7951 enrolled 32 eligible Ewing sarcoma patients with bone and/or marrow metastases from 1996 to 1998 (Meyers et al. 2001). All patients received five courses of intensive chemotherapy and RT to the primary and metastatic sites delivered immediately prior to TMI and HDCT (melphalan and etoposide) and autologous HCT. Nine patients did not receive HDCT due to persisting or progressive disease ($n=4$), excessive early toxicity or death during induction chemotherapy ($n=3$), patient refusal ($n=1$), or inadequate data on treatment delivered ($n=1$). The 2-year EFS was similar for all 32 eligible patients and the subgroup of 23 patients who received HDCT (20 and 24 %, respectively). For outcome comparison, a contemporary control group (63 Ewing sarcoma with bone or marrow metastases treated with conventional therapy) was identified (Miser et al. 2004); the two groups had identical results. Because all eligible patients were accounted for from the time of study enrollment, selection bias for allocation to HCT was eliminated, strengthening the authors' conclusion that HDCT was not beneficial for Ewing sarcoma with bone or marrow metastases.

More encouraging results were reported from combined analysis of two consecutive prospective studies by the German/Austrian Meta European Intergroup Cooperative Ewing Sarcoma Study Group (Burdach et al. 2003). From 1986 to 1994, 26 Ewing sarcoma patients with bone or marrow metastases or recurrent Ewing sarcoma received TBI, melphalan, and etoposide (HyperME), with carboplatin in eight patients. From 1995 to 2000, 28 similar Ewing sarcoma patients received tandem courses of melphalan and etoposide (TandemME). In addition, 22 patients received interleukin-2. Five-year EFS was 22 and 29 % for HyperME and TandemME, respectively. HyperME had a higher rate of fatal complications, including secondary malignancies, compared to TandemME (23 % versus 4 %). No difference in EFS was seen between those who did and did not receive interleukin-2. The lack of a contemporary comparison group limited the ability to determine the benefit of HDCT over conventional treatment. The authors concluded that including TBI in a preparative regimen increased the risk of fatal complications and did not improve outcome.

The French Société Française des Cancers de l'Enfant trial included 97 patients with metastatic Ewing sarcoma (including both those with isolated pulmonary and bone/marrow metastases) from 1991 to 1999 (Oberlin et al. 2006). All patients received seven courses of chemotherapy, with timing of local treatment individualized to the patient. Seventy-five patients received BuMel as HDCT followed by autologous HCT with either PBSC ($n=58$), bone marrow ($n=13$), or

both ($n=4$). Patients did not receive whole lung RT despite the presence of pulmonary metastases. Twenty-two patients had persistent or progressive disease during induction precluding HDCT, all of whom died. For all 97 patients, the 5-year EFS was 37 %; for the 75 patients who were able to undergo HDCT with autologous HCT, the 5-year EFS was 47 %. Among patients with isolated pulmonary metastases, the 5-year EFS was 52 %. In multivariate analysis, age >15 years, fever at diagnosis, and marrow involvement were each independently associated with inferior outcome. No contemporary comparison to a control group of patients treated with conventional therapy was included in the analysis. However, the similar results relative to other HDCT series without TBI or whole lung RT encouraged the authors to conclude that BuMel was a promising preparative RT-free regimen, particularly for patients with isolated pulmonary metastases, and supported the randomized R2pulm design of EuroEWING99.

The largest prospective HDCT with autologous HCT trial for Ewing sarcoma to date was the pan-European EuroEWING99, which included 281 patients with bone or marrow metastases (R3) from 1999 to 2005 (Ladenstein et al. 2010). The study design included six courses of VIDE and one or more VAI prior to HDCT with BuMel or TandemME followed by autologous HCT. The timing and extent of local treatment to the primary and metastatic sites were individualized to the patient. Only 169 patients (60 %) received either BuMel ($n=136$), TandemME ($n=13$), or other HDCT ($n=20$). The reasons for omitting HDCT were early progression ($n=44$) or other/unknown causes ($n=68$). The 3-year EFS overall was 27 %. Using clinical features present at diagnosis (including age, number of bone metastases, primary tumor size, and presence of marrow or lung metastases), the authors developed a prognostic scoring model to predict the probability of EFS ranging from 8 to 40 %. The prognostic scoring model was independently confirmed in a French dataset of similar patients. No comparison was made between patients who did or did not receive HDCT because of the unequal distribution of clinical risk factors at diagnosis and high rate of early progression in the group that did not receive HDCT. In addition, local treatment was only delivered in 54 % of patients who did not receive HDCT, compared to 88 % of patients who did receive HDCT. Systematic use of local therapy was associated with improved outcome even in patients with extrapulmonary metastatic disease (Haeusler et al. 2010). Because of the non-randomized nature of the study, it is not possible to determine whether HDCT with autologous HCT improved outcome compared to conventional treatment. However, the prognostic scoring model developed from the study demonstrated that the outcome is heterogeneous for Ewing sarcoma patients with extrapulmonary metastases. For this reason, non-randomized comparison to historic control may be compromised unless controlled for clinical risk factors.

A combined Italian Sarcoma Group and Scandinavian Sarcoma Group trial was the only completed prospective study to evaluate the role of HDCT with autologous HCT for localized Ewing sarcoma with a poor response to neoadjuvant chemotherapy (Ferrari et al. 2011). Poor response was defined as either macroscopic residual tumor histologically or persistence of a soft tissue mass in unresected primary tumors, both assessed after neoadjuvant chemotherapy. Among 300 patients with localized disease, 104 (51 %) were poor responders, of whom only 126 received HDCT (consisting of BuMel) with autologous HCT. The reasons for a poor responding patient not receiving HDCT were early tumor progression ($n=10$), institutional choice ($n=7$), inadequate PBSC collection ($n=5$), patient refusal ($n=4$), and medical contraindications ($n=3$). The 5-year PFS for patients with poor response who received HDCT with autologous HCT was 72 %, which was similar to the 5-year PFS for patients with good response (75 %). For comparison, the 5-year PFS for patients with poor response who did not receive HDCT with autologous HCT (excluding those with early progression) was 33 %, which was similar to the expected PFS for poor responding patients based upon historic data (Bacci et al. 2004; Oberlin et al. 2001; Paulussen et al. 2001).

The authors concluded that HDCT with autologous HCT resulted in improved outcome for poor responding patients, although the study lacked a contemporary randomized control group.

11.4.1.3 Registries of HDCT with Autologous HCT in Ewing Sarcoma

Two multi-institutional retrospective registry studies have evaluated the role of HDCT with autologous HCT in metastatic Ewing sarcoma. The European Bone Marrow Transplantation Registry for Solid Tumours (EBMT-STR) reported results from 21 transplant centers for Ewing sarcoma patients with either initially metastatic disease ($n=32$) or recurrent disease with second CR ($n=31$) from 1982 to 1992 (Ladenstein et al. 1995). Most patients received autologous bone marrow, although two received allogeneic HCT. HDCT included more than 20 different preparative regimens, with 93 % of patients receiving melphalan and 30 % of patients receiving TBI. Nine patients received tandem HDCT. Overall, the 5-year EFS from time of HDCT was 21 and 32 % for patients with initially metastatic and recurrent disease, respectively. Because of the variable and non-randomized nature of the study population, prior treatment, and conditioning regimens, the ability to draw conclusions from the series was limited. In addition, there was no concurrent control group of patients who did not receive HDCT. Within the study population, however, improved outcome was seen in patients who did not receive TBI (particularly within the initially metastatic group), recurrent patients after initially localized disease, and non-ifosfamide containing initial therapy. There was no improvement in outcome for patients who received tandem HDCT. Nine deaths from treatment (16 %) were observed. The authors concluded that HDCT improved the outcome for Ewing sarcoma patients in general, but its role in specific risk groups required further exploration, including those with isolated pulmonary recurrence, large primary tumors without metastatic disease, and poor response to initial therapy. Although it was not possible to conclude that one preparative regimen was superior to another, TBI did not appear to offer any advantage over HDCT alone.

The second multi-institutional retrospective study was conducted by the Center for International Blood and Marrow Transplantation Research (CIBMTR) from 39 North and South American centers from 1989 to 2008 (Gardner et al. 2008c). Included in the analysis were 116 total patients: 50 who received HDCT with autologous HCT for metastatic disease prior to recurrence, 27 HDCT with autologous HCT for localized disease prior to recurrence, 36 who received HDCT with autologous HCT for recurrent disease, and three with unclassified status. The rationale for HDCT with autologous HCT for localized patients without prior relapse was not provided. Preparative regimens were heterogeneous, with 59/116 patients (51 %) receiving TBI. The 5-year PFS were 49, 34, and 14 % for patients with localized disease without prior recurrence, metastatic disease without prior recurrence, and localized with recurrence, respectively. Only one of five patients with initially metastatic disease who received HDCT with autologous HCT after relapse was free of second relapse. In multivariate analysis, initially metastatic disease, lower performance status, and relapse prior to HDCT were associated with inferior PFS. No concurrent control group treated with conventional therapy was included in the analysis, but the authors concluded that the outcome for each patient group was similar to those published without HDCT. Both registry studies provide useful information regarding the commonly used conditioning regimens and indications for HDCT with autologous HCT in Ewing sarcoma. However, patient selection bias limits any generalized interpretation of the outcome data to metastatic or recurrent Ewing sarcoma patients.

11.4.1.4 Allogeneic HCT for Ewing Sarcoma

Intensification of therapy to increase cytotoxicity against Ewing sarcoma has been investigated in many settings, as previously discussed. When

HDCT is utilized, autologous HCT is most often used to rescue the patient following bone marrow ablation. However, as the treatment-related mortality of allogeneic HCT has decreased, transplant centers have piloted studies to determine whether allogeneic HCT is effective in Ewing sarcoma and other solid tumors. A review of transplantation for solid tumors in EBMT from 1991 to 2002 revealed only 36 patients with Ewing sarcoma who underwent allogeneic HCT, while 1,860 received autologous HCT (Gratwohl et al. 2004). Although the benefit from allogeneic HCT over autologous HCT for pediatric solid tumors is unproven, there are some potentially encouraging results in very high-risk Ewing sarcoma.

There are three basic premises behind the strategy of allogeneic HCT for malignancies: (1) intensification of chemotherapy consolidation, (2) avoidance of the problems related to tumor contamination of autologous product, and (3) the potential for graft-versus-tumor (GVT) effect. The rational for HDCT prior to allogeneic HCT is the same as prior to autologous HCT. However, HDCT in heavily pretreated patients carries increased risk for transplant-related mortality (TRM) in the allogeneic HCT setting. Care should be taken in selecting the patient most likely to tolerate potentially toxic therapies. Patients with rapidly progressive disease are not well suited as candidates for allogeneic HCT, as the HDCT is rarely able to fully control growth of refractory macroscopic disease. Instead, HDCT in the setting of an allogeneic HCT appears to be better suited as part of consolidation in a patient with no evidence of disease on scans or a very good partial response to prior multimodality therapy. The choice of autologous HCT versus allogeneic HCT following a HDCT regimen should be considered based on availability of product and/or trial. In some trials (Burdach et al. 2000), the assignment to allogeneic HCT or autologous HCT was biologic, based on whether the patient had a matched sibling donor, while other trials only enrolled patients eligible for allogeneic HCT (Baird et al. 2012; Pedrazzoli et al. 2002; Lang et al. 2006).

The most common HDCT utilized in series of allogeneic HCT in Ewing sarcoma are similar to those regimens used for autologous HCT (Table 11.2). Conditioning regimens included busulfan, melphalan, and thiotepa or fludarabine. The reported adverse events included the typical side effects of nausea, mucositis, and profound neutropenia with risk for infection. As transplant support has continued to evolve with improvements in HLA typing and supportive care, the TRM has declined from rates of up to 40 % in the 1990s to 5–16 % in more recent series of sarcoma patients. TRM is one of the primary reasons that allogeneic HCT studies are limited to patients with high-risk Ewing sarcoma, such as those with widely metastatic disease at diagnosis, early relapse, or multiple relapses.

Circulating tumor cells are frequently identified in autologous products used for treatment of solid tumors (Matthay et al. 1993 ; Ljungman et al. 2010 ; Merino et al. 2001). When available, purging strategies have decreased the number of contaminating tumor cells to below level of detection (Matthay et al. 1993). CD34+ selection on peripheral blood products may decrease the presence of tumor cells in the autologous HCT product. Ewing sarcoma cells were able to be purged from a peripheral stem cell product using an 8H9 antibody that binds most Ewing sarcoma cells (Merino et al. 2001). However, specific tumor purging strategies are not universally available or utilized for Ewing sarcoma trials. In published reports of neuroblastoma HDCT, recipients of purged autologous products have similar disease control as do recipients of allogeneic products, suggesting that any remaining contamination does not add to relapse (Matthay et al. 1994). The similar outcome with either purged or unpurged autologous HCT in a large, prospective, randomized trial in neuroblastoma suggests that tumor contamination of stem cell product does not contribute to post-HDCT relapse (Kreissman et al. 2013). The presence of detectable tumor cells may actually help to stimulate an immunologic antitumor response in consolidation autologous HCT for neuroblastoma (Handgretinger et al. 2003).

Since autologous products are often collected in the setting of continued disease and Ewing sarcoma is not a localized disease, Ewing sarcoma

Table 11.2 Allogeneic HCT for Ewing sarcoma

	n	CR prior to HCT?	Prep, GVHD proph	Type	Outcome	TRM	GVHD	Notes
Hawkins et al. (2000)	1 allo 1 syn 14 auto	PD CR2	Bu/Mel/TT+/– TMI	MSD	DOD CR3 @ 62 mo	VOD @1 mo		HD therapy yielded long term CR in syngeneic
Burdach et al. (2000)	10 allo 26 auto	6 CR	Mel/Etop/TBI	MSD	2 CR/4 DOD	4 DOC		Overall 9 of 36 surviving @ median of 89 mo Relapse rate similar in auto versus allo
Lucas et al. (2008)	1	no	Bu/Mel (CsA, MTX)	10/10 mother	AWD @ 9 mo			Decrease in nodule size temporally associated with GVHD
Koscielniak et al. (2005)	1	no	Bu/TT/Flu/Cyclo OKT3	Haplo	CRx3.5 yr Died of relapse @ 43 mo		Grade II/IV gut and skin	Posttransplant IL2 resulted in GVHD but also regression of lesions
Lang et al. (2005)	1 (+5 other tumors)	no	Mel/TT/Flu/OKT3 (MMF)	Haplo	DOD @ 7 mo		Grade II in 4 patients	Prospective trial based on prior case report
Fagioli (2010)	4 (+17 sarcoma)	no	TT/Mel/Flu or Cyclo (CsA ± ATG ± MTX)	MSD (14) MUD (7)	7 DOD	7 DOC	GVHD II–IV in 6 patients	
Pedrazzoli et al. (2002)	1 (+16 other tumors)	no	Cy-Flu (CsA)	RIC MSD	DOD @ 13 mo		aGVHD	2 CR (in RMS and HD)
Castagna et al. (2005)	1 (+9 other sarcomas)	PR	Cy/Flu (CsA)	RIC MSD	77 % PD	DOC d+12	75 % aGVHD	
Hosono et al. (2008)	1	no	Bu/Flu (CsA)	RIC MSD	CR @ 8 mo			CNS relapse @ 14 mo
Thiel et al. (2011)	50 (RIC) 37 (HIC)	22 20			33 DOD 17 DOD	4 DOC 16 DOC	10 6	Retrospective EBMT review; RIC decreases TRM but does not increase OS
Baird et al. (2012)	17 (+6 other sarcoma)	7	Cy/Flu/Mel (CsA or Tacro/siro)	RIC MSD	1 CR @ 61 mo		High rate mild-mod acute, chronic	Indolent tumor growth with increased chemo responsiveness post-allogeneic HCT

Abbreviations: *allo* allogeneic, *auto* autologous, *HCT* hematopoietic cell transplant, *Bu* busulfan, *CR* complete response, *CsA* cyclosporine A, *DOC* dead of complications, *DOD* dead of disease, *Flu* fludarabin, *GVHD* graft-versus-host disease, *HD* Hodgkin disease, *HIC* high-intensity conditioning, *Mel* melphalan, *MSD* matched sibling donor, *MUD* matched unrelated donor, *MTX* methotrexate, *OS* overall survival, *yr* year, *mo* month, *PD* progressive disease, *Proph* prophylaxis, *RIC* reduced intensity conditioning, *RMS* rhabdomyosarcoma, *syn* syngeneic, *TT* thiotepa, *TRM* transplant-related mortality, *VOD* venous occlusive disease, *TBI* total body irradiation, *TMI* total marrow irradiation, *Tacro* tacrolimus, *siro* sirolimus, *CNS* central nervous system, *aGVHD* acute GVHD, *Cy* cyclophosphamide, *haplo* haploidentical, *EBMT* European Bone Marrow Transplantation Registry, *ATG* anti-thymocyte globulin, *MMF* mycophenolate mofetil, *cyclo* cyclosporine, *AWD* alive with disease

cells are likely to be in the leukapheresis product obtained for autologous HCT. Using nested polymerase chain reaction (PCR), EWSR1-FLI1 transcript was found in 75 % of samples from high-risk patients on an immunotherapy protocol (Merino et al. 2001). Despite CD34 selection, autologous progenitor cells from the peripheral blood of patients with Ewing sarcoma contained translocation positive cells in 54 % of samples (Toretsky et al. 1995). Allogeneic HCT strategies do not require purging of tumor cells and therefore provide a decreased risk of tumor transfer. An additional potential benefit is the lack of any pro-tumor survival or tolerizing factors that may be secreted by contaminating tumor cells.

Perhaps the most relevant rationale for allogeneic HCT is the potential for additional GVT effect. Not only do allogeneic donor stem cells provide a naïve population of T-cells with potential to respond to Ewing sarcoma specific tumor antigens, but the mismatch of minor antigens leads to a population of allo-reactive T-cells that can be active against tumor as well. This allogeneic reactivity is a double-edged sword, however, because it is not tumor specific and is accompanied by graft-versus-host disease (GVHD) toxicities. The de-coupling of GVT from GVHD is an area of intense preclinical investigation, and hopefully future trials will have mechanisms that can increase GVT while decreasing GVHD.

Immune reactivity in allogeneic HCT for hematopoietic malignancies has been well established, with graft-versus-leukemia playing a large role in the efficacy of allogeneic HCT against chronic myelogenous leukemia and acute myelogenous leukemia, and potentially in some acute lymphoid leukemias. Laboratory models of allogeneic HCT for solid tumors have shown that the posttransplant setting may be well suited for immune reactivity of donor immune cells against weak cancer antigens. T-cell and natural killer (NK) survival factors IL7 and IL15 are elevated in the engraftment period following allogeneic HCT and play a role in GVT (Thiant et al. 2010, 2011; Lang et al. 2006).

Although not routinely mentioned when discussing immune responsive malignancies such as melanoma or renal cell carcinoma, there is evidence that pediatric solid tumors such as neuroblastoma and Ewing sarcoma can be targets of immunocytotoxicity. When appropriately stimulated *ex vivo*, Ewing sarcoma reactive T-cells can be expanded to control in vitro and in vivo growth of both autologous and allogeneic Ewing sarcoma cells (Zhang et al. 2003). Patients with Ewing sarcoma who have absolute lymphocyte counts of >500 on cycle 1 day 15 have a better prognosis than patients with lower lymphocyte counts following initial chemotherapy (De Angulo et al. 2007). Although the exact mechanism is not understood, this correlation suggests that immune activity against Ewing sarcoma may be an important denominator of successful treatment against these aggressive tumors. Since the patient with Ewing sarcoma is lymphopenic following standard chemotherapy, consolidation of therapy with allogeneic HCT may increase antitumor capacity by engraftment of donor alloreactive T-cells. Ewing sarcoma may be a different and perhaps better target for immune-mediated killing since it expresses higher levels of major histocompatibility complex (MHC), costimulatory molecules, and also has been reported to express specific cancer testes antigens that can be targets of immunotherapy (Zhang et al. 2003; Shamamian et al. 1994).

Evidence supporting possible GVT is apparent in some of the allogeneic HCT reported (Table 11.2). Lucas reported a case study of one patient who had post-allogeneic HCT tumor regression that was associated with GVHD (Lucas et al. 2008). Other groups have manipulated the allogeneic setting by using haploidentical donors in order to increase the allogeneic reactive T-cells. The initial case study by Koscielniak described use of IL2 post-haploidentical allogeneic HCT, which induced grade II/IV GVHD of the gut and skin but also resulted in regression of lesions present at time of transplant (Koscielniak et al. 2005). The patient had a prolonged disease-free interval of >3 years before relapse. This case was the basis for a prospective pilot study of haploidentical allogeneic HCT that enrolled one patient with Ewing sarcoma who had already received HDCT plus

autologous HCT as well as five patients with other solid tumors (Lang et al. 2006). The one Ewing sarcoma patient did not achieve a CR and died of disease at 7 months following allogeneic HCT. Although not a curative outcome, the trial did look at several biological endpoints that do reveal some GVT. Patients had an early reconstitution of NK cells with an elevation of cells lasting approximately1–2 months. T-cell reconstitution took longer with significant rise only after 3–5 months. Growth of tumor in the early time points is unlikely to be controlled by such normal immune reconstitution following allogeneic HCT, reinforcing the idea that allogeneic HCT should not be used as a treatment for refractory Ewing sarcoma.

Reduced intensity allogeneic HCT has been shown to be a feasible and well-tolerated therapy in other solid tumors with comparable tumor response and disease control to those observed using conventional approaches (Todisco et al. 2007; Secondino et al. 2007). Reduced intensity conditioning (RIC) meets two goals of allogeneic HCT for Ewing sarcoma. First, it decreases the toxicity associated with the preparative regimen in these heavily pretreated patients, and second, it allows for a more rapid engraftment of donor immune system. Several groups have investigated allogeneic HCT with RIC for Ewing sarcoma with cyclophosphamide plus melphalan being the most common regimen (Table 11.2) (Baird et al. 2012; Castagna et al. 2005; Thiel et al. 2011; Hosono et al. 2008). Overall, the patients have shown full donor lymphocyte chimerism at earlier times than high-intensity conditioning allogeneic HCT. In a comparison of RIC and high-intensity preparative regimens from the EBMTR, RIC was associated with decreased TRM but did not lead to increased overall survival (Thiel et al. 2011). High rates of moderate acute and chronic GvHD were seen in the initial cohort reported by Baird et al. using only cyclosporin for GvHD prophylaxis (Baird et al. 2012). A second cohort received tacrolimus and sirolimus for prophylaxis with a reduction in the incidence and severity of GvHD. Patients in CR at time of allogeneic HCT fared better than patients with bulk disease, and one high-risk patient who underwent allogeneic HCT with RIC in CR1 is still disease-free over 5 years later.

Overall disease-free survival was still quite low when all 125 reported allogeneic HCT for Ewing sarcoma were combined. Fifty-five patients were in CR at time of allogeneic HCT, most from multimodality therapy prior to transplant regimen, although there were a few responses reported to the conditioning regimen. Follow-up varies widely in the series and case reports and alive with disease is not always distinguishable from continued CR, but a conservative estimate of patients alive at time of report shows only approximately 25 % of patients surviving following allogeneic HCT. The most likely cause of death in all reports is progression of disease. Whether selecting only patients in CR for transplant would improve these numbers is speculative.

11.4.1.5 Conclusions

The chemotherapy sensitivity of Ewing sarcoma and uncontrolled case series with survival rates of 20–70 % among patients with metastatic, localized with poor histologic response, or recurrent disease have provided support for HDCT with autologous HCT. However, case-control series comparing outcome between HDCT and conventional treatment are either negative or have the potential for significant bias. Comparisons between the historic results with conventional treatment and single and multi-institutional clinical trials and retrospective registries using HDCT with autologous HCT are also confounded by patient selection bias that prevents unambiguous comparison, especially because of the variable outcome seen among metastatic, localized, and recurrent Ewing sarcoma patients. Only the EuroEWING99 trial will provide definitive evidence to support the benefit of HDCT with autologous HCT in the frontline therapy for isolated pulmonary metastatic disease (R2pulm) or poor response to initial therapy (R2loc). In the absence of new data, HDCT with autologous HCT for metastatic, poorly responding, or recurrent Ewing sarcoma should be restricted to prospective clinical trials.

11.4.2 Rhabdomyosarcoma

Collectively, soft tissues sarcoma are the most common extracranial solid tumor type in children, accounting for 7.4 % of all pediatric cancers (Li et al. 2008a; Gurney 1999a). Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma, with an incidence in children less than 20 years old of 4.3 per million per year or approximately 350 children and adolescents annually in the United States (Gurney 1999). Although predominantly a disease of children, 41 % of all patients diagnosed with RMS are older than 19 years (Sultan et al. 2009). RMS can be broadly divided into one of two major histologic subtypes, embryonal (ERMS) and alveolar (ARMS), which are clinically and biologically distinct (Missiaglia et al. 2012; Pappo et al. 1995; Newton et al. 1995; Maurer et al. 1988; Davicioni et al. 2009; Williamson et al. 2010). The optimal initial treatment for RMS is determined by clinical risk stratification based on pretreatment staging, surgical/pathologic clinical group, and tumor histology, each of which is independently associated with outcome (Malempati and Hawkins 2012; Meza et al. 2006). Depending upon the risk group, RMS patients are typically treated with vincristine, dactinomycin, and cyclophosphamide (VAC) or ifosfamide (VAI), in combination with surgery and/or RT for local control (Malempati and Hawkins 2012; Pappo et al. 1995).

Among three distinct RMS risk groups, the high-risk group (defined by the presence of distant metastases, such as bone, bone marrow, or lung) has long-term EFS of 24 % (Oberlin et al. 2008). A pooled analysis of metastatic RMS from North American and European cooperative groups identified clinical features (including age <1 or >10 years, unfavorable primary site, bone or marrow involvement, and >2 sites of distant metastases) as being associated with particularly inferior outcome (Oberlin et al. 2008). Depending upon the number of unfavorable risk factors, metastatic RMS patients have EFS that ranges from 5 to 50 %. From 1988 to 2004, the Intergroup Rhabdomyosarcoma Study Group (IRSG) and later the COG-treated metastatic RMS patients on a series of phase II window studies to identify active agents or drug pairs, followed by VAC after assessing initial response in the phase II window (Pappo et al. 2001, 2007; Breitfeld et al. 2001; Sandler et al. 2001; Lager et al. 2006; Walterhouse et al. 2004). Although active agents or drug pairs were identified, no improvement in EFS was seen. More recently, COG has combined the most active drug pairs in an intensive combination, potentially improving the outcome for metastatic ERMS (Weigel et al. 2010, 2012).

In addition to metastatic disease at diagnosis, additional clinical features have been associated with inferior outcome. Recurrent RMS has a particularly poor prognosis, with a 5-year post-relapse overall survival of 17 % (Chisholm et al. 2011; Pappo et al. 1999). Two independent retrospective analyses both identified alveolar histology, intensive initial treatment, and advanced initial clinical group and stage as associated with worse post-relapse survival. It is possible to identify a minority of patients with a more favorable post-relapse survival, including ERMS with limited prior chemotherapy and no history of RT. Using these results as a baseline, COG study ARST0121 evaluated protocol-driven therapy stratified by post-recurrence risk but was unable to demonstrate an improvement in outcome compared to historic results (Mascarenhas et al. 2010). Several RMS clinical trial groups, including the Cooperative Soft Tissue Sarcoma (CWS) (Koscielniak et al. 1999; Koscielniak et al. 1992) and the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor (MMT) (Oberlin et al. 2012; Stevens et al. 2005) studies, have used early anatomic response to tailor subsequent therapy, based upon observations that change in tumor volume is associated with outcome (Koscielniak et al. 1999). However, COG RMS trials showed that neither early (Burke et al. 2007) nor end of treatment (Rodeberg et al. 2009) radiographic response was prognostic for future recurrence, even among patients with no response (<50 % reduction in tumor size). Given the conflicting literature on the significance of radiographic response, change in tumor size is of unclear importance in determining risk for recurrence.

Metastatic RMS has been an attractive candidate population for HDCT with autologous HCT. Even patients with widespread metastatic disease are highly likely to respond to initial chemotherapy with both alkylator- and non-alkylator-based regimens (Lager et al. 2006; Pappo et al. 2007). Preclinical RMS models identified melphalan as a particularly effective agent (Houghton et al. 1985), with hematopoietic toxicity limiting its use without autologous HCT (Breitfeld et al. 2001). In contrast to neuroblastoma and Ewing sarcoma, no randomized trials comparing conventional therapy to HDCT with autologous HCT have been conducted in RMS. Instead, the evidence supporting the benefit of HDCT over standard treatment is based upon comparison to historic cohort with similar disease features. Because of patient selection bias, direct comparisons between HDCT with autologous HCT and conventional therapy are inherently limited. A systematic review of the role of HDCT for metastatic RMS by the Cochrane Collaboration concluded that the literature did not support the routine use of HDCT with autologous HCT in metastatic RMS (Admiraal et al. 2010).

11.4.2.1 Prospective HDCT with Autologous HCT Trials in RMS

Much of the literature for HDCT with autologous HCT consists of retrospective case series with less than ten patients from single institutions. Stronger levels of evidence for the role of HDCT with autologous HCT come from two larger institutional studies and four multi-institutional trials, all of which were prospective. Horowitz et al. reported the long-term results from three consecutive clinical trials conducted at the NCI from 1981 to 1986 for 25 patients with high-risk RMS (Horowitz et al. 1993). The study design is discussed above under Ewing sarcoma (see Sect. 11.4.1.2). The 6-year EFS was 28 % for localized and metastatic RMS combined. These long-term results were considered to be similar to historic results achieved with conventional treatment and suggested little role for TBI as consolidation in high-risk RMS. A similar institutional trial was conducted from 1990 to 1994 at MSKCC. Eligible patients included RMS ($n=21$), undifferentiated sarcoma ($n=3$), and extraosseous Ewing sarcoma ($n=2$) with stages II–IV (Boulad et al. 1998). The study design included induction chemotherapy and local RT, followed by consolidation with melphalan and etoposide, then autologous HCT using bone marrow treated *ex vivo* with 4-hydroperoxycyclophosphamide. Like the NCI series, this study accounted for all patients from the time of diagnosis, including patients who did not undergo autologous HCT (progressive disease or no response, $n=7$). For the entire study population, the 2-year overall survival and PFS were 56 and 53 %, respectively, which was similar to a historic MSKCC cohort. Restricting the analysis to metastatic patients (all histologies combined), the 2-year overall survival was 50 %, compared 32 % in the historic MSKCC cohort. The authors of the NCI and MSKCC series concluded that results with HDCT consolidation for RMS were similar to historic outcome with conventional treatment.

Four European multi-institutional trials have evaluated the role of HDCT with autologous HCT in metastatic RMS. The first trial, SIOP Malignant Mesenchymal Tumor (MMT)4-91, included three cycles of induction chemotherapy and local treatment, followed by consolidation treatment with either HDCT (most frequently a single dose of melphalan 200 mg/m^2 ($n=42$), but also various combinations with etoposide, carboplatin, busulfan, and thiotepa ($n=10$)) and autologous HCT or a fourth cycle of conventional chemotherapy ($n=44$) (Carli et al. 1999). The selection of HDCT or a fourth cycle conventional chemotherapy was by institutional preference and was not randomized, although the analysis was restricted to patients who achieved a CR after three cycles of treatment. Among patients who achieved a CR, there was no difference in 3-year EFS between those who received HDCT and those who did not (29.7 % versus 19.2 %, $p=0.3$), with both groups having a similar outcome to historic results for metastatic RMS without HDCT. The authors concluded that HDCT might delay the time to progression in metastatic RMS but did not improve ultimate outcome.

Similar to SIOP MMT4-91, CWS conducted a prospective trial to evaluate the role of tandem HDCT, HD CWS-96, from 199 to 2003 for 295 patients with metastatic soft tissue sarcoma

(Klingebiel et al. 2008). Patients received 7 cycles of conventional chemotherapy and local treatment prior to either tandem HDCT (first thiotepa and cyclophosphamide, then melphalan and etoposide, both followed by autologous HCT) or two additional cycles of conventional chemotherapy followed by four cycles of oral maintenance therapy (OMT) consisting of trofosfamide, etoposide, and idarubicin. Like the SIOP MMT4-91 trial, the selection of tandem HDCT or OMT was by institutional preference rather than randomized. Of the initial 295 patients, 199 were not evaluable due to insufficient treatment records ($n=37$) or failure to follow one of the two treatment plans ($n=162$). Of the remaining 96 patients, only 74 had ARMS or ERMS. For patients with RMS, OMT had a superior 5-year overall survival compared to HDCT (52 % versus 15 %, $p=0.001$). The benefit of OMT was seen in patients without bone or marrow involvement, although no benefit was seen in those with bone or marrow involvement. The poor compliance with the study therapy and its non-randomized nature confound the interpretation of the comparison between the HDCT and OMT arms. Nonetheless, the authors conclude that HD CWS-96 did not support the routine use of HDCT in metastatic RMS.

Three cycles of HDCT with autologous HCT were tested in the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) trial, RMS4.99, which enrolled 70 metastatic RMS patients from 1999 to 2006 (Bisogno et al. 2009). In contrast to SIOP MMT4-91 and HD CWS-96, RMS4.99 included only four cycles of conventional chemotherapy prior to HDCT, with local treatment and additional maintenance chemotherapy after HDCT. The triple HDCT consisted of first thiotepa with melphalan, then cyclophosphamide with thiotepa, then melphalan alone, each followed by autologous HCT. Of the initial 70 patients, eight did not receive HDCT due to progressive disease, poor overall condition, or persisting marrow disease. The 3-year PFS was 35.3 % for the entire study population. Dividing the patients by presence of 0–1 or 2 or more risk factors (Oberlin et al. 2008), the outcome for RMS4.99 was similar to historic results. The authors concluded that even three cycles of HDCT with autologous HCT did not improve the outcome for metastatic RMS compared with conventional treatment.

SIOP MMT investigated the role of HDCT with autologous HCT again in MMT-98, enrolling 146 metastatic RMS patients from 1998 to 2005 (McDowell et al. 2010). Patients were stratified into standard (SRG) and poor risk groups (PRG), with age >10 years or the presence of bone or marrow involvement defining PRG. Both risk factors used to define PRG were identified as independently associated with outcome in an international metastatic RMS dataset (Oberlin et al. 2008). SRG patients ($n=45$) received 18 cycles of conventional chemotherapy with local treatment, resulting in a 51 % 5-year EFS. PRG patients ($n=101$) either received initial conventional chemotherapy like SRG patients or one of three phase II window therapies, followed by four sequential high doses of single agents every 14 days regardless of blood count recovery, with autologous HCT infused after the fourth single-agent course only. The four sequential single-agent courses were cyclophosphamide 2 g/m^2/day IV for 3 days, etoposide 800 mg/m^2/day for 3 days by continuous IV infusion, cyclophosphamide 2 g/m^2/day IV for 3 days, and carboplatin with a target AUC = 20 IV over 5 days. Only 79/101 PRG patients received the four sequential courses of HDCT; the reasons for omitting HDCT in 22 PRG patients were not stated. The 3-year EFS was 18 and 6.9 % for PRG patients who received or did not receive HDCT, respectively. The authors conclude that four sequential courses of HDCT with a single autologous HCT did not improve outcome for PRG patients compared to historic results for similar patients.

11.4.2.2 Registries of HDCT with Autologous HCT in RMS

Two multi-institutional retrospective registry studies have evaluated the role of HDCT with autologous HCT in metastatic RMS. The German/Austrian Pediatric Bone Marrow Transplantation Register reported combined outcome for RMS patients with either initially metastatic disease ($n=27$) or recurrent disease ($n=9$) from 1986 to

1994. Eligible patients received a variety of stem cell sources, including five with allogeneic HCT (Koscielniak et al. 1997). HDCT was heterogenous, although the most common conditioning regimen was melphalan with TBI ($n=26$). Because of the variable nature of included patients and treatment, the ability to draw conclusions from the series is limited. Overall, 19 % (5/27) of the initially metastatic patients and 44 % (4/9) of the patients with recurrent disease were reported to be alive without recurrence. There were no significant differences in outcome by histology (ERMS versus ARMS), by use of TBI or by infusion of interleukin-2 post-autologous HCT. None of the five who received allogeneic HCT survived. Only one death from treatment was observed. The authors concluded that HDCT was investigational and of unproven benefit for RMS and should be only given in the context of a prospective clinical trial. CIBMTR reported the outcome for 62 RMS patients from 30 worldwide transplant centers who received HDCT with autologous HCT from 1989 to 2003 (Stiff et al. 2010). Similar to the earlier German/Austrian registry, the CIBMTR series included patients with heterogenous prior therapy, disease status at the time of HDCT (including 67 % with initially metastatic disease), and conditioning regimen (including 44 % receiving melphalan, 84 % receiving etoposide, and none reported to receive TBI). For all patients, the 5-year PFS was 29 %, with similar outcome for those receiving HDCT with autologous HCT prior to relapse (32 %) compared to those after relapse (26 %). Like the German/Austrian registry, the CIBMTR series had no conventional therapy control group for comparison. The CIBMTR authors conclude that their results support a randomized trial of HDCT with autologous HCT in high-risk RMS in remission or after recurrence. However, both registry studies are limited by inherent selection bias and by measuring outcome from the time of autologous HCT rather than diagnosis, confounding direct comparisons to historic outcome with conventional therapy.

11.4.2.3 Conclusions

Although the chemotherapy sensitivity of RMS makes it an attractive candidate for HDCT with autologous HCT, its role is unproven. No randomized, prospective trial has compared outcome between HDCT and conventional treatment in RMS. Comparisons between the results from single and multi-institutional clinical trials and retrospective registries using HDCT with autologous HCT and standard therapy are confounded by patient selection bias that prevents unambiguous comparison, especially because of the variable outcome seen among metastatic and recurrent RMS patients. Overall, the outcome from most HDCT with autologous HCT series is similar to those seen with conventional treatment. In the absence of new data, HDCT with autologous HCT for metastatic or recurrent RMS should be restricted to prospective (and preferably randomized) clinical trials.

11.4.3 Desmoplastic Small Round Cell Tumor

Gerald and Rosai first described desmoplastic small-round-cell tumor (DSRCT) in 1989 (Gerald and Rosai 1989), as clinically distinct from Ewing sarcoma because it was highly aggressive, tended to occur in the abdomen and metastasize throughout the peritoneum (Gerald et al. 1991). With a peak incidence in the second and third decade, the overall DSRCT incidence has not been clearly defined but is likely to be approximately 50 patients or less annually in the United States and accounts for less than 1 % of sarcomas. DSRCT spread occurs on mesothelial surfaces in the peritoneum in a pattern resembling peritoneal carcinomatosis from ovarian cancer. Instead of being confined to one organ, macroscopic disease in DSRCT is often identified in omentum, liver, or lymph nodes. DSRCT is more common in males than females. While most common in the abdomen and pelvis, DSRCT has been described outside of the abdomen or metastatic to CNS, lungs, or bone marrow (Backer et al. 1998; Yoshida et al. 2008; Tison et al. 1996; Neder et al. 2009). Patients with widespread disease can present with ascites and/or pleural effusions. [F-18]-fluorodeoxy-D-glucose positron-emission tomography (FDG PET) is a good modality for identifying and following sites of disease (Magnan et al. 2012).

DSRCT histologically appears in clusters or sheets with hyperchromatic nuclei and scant cytoplasm and is distinct from the cellular stroma, with a classic desmoplastic reaction (Gerald et al. 1998). DSRCT is often highly vascularized. Immunohistochemistry reveals markers of both mesenchymal and epithelial differentiation, which distinguish it from Ewing sarcoma, RMS, or other small round blue cell tumors. DRSCT can stain positive for keratin, epithelial membrane antigen, vimentin, desmin, neuron-specific enolase, and GD2 (Modak et al. 2002) but also can sometimes express CD99. DSRCT cells will stain positive for nuclear WT1 using a carboxy-specific antibody. Most DSRCT have the pathognomonic translocation chromosomal abnormality t(11;22)(p13;p12), which fuses *EWSR1* and *WT1*(Ladanyi and Gerald 1994; Gerald et al. 1995; de Alava et al. 1995). The fusion of the first 7–10 exons of the *EWSR1* gene to a breakpoint in the *WT1* gene between exons 7 and 8 yields a fusion protein that contains three zinc-finger domains of WT1. The EWSR1-WT1 fusion thus results in a DNA-binding oncoprotein that has been shown to affect transcription of many genes, including *PDGFA* (Lee et al. 1997) and *ENT4* (Li et al. 2008a, b).

Unlike many of the other pediatric small round blue cell tumors, DSRCT has poor initial response to standard chemotherapy. No CR have been described following chemotherapy alone. A multimodal approach including aggressive debulking is required to achieve any possibility of long-term remission. There is no single standard of care for newly diagnosed patients with DSRCT, but most are treated with the five-drug chemotherapy regimen used for other high-risk sarcoma tumors, including VDC/IE. Therapy often includes high-dose alkylators and aggressive surgical debulking, as detailed in the largest patient cohort report of 66 patients with overall survival of 15 % at 5 years (Lal et al. 2005). Irinotecan-based chemotherapy has shown activity against DSRCT in several case reports, and its use in upfront trials or recurrent disease is warranted (Aguilera et al. 2008; Neder et al. 2009).

In several series, the ability to achieve a CR is required to achieve any meaningful disease-free interval (Lal et al. 2005; Cook et al. 2012). However, recurrence with metastases to liver, lymph nodes, and lung is unfortunately common following completion of initial treatment. Based on the rationale that surgery alone is unlikely to fully eliminate microscopic tumor spread, consolidation therapy has been investigated following aggressive multimodality induction therapy for these very high-risk patients. Consolidative intensity-modulated RT is one strategy that has been used in many patients but has not been evaluated in a prospective fashion (Desai et al. 2013; Pinnix et al. 2012). Hyperthermic intraperitoneal chemotherapy (HIPEC) administration has been shown to be an effective therapy for peritoneal surface spread of other malignancies such as adenocarcinoma of the colon or peritoneal mesothelioma (Yan et al. 2009). In a similar fashion, HIPEC has been used with some encouraging results following cytoreductive surgery for DSRCT (Hayes-Jordan et al. 2007), and a phase II trial is underway to assess efficacy (NCT01277744).

An early report by Kushner et al. established that intensive chemotherapy in the setting of multimodality aggressive therapy was beneficial for patients with DSRCT (Kushner et al. 1996). Although no patients achieved a CR to chemotherapy alone, 70 % of newly diagnosed patients had a PR to a regimen containing high-dose alkylators. In that series, two patients that had previously received low-dose chemotherapy were also able to obtain a very good partial response to high-dose cyclophosphamide, doxorubicin, and vincristine. Thus it was concluded that DSRCT could be sensitive to intensive chemotherapy. The largest series of DSRCT included 66 patients and concluded that patients treated with intensive alkylator therapy had better overall survival than other treatment regimens (Lal et al. 2005). However, it must be noted that the 5-year survival for the intensive alkylator regimen was still only approximately 20 %. The retrospective review also established that complete surgical resection was important for overall survival.

11.4.3.1 HDCT with Autologous HCT for DSRCT

Based on these initial findings, treatment strategies were designed that combined intensive

induction chemotherapy with aggressive surgery and consolidation with HDCT and autologous HCT. Four patients in the initial MSKCC series received HDCT with autologous HCT, and two were reported to have long-term CR (Kushner et al. 1996). Two subsequent reports also suggested that HDCT with autologous HCT might improve outcome after achieving minimal residual disease in this high-risk population (Kushner et al. 2001; Mazuryk et al. 1998). Prospective but non-randomized trials further examined the efficacy of HDCT with autologous HCT (Bertuzzi et al. 2002; Fraser et al. 2006; Bisogno et al. 2010). In one of the trials that allowed patients with less than CR to undergo HDCT with autologous HCT, the majority of patients had response to the HDCT regimens, suggesting that intensification of chemotherapy may provide increased antitumor cytotoxicity (Bisogno et al. 2010).

Three prospective studies of HDCT with autologous HCT in DSRCT have been published, with mixed results (Table 11.3). In addition, a retrospective review through CIBMTR identified 36 patients in North America who underwent HDCT with autologous HCT for DSRCT (Cook et al. 2012). HDCT with autologous HCT reports has several consistent findings. As with many other transplant settings, a CR prior to consolidation with HDCT with autologous HCT is important for best overall survival. The CIBMT data showed that patients with a CR had a 3-year overall survival of 57 % compared to 28 % for those patient who were not in a CR at time of HDCT with autologous HCT. The first prospective HDCT with autologous HCT trial included three patients with DSRCT who had PR to conventional chemotherapy (Bertuzzi et al. 2002). No CR was achieved on the trial. In contrast, the Minnesota experience included four patients with DSRCT, two with CR, and two with PR prior to HDCT with autologous HCT (Fraser et al. 2006). Using a preparative regimen of BuMelTt, three patients achieved long-term CR following HDCT with autologous HCT. The largest prospective series included ten DSCRT patients (Bisogno et al. 2010). Bisogno et al. showed that the majority of patients had tumor response to the sequential HDCT with autologous HCT regimen, but most had early relapses, with 3-year overall survival of 38.9 %. Bisogno et al. conclude that HDCT with autologous HCT did not significantly improve the overall outcome compared to the reported 3-year survival rate of 44 % reported by Lal et al. (Lal et al. 2005). However, the sequential HDCT with autologous HCT occurred after chemotherapy induction prior to surgical resection to remove macroscopic disease.

11.4.3.2 Conclusion

Overall, it is clear that DSRCT is an aggressive disease with poor outcomes despite intensification of therapy. The inclusion of consolidative HDCT with autologous HCT in a select patient population when CR has been reached may be beneficial but remains to be proven. Future translational work will reveal new effective therapies targeting EWSR1/WT1 or its downstream targets that can be added to current regimens in order to improve upon the outcomes of chemotherapy intensification.

11.5 Retinoblastoma

Retinoblastoma is the most common intraocular malignancy of infancy and childhood, with an incidence of 1/15,000–20,000 live births. In 60 % of cases, the disease is unilateral and the median age at diagnosis is 2 years. Among unilateral cases, 15 % are hereditary. Retinoblastoma is bilateral in about 40 % of cases with a median age at diagnosis of 1 year. All bilateral and multifocal unilateral forms are hereditary.

Treatment of retinoblastoma is based on the bilateral or unilateral characteristics of the retinoblastoma, the staging performed by fundoscopy (Murphree 2005; Reese and Ellsworth 1963) and the extent of the disease (Chantada et al. 2006). Patients diagnosed with intraocular retinoblastoma in the more industrialized countries have an excellent (>95 %) overall survival, and development of extraocular disease is rare following enucleation or chemo-reduction (Chantada et al. 2010). The most likely explanation for these excellent results is early diagnosis, facilitated by adequate access to health care and early

Table 11.3 HDCT with autologous HCT for desmoplastic small-round-cell tumor

	# DSRCT	# HCT	Prep regimen	Outcome	Notes
Kushner et al. (1996)	12	4	Thiotepa/carbo	CR @ 13 mo CR @ 34 mo	Majority had response to CAV but no CR to chemo alone HDCT may be beneficial
Mazuryk et al. (1998)	1	1	Bu/Mel	CR @ 19 mo	
Kushner et al. (2001)	1	1	HD Cyclo/HD cisplat/topotecan	PD @ 8 mo	
Bertuzzi et al. (2002)	7	3	Mel/thiotepa or Mitox/thiotepa	PD in 2 patients Debulking, then allogeneic HCT in other	Prospective phase II study No CR achieved prior to autologous HCT
Fraser et al. (2006)	4	4	Bu/Mel/thiotepa	3 CR 1 relapse @ 9 mo	Prospective transplant trial Only non-Ewing sarcoma disease on trial that had this degree of response
Livaditi et al. (2006)	5	2	Not reported	Relapsed @ 9 mo Relapse @ 1 yr	
Al Balushi et al. (2009)	5	3	Thiotepa/carbo	CR @ 6 yr CR @ 2 yr Relapse @ 18 mo	Only patient with CR went to autologous HCT
Houet et al. (2010)	1	1	HD chemo	CR @ 10 yr	EWSR1-WT1 detected by PCR in PB collection prior to CD34 selection
Bisogno et al. (2010)	14	10	Thiotepa/Mel	CR @ 33 mo CR @ 49 mo CR @ 8 mo	Prospective study 7/8 with disease had response to preparative regimen with HDCT
Cook et al. (2012)	36	36	Multiple centers and regimens	3 yr OS 40 % (57 % OS if CR at time of HCT)	CIBMTR retrospective study CR at time of HCT is important

Abbreviations: *HDCT* high-dose chemotherapy, *HCT* hematopoietic cell transplant, *DSRCT* desmoplastic small-round-cell tumor, *Carbo* carboplatin, *Bu* busulfan, *Mel* melphalan, *HD* high dose, *Cisplat* cisplatin, *HD* chemo: specific high-dose chemotherapy regimen not specified, *CR* complete response, *PD* progressive disease, *OS* overall survival, *yr* year, *mo* month, *CAV* cyclophosphamide, doxorubicin, vincristine, *PCR* polymerase chain reaction, *CIBMTR* Center for International Blood and Marrow Transplantation Research, *PB* peripheral blood

consultation with specialists that lead to detection of the disease well before it disseminates outside the eye (Aerts I et al. 2013). Rarely, extraocular retinoblastoma may involve the soft tissues of the orbit, pretragal and cervical lymph nodes (International Retinoblastoma Staging System stage 3), metastases to bone or bone marrow (International Retinoblastoma Staging System stage 4a), or the CNS (International Retinoblastoma Staging System stage 4b). Metastatic retinoblastoma at presentation is uncommon in most industrialized countries but is more frequent and a major cause of mortality due to retinoblastoma in less developed countries (Canturk et al. 2010; Antoneli et al. 2003; Chantada et al. 2003). The occurrence of metastatic disease at diagnosis in retinoblastoma appears to be critically influenced by delays in diagnosis, which are themselves related to poor sociocultural conditions (Canturk et al. 2010). In addition, in less developed countries, many families of children with intraocular retinoblastoma opt out of recommended treatment, therefore leading to subsequent metastatic dissemination and death (Sitorus et al. 2009).

Survival of metastatic retinoblastoma was traditionally poor, until the advent of HDCT

regimens followed by autologous HCT. The effectiveness of autologous HCT has been reported in non-randomized case series by different groups from United States and Europe (Dunkel et al. 2000, 2010a, c; Kremens et al. 2003; Matsubara et al. 2005; Rodriguez-Galindo et al. 2003). Most single-institution reports included single cases or small series with fewer than five patients. Only three reports included more than 10 patients, each with the conclusion that consolidation with high-dose therapy and autologous HCT provides a 60–70 % probability of cure, especially for children with metastatic disease outside the CNS (stage 4a) (Dunkel et al. 2010c; Namouni et al. 1997; Palma et al. 2011) whose disease previously responded to conventional chemotherapy. CNS dissemination of retinoblastoma (stage 4b) (Dunkel et al. 2010a) and trilateral retinoblastoma (Dunkel et al. 2009) have been associated with even more inferior outcome, although cure has been reported with HDCT with autologous HCT in two small series (Dunkel et al. 2009, 2010a). Because of early detection, HDCT for retinoblastoma is rare in industrialized countries. However, HDCT with autologous HCT is available in some middle income countries like Argentina, Chile, and Uruguay (Palma et al. 2011). Other debated indictions for HDCT with autologous HCT include incomplete microscopic resection after enucleation (International Retinoblastoma Staging System stage 2: positive optic nerve margin, extra-scleral extension, and optic nerve involvement), as well as in case of locoregional disease (stage 3) (Bellaton et al. 2003; Doz et al. 1994; Honavar and Singh 2005; Namouni et al. 1997; Goble et al. 1990; Schvartzman et al. 1996). The optimal conditioning regimen for retinoblastoma is undefined, although all share combinations of carboplatin or cisplatin with etoposide and alkylating agents (including melphalan, thiotepa, cyclophosphamide) (Dunkel et al. 2000; Kremens et al. 2003; Matsubara et al. 2005; Namouni et al. 1997; Rodriguez-Galindo et al. 2003).

The variable therapy used in multiple small case series has left multiple areas of uncertainty in the optimal management of metastatic retinoblastoma with HDCT with autologous HCT. To better determine the role of intensive chemotherapy in the treatment of patients with metastatic retinoblastoma, COG is coordinating an international study, ARET0321 (http://cancer.gov/clinicaltrials/COG-ARET0321). This prospective, multicenter study includes patients with stage 4a, stage 4b, and trilateral retinoblastoma who receive four cycles of induction chemotherapy (vincristine, cisplatin, cyclophosphamide, and etoposide), followed by a single course of HDCT with carboplatin, thiotepa, and etoposide with autologous HCT. After high-dose therapy, radiation treatment is adjusted by response. Thiotepa was selected for this regimen due to its favorable toxicity profile and excellent CNS penetration. Despite its non-randomized design, ARET0321 should help define the role of HDCT in retinoblastoma. Pending the completion of ARET0321, the indications of HDCT in retinoblastoma may be limited to patients with extraocular, metastatic, or recurrent disease.

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Future Directions

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Franklin O. Smith, Judy M. Racadio,
and Gregory H. Reaman

Contents

F.O. Smith, MD (✉)
Division of Hematology/Oncology,
Department of Internal Medicine,
University of Cincinnati College of Medicine,
University of Cincinnati Cancer Institute,
Cincinnati, Ohio, USA
e-mail: smithfo@ucmail.uc.edu

J.M. Racadio, MD
Division of Hematology/Oncology,
Department of Internal Medicine,
University of Cincinnati College of Medicine,
Madeira, Ohio, USA

G.H. Reaman, MD
Division of Oncology,
George Washington University,
School of Medicine and Health Sciences,
Children's National Medical Center,
Washington, D.C., USA
e-mail: gregory.reaman@fda.hhs.gov

Our ability to cure children with cancer has improved dramatically over the past six decades. In the 1950s, when E. Donnall Thomas began his extraordinary pioneering work in hematopoietic cell transplantation (HCT), few children with cancer survived. Today, more than 80 % of children with cancer are cured of their disease. This profound success, one of the greatest stories in the history of medicine, is the result of numerous factors, including the development of the pediatric cooperative group mechanism; the development of a culture that integrates clinical research with clinical care; an emphasis on biology-based discovery with rapid translation of positive observations to the clinic resulting in new standards of care; dedicated investigators, and institutions; and finally, the courage of parents and children to participate as research participants.

Successful treatments for children with cancer have been developed based in multimodality approaches that include conventional chemotherapy, surgery, radiation, and hematopoietic cell transplantation, with the more recent addition of biologically targeted therapies. All of these approaches have been further enhanced by improvements in supportive care.

However, despite these great successes, recent data suggest that progress in improving the outcome for children with hematologic malignancies has slowed, and progress for most solid tumors has almost ceased (Smith et al. 2010). These data may suggest that over the past six decades, we have optimized conventional chemotherapy, surgery, radiation, and HCT. Based

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on this assumption, most paradigms for the future of cancer treatment depend heavily on biologically based targeted therapy and immune system manipulation in combination with chemotherapy, surgery, radiation, and transplantation. While this new approach holds great promise, many believe that there may still remain opportunities for improving conventional approaches to cancer treatment, including HCT.

Over the past several decades, there have been several improvements in how HCT is performed that have had a profound impact on outcomes in children and adults. These remarkable advances include improved human leukocyte antigen (HLA) typing methods with the identification of the importance of HLA-A, HLA-B, DRB1, and more recently HLA-C, DQ, and DP; the expanded possibilities for stem cell sources including bone marrow, mobilized peripheral blood, and cord blood; and the growth of the National Marrow Donor Program and a number of public unrelated donor cord blood banks. The refinement of total body irradiation (TBI) and the development of non-TBI conditioning regimens that constitute both myeloablative and non-myeloablative or reduced intensity approaches have expanded the potential indications for HCT and contributed to decreased morbidity. Effective approaches to graft-versus-host disease prophylaxis and treatment, including the development of cyclosporine, tacrolimus, and mycophenolate, have made a significant impact on improved transplant outcomes. Importantly, advances in supportive care, in particular the development and evidence-based use of ganciclovir for cytomegalovirus, acyclovir for herpes simplex virus, and an increasingly large number of drugs directed at combating opportunistic yeast and fungus, have reduced the incidence and severity of transplant complications that have traditionally been a major contributing factor to both morbidity and mortality.

However, perhaps the greatest advance has been an increasing recognition of how to most effectively use HCT (e.g., who, how, and when). Transplantation has evolved from its original use as a salvage therapy for patients in desperate circumstances to being the treatment of choice for many diseases. We are learning how to use HCT in only patients who are likely to benefit from the procedure, defining the approach to transplantation that is likely to be most effective in a given patient and learning when to use transplantation in the context of the patient's treatment.

Specific examples of how we have learned, and will continue to learn, and how to best utilize HCT in a risk-directed approach include no use of HCT in children with acute myeloid leukemia (AML) in complete remission (CR)1 who have core-binding factor abnormalities (i.e., HCT offers no advantage over chemotherapy alone), the use of HCT in children with intermediate-risk AML in CR1 (i.e., proven benefit of HCT over chemotherapy alone), HCT in all children with AML with an identified donor after relapse of disease (i.e., HCT is the only known effective therapy), no use of HCT in children with ALL not in remission (i.e., HCT is ineffective), the increasing use of non-TBI containing preparative regimens in children with AML (i.e., equally effective approach with reduced toxicity), and the continued use of TBI in children with acute lymphoblastic leukemia (ALL) (i.e., alternative approaches have not proven as effective).

Despite these great accomplishments, progress has been challenged in a number of clinically important areas. Even with an enormous investment in research over the past several decades, several critical areas have remained challenging, including a continued inability to eradicate malignant cells in many patients; an inability to identify suitable stem cell donors for ethnic minorities; ineffective treatments for patients with acute and chronic graft-versus-host disease; inability to enhance and facilitate immune reconstitution; an inability to harness the powerful allogeneic graft-versus-leukemia and graft-versus-tumor effect; and, finally, the inability to effectively treat invasive mold infections.

Therefore, it is likely that the future of HCT must continue to focus on these challenging areas.

Despite these ongoing challenges, several recent advances suggest a potential for paradigm-shifting approaches to cellular therapy. Perhaps the most exciting of these recently reported approaches is the development of chimeric antigen receptor-modified T cells (CAR-T cells) for the treatment of children with high-risk ALL (Grupp et al. 2013). With this approach, genetically modified T cells are created that are capable of killing treatment-resistant and treatment-refractory ALL. While this approach remains highly experimental, early results suggest that new methods for cellular graft engineering, after many decades of development, may ultimately prove to be a new and powerful approach to treating children with high-risk leukemias.

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