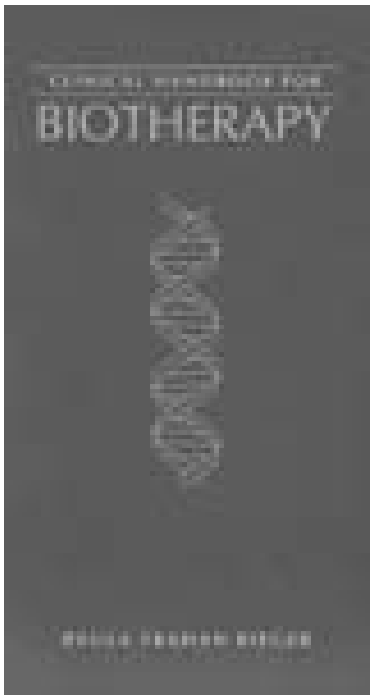

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Clinical Handbook for Biotherapy

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PREFACE

The use of biological agents in the management of patients with cancer and other diseases has grown tremendously since the first regulatory approval of a biological agent in 1986. Many nurses, regardless of their specialty, may come in contact with a patient who has received or may receive biotherapy. Given the environment in which nurses must practice today, resources that provide timely information in a quick and clinically useful format are vital. This need was the impetus for the development of the *Clinical Handbook for Biotherapy.*

This pocket-sized reference was developed from *Biotherapy: A Comprehensive Overview,* published in 1995. Information specific to drugs with regulatory approval was generated from the following resources: the World Wide Web; *The Physician's Desk Reference, 52nd edition* (1998); and *Drug Facts and Comparison: Loose Leaf Drug Information Service* (1998).

The content of this handbook follows the general outline of *Biotherapy: A Comprehensive Overview,* with the addition of a new chapter on diseases commonly treated with biotherapy. Each chapter is arranged in an outline format with general questions to guide location of information. Each chapter discussing major agents has incorporated Quick Summary pages to provide easy-to-locate information on the administration of biological agents with regulatory approval and resources materials. Each chapter on categories of agents also uses a Clinical Pearls summary to guide practice for managing patients receiving a given type of agent. Suggested readings and websites are provided to direct the reader to more comprehensive information on a variety of topics. The appendixes include a care plan and an example of a patient education plan for patients receiving biotherapy.

Italicized words in the text are defined in the Glossary.

It is my hope that this handbook will serve as a clinically useful resource to locate information on the care of patients receiving biotherapy in the many settings and for the many diseases in which that may occur.

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The drug information presented in the *Clinical Handbook for Biotherapy* has been derived from standard reference sources, recently published data, and respected pharmaceutical texts. The writers and publishers of this book have made every effort to ensure that information and dosage regimens presented are accurate and in accord with current labeling at the time of publication. However, in view of the constant and rapid flow of information resulting from ongoing research and clinical experience, as well as changes in government regulations, readers are urged to check the package insert and consult with a pharmacist, if necessary, for each drug they plan to administer to be certain that changes have not been made in its indications or contraindications, or in the recommended dosage for each use. While the drugs included in this publication were chosen on the basis of frequency of use and appropriate indications, the publisher and authors do not necessarily advocate, and take no responsibility for, the use of products described herein.

The inclusion of information in the Quick Summary pages for professional and patient resources represents a selection of materials that were readily available at the time of publication of this handbook and is not meant to be all-inclusive. For complete information on resources that are available from a pharmaceutical company related to a given product, contact the product sales representative.

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CHAPTER 1

BIOTHERAPY: AN OVERVIEW

The use of biological agents or approaches for the treatment of cancer is known as *biotherapy.* In the last twenty years, astounding progress has occurred in the discovery, clinical investigation, and regulatory approval of biological agents. Today, biotherapy stands as the fourth modality of cancer therapy along with surgery, radiotherapy, and chemotherapy.

The history of biotherapy, or *immunotherapy* as it was originally termed, can be traced to the 1800s. In 1894 William B. Coley found that patients with high fevers after cancer surgery were more likely than others to remain tumor-free. Coley administered extracts of erysipelas-causing streptococci to patients with inoperable sarcomas and observed regression of their disease.

Many years later, work was initiated using bacterial extracts to nonspecifically stimulate the immune system. These agents seemed to be effective only in patients with a minimal tumor burden. In general, clinical outcomes were poor.

Several technological advances in the 1980s established biotherapy as a recognized treatment modality:

- Greater understanding of the immune system and the biology of cancer
- Refinements in recombinant *deoxyribonucleic acid (DNA)* and *hybridoma* technology
- Success in producing large volumes of effector cells in culture
- Purification of new biological products aided by computers

Biotherapy is now well integrated into the clinical management of patients with cancer and other diseases. All nurses are likely, at some time in their careers, to encounter a patient who has or will receive a biological

agent to treat their disease or assist in its management. Table 1.1 outlines the key events that have occurred in the evolution of biotherapy.

Table 1.1 Key Events in Biotherapy

Late 1800s to mid-1900s
- Impure vaccines
- Coley's toxins
- Interferon discovered, 1957

1960s to early 1970s
- Clinical trials of bacterial agents
  - Used to nonspecifically stimulate the immune system
  - Examples: bacille Calmette Guérin (BCG), *Corynebacterium parvum*
- Early immunotherapy trials
- Limitations in studies related to:
  - Impure agents
  - Variability in experimental procedures
  - Incongruence between animal and human studies
  - Lack of generalizable results

Late 1970s to mid-1980s
- Major technological advances aid quest
  - Increased understanding of immune system
  - Advances in genetic engineering
  - Ability to mass-produce biological proteins and antibodies
    - Recombinant DNA technology
    - Hybridoma technology
  - Continued advances in molecular biology
  - Advances in laboratory methods and processes and computer systems
  - Single-agent cytokine studies initiated
  - Biological response modifier program initiated by the National Cancer Institute
- First biological agent (IFN-α) approved by the FDA (1986)

Late 1980s to the present
- Discovery and isolation of a variety of immune system products
- Numerous agents recombinantly produced for clinical trials
- Multisite clinical trials initiated and ongoing
- Combination cytokine therapy clinical trials initiated and ongoing
- Combination cytokine and chemotherapy clinical trials initiated and ongoing
- Regulatory approval for all categories of biological agents

Reprinted with permission from Jassak, P. 1995. An Overview of Biotherapy. In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview*. Boston: Jones and Bartlett.

WHAT IS BIOTHERAPY?

Originally, the term used to describe the use of agents that modulated the immune system for the treatment of cancer was *immunotherapy.* As technological advances allowed for the identification of new molecules and approaches and expansion of this modality beyond just the immune system, the terms *biotherapy* or *biological therapy* became more commonly accepted.

Biotherapy uses agents derived from biological sources or agents that affect biological responses. In 1983 the National Cancer Institute defined the term *biological response modifiers (BRMs)* as "agents or approaches that will modify the relationship between tumor and host by modifying the host's biologic response to tumor cells, with resultant therapeutic benefit." The term BRM is still used, although today *biological agent* is used more frequently to describe the agents used in this therapeutic modality.

HOW IS BIOTHERAPY DIFFERENT THAN CHEMOTHERAPY?

Chemotherapy uses drugs or chemical agents for the treatment of cancer. Agents used in biotherapy are primarily products of the mammalian genome.

The majority of biological agents in use clinically are *cytokines*, a broad class of protein cell regulators produced by the immune system. Cytokines

- Have a low molecular weight and a polypeptide structure; they are often *glycosylated*
- Act at short range on cells that produce them or on nearby cells
- Play a role in immune responses by functioning as a signaling system, controlling the growth, mobility, and differentiation of immune cells
- Interact with high-affinity receptors on the surface of cells to alter synthesis of proteins

Most cytokines possess multiple *(pleiotropic)* effects. The production or administration of one cytokine influences the production of others in a cascade effect.

Cytokine is an umbrella term for this class of proteins. Cytokines produced by lymphocyte cells are known as *lymphokines;* cytokines produced by monocytes are known as *monokines.*

Clinical evaluation of biological agents in the 1980s enabled investigators to identify several principles of cytokine therapy (Table 1.2).

Table 1.2 Principles of Cytokine Therapy

- Simple dose-response relationship may not always occur (less may be better).
- Cytokine-responsive tumors may require longer periods to achieve therapeutic response.
- Stable disease may be acceptable outcome.
- Toxic effects: severity may vary by agent, dose, and other factors.

In summary, biotherapy is a modality that capitalizes on the use of natural body proteins and their inherent functions to fight cancer.

WHAT IS THE RATIONALE FOR THE USE OF BIOTHERAPY IN TREATING CANCER?

The theory of immune surveillance forms the historical basis for the use of biological agents in the treatment of cancer. The principles of this theory are as follows:

- Cancer arises from a stepwise series of mutations in genes that control the growth, differentiation, and death of cells.
- Cancer cells express antigens on the surface of the cell (tumor-associated antigens) that cause the cell to look different from normal cells ("self ").
- The expression of these antigens occurs as a result of mutations.
- The immune system can recognize and provide a defense against these "nonself" cancer cells.

Although the theory is controversial and remains unproven, evidence suggests that the same immune mechanisms used to destroy bacteria and viruses are also targeted toward cancer cells. Also, persons who are immunosuppressed for long periods exhibit a higher incidence of certain types of malignancies; for example, patients with acquired immune deficiency syndrome (AIDS) have a high incidence of lymphoid malignancies.

HOW ARE BIOLOGICAL AGENTS CLASSIFIED?

Chemotherapy agents are classified according to their mechanism of action. The same can be done for biological agents, although this becomes difficult because each agent has multiple biological functions. Thus, agents can be placed in more than one category. Biological agents can produce immunologic actions, other biological effects, or a combination of these.

Biological agents exert at least one of the following three effects:

1. They augment, modulate, or restore the host's immune response.
2. They have direct cytotoxic or antiproliferative (cytostatic) activity.
3. They produce biological effects, such as differentiation of cells or interference with tumor metastasis.

Another classification system, primarily focused on the immune system, is shown in Table 1.3.

Table 1.3 Biotherapy's Effects on the Immune System

- *Active:* stimulates host's intrinsic function

  nonspecific: use of microbial or chemical agents to activate general host defense systems (e.g., BCG)

  specific: use of vaccines to augment host response to tumor cells or antigens (e.g., tumor-associated antigens)

- *Adoptive:* transfer of immune cells with antitumor properties to tumor-bearing host (e.g., lymphokine activated killer [LAK] cells, tumor infiltrating lymphocytes [TILs])

(continued)

Table 1.3 Biotherapy's Effects on the Immune System *(cont.)*

- *Restorative:* restores deficient immunologic subpopulation (e.g., thymic factors)
- *Passive:* transfer of antibodies or short-lived antitumor "factors"
- *Cytomodulatory:* agents that increase recognition of antigens and histocompatibility (HLA) antigens on tumor cells (e.g., interferon)

Source: Data from Mitchell, M. 1992. Chemotherapy in combination with biomodulation: A 5-year experience with cyclophosphamide and interleukin-2. *Seminars in Oncology* 19(2, suppl. 4): 8–87.

HOW ARE BIOLOGICAL AGENTS PRODUCED?

Two technological advances, recombinant DNA technology and hybridoma technology, have provided the means for the mass production of pure proteins and immunoglobulins, respectively. Prior to the availability of these technologies for producing biological molecules, the use of natural body proteins in the treatment of cancer was limited because proteins produced were impure, and quantities produced were not sufficient for large-scale clinical trials.

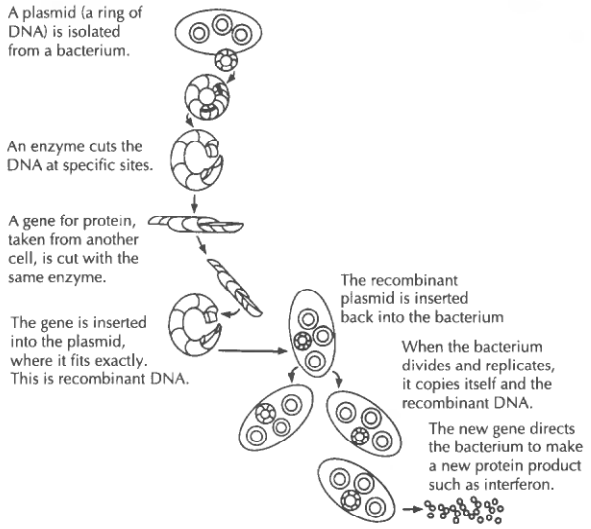
Process of Recombinant DNA Technology

Simplistically, the main steps are as follows:

1. The gene coding for a desired protein (e.g., insulin or interferon) is identified.
2. The gene is incorporated into the DNA of another organism (e.g., a bacteria or a yeast).
3. The organism then serves as a "factory" and produces the desired protein.
4. The protein goes through a purification process.

Many recombinant proteins are currently used in clinical medicine, the majority in cancer care. A small "r" placed before the drug name denotes that the protein was produced by recombinant DNA technology. Figure 1.1 depicts this process.

Figure 1.1 Recombinant DNA Technology



Source: Schindler, L. 1988. *Understanding the Immune System.* NIH publication number 88-529. Bethesda, MD: U.S. Department of Health and Human Services, p. 29

Hybridoma Technology

Hybridoma technology, discovered in 1975 by Köhler and Milstein, is used to produce monoclonal antibodies (MABs). These are highly specific antibodies targeted toward a single antigen and produced by clones of a single cell. The technique was originally perfected using mice; thus murine MABs were produced. The process is as follows:

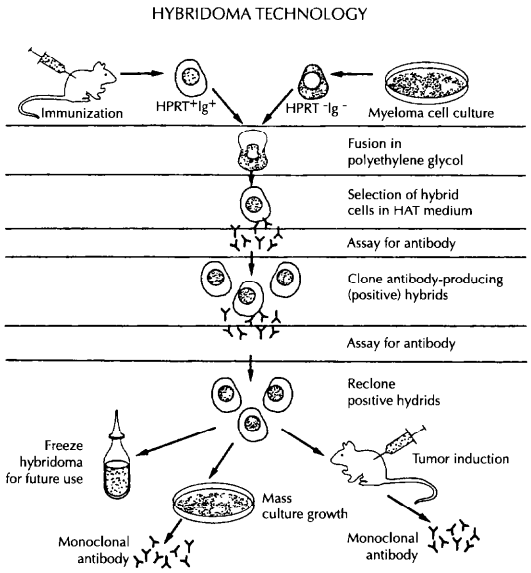
1. A mouse is immunized with a desired target antigen.
2. The mouse's immune system recognizes the antigen as foreign, and its B lymphocytes begin producing antibodies toward the antigen.
3. The mouse's spleen is removed to obtain the lymphocytes.

4. The B lymphocytes are fused in culture with cells from a malignant mouse myeloma cell to form a new cell known as a "hybridoma." Myeloma cells impart immortality, ability to grow indefinitely in culture; B lymphocytes impart specificity.
5. The culture is assayed and purified for the desired clone producing antibody toward the desired antigen.

This technique has now been refined with genetic engineering techniques for the production of MABs that are part human and part murine.

See Figure 1.2 for an overview of hybridoma technology.

Figure 1.2 Hybridoma Technology



Source: Reprinted with permission from DiJulio, J. 1988. Treatment of B-cell and T-cell lymphomas with monoclonal antibodies. *Seminars in Oncology Nursing,* 4:103.

HOW ARE BIOLOGICAL AGENTS DEVELOPED?

The Food and Drug Administration (FDA) requires preclinical and clinical evaluation of all chemical and biological agents before their commercial approval. The preclinical development of a biological agent involves the following three steps:

1. Producing the new agent, determining its physiologic role, and developing early models
2. Developing the drug and analyzing its toxicity, pharmacology, and application
3. Filing an investigational new drug (IND) application with the FDA

Once IND status is granted, the agent enters clinical trials, which consist of three phases (Table 1.4). The first step in evaluating a new drug is determining its maximum tolerated dose (MTD). The agent may exert the best antitumor effect at the MTD. The MTD, however, may not be the same as the optimal biological dose (OBD), which is the dose that "produces the optimal desired responses for the parameters deemed important with respect to a particular biological agent."

Table 1.4 Three Phases of a Clinical Trial

Phase I

- Defines toxic effects
- Determines MTD and dose-limiting toxicity
- Uses escalating doses
- Determines pharmacokinetics
- Range 3 to 6 patients/dose level
- Generally single-institution trials

End points; Unacceptable toxic effects define MTD

Determination of dose schedules and toxicities

Phase II

- Determines antitumor activity at given dose and schedule
- Further defines toxicity

(continued)

Table 1.4 Three Phases of a Clinical Trial *(cont.)*

- Refines toxicity interventions/management
- Usually 30 patients at fixed dose
- Involves multiple institutions

End points: Substantial information obtained about drug's best dose, route, and administration

Identification of tumor types for which treatment appears promising

Phase III

- Compares therapeutic efficacy
- Randomized study design
- Large numbers of patients
- Cooperative study groups

End point: comparing a new treatment to standard treatment

Specific to Biological Agents

Phase I

- Determines OBD
- Correlates clinical responses with biological end points
- 5 to 15 patients/dose level
- Immunologic monitoring

Phase II

- Given dose and schedule can be at MTD or OBD

Phase III

- In many diseases: no effective standard therapy exists. Thus, some biological agents may be approved after analysis of phase II data.

Adapted with permission from Jassak, P. 1995. "An Overview of Biotherapy." In P. Rieger (ed.) *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

Two major differences between drugs and biological agents have been identified:

1. Biological agents are derived from natural products in mammalian or human genes.
2. Biological agents have preprogrammed mechanisms and receptors within the body.

To evaluate a biological agent's activity, clinical trials measure bioavailability, pharmacokinetics, biological effects, and toxicity. They also examine the study population, monitor toxic effects, and the use of immunologic assays to measure effects on immune function.

WHAT ARE THE MAJOR BIOLOGICAL AGENTS IN CLINICAL USE?

Categories of Biologic Agents in Clinical Use

- **Cytokines**
  - Interferons
  - Interleukins
  - Hematopoietic growth factors
  - Tumor necrosis factor
- **Monoclonal antibodies**
- **Differentiation agents**
  - Retinoids
- **Cellular therapies**
  - Lymphokine-activated killer cells (LAKs)
  - Tumor-infiltrating lymphocytes (TILs)
- **Immunostimulants**
  - Nonspecific
    - Bacillus Calmette Guérin (BCG)
    - Levamisole
  - Specific
    - Vaccines
- **Gene therapy**

Interferons

In 1957 two virologists, Isaacs and Lindenmann, isolated interferon (IFN), a protein that interfered with viral activity in cells. It is now known that interferon is actually a family of proteins produced by the body in response to a variety of potentially threatening cellular or viral stimuli. The IFNs are cytokines and possess a variety of biological effects including antiviral activity, antiproliferative properties, and immunomodulatory effects.

IFN-alpha (IFN-α) was the first biological agent approved by the FDA (in 1986). Currently, there are

numerous types of IFN available for commercial or research use:

- IFN-α (Alferon®, Roferon®-A, Intron®A, Infergen®)
- IFN gamma (IFN-γ) (Actimmune®)
- IFN beta (IFN-β) (Betaseron®, Avonex®)

Interleukins

Interleukins *(ILs)* are a family of cytokines that are primarily involved in signaling or communicating between cells of the immune system. They are named numerically in the order of their discovery. They have been clinically investigated in the treatment of cancer, as supportive agents to diminish the deleterious effects of chemotherapy, and in the treatment of a variety of autoimmune diseases. As of December 1998, 18 have been isolated, but only IL-2 and IL-11 have been approved by the FDA.

Commercially available ILs include

- IL-2 (aldesleukin) (Proleukin®)
- IL-11 (oprelvekin) (Neumega®) (See HGFs)

Hematopoietic Growth Factors

Hematopoietic growth factors (HGFs) are glycoprotein hormones responsible for the differentiation, proliferation, maturation, and functioning of hematopoietic cells. They are primarily used as supportive therapy following chemotherapy or bone marrow transplantation. The HGFs remain under clinical investigation for the treatment of primary and secondary bone marrow failure states.

The following HGFs have been approved by the FDA:

- Granulocyte–colony stimulating factor (G-CSF) (filgrastim) (Neupogen®)

- Granulocyte-macrophage CSF (GM-CSF) (yeast-derived) (sargramostim) (Leukine®)
- Erythropoietin (EPO) (epoetin alfa) (Epogen®, ProCrit®)
- Interleukin 11 (IL-11) (oprelvekin) (Neumega®)

Monoclonal Antibodies

The use of antibodies to deliver drugs and toxins to tumor cells was first proposed by Paul Ehrlich in 1910. In 1975, Köhler and Milstein produced large volumes of antibodies from a single clone of cells. These antibodies are called *monoclonal antibodies* (MABs). The widespread availability of MABs has fostered their investigation or use in a variety of ways in cancer care:

- They are under investigation in bone marrow transplantation for the prevention of graft-versus-host disease or to remove cancer cells from the marrow prior to autologous transplantation.
- They are used by pathologists to classify leukemias and lymphomas or to help diagnose tumors that look alike on examination by light microscope.
- They are used or are under investigation in both conjugated (e.g., drug, toxin, or radioisotope attached) or unconjugated form for the treatment of both solid tumors and hematologic malignancies.
- They are used for the detection and imaging of tumors.

Several MABs currently have regulatory approval:

- Muromonab-CD3 (Orthoclone OKT-3®)
- Satumomab pendetide (OncoScint® CR/OV)
- Capromab pendetide (ProstaScint®)
- Rituximab (Rituxan®)
- Trastuzumab (Herceptin®)

Retinoids

Retinoids are a group of natural and synthetic analogues of vitamin A that perform a significant role in vision, growth and reproduction, epithelial cell differentiation, and immune function. They represent an active area of research in chemoprevention, that is, the attempt to arrest or reverse the process of carcinogenesis to prevent cancer invasion and metastasis and also in the treatment of cancer.

One retinoid has regulatory approval:

- Tretinoin (Vesanoid®)

Tumor Necrosis Factor

Tumor necrosis factor (TNF) is a potent molecule that targets and destroys malignant cells by causing hemorrhagic necrosis. Two types of TNF have been isolated: TNF-α, produced mainly by macrophages, and TNF-β, produced mainly by lymphocytes. Numerous clinical trials have evaluated the efficacy of TNF in the treatment of cancer and have found no consistent clinical benefit. In addition, significant toxicity is associated with the administration of TNF. To date, TNF has not received regulatory approval.

Current investigation is focused on the role of TNF in the pathophysiology of sepsis and cachexia and other approaches (such as gene therapy that inserts the gene coding for TNF into immune cells) that will lessen toxicity while maintaining clinical benefit.

See Table 1.5 for major biological agents with regulatory approval.

Table 1.5 Major Biological Agents with Regulatory Approval

Agent	Regulatory Approval
Interferons	
Interferon-α	
Interferon-α-2a (Roferon®-A, Roche Laboratories)	Hairy-cell leukemia; AIDS-related Kaposi's sarcoma; chronic myelogenous leukemia; hepatitis C
Interferon-α-2b (Intron®A, Schering Corporation)	Hairy-cell leukemia; AIDS-related Kaposi's sarcoma; condylomata acuminata; chronic hepatitis C; chronic hepatitis B; adjuvant therapy for melanoma (high risk for recurrence); and in conjunction with anthracycline-containing combination chemotherapy for the initial treatment of patients with clinically aggressive non-Hodgkin's lymphoma, a cancer of the lymphatic system.
Interferon-α leukocyte (Alferon®, Interferon Sciences, Inc.)	Condylomata acuminata
Interferon alfacon-1 (Infergen®, Amgen), is a bioengineered, non–naturally occurring type I interferon	Treatment of chronic hepatitis C viral infection
Hematopoietic Growth Factors	
GM-CSF (sargramostim) (Leukine®,Immunex, a subsidiary of American Home Products)	Acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma; acute lymphoblastic leukemia; and Hodgkin's disease patients undergoing autologous bone marrow transplantation (BMT); BMT failure or engraftment delay; after induction chemotherapy in acute myelogenous leukemia in elderly patients; use in mobilization and following transplantation of autologous peripheral blood progenitor cells; acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors
G-CSF (filgrastim) (Neupogen®, Amgen)	Decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs; to reduce the duration of neutropenia and neutropenia-associated sequelae in patients with nonmyeloid malignancies who are receiving myeloablative chemotherapy followed by BMT; mobilize peripheral blood stem

(continued)

Table 1.5 Major Biological Agents with Regulatory Approval *(cont.)*

	cells for transplantation; to support treatment of patients with acute myeloid leukemia following induction or consolidation chemotherapy; and for use in patients with severe chronic neutropenia
Erythropoieitn (epoetin alfa) Epogen® (Amgen)	Treatment of anemia in patients with chronic renal failure on dialysis
Procrit® (Ortho-Biotech)	FDA approved for the reatment of anemia in patients with chronic renal failure; anemia related to therapy with zidovudine (AZT) in HIV-infected patients; the treatment of anemia in cancer patients on chemotherapy; and anemic patients undergoing elective noncardiac, nonvascular surgery to reduce the need for allogenic blood transfusion.
rh Interlukin-11 (oprelvekin) Neumega® (Genetics Institute, a subsidiary of American Home Products)	Prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia
Interleukins	
Interleukin-2 (Proleukin®, Chiron Therapeutics)	Renal cell cancer; metastatic melanoma
MONOCLONAL ANTIBODIES	
Satumomab pendetide (OncoScint®, Cytogen)	Imaging of colon and ovarian cancer
Capromab pendetide (ProstaScint®, Cytogen)	Imaging of prostate cancer
Rituximab (Rituxan™, Genentech)	Treatment of relapsed or refractory low-grade or follicular, CD20-positive B-cell non-Hodgkin's lymphoma
Trastuzumab (Herceptin®, Genentech)	Treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein.
Muromonab-CD3 (Orthoclone Okt-3, Ortho Biotech)	Treatment of rejection in organ transplants

Source: Adapted with permission from Rieger, P. T. 1994. Biotherapy. In *Oncology nursing*, ed. S. Otto. 2d ed. St. Louis: Mosby.
For full indications and prescribing information, please refer to package insert.

SUMMARY

Our current understanding of biotherapy rests on the following observations:

- The majority of biological agents are produced by more than one type of cell.
- Each biological agent has its own receptors but produces overlapping effects.
- Most biological agents possess pleiotropic effects.
- Biological agents stimulate production of other agents, modulate receptor sites, and enhance or inhibit the biological activity of other cytokines.

Significant achievement has occurred in a relatively short time in the use of biological agents to treat cancer. The following challenges must be addressed so that the full potential of these molecules may be realized:

- Management of toxicity
- Cost-effective treatment plans and development of guidelines
- Resolution of issues related to dosing and scheduling so that the OBD may be maximized
- Development of optimal combination therapies

Technological changes are progressing at an unprecedented rate. This assures the ongoing discovery of new biological agents and approaches that will continually be integrated into the management of patients with cancer and other diseases. The need for nurses who are knowledgeable in this area and able to direct the care of patients receiving biotherapy has never been greater.

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RESOURCES

Website

Website for listing of biopharmaceuticals by company: www.biopharma.com/biopharmco.html

CHAPTER 2

THE IMMUNE SYSTEM

WHAT IS THE IMMUNE SYSTEM?

The immune system is the body's complex and dynamic set of defense mechanisms. Its primary purpose is to protect against pathogenic organisms; however, it also destroys worn, damaged, or malignant cells. In autoimmune diseases, the immune system attacks the body itself.

Functions of the Immune System

• Protection	Destruction of antigens (e.g., foreign proteins, viruses, bacteria, parasites, and fungi). Antigens are molecules on the microorganism or tumor cells that are recognized as foreign, "non-self."
• Surveillance	Destruction of malignant cells.
• Homeostasis	Destruction of worn and damaged cells.
• Tolerance	Recognition of self components.
• Regulation	Augmentation and depression of immune responses.

ARE THERE DIFFERENT TYPES OF IMMUNITY?

Immune responses involve a number of different cell types and their products. These responses are divided into two basic types.

Types of Immunity: Innate vs. Adaptive

Innate immunity (also called natural or nonspecific immunity) is the first line of defense against pathogens.

Features:	Mechanical barriers (skin, mucous membranes) and chemical barriers
	The inflammatory response
	Fever
	Phagocytic cells
	Soluble factors (acute phase proteins, cyto-kines)
Hallmarks:	Non-specific
	No memory

Action:

1. The body's first line of defense is a mechanical barrier such as the skin or mucous membranes. If it is breached, as in a wound or bacterial infection, an inflammatory response attempts to limit the colonization of the microbe.
2. The inflammatory response involves the physiological processes of capillary dilatation, exudation of fluid and plasma proteins into the tissues, and accumulations of neutrophils at the site of infection.
3. Clinical signs of inflammation are heat, redness, swelling, pain, and loss of function.
4. The white blood cells involved in this response are phagocytes (e.g., granulocytes, monocytes, or macrophages).
5. The serum proteins contained in the exudate have antibacterial properties.
6. The phagocytes engulf the bacteria and destroy it.

Adaptive immunity is also called specific or acquired immunity.

Features:	B lymphocytes—humoral immunity
	T lymphocytes—cellular immunity

Hallmarks: Specificity
Memory

Types of Adaptive Immunity:

Cell-Mediated Immunity: T cells, one type of lymphocyte, protect against intracellular organisms, provide immune surveillance, are responsible for rejection of transplanted organs, and modulate the immune response. For a T cell to recognize a molecule as foreign, the molecule must first be phagocytized. Monocytes generally perform this function. The antigen is then "presented" to the T cell linked to self molecules or major histocompatibility (MHC) molecules on the accessory cell (i.e., the cell presenting the antigen).

Humoral response: Other lymphocytes, called B cells, interact with antigen through antibodies displayed on their surface. The B cells then differentiate into antibody-secreting plasma cells. The secreted antibody binds to the antigen and facilitates its clearance from the body.

Action:

1. If the innate immune system fails to provide resistance to an antigen, the adaptive or specific immune system responds.
2. Lymphocytes recognize foreign (non-self or altered self) molecules—on a tumor, for example.
3. A small area of the antigen (called the *antigenic determinant* or *epitope*) binds to the lymphocyte receptor, stimulating an immune response.
4. The immune response on the second exposure to the same specific antigen is heightened and faster. This response is called *memory* or *anamnestic* response.

For a review of the body's defense mechanisms, see Figure 2.1.

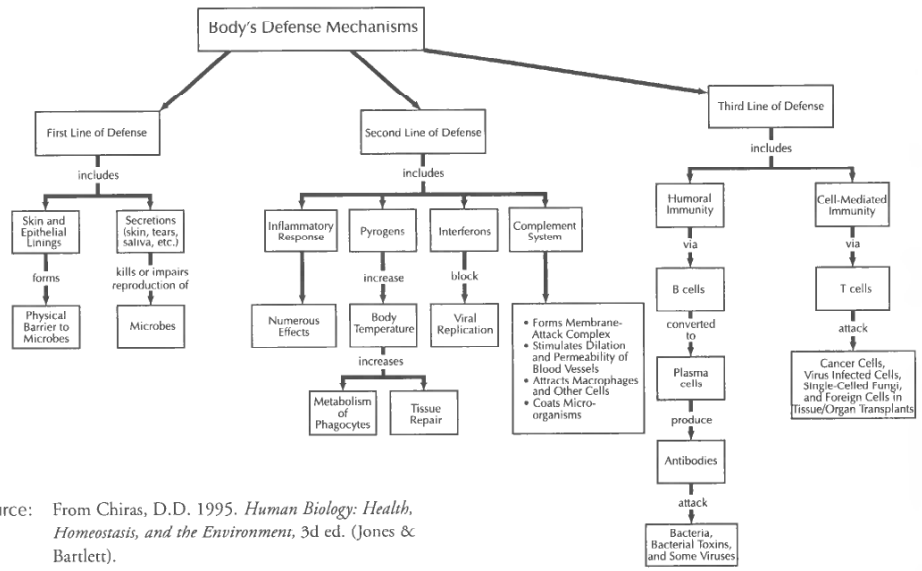


Figure 2.1 The Body's Defense Mechanisms

Source: From Chiras, D.D. 1995. *Human Biology: Health, Homeostasis, and the Environment,* 3d ed. (Jones & Bartlett).

WHAT ARE ANTIGENS?

An antigen is a foreign molecule from a bacteria or other invader. The immune system "learns" the distinction between self and non-self molecules in utero, where it is exposed to the molecules it will later recognize as self. The non-self molecules are antigens of various types:

- Immunogens are molecules that induce a specific immune response.
- Allergens induce allergic response.
- Tolergens induce immunologic unresponsiveness.
- Alloantigens distinguish one individual from another of the same species (e.g., blood group antigens or MHC antigens).
- Mitogens can activate lymphocytes.
- Super antigens are potent T-cell mitogens that stimulate T-helper cells.

HOW DO CELLS OF THE IMMUNE SYSTEM COMMUNICATE?

Cells of the immune system communicate through the secretion of cytokines. *Cytokines* are molecules released in inflammatory and specific immune responses. They act on target cells to produce effects such as activation, proliferation, or differentiation of cells.

Overview of Cytokines

- *Definition:* Soluble proteins produced by cells, including such polypeptide molecules as interleukins, lymphokines, monokines, interferons, tumor necrosis factor, and transforming growth factor.

- *Characteristics:*
  - Biologically active
  - Short half lives
  - Functional at low concentrations
- *Function:*
  - Regulate immune and inflammatory responses
  - Bind to plasma membrane receptors
  - Affect growth and differentiation of white blood cells
- *Interaction with neuroendocrine system:*
  - Interferon-α can increase levels of cortisol.
  - Interleukin-2 can cause fatigue and depression.
  - Changes in the neuroendocrine system can heighten or diminish immune responses. Some hormones may depress immune responses, whereas growth hormone and thymosin enhance T-cell responses.
- *Area of Action:*
  - *Autocrine* action: Cytokines exert effect in same cell where secreted.
  - *Paracrine* action: Cytokines affect cells in the immediate area.
  - *Endocrine* action: Cytokines act as signals to distant cells.

Cytokine cascade: One cytokine can potentiate (or inhibit) the action of another.

- *Attributes:*

Pleiotropy: One cytokine affects several target cells different ways.

Redundancy: Different cytokines affect one cell the same way.

Synergy: Two cytokines act together to induce an effect.

Antagonism: One cytokine blocks effect of another.

- *Nomenclature:* Many cytokines have more than one name because when they were first studied, they were named for their actions (e.g., tumor necrosis factor) rather than chemical or genetic make-up. But since 1986 the nomenclature has been standardized and these proteins are now given an *interleukin* designation once the DNA sequence coding for the protein is determined.

WHAT IS THE MAJOR HISTOCOMPATIBILITY COMPLEX?

Individual genetic makeup plays a part in the body's immune response.

- **Major histocompatibility complex (MHC)** is the collection of genes coding for cell surface compatibility antigens. It also has a role in determination of the immune response. The MHC includes 40 to 50 genes.
- **Human leukocyte antigen (HLA) complex** is the name of MHC in humans.
- **Locus:** HLA genes are located on the short arm of chromosome 6.
- **Classes:** HLA is divided into class I, II, and III regions and the genes code for class I, II, or III molecules. Classes I and II are considered part of the immunoglobulin superfamily.

  Class I molecules are present on most nucleated cells. Class I molecules must bind to an antigen, forming a complex, for that antigen to be recognized by a cytotoxic T cell.

  Class II molecules are present primarily on cells of the immune system. The major role of these molecules is to bind to antigens, forming a complex which in turn binds to and stimulates T-helper cells.

  Class III genes code for some of the proteins involved in the complement pathway and have no role in presentation of the antigen.

WHICH TISSUES AND CELLS ARE PART OF THE IMMUNE SYSTEM?

The Lymphoid System

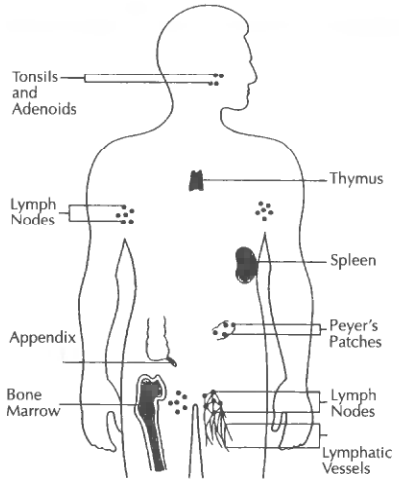
The cells responsible for the immune response are tissues and organs of the lymphoid system. Lymph nodes filter material draining from body tissues, the spleen filters

antigens in the blood, and the unencapsulated lymph tissue monitors mucosal surfaces.

- *Primary lymphoid tissue:* Lymphocytes develop and mature in the primary organs—the bone marrow and the thymus.
- *Secondary lymphoid tissue:* Lymphocytes are stored in the secondary organs—lymph nodes, lymph vessels (nodes are located at junctions of lymph vessels), spleen, tonsils, and unencapsulated lymphoid tissue lining the respiratory, alimentary, and genito-urinary tract.

See Figure 2.2.

Figure 2.2 Organs of the Immune System



Source: From Shindler, L. W. 1996. *The Immune System—How It Works.* NIH Publication 96-3229. Bethesda, MD: U.S. Department of Health and Human Services, April 1996, p. 3.

Cells of the Immune System

White blood cells (WBC) are *leukocytes* and include granulocytes, monocytes, and lymphocytes.

- *Formation:* Derived from bone marrow stem cells in children and adults in the process of differentiation called *hematopoiesis.* Four main types of hematopoietic growth factors, called colony-stimulating factors, are necessary at different stages of maturation and differentiation of blood cells.
- Two main kinds:

1. *Polymorphonuclear (PMN) leukocytes,* also called granulocytes, are of three types: neutrophils, basophils, and eosinophils.

   Granulocytes are polymorphonuclear (PMN) leukocytes. Important early in the inflammatory process and in acute infections, they are 50–70% of circulating white cells.

   Neutrophils migrate from blood stream into tissue, where they phagocytize pathogens and cellular debris.

   Basophils contain granules and mediators such as histamine, which act in allergic reactions. In tissues, cells similar to basophils are called mast cells.

   Eosinophils are phagocytes that respond to parasitic worms.

2. *Mononuclear (MNL) leukocytes* are of two types: lymphocytes (B lymphocytes, T lymphocytes, and Non-T, Non-B lymphocytes) and mononuclear phagocytes.

   Monocytes are large phagocytes that make up 3–7% of the white blood cells. Their functions:

   1. *Phagocytosis:* Present late in the inflammatory process and in chronic infections. Tissue monocytes (macrophages) are often designated a monocytic infiltrate on histologic examination. Macrophages contain many granules and lysosomes and are effective in removing cellular debris.

2. *Adaptive immune response:* Macrophages phagocytize antigens and present them to lymphocytes. The lymphocyte specific for that antigen then binds to the antigenic determinant and is activated. Macrophages can also bind antibodies on their cell surfaces, becoming more efficient in destroying specific invading microorganisms.

Lymphocytes:

Quantity: 20–40% of circulating white blood cells.

Location: In lymphatic tissues throughout the body: tonsils, adenoids, lymph nodes, thymus, spleen, appendix, bone marrow, and underlining the mucous membranes

MALT: mucosa-associated lymphatic tissue

BALT: bronchus-associated lymphatic tissue

GALT: gut-associated lymphatic tissue

Function: Recognition of antigens and induction of adaptive immune responses. Recirculate throughout the body and infiltrate tissues.

Three main subpopulations of lymphocytes: B lymphocytes and T lymphocytes are responsible for specific immune responses, and non-B, non-T lymphocytes (e.g., NK [natural killer] cells) are involved in innate immune responses to viruses and tumor cells. Distinguished by surface molecules called cluster of differentiation (CD) antigens (or CD markers).

B Lymphocytes:

Formation: B cells develop in the bone marrow in humans and when mature migrate to peripheral tissues. Make up 5–15% of circulating lymphocytes.

Function: Secrete antibodies for specific immune responses to extracellular microorganisms. Molecules called immunoglobulin (IG) on B cells' surface bind soluble antigens. On any B cell these IG receptors are identical in structure and bind only one type of antigen.
Plasma cells: Most mature B lymphocytes. Antibodies or immunoglobulin are found in the plasma, the liquid part of the blood, so specific immunity mediated by B cells is historically called humoral immunity.
Monoclonal antibodies: Produced by the daughter cells of one B cell.

T Lymphocytes

Formation: Migrate from the bone marrow in the fetus and childhood to the thymus, where they mature and then migrate to the lymphatic tissue. Make up 70–80% of circulating lymphocytes.
Function: Immune reactions such as graft rejection, graft-versus-host disease, contact skin sensitivity, and delayed hypersensitivity reactions. Also help regulate the immune response. Can recognize and bind to specific antigens only if antigen is linked to a self-molecule on another cell. Particularly effective for eliminating intracellular pathogens, such as cells infected with a virus.

T-helper lymphocytes: One of the four populations of T-cells, the T4 cell is called T-helper/inducer lymphocyte because it secretes cytokines called lymphokines that stimulate the growth and differentiation of B lymphocytes or activate macrophages. Lymphokines also induce the generation of cytotoxic T lymphocytes. Human immunodeficiency virus (HIV) binds to CD4 molecules expressed on T-helper cells causing their demise and disabling the immune system. T-helper lympho-

cytes can be divided into subpopulations (e.g., TH0, TH1, TH2) based on the types of lymphokines secreted.

Cytotoxic T cells: Release a variety of mediators that cause lysis of the target cell. Express CD8 markers.

Suppressor T cells: Inhibit or down-regulate both T- and B-cell immune reactions and are responsible for tolerance to self.

Other lymphocytes: Null, natural killer, killer, lymphokine activated killer (LAK), and tumor infiltrating lymphocytes (TIL) cells. May represent more mature forms of other lymphocytes, which have lost some markers and gained others.

Null cells: Lack both T- and B-cell markers.

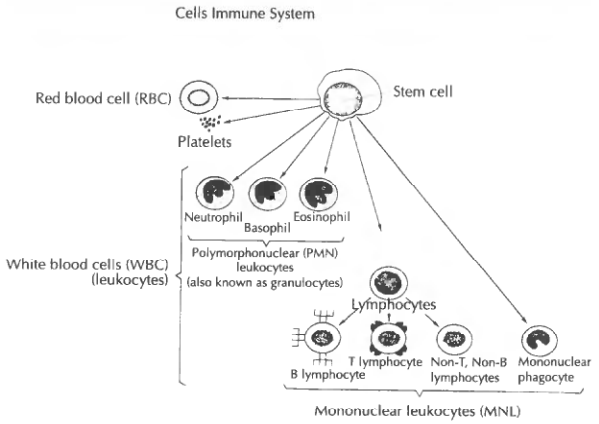
Natural killer cells: Large lymphocytes with membrane-bound granules containing hydrolytic enzymes. They make up 15% of circulating lymphocytes. NK cells can destroy tumor cells without prior exposure and are not MHC-restricted. They destroy tumors by direct contact and release of perforins, molecules that form doughnut-shaped pores in the target cell membrane. Killer cells also destroy target cells by *antibody-dependent cell-mediated cytotoxicity (ADCC).* When antibodies on the surface of killer cells bind to the tumor antigens, cytotoxic enzymes are released, destroying the tumor cells. NK cells have potent antitumor activity early in tumor development and prevent metastasis.

Lymphokine activated killer (LAK) cells: Destroy tumor cells more efficiently than normal lymphocytes.

Tumor-infiltrating lymphocytes (TIL): Isolated from the tumor and are specific for killing tumor cells derived from the host.

For a review of cells of the immune system, see Figure 2.3.

Figure 2.3 Cells of the Immune System



Source: Reprinted with permission from Gallucci, B. B., and D. McCarthy. 1995. "The Immune System." In P. Rieger (ed.), *Biotheraphy: A Comprehensive Overview.* Boston: Jones and Bartlett.

HOW DOES THE SPECIFIC IMMUNE RESPONSE WORK?

The type of immune response depends on the antigen, which lymphocytes are activated, and the characteristics of the individual. The way the antigen is recognized determines which responses occur.

- **B-Cell Responses**

  Activation of B Lymphocytes: Receptors on the surface of B cells bind with matching antigen, which is then engulfed and digested by the B cell. A piece of the antigen, bound to protein (an MHC class II molecule), is then presented on the surface to a mature T-helper cell. The T-helper cell is then stimulated to release interleukins that transform the B-cell into antibody-secreting plasma cells. When released into the bloodstream, anti-

bodies lock onto matching antigens. The antigen-antibody complex is then eliminated by the complement cascade or by the liver and the spleen.

Immunoglobulins

Definition: Another name for antibodies, which are proteins that bind to an antigen, causing it to lyse, precipitate out, or be phagocytized.

Five classes: IgG, IgM, IgA, IgD, and IgE

IgM: Antibody that is formed first. It is a large molecule composed of five monomers and is efficient in agglutinating (causes clumping) viruses.

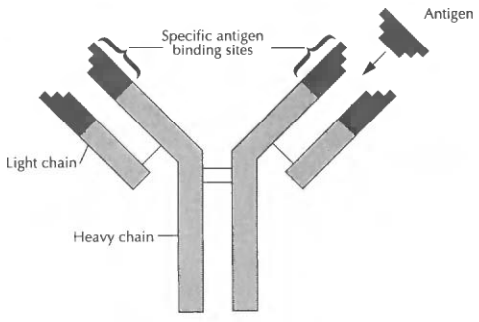
IgA: Found primarily in secretions, it helps prevent antigens from entering the bloodstream.

IgG: Present in highest concentration in the plasma and is responsible for most antibody reactions in adults. It is secreted in the secondary response and is passed from a mother to the fetus.

IgE: Present in allergic reactions and parasitic infections. In tissues it is bound to the surface of mast cells.

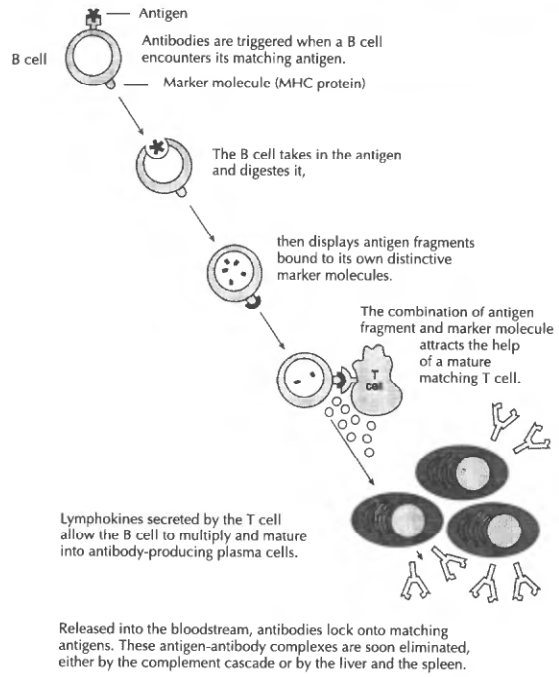
See Figures 2.4 and 2.5 and Table 2.1.

Figure 2.4 Antibody Structure



Source: From Chiras, D.D. 1995. *Human Biology: Health, Homeostasis, and the Environment* 3d ed. (Jones and Bartlett).

Figure 2.5 Activation of B Cells to Produce Antibody



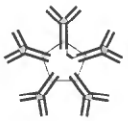
Source: From Shindler; L. 1992. Understanding the Immune System. NIH pub. no. 92-3229. Bethesda, MD: U.S. Department of Health and Human Services, June 1992, p. 12.

Primary and Secondary Responses: The first response takes longer to develop and is not as specific or as sustained as a secondary response.

Complement: A system that is a series of about 20 plasma proteins that act as a bridge between a specific antibody response and a nonspecific inflammatory response. Complement proteins circulate as proenzymes or inactive enzymes. When the complement cascade is triggered, often by an antigen-antibody complex, the proteins become active in a series of enzymatic reactions that resemble the clotting cascade.

The end product is the membrane attack complex, which forms a doughnut-shaped channel in the membrane of the target cell on which the antibody-antigen complex is attached, thus enabling lysis of the cell.

Table 2.1 Types and Functions of the Immunoglobulins

Class	Location and Function	
IgD	Monomer	Present on surface of many B cells, but function uncertain; may be a surface receptor for B cells; plays a role in activation of B cell
IgM	 Pentamer	Found on surface of B cells and in plasma; acts as a B-cell surface receptor for antigen, secreted early in primary response; powerful agglutinating agent
IgG	Monomer	Most abundant immunoglobulin in the blood plasma; produced during primary and secondary response; can pass through the placenta, entering fetal bloodstream, thus providing protection to fetus
IgA	Dimer	Produced by plasma cells in the digestive, respiratory, and urinary systems, where it protects the surface linings by preventing attachment of bacteria to surfaces of epithelial cells; also present in tears and breast milk; protects lining of digestive, respiratory, and urinary systems
IgE	Monomer	Produced by plasma cells in skin, tonsils, and the digestive and respiratory systems; responsible for allergic reactions, including hay fever and asthma

Source: From Chiras, D.D. 1995. *Human Biology: Health, Homeostasis, and the Environment.* 3d ed. (Jones and Bartlett).

- **T-Cell Responses**

The T cell is responsible for cell-mediated immunity. T cells are also responsible for immunoregulation. T-cell responses can be broadly divided into the cytotoxic response and the T-helper response.

Activation of T cells: After a macrophage internalizes and processes an antigen, it presents an antigen fragment on its surface in conjunction with class II proteins to the helper T cell. Cytokines secreted by the macrophage help the T cell to mature. The activated T cell then secretes additional lymphokines that attract other immune cells to the area, activate cytotoxic T cells, and cause the growth of more T-helper cells.

T-Helper Cell Responses: The T-helper response causes a delayed hypersensitivity reaction, the prototype of which is the positive *PPD* reaction. The results of the PPD test are read after 36 to 72 hours.

Cytotoxic T-Cell Responses: The cytotoxic T-cell response requires physical contact between a cytotoxic T cell (CD8 lymphocyte) and a target cell. CD8 cells target cells with MHC class I antigens on their surfaces. Almost every cell can be killed by cytotoxic T cells.

See Figure 2.6.

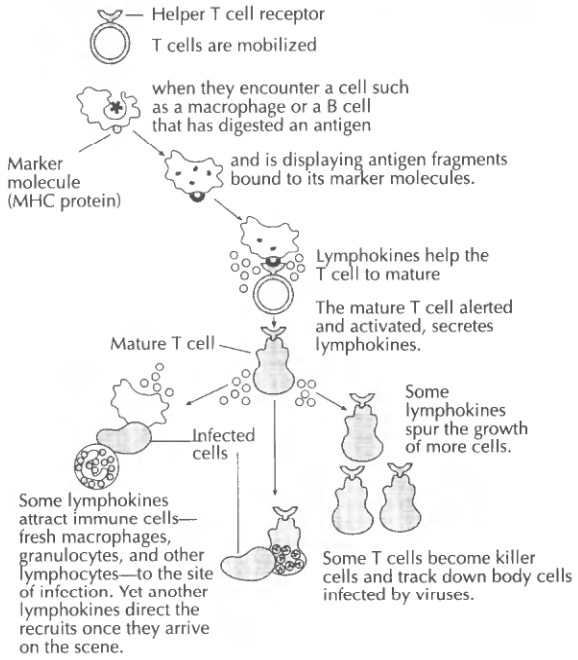
HOW DOES THE IMMUNE SYSTEM PROTECT AGAINST CANCER?

Tumor Immunology

To understand the immune responses to tumors, infections, and transplantation, one must first understand tolerance to self-molecules.

- *Immune surveillance:* The immune surveillance theory holds that (1) all individuals form tumor cells; (2) not everyone develops a malignancy; and (3) the immune system prevents the development of tumors. This theory implies that tumors have antigens that under appropriate circumstances can be identified by the immune system.

Figure 2.6 Overview of Cellular Immunity



Source: From Shindler, L. 1992. Understanding the Immune System. NIH pub. no. 92-3229. Bethesda, MD: U.S. Department of Health and Human Services, June 1992, p. 13.

One way to study tumor rejection and tumor-associated transplantation antigens is to inject nonviable tumor cells (obtained from another animal of the same inbred line) into an animal as a vaccine. When the animal is later given live tumor cells, it is able to reject the tumor. A control animal without prior exposure to the vaccine is unable to reject the live tumor cells.

- *Tumor-associated antigens:* Genetic changes occur during the process of carcinogenesis that lead to the expression of altered proteins on the surface of a cell. These altered proteins can potentially be recognized by the immune system and may become a target for chemotherapy or biological agents. Very few antigens in humans are associated exclusively with malignancy. Most antigens are also present in other pathologic states or in the fetus. Those found in the fetus are termed *oncofetal antigens.*
- *Screening tumor progression:* Two tumor-associated antigens that are clinically useful are alpha fetoprotein (AFP), found in hepatocellular and testicular cancer, and carcinoembryonic antigen (CEA), found in gastrointestinal and breast cancers. After tumor surgery, the concentration of the oncofetal antigen usually drops. A rise in CEA might indicate a relapse.

  Monoclonal antibodies can be used to screen and observe tumor progression or to diagnose tumor type. The CD10 antigen appears in leukemic cells of 70% of children with acute lymphocytic leukemia. Tumor antigens can help determine T- or B-cell lineage and the differentiation state of leukemias. Monoclonal antibodies help determine the tissue of origin in undifferentiated tumors and help distinguish tumors of epithelial and connective tissue.
- *Immune responses to tumors:* Almost every immune response is also generated as a response to tumor cells. Probably the most protective responses are cellular responses, which involve cytotoxic T-cells, macrophages, NK-cells, and antibody-dependent cytotoxic cells. Some tumors have marked infiltrates, seen in biopsied tissue specimens, which suggest the tumor has stimulated an immune response. Sometimes a mononuclear infiltrate means a more favorable prognosis. Other clinical signs of an immune response are the waxing and waning of tumors as the immune response eliminates a tumor from one area but not another. Immune mechanisms

offer the best explanation for the rare spontaneous regression of cancer.

Cell-mediated cytotoxicity: Cytotoxic T-cells destroy malignant cells the same way they destroy cells infected by viruses. The T-cell receptor attaches to the tumor antigen; enzymes are released and the tumor cell is lysed in minutes. T-helper cells release lymphokines, which activate macrophages. The macrophages release lytic enzymes, proteases, and reactive oxygen intermediates that destroy tumor cells.

Antitumor antibodies: Injecting tumor cells into animals results in antitumor antibody production. These antibodies bind to macrophages and lead to tumor cell lysis. The binding of antibodies to tumor cells may also activate the complement system. The use of vaccines to stimulate the production of antitumor antibodies is an active area of clinical research.

Cytokines: These regulatory proteins are lymphokines if produced by lymphocytes; if produced by monocytes, they are monokines. Several cytokines have antitumor effects (for example, interferons, tumor necrosis factor, and interleukin-2). The interferons are antiproliferative agents and can increase the expression of MHC antigens. Tumor necrosis factor can directly lyse tumor cells and act in a synergistic fashion with interferon.

Tumor Escape Mechanisms

Tumors evade the immune system through several known mechanisms:

- Antigenic modulation is readily observed in animals. Antibodies form complexes with the tumor antigen and are taken into the cell. Since the antigen is lost from the tumor surface, it cannot be recognized by a cytotoxic T-cell and the tumor cell cannot be killed by it.

- According to another theory, so few cells and tumor antigens are present early in the growth of a tumor that the immune system is not stimulated. Later, there is enough tumor antigen to stimulate the immune system, but by then the tumor is too large to be controlled by an immune response.
- Cell-adhesion molecules are expressed on most body cells and help hold cytotoxic cells to a target cell before lysis ensues. As tumor cells grow, they lose these cell-adhesion molecules. Therefore, cytotoxic cells cannot bind as well to malignant cells and thus the tumor escapes surveillance.
- Class I MHC molecules on the target cell and antigen are needed for cytotoxic T-cell killing. As cells change from normal to malignant, the expression of class I MHC molecules decreases, allowing the tumor cell to escape recognition by the cytotoxic cell.
- Tumor cells may produce factors that inhibit immune responsiveness, such as prostaglandins.

AUTOIMMUNE DISEASES

Biological therapies also hold great promise for the treatment of autoimmune diseases, which affect 6% of people.

- *Definition:* When the immune system reacts against self-antigens, the ensuing state is called *autoimmunity*, the loss of self-tolerance. These diseases are classified as (1) organ-specific diseases or (2) systemic diseases. Current therapies employ drugs, plasmapheresis, lymph node irradiation, and thymectomy.
- *Self-tolerance:* Most adults have *clonal anergy*, that is, lymphocytes that can react against self-molecules do not react. This state of self-tolerance must be maintained through regulation of immune responses.
- *MHC alleles research:* Research is now being done to determine the roles of MHC antigens and T-cell receptors in autoimmune diseases. Many autoimmune diseases are associated with MHC class II genes. The

risk of developing an autoimmune disease is high for people with certain MHC alleles. Cytokines that down-regulate the immune response or antibodies that react with immune effector cells involved in autoimmune reactions are being investigated as therapeutic strategies for autoimmune disease.

SUMMARY

- The immune system is the body's defense system.
- Innate or nonspecific defenses involve such mechanisms as intact skin and mucous membranes, the acidic environment of the stomach, the cleansing effect of tears and saliva, exfoliation of the skin, and the inflammatory response.
- If innate immunity fails, adaptive immunity is enlisted. Specific immune responses recognize foreign antigens. The hallmarks of adaptive immunity are memory and specificity and their ability to react in a more specific and sustained fashion upon the second encounter with an antigen. Lymphocytes and macrophages are involved in specific immune reactions.
- The immunoglobulin receptor on the B-cell and the T-cell receptor are responsible for the recognition of an antigen.
- Histocompatibility genes control interactions among cells of the immune system. These genes code for molecules (MHC antigens) on cell surfaces that are recognized by T lymphocytes.
- Cytokines are powerful mediators released during immune reactions.
- According to the theory of immune surveillance, a diagnosed tumor has evaded the immune surveillance system. Under appropriate conditions the immune system should recognize tumor-associated antigens.
- T-cell responses to tumor cells resemble responses to viruses. B-cell responses also occur. Both activated macrophages and natural killer cells can lyse tumor cells.

- Biological proteins currently being used for cancer treatment include cytokines such as interferons, interleukins, hematopoietic growth factors, and tumor necrosis factor and monoclonal antibodies.
- In the future, biologicals may be used to control autoimmune diseases.

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CHAPTER 3

THE INTERFERONS

WHAT ARE THE INTERFERONS?

The interferons (IFNs) are a family of protein and glycoprotein (protein molecule with a sugar attached) hormones with a wide variety of biological effects.

Discovery:

- In 1957 by Isaacs and Lindenmann, two virologists
- Named a protein produced by virally infected cells "interferon" because it protected other cells from attack by virus

Subtypes:

- Three major subspecies exist: alpha (α), beta (β), and gamma (γ)
- IFN-α is produced primarily by leukocytes after exposure to B-cell antigens, viruses, foreign cells, or tumor cells.
- Interferon-β is produced primarily by fibroblasts after exposure to viruses or foreign nucleic acids.
- Interferon-γ is produced primarily by T lymphocytes after stimulation with T-cell mitogens, specific antigens, or interleukin-2.

Interferons are classified as either type I or type II; the two types differ in structure and in their interaction with cell surface receptors. Type I IFNs are more effective in inducing an antiviral state in cells, whereas type II IFNs are more associated with the proper functioning of the immune system. Type I IFNs include the subtypes IFN-α, IFN-β; and type II includes IFN-γ.

HOW DOES INTERFERON WORK?

The precise physiologic role of each subtype of interferon remains unclear. Each possesses numerous biological effects. The exact mechanism of action for the use of IFN in different diseases is still not known, but it most likely differs between diseases and possibly even between patients. These biological effects include:

Antiviral Effects

- The IFNs have high antiviral activity and are protective against DNA and RNA viruses.
- When a cell is infected with a virus, it releases interferon. The IFN binds to receptors on other cells, which then produce enzymes to regulate viral protein synthesis.

Intercellular Protein Changes

- An IFN molecule binds to a cell-surface receptor and is internalized and then degraded. IFN-α and IFN-β use the same cell-surface receptor, whereas IFN-γ interacts with a different receptor.
- Anticancer activity may result from the induction (stimulated production) of intracellular proteins, enhancement of immune effector cells, and changes in cell-surface structures.
- Two enzymes play major roles: 2'-5'-oligoadenylate synthetase, which affects RNA transcription and translation, and the protein kinases, which inhibit peptide chain initiation.

- IFN causes an increase in human leukocyte antigen expression and also an increase in the number of tumor-associated antigens expressed on the cell's surface. This may help make cancer cells more recognizable by the immune system.

Antiproliferative Effects

- The IFNs have antiproliferative effects on tumor cells.
  - Demonstrated in: Burkitt's lymphoma, lymphocytic lymphoma, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and multiple myeloma.
  - Studies suggest that IFN-α inhibits cells of hematopoietic origin more than either IFN-β or IFN-γ.
- Nondividing tumor cells may have increased sensitivity to the antiproliferative activity of IFN.
  - IFN causes extension of all phases of the cell cycle, and prolongation of overall cell generation time. This is termed a "cytostatic" effect.

Immunomodulatory Activity

- A variety of changes in the immune system have been described:
  - IFN recruits pre–natural killer (NK) cells.
  - IFN enhances the cytotoxic activity of activated NK cells.
  - Both the dose and the route of administration of IFN affect NK cell activity (i.e., lower dosages may result in greater NK cell activity).
  - IFN-γ, more than IFN-α or IFN-β, seems to enhance macrophage activity (e.g., phagocytosis).
  - IFN may inhibit the expression of oncogenes.

Differentiation

- Interferons have shown a variety of effects on the differentiation of cells.

The effects on differentiation may contribute to the antineoplastic effect of IFN.

HOW IS INTERFERON MADE?

In the early 1970s, Cantell and coworkers in Finland developed a technique to produced IFN-α from donated human white blood cells stimulated by virus. This method was costly and time consuming, and it resulted in the production of only small amounts of impure product. The birth of recombinant DNA technology in 1981 allowed for the production of large amounts of purified IFNs of all subtypes. This facilitated large-scale clinical trials to evaluate the efficacy of IFN in the treatment of cancer and other diseases.

See Table 3.1 for a listing of the interferon types in clinical use today.

Table 3.1 Interferon Types in Clinical Use

Type	Subtype	Manufacturer
Alpha (α)	Recombinant IFN-alfa-2a	Roche Laboratories
	Roferon®-A	
	Recombinant IFN-alfa-2b	Schering-Plough
	Intron® A	
	Interferon alfacon-1	Amgen Inc.
	Infergen®	
	Interferon alfa-n3, human leukocyte–derived	Interferon Sciences, Inc.
	Alferon® N	
Beta (β)	Recombinant IFN-beta-1b	Chiron Corporation (manufacturer)
	Betaseron®	Berlex Laboratories (distributor)
	Recombinant IFN-beta-1a	
	Avonex®	Biogen
Gamma (γ)	Recombinant IFN gamma	Genentech
	Actimmune®	

Adapted with permission from Moldawer, N. P., and R. A. Figlin. 1995. "The Interferons." In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

WHICH DISEASES ARE TREATED WITH INTERFERON?

After numerous years and clinical trials, the IFNs have now been approved for treatment of 10 diseases, with the majority of approvals in cancer care. IFN has regulatory approval for viral diseases such as condylomata acuminata (genital warts), hepatitis C, and hepatitis B. Chronic granulomatous disease, an inherited immune disease, is characterized by infections of the skin, lymph nodes, liver, lungs, and bone. Treatment with IFN-γ led to a 70% reduction of infections. Multiple sclerosis, a common neurologic disease that causes severe disability, is treated with IFN-β. IFNs are now licensed in more than 40 countries.

CLINICAL EXPERIENCE: INTERFERON-α

The following overview presents diseases in which IFN has regulatory approval or major clinical benefits have been seen in clinical trials.

Hematologic Malignancies and Lymphomas

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a rare, chronic lymphoproliferative disorder affecting mostly middle-aged men. Its features include splenomegaly, pancytopenia, and irregular projections on lymph cells in bone marrow, peripheral blood, and reticuloendothelial system.

- Traditional therapy: splenectomy.
- In 1984, IFN-α was used first to treat HCL.
- IFN treatment of HCL leads to a high overall response rate (80%), with normalization of peripheral blood counts but few complete bone marrow remissions (<5%).
- Interferon treatment lasts about 12 months; patients experience only minor toxic effects.

Newer therapies for HCL are now used more frequently than IFN.

- Treatment of HCL with pentostatin yields a higher percentage of complete remissions.
- Pentostatin (Nipent®) is now approved by the FDA for the treatment of IFN-α refractory HCL.
- The FDA approved cladribine (Leustatin®) for the treatment of HCL in 1993.
- Cladribine, or 2-CdA, is a chlorinated purine nucleoside that is incorporated into DNA and ultimately results in DNA strand breakage.
- Single 7-day course of treatment.

Myeloproliferative Disorders

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is characterized by the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22. The disease occurs in three phases: a chronic phase characterized by increased granulocytes with normal cellular maturation; an accelerated phase characterized by increased peripheral blasts and basophils; and an acute phase characterized by more than 30% blasts in the marrow or peripheral blood. Blastic transformation precedes acute leukemia and is uniformly fatal.

- Traditional treatment with single-agent hydroxyurea or busulfan.
- Neither hydroxyurea or busulfan suppresses the positive Philadelphia (Ph1) chromosome nor prevents progression to blast crisis.
- A significant number of patients (>50%) have achieved a hematologic complete remission after treatment with IFN-α.
- The Ph1 chromosome has been suppressed to varying degrees in 35–40% of patients on IFN-α.

Approval for the treatment of chronic phase CML in 1995.

Median response time is 12 months.

Essential Thrombocythemia and Polycythemia Vera

Essential thrombocythemia is characterized by an increase in circulating platelets. In low doses, IFN-α reduces platelet counts. Also, patients with polycythemia treated with IFN had reductions in the number of phlebotomies needed to reduce platelet counts. Doses of 3 to 5 MIU/m² three times weekly are well tolerated. Patients with these disorders survive long periods, but they are unlikely to tolerate IFN for prolonged periods.

B-Cell Malignancies

Multiple Myeloma

Multiple myeloma is characterized by uncontrolled proliferation of malignant plasma cells. Early trials showed that IFN therapy affected abnormal serum proteins and modified this disease in some patients. Recombinant IFN-α produces response rates of 10 to 20% as single agent treatment in patients with myeloma. However, IFN-α does not have a significant impact overall when used as a single agent. Several strategies have now been investigated for the treatment of multiple myeloma with IFN-α.

Maintenance therapy with IFN-α following chemotherapy has demonstrated improved response duration and median survival. Randomized clinical trials continue to evaluate the role of IFN-α in combination with chemotherapy as induction therapy for multiple myeloma, or as maintenance therapy.

Non-Hodgkin's Lymphoma

As a single agent, IFN-α has shown efficacy in patients with lymphoma, with the majority of successes seen in patients with low-grade lymphomas. Patients previously treated with chemotherapy or radiation have even

responded well to IFN-α. Both low-dose and high-dose therapy have been used, although the latter is generally poorly tolerated. Data from randomized clinical trials have demonstrated that IFN-α adds to the treatment of follicular lymphoma either when combined with anthracycline containing chemotherapy regimens or as long-term maintenance therapy.

In 1997, IFN-alfa-2b was approved by the FDA for use in combination with CHOP (cyclophosphamide, adriamycin, vincristine and prednisone)–like regimens in patients with advanced low-grade follicular non-Hodgkin's lymphoma.

Cutaneous T-Cell Lymphomas

Cutaneous T-cell lymphomas are non-Hodgkin's lymphomas characterized by malignant helper T cells. They present with skin infiltration and an indolent clinical course.

Effective therapies are topical mechlorethamine, psoralen plus ultraviolet light, total skin electron-beam irradiation, and systemic chemotherapy. Although high response rates may be seen, remissions are difficult to maintain.

Numerous clinical trials with IFN-α have been performed with varying response rates: about 79% of previously untreated patients respond; between 45% and 70% of pretreated patients respond. It appears that a dose-response relationship exists.

Solid Tumors

In solid tumors, response rates for treatment with single-agent IFN have not been as high as for hematologic malignancies and lymphomas. However, IFN has shown significant activity, often when combined with cytotoxic chemotherapy or other biological or differentiating agents.

AIDS-Related Kaposi's Sarcoma

Kaposi's sarcoma, once a rare malignancy of the skin, is now the most frequent malignancy in male patients with acquired immune deficiency syndrome (AIDS). Although chemotherapy induces responses, it is often not used because of poor bone marrow tolerance and the risk of further immunosuppression. Radiation therapy is a choice for those with a limited number of lesions. Prognosis is poor for those with progressive disease, generally less than 6 months.

- IFN-α as single-agent therapy has demonstrated efficacy in the treatment of Kaposi's sarcoma with response rates as high as 30% in high-dose therapy. In general, a dose-response relationship exists.
- Regulatory approval was received in 1987.
- IFN-α is useful predominantly in patients with mucocutaneous disease who have limited lymphadenopathy, no history of opportunistic infections, an absence of B symptoms (fever, night sweats, cachexia, and diarrhea), and an intact immune system (T-helper cell ($CD4^+$)-count greater than 220/mm^3).

Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the most common malignancy of the kidney. Only half of patients with RCC are cured by surgery, and those with metastatic disease have a survival of about 10 months. Neither chemotherapy nor radiation plays a significant role in the treatment of RCC.

- Response rates with IFN-α as single-agent therapy are in the range of 15 to 20%.
- Responses correlate with prior nephrectomy, good performance status, a long disease-free interval, and the lungs as the main metastatic site. The duration of response averaged 6 to 10 months, with few complete remissions.

As of December 1998 no regulatory approval.

IFN-α is often used in combination with other biologics such as interleukin-2 and/or chemotherapy for the treatment of RCC.

Metastatic Melanoma

Melanoma is the most deadly type of skin cancer. It is estimated that the risk for developing melanoma will be 1 in 75 by the year 2000. When found early, surgical therapy is generally curative. However, when discovered at a more advanced stage, the outlook is less positive. The treatment of metastatic melanoma (stage IV) disease is often disappointing. Median survival is generally 5 to 6 months, with only 20% of patients surviving 1 year. Many chemotherapeutic regimens are available, but rates of response range from 15 to 40%. Few complete responses occur, and the majority are short-lived.

Clinical studies with IFN-alfa-2a or IFN-alfa-2b as a single agent have response rates between 10% and 20%.

In 1995 IFN-alfa-2b received regulatory approval for use as adjuvant therapy in patients with high-risk, resected, cutaneous melanoma.

Research continues to evaluate the use of IFN-α in conjunction with other biological agents such as interleukin-2 and/or chemotherapy.

Nononcologic Indications for Interferon-α Therapy

Hepatitis

Chronic viral hepatitis is the primary cause of serious liver disease in the world and is now the primary reason for liver transplantation in adults. It is also associated with the development of hepatocellular carcinoma and cirrhosis. Chronic disease is most frequently associated with hepatitis virus B, C, and D. Prior to 1989, most cases of hepatitis C were called hepatitis non-A, non-B

because the causative agent had yet to be identified.

In chronic hepatitis B infection, 30–50% of patients will respond to IFN-α therapy. Remissions are long and often associated with loss of viral hepatitis B surface antigen. Treatment with IFN-α for at least 6 months slows the disease and may often result in long-term remission.

IFN-α now has regulatory approval for the treatment of hepatitis B and C.

Recombinant consensus IFN (IFN alfacon-1) gained approval for the treatment of hepatitis C in 1997.

On March 26, 1997, the National Institutes of Health convened a consensus conference on chronic hepatitis C infection, which concluded that initial therapy of chronic hepatitis C infection should consist of a 12-month regimen of IFN-α therapy in order to reap the greatest potential benefits of treatment. Hepatitis C currently affects an estimated 4 million Americans and puts them at risk of developing liver cancer and cirrhosis of the liver. Preliminary data presented to the consensus conference panel indicate that IFN-α therapy is cost-effective, falling well within the range of costs per adjusted-life-year gained of generally accepted therapies (e.g., agents for hypertension).

Condylomata Acuminata

- Condylomata acuminata, also known as genital warts, is caused by the human papillomavirus (HPV).
- HPV is contagious and is usually transmitted by direct sexual contact.
  - *Women:* warts usually appear on the external genitalia, but they may also occur in the vagina and on the cervix.
  - *Men:* warts generally appear on the penis.
- Usually painless, but some people may have itching, burning, or slight bleeding from these areas.
- Time between exposure to the virus and the appearance of warts is unknown, ranging from several weeks to several years before symptoms occur.

- HPV infection has been associated with an increased risk of cervical cancer. Annual Pap smears are recommended.
- Treatment
  - Freezing of the tissue (cryosurgery)
  - Electrical cautery or lasers
  - Chemical treatment with podophyllin or trichloroacetic acid (TCA)
  - IFN-α

CLINICAL EXPERIENCE: INTERFERON-β

The effects of interferon-β are similar to those of IFN-α: antiviral, immunomodulatory, and antiproliferative. The use of IFN-β in cancer treatment remains investigational.

Multiple Sclerosis

Multiple sclerosis (MS) is a neurologic disease of unknown etiology, although an immunologic basis has been suggested. Results of trials with IFN-α or IFN-β have demonstrated reduced exacerbations and disease activity in patients receiving one of these agents. Using IFN-beta-1b in 372 patients with relapsing-remitting MS resulted in significant reductions in exacerbations, severity, and accumulation of abnormalities seen by magnetic resonance imaging. Therapy was generally well tolerated. The mechanism of action is unknown. The FDA has approved IFN-β for use in patients with MS.

CLINICAL EXPERIENCE: INTERFERON-γ

IFN-γ shares many properties with type I IFNs, but it demonstrates greater antiproliferative activity and is a more potent immune stimulator of monocytes. The use of IFN-γ in the treatment of cancer remains investigational, with modest activity noted in biologically active doses in renal cell cancer.

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is an inherited abnormality of certain cells of the immune system that "ingest" bacteria and kill them (phagocytic cells); the abnormality results in chronic infection by certain types of bacteria. Transmitted as a sex-linked recessive trait, CGD almost universally affects males, although it is possible for a woman to have two affected X chromosomes and subsequently develop CGD. In this disease, the inability of phagocytic cells to kill certain bacteria and fungi leads to long-term (chronic) and repeated (recurrent) infections appearing in the first years of life. Milder forms may appear in adolescence. In 1990 Genentech received FDA approval to market Actimmune® (Interferon gamma-1b) for the treatment of CGD.

REGULATORY APPROVALS

For a summary of regulatory approvals in the United States for the IFNs, see Table 3.2.

Table 3.2 Interferon Therapy Approved by the FDA

Disease	Agent
Hairy cell leukemia	IFN-α
Kaposi's sarcoma in AIDS	IFN-α
Chronic myelogenous leukemia	IFN-α
Non-Hodgkin's lymphoma	IFN-α
Melanoma	IFN-α
Hepatitis B	IFN-α
Hepatitis C	IFN-α
Condylomata acuminata	IFN-α
Multiple sclerosis	IFN-β
Chronic granulomatous disease	IFN-γ

Adapted with permission from Moldawer, N. P., and R. A. Figlin. 1995. "The Interferons." In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

WHAT ARE THE SIDE EFFECTS OF INTERFERONS?

The toxicity of IFN depends on the dose, the route of administration, the schedule, and the administration of concomitant therapies such as chemotherapy or interleukin-2. See Table 3.3 for a summary of common IFN-associated side effects.

Table 3.3 Toxicity Profile of Interferon

Frequent	Less Frequent
Acute	
Fever	Nausea
Chills	Vomiting
Malaise	Diarrhea
Headache	
Anorexia	
Chronic	
Fatigue	Mild neutropenia
Weight loss	Elevated liver enzymes
Alopecia (hair thinning, mild)	Thrombocytopenia
	Central nervous system
	Depression
	Confusion
	Mental slowing
	Mild proteinuria

Adapted with permission from Moldawer, N. P., and R. A. Figlin. 1995. "The Interferons." In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

- **Flulike** symptoms are almost universal following initial injections; the appearance of *tachyphylaxis* (gradual lessening over time of side effects) depends on the type of IFN used, the dose, the route, and the schedule. Symptoms are controlled with acetaminophen given prior to IFN therapy and every 4 to 6 hours with the initial injections.
- **Fatigue** is a common side effect. It may be dose-limiting and is most commonly seen at moderate to higher doses. Nursing management includes assessment, patient education, and interventions targeted toward adequate nutrition and hydration, management of coexisitng symptoms such as anemia and pain, and

balancing activity and rest. Giving IFN in the evening may minimize the effects of both flu-like symptoms and fatigue.

- **Anorexia** is also seen commonly with IFN therapy. Patients often report that they have lost the desire to eat or that food tastes different. Nursing management includes assessment, especially for weight loss of more than 10% of body weight, small frequent meals, caloric supplements, and experimentation to determine which foods remain appealing.
- **Mental status changes** are seen frequently with IFN and are evidenced as cognitive dysfunction (trouble with calculations, forgetfulness, slowed thinking), depression, anxiety, and sexual dysfunction. Important nursing interventions are a baseline assessment and periodic assessment for the development of such toxicity, and patient education. Medical management with antidepressive medications may be helpful. Interventions to promote patient safety are also important.
- **Hematologic effects** include leukopenia, anemia, and thrombocytopenia. White blood cell counts are lowered by 40 to 60% but rebound rapidly after therapy stops. Infectious sequelae do not increase in IFN-induced leukopenia; granulocytopenia is rarely dose-limiting. Anemia (not severe) occurs with chronic therapy. Mild thrombocytopenia occurs in 5 to 50% of patients. Patients treated with chemotherapy or radiation are more susceptible to these side effects.

QUICK SUMMARY

AGENT: Interferon alfa-2a (Roferon®-A)
Manufacturer: Roche Laboratories, Nutley, N.J.

Roferon® is a highly purified protein, biosynthetic human interferon produced by recombinant DNA technology using genetically engineered *Escherichia coli (E. Coli)* bacterium.

WEBSITE: www.roche.com

First approved by FDA in 1986.

REGULATORY APPROVALS

Disease	*Dosing*
Hairy cell leukemia	Induction: 3 MIU daily SC or IM injection for 16 to 24 weeks Maintenance: 3 MIU three times per week (TIW)
Kaposi's sarcoma	Induction: 36 MIU daily IM or SC injection Maintenance: 3 MIU three times per week (TIW) (Gradual dose escalation starting from 3 MIU to 9 MIU to 18 MIU, then to 36 MIU, may help decrease initial toxicity)
Chronic myelogenous leukemia (CML)	9 MIU daily by SC or IM injection (Gradual dose escalation starting from 3 MIU for 3 days to 6 MIU for 3 days

	to 9 MIU may help decrease initial toxicity)
Hepatitis C	3 MIU administered SC or IM injection for 12 months (48 to 52 weeks), three times per week.

PHARMACOKINETICS

Absorption: Maximum serum concentration for IM or SC injection occur 3 to 8 hours after administration. After IV use, concentrations peak at the end of the infusion.

Half-life: Elimination half-lives are approximately 2 to 3 hours.

Metabolism/excretion: It is believed that proteolytic degradation occurs in the kidney, where most of the drug is catabolized.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

Hematologic survey, routine blood chemistries to include liver function studies, assay for presence of hepatitis virus (with hepatitis).

ADMINISTRATION

Vial Sizes

Single-use injectable solution

3MIU per mL; 6MIU per mL; 9MIU per mL; 36 MIU per mL

Multidose injectable solution 9MIU;

18 MIU (use within 30 days once vial is entered)

Sterile powder with diluent 18 MIU.

Roferon®-A *continued*

Store in the refrigerator at 2° to 8°C.
Do not freeze. Do not shake.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Should not be used in patients with a history of severe psychiatric disorders, and therapy should be discontinued in patients who develop severe depression, suicidal ideation, or other severe psychiatric disorders. Should be used with caution in patients with a history of cardiac disease or debilitating medical conditions such as pulmonary disease or diabetes mellitus prone to develop ketoacidosis; in patients with abnormally low peripheral blood cell counts; in patients who are receiving agents known to cause myelosuppression; and in patients with a history of endocrine disorders. Exacerbation of autoimmune disease has been reported. Monitor renal and hepatic function.

RESOURCES FOR PATIENTS

The new Roferon®-A HCV Patient Support System is designed to educate patients about the side effects of therapy with Roferon®-A. The kit contains an educational brochure and a Spanish- and English-language video; a booklet, "Frequently Asked Questions about Hepatitis C"; and a workbook/diary so that patients can monitor their responses to therapy.

PATH (Partners Allied in the Treatment of Hepatitis) Compliance Kit can be obtained by calling 1-800-LAROCHE.

RESOURCES FOR PROFESSIONALS

1-800-526-6367	1-800-7ROFERON
Option 1: Product use line	Can request a videotape, booklet, and personal care kit (syringes, cooler, etc.) specific to Roferon®-A and suitable for patients or professionals.
Option 2: Adverse drug reaction, safety issues line	
Option 3: Report a product complaint line	
Option 4: Medical Needs Program*	

* Physician must submit request for application for a patient with financial need for covering drug expenses.

QUICK SUMMARY

AGENT: Interferon-alfa-2b, recombinant (Intron® A)
Manufacturer: Schering Corporation, Kenilworth, N.J.

Intron® is a highly purified protein, biosynthetic human interferon produced by recombinant DNA technology using genetically engineered *E. coli* bacterium.

WEBSITES:
For product information:
www.sp-research.com
For corporate information:
www.schering-plough.com

First received regulatory approval in 1986.

REGULATORY APPROVALS

Disease	*Dosing*
Hairy cell leukemia	2 MIU/m^2 SC or IM injection three times per week (TIW)
Kaposi's sarcoma	30 MIU/m^2 SC or IM injection three times per week (TIW)
Hepatitis B	30 to 35 MIU/week SC or IM daily as either 5 MIU daily or 10 MIU three times per week for 16 weeks

Hepatitis C	3 MIU SC or IM injection three times per week (TIW)
Condylomata acuminata	10 MIU/1.0 cc Inject 0.1 cc per lesion three times per week for 3 weeks
Melanoma	Induction: 5 days/week for 4 weeks 20 MIU/m^2 IV (Place appropriate dose of reconstituted IFN into a 100-mL bag of 0.9% sodium chloride injection, USP. Infuse over 20 minutes). Maintenance: 10 MIU/m^2 SC or IM injection three times per week (TIW) for 48 weeks
Follicular lymphoma	5 MIU SC injection three times per week for up to 18 months in conjunction with an anthracycline-containing chemotherapy regimen

PHARMACOKINETICS

Absorption: Maximum serum concentrations for IM or SC injection occur 3 to 12 hours after administration. After IV use, concentrations peak at the end of the infusion.

Half-life: Elimination half-lives are approximately 2 to 3 hours.

Metabolism/excretion: It is believed that proteolytic degradation occurs in the kidney, where most of the drug is catabolized.

Intron® A *continued*

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

Hematologic survey, routine blood chemistries to include liver function studies (especially important during induction phase for malignant melanoma), assay for presence of hepatitis virus (with hepatitis).

ADMINISTRATION

Vial Sizes

Solution:

- Single-use injectable solution 3MIU per 0.5 mL; Pak-3 (six 3-MIU vials, syringes, and alcohol)
- Single-use injectable solution 5 MIU per 0.5 mL; Pak-5 (six 5-MIU vials, syringes, and alcohol)
- Single-use injectable solution 10 MIU per 1.0 mL; Pak-10 (six 10-MIU vials, syringes, and alcohol)
- Multidose injectable solution 18 MIU; 25 MIU (use within 30 days once vial is entered)
- 3 MIU multidose pen (6 doses × 3 MIU/0.2 mL)
- 5 MIU multidose pen (6 doses × 5 MIU/0.2 mL)
- 10 MIU multidose pen (6 doses × 10 MIU/0.2 mL)

Sterile Powder:

- Sterile powder with diluent 3 MIU; Pak-3 (six 3-MIU vials, six syringes of diluent)
- Sterile powder with diluent 5 MIU, 10 MIU, 18 MIU, 25 MIU, 50 MIU
- Swirl gently to mix. *Do not shake.*

Combinations:

For use in the treatment of hepatitis C:

Rebetron™ 1200/Pak-3 combination therapy
- 84 Rebetol® 200-mg capsules
- Intron® A 3-MIU pack (6 vials of 3-MIU/0.5 mL)

Rebetron™ 1000/Pak-3 combination therapy
- 70 Rebetol® 200-mg capsules
- Intron® A 3-MIU pack (6 vials of 3-MIU/0.5 mL)

Rebetron™ 600/Pak-3 combination therapy
- 42 Rebetol® 200-mg capsules
- Intron® A 3 MIU pack (6 vials of 3-MIU/0.5 mL)

Rebetron™ 1200/MDV
- 84 Rebetol® 200-mg capsules
- Intron® A 18-MIU pack (6 doses of 3-MIU/0.5 mL)

Rebetron™ 1000/MDV
- 70 Rebetol® 200-mg capsules
- Intron® A 18-MIU pack (6 doses of 3-MIU/0.5 mL)

Rebetron™ 600/MDV
- 42 Rebetol® 200-mg capsules
- Intron® A 18-MIU pack (6 doses of 3-MIU/0.5 mL)

Rebetron™ 1200/3-MIU pen
- 84 Rebetol® 200-mg capsules
- Intron® A 3-MIU multidose pen (6 doses × 3 MIU/0.2 mL)

Rebetron™ 1000/3-MIU pen
- 70 Rebetol® 200-mg capsules
- Intron® A 3-MIU multidose pen (6 doses × 3 MIU/0.2 mL)

Intron® A *continued*

Rebetron™ 600/3-MIU pen

42 Rebetol® 200-mg capsules

Intron® A 3-MIU multidose pen (6 doses × 3 MIU/0.2 mL)

Store in the refrigerator 2° to 8°C.
Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Should not be used in patients with a history of severe psychiatric disorders, and therapy should be discontinued in patients who develop severe depression, suicidal ideation, or other severe psychiatric disorders. Should be used with caution in patients with a history of cardiac disease or debilitating medical conditions such as pulmonary disease or diabetes mellitus prone to develop ketoacidosis; in patients with abnormally low peripheral blood cell counts; in patients who are receiving agents known to cause myelosuppression; and in patients with a history of endocrine disorders. Exacerbation of autoimmune disease has been reported. Monitor renal and hepatic function.

RESOURCES FOR PATIENTS

Package insert available for patients.

"Crossing Bridges: Your Link to a World of Support and Caring" (pamphlet)

Crossing Bridges is a voluntary therapy compliance program available at no cost to malignant melanoma patients on INTRON® A. Designed to supplement the advice of oncologists and their nurses, the program provides patients with up-to-date medical information regarding their treatment as well as resources to help manage their treatment challenges—side effects such as depression, fatigue, nausea, and loss of appetite. The program is a research study for malignant melanoma patients who are prescribed INTRON® A.

Be in Charge: A Program to Help You Get through Intron® A Therapy

Commitment to Care Program: assistance and reimbursement program for indigent patients

Interferon information sheet

Cancer Care brochure

Melanoma Fact/Fiction Card

Patient Guide for Melanoma

Side Effects Card

www.crossingbridges.com

RESOURCES FOR PROFESSIONALS

Drug Information Service (1-800-526-4099), Monday through Friday, 9:00 A.M.–4:00 P.M. EST

Provides literature search and general product information

Intron® A *continued*

Patient Care Consultant Program

Provides nurses with specialty backgrounds for consultation and education to nurses working in doctors' offices.

QUICK SUMMARY

AGENT: Interferon alfacon-1 (Infergen®)
Manufacturer: Amgen Inc., Thousand Oaks, Calif.

Infergen® is a recombinant non–naturally occurring type 1 IFN. The 166-amino acid sequence of IFN alfacon-1 was derived by scanning the sequences of several natural IFN-α subtypes and assigning the most frequently observed amino acid in each corresponding position. Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using chemical synthesis methodology. IFN alfacon-1 is produced in *E. coli* cells that have been genetically altered by insertion of a synthetically constructed sequence that codes for IFN alfacon-1.

WEBSITE: www.amgen.com

Received regulatory approval in October 1997.

REGULATORY APPROVALS

Disease	*Dosing*
Chronic hepatitis C virus infection	9-mcg SC injection three times per week (TIW). At least 48 hours should elapse between doses.

Infergen® *continued*

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

Hematologic survey, routine blood chemistries to include liver function studies, assay for presence of hepatitis virus, triglycerides, thyroid functions.

ADMINISTRATION

Vial Sizes

Single-dose, preservative-free vials 9 mcg per 0.3 mL; or 15 mcg per 0.5 mL

Use only one dose per vial; do not reenter the vial.

Discard unused portions. Do not save unused drug for later administration.

Store in the refrigerator at 2° to 8°C.

Do not freeze. Do not shake.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Should not be used in patients with a history of severe psychiatric disorders, and therapy should be discontinued in patients who develop severe depression, suicidal ideation, or other severe psychiatric disorders. Should be

used with caution in patients with a history of cardiac disease; in patients with abnormally low peripheral blood cell counts who are receiving agents known to cause myelosuppression; and in patients with a history of endocrine disorders. Exacerbation of autoimmune disease has been reported. Monitor renal and hepatic function. Do not treat patients with decompensated hepatic disease.

RESOURCES FOR PATIENTS

Patient Center accessed through the Web site. Includes a therapy guide, called "Infergen and You," for patients taking Infergen, and the quarterly newsletter "Living Well" for patients with chronic hepatitis C.

"Safety Net® Program": Patient assistance program to help medically indigent patients with chronic hepatitis C. Accessed via the COMPASS™ Support Line at 1-888-508-8088. Ask to speak with a reimbursement specialist. Open 7 days per week, 24 hours per day.

RESOURCES FOR PROFESSIONALS

Infergen® Fact Sheet

Infergen® Prescribing Information

Resource guide for treatment with Infergen®, a link to continuing education programs for pharmacists offered by the University of Wisconsin, and "Hepatitis Care Views," a quarterly newsletter for hepatology nurses and health care professionals.

QUICK SUMMARY

AGENT: Interferon alfa-n3, human leukocyte–derived (Alferon® N)
Manufacturer: Interferon Sciences, Inc., New Brunswick, N.J.

WEBSITE: www.interferonsciences.com

Alferon® N is a sterile aqueous formulation of purified, natural, human IFN-α proteins for use by injection. It is manufactured from pooled units of human leukocytes induced by incomplete infection with an avian virus (Sendai virus) to produce interferon alfa-n3.

REGULATORY APPROVALS

Disease	*Dosing*
Condylomata acuminata	Intralesional injection 250,000 IU/wart 2×/week for up to 8 weeks. Inject into the base of each wart, preferably using an 18 gauge needle.

PHARMACOKINETICS

In a study of intralesional use of interferon alfa-n3 injection for the treatment of condylomata acuminata, plasma concentrations were below the detection limit of the assay.

SETTING: Physician's office or ambulatory clinic

DIAGNOSTIC/LABORATORY TESTS

In patients with condylomata acuminata, decreased white blood cell counts were seen approximately 11% of the time.

ADMINISTRATION

Vial Sizes

5 MIU/1.0 mL vials.
Store in refrigerator at 2° to 8°C.
Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Contraindicated in patients with hypersensitivity to human IFN-α or any component of the product and in patients who have anaphylactic sensitivity to mouse immunoglobulin, egg protein, or neomycin. Use with caution in patients with debilitating medical conditions because of flulike symptoms. Caution fertile women to use effective contraception during use.

Alferon® N *continued*

RESOURCES FOR PATIENTS

Patient Assistance Program (1-888-Alferon)

Request patient-specific product information on-line or by calling 1-888-Alferon

RESOURCES FOR PROFESSIONALS

The ALFERON Access Program™ consists of three components:

Distribution Services: a centralized distributor for wholesalers, home care agencies, pharmacies, hospitals, and physician offices

Clinical and Product Information Services: where clinicians and patients can learn more about Alferon N Injection®

Reimbursement Information Services: offers assistance with reimbursement issues

1-888-ALFERON. The ALFERON Access Program™ is staffed from 8:00 A.M. to 7:00 P.M. EST.

For additional information about the program, you can also request information via fax at 1-888-FAXXAFN.

QUICK SUMMARY

AGENT: Interferon beta-1a, recombinant (Avonex®)
Manufacturer: Biogen, Cambridge, Mass.

WEBSITE: www.biogen.com

Approved May 1996.

Avonex® is a purified, sterile, lyophilized protein product produced by recombinant DNA technology and formulated for use by injection. It is produced by mammalian cells (Chinese hamster ovary cells) into which the human IFN-β gene has been introduced. The amino acid sequence of IFN-beta-1a is identical to that of natural human IFN-β. The mechanism of action by which it exerts its actions in multiple sclerosis (MS) is not clearly understood.

REGULATORY APPROVALS

Disease	*Dosing*
Multiple sclerosis (relapsing/ remitting)	30 mcg IM once per week

PHARMACOKINETICS

Peak serum concentrations occurred between 1 and 8 hours, with an elimination half-life of 8 to 10 hours, depending on the route of administration (SC or IM).

SETTING: Primarily ambulatory

Avonex® *continued*

DIAGNOSTIC/LABORATORY TESTS

Hemoglobin, complete and differential WBC counts, platelet counts, and blood chemistries including liver function tests. Recommended prior to initiation of therapy and at periodic intervals thereafter.

ADMINISTRATION

Vial Sizes

Powder for injection, lyophilized 33 mcg (6.6 MIU). Preservative-free, Single-use vial.

Reconstitute with provided diluent 1.1 mL and swirl gently to dissolve.

AVONEX® is available in the following package configuration: Package (Administration Pack) containing 4 Administration Dose Packs (each containing one vial of AVONEX®, one 10 mL (10 cc) diluent vial, two alcohol wipes, one 3-cc syringe, one Micro Pin® vial access pin, one needle, and one adhesive bandage).

Store in the refrigerator at 2° to 8°C. If unavailable, may be stored at room temperature for up to 30 days. Following reconstitution, use as soon as possible (within 6 hours or less).

Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Contraindicated in patients with known hypersensitivity to natural or recombinant IFN-β, human albumin, or any other component of the formulations. Use with caution in patients with depression or history of depression, preexisting seizure disorders, debilitating conditions such as cardiac conditions.

RESOURCES FOR PATIENTS

Training materials: patients first receive AVONEX® Patient Instruction Materials, including a video cassette and a manual that describe the appropriate ways to store AVONEX®, prepare for injections, and administer the drug. To order AVONEX® Patient Instruction Materials, call 1-800-456-2255.

The Avonex Alliance

The Avonex Alliance was developed by Biogen as an ongoing, comprehensive support program to help people with relapsing MS, their care partners, and health care professionals work together to help manage MS with AVONEX® (Interferon beta-1a).

RESOURCES FOR PROFESSIONALS

The Avonex Support Line

A toll-free Avonex Support Line provides product information, reimbursement counseling, and information about Biogen's optional distribution and training programs. The number is 1-800-456-2255, and information is available Monday through Friday, 8:30 A.M. to 8:00 P.M. EST.

Avonex® *continued*

Biogen's Special Distribution Options

In addition to offering AVONEX® through traditional retail channels, Biogen has established two special distribution options that provide direct billing of patients' health plans (referred to as "assignment of benefits") so that patients can avoid having to pay for the drug up-front and then filing claims for reimbursement. The Avonex Pharmacy Network, a service of Olsten Health Services, provides assignment of benefits for patients wishing to pick up AVONEX® at a local pharmacy. Avonex Direct Delivery, a service of Nova Factor, provides assignment of benefits for patients who prefer the convenience of direct shipment to their home or workplace.

QUICK SUMMARY

AGENT: Interferon beta-1b, recombinant (Betaseron®)
Manufacturer: Chiron
Distributor: Berlex, Richmond, Calif.

WEBSITE: www.berlex.com

Approved July 1993.

Betaseron® is a purified, sterile, lyophilized protein product produced by recombinant DNA technology and formulated for use by injection. It is produced by bacterial fermentation of a strain of *E. coli* that bears a genetically engineered plasmid containing the gene for human IFN-β_{ser17}. The native gene is altered in a way that substitutes serine for cysteine at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids. The mechanism of action by which it exerts its actions in multiple sclerosis (MS) is not clearly understood.

REGULATORY APPROVALS

Disease	*Dosing*
Multiple sclerosis (relapsing/ remitting)	0.25 mg (8 MIU) SC every other day

PHARMACOKINETICS

Peak serum concentrations occurred between 1 and 8 hours, with an elimination half-life of 8 to 10 hours, depending on the route of administration (SC or IM). With IV administration, half-life values range from 8 minutes to 4 hours.

GENERAL PRECAUTIONS (see package insert for details)

- Contraindicated in patients with known hypersensitivity to natural or recombinant IFN-β, human albumin, or any other component of the formulations. Use with caution in patients with depression or history of depression, preexisting seizure disorders, debilitating conditions such as cardiac conditions.

RESOURCES FOR PATIENTS

Training materials: patients first receive AVONEX® Patient Instruction Materials, including a video cassette and a manual that describe the appropriate ways to store AVONEX®, prepare for injections, and administer the drug. To order AVONEX® Patient Instruction Materials, call 1-800-456-2255.

The Avonex Alliance

The Avonex Alliance was developed by Biogen as an ongoing, comprehensive support program to help people with relapsing MS, their care partners, and health care professionals work together to help manage MS with AVONEX® (Interferon beta-1a).

RESOURCES FOR PROFESSIONALS

The Avonex Support Line

A toll-free Avonex Support Line provides product information, reimbursement counseling, and information about Biogen's optional distribution and training programs. The number is 1-800-456-2255, and information is available Monday through Friday, 8:30 A.M. to 8:00 P.M. EST.

Betaseron® *continued*

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

Hemoglobin, complete and differential WBC counts, platelet counts, and blood chemistries including liver function tests. Recommended prior to initiation of therapy and at periodic intervals thereafter.

ADMINISTRATION

Vial Sizes

Powder for injection, lyophilized 0.3 mg (9.6 MIU). Preservative-free, single-use vial. Discard unused portions. Reconstitute with provided diluent 1.2 mL and swirl gently to dissolve. Use within 3 hours of reconstitution.

Store in the refrigerator at 2° to 8°C.

Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Contraindicated in patients with known hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component

of the formulations. Use with caution in patients with depression or a history of depression, preexisting seizure disorders, or debilitating conditions such as cardiac conditions.

RESOURCES FOR PATIENTS

A patient information sheet is provided with the product.

Betaseron® patient handbook

MS Pathways Program: offers comprehensive patient programs, including resource center, brochures "Caring for a Loved One with MS" and "MS Management Gets Personal," peer support groups, newsletter "Messages," reimbursement options, Betaseron® starter kit (personal journal, videotape on learning to use Betaseron®, administration supplies, patient guide "Your Guide to Starting Therapy with Betaseron®," and information regarding financial assistance.

Access above resources by calling 1-800-788-1467.

RESOURCES FOR PROFESSIONALS

www.berlex.com/healthprofs.html

Health Professionals' Forum is a dynamic section designed for health professionals such as physicians, nurses, nurse-practitioners, and pharmacists who are involved in the care and treatment of patients with MS. In this section, Continuing Medical Education (CME) and other educational programs will be offered to aid such caregivers in their professional development and in their care of MS patients.

Betaseron® *continued*

The Betaseron® Training Program

The Betaseron® Training Program provides a registered nurse to conduct a personalized training session on the administration of Betaseron® to all patients referred by their physician. In addition to the initial training session, the program includes three follow-up telephone calls to answer questions that the patient or caregiver may have and to encourage compliance with Betaseron® therapy. Physicians can refer patients to this program by calling 1-800-788-1467.

Berlex Professional Services Department, 1-800-888-4112, available between 7:30 A.M. and 5:00 P.M. PST. Offers product-related clinical information about Betaseron®.

To report adverse events caused by Betaseron® therapy, call 1-888-237-5394.

On-line MS Resource Library to order copies of recently published MS-related articles.

QUICK SUMMARY

AGENT: Interferon gamma-1b, recombinant (Actimmune®)
Manufacturer: Genentech Inc., San Francisco, Calif.

WEBSITE: www.gene.com

(Actimmune® is not listed as a product because the rights to the drug have been bought by Kinetics and it is currently in a transition phase. The only information currently available is the package insert.)

Actimmune® is a single-chain polypeptide containing 140 amino acids. It is produced by fermentation of a genetically engineered *E. coli* bacterium containing the DNA that encodes for the human protein.

REGULATORY APPROVALS

Disease	*Dosing*
Chronic granulomatous disease (to decrease frequency and severity of infections)	50 mcg/m² (1.5 MIU/m²) for patients whose body surface area is 0.5 m² or greater and 1.5 mcg/kg/dose for patients whose body surface area is ≤ 0.5 m². Administer SC three times per week (TIW)

Actimmune® *continued*

PHARMACOKINETICS

The mean elimination after IV administration was 38 minutes. After IM and SC dosing, the mean half-life was approximately 3 and 6 hours, respectively.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

In addition to tests normally required for monitoring patients with chronic granulomatous disease, it is recommended that hematologic tests including complete blood counts, differential and platelet counts, blood chemistries including renal and liver function tests, and urinalysis be done prior to initiation of therapy and every 3 months during treatment.

ADMINISTRATION

Vial Sizes

100-mcg (3 MIU) single-dose vials. Discard unused portions once vial is entered. Stable for a maximum of 12 hours at room temperature.

Store in the refrigerator at 2° to 8° C.

Do not freeze. Do not shake.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Contraindicated in patients with known hypersensitivity to natural or recombinant IFN-γ, *E. coli*–derived products, or any other component of the formulations. Use with caution in patients with depression or a history of depression, preexisting seizure disorders, or compromised CNS function or debilitating conditions such as cardiac conditions. Exercise caution when administering IFN-γ in combination with other potentially myelosuppressive agents.

RESOURCES FOR PATIENTS

A patient information sheet is provided with the product.

RESOURCES FOR PROFESSIONALS

Drug/medical information line: 1-800-448-3405; reimbursement assistance: 1-800-879-4747.

Clinical Pearls

1. Upon initiation of therapy, patients will experience flulike symptoms. The intensity and duration will vary according to the dosing schedule. Over time, patients generally develop a tolerance to these side effects, which is termed *tachyphylaxis*.
2. The need for monitoring a patient following his or her initial dose of IFN should be guided by clinical judgment and the patient's underlying medical condition.
3. Premedication should be used to lessen flulike symptoms. Acetaminophen is generally given 1 hour before injection or IV administration, and every 4 to 6 hours as needed. If this is ineffective, nonsteroidal anti-inflamatory agents (NSAIDS) are sometimes used. Check with physician prior to administration.
4. Fever may be preceded by chills and rigors. If rigors are unusually severe, meperidine is effective for symptom control.
5. Although not well substantiated through research, bedtime administration may be useful for decreasing flulike symptoms.
6. It is important that patients maintain adequate hydration, because significant fluid loss can occur following defervescence.
7. Other comfort measures include use of warm clothing, blankets, warm fluids, and visualization (e.g., thinking of a warm beach).

8. Patients should be monitored closely over the duration of therapy for chronic side effects such as fatigue, anorexia, and mental status changes. Working closely with the patient and family to design a plan of care that manages these side effects is essential.
9. Product interchange: Because of the manufacturing process, strength and type of IFN may vary for different IFN formulations; a change in brands may require a change in dosage. Therefore, physicians are cautioned not to change from one IFN product to another without considering these factors.
10. Patient and/or family education to learn medication self-administration should be instituted as soon as possible.
11. In general, patients receiving IFN-α do not experience inflammatory reactions at the injection site. Injection site reactions are seen more frequently in patients receiving IFN-β.
12. With IV administration, especially during acute flulike symptoms, nausea and vomiting may be seen more frequently. Premedication with antiemetics may be helpful.

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CHAPTER 4

THE INTERLEUKINS

WHAT ARE THE INTERLEUKINS?

The interleukins (ILs) are a family of molecules that act primarily in signaling or communicating between cells of the immune system. The main function of ILs is the *immunomodulation* and *immunoregulation* of leukocytes. Most have *pleiotropic* (more than one) function and are also produced by leukocytes. Many originally had several names, based on their biological function. Now ILs are given a numerical designation by the order in which they were identified (IL-1, IL-2, IL-3, etc.). Table 4.1 summarizes the biological activities of ILs discovered to date.

Table 4.1 Biological Activities of Interleukins

Interleukin	Biological Activities
Interleukin-I	Activates resting T cells
	Mediates inflammation
	Activates endothelial cells and macrophages
	Functions as a cofactor for hematopoietic growth factors
	Induces sleep, fever, ACTH release, acute phase response
	Enhances activity of NK cells
	Chemotactically attracts neutrophils and macrophages
	Stimulates the synthesis of lymphokines
Interleukin-2	Induces the synthesis and secretion of lymphokines
	Induces proliferation of antigen-primed T cells
	Acts as a cofactor for growth and differentiation of B cells
	Augments LAK activity
	Enhances NK activity

continued

Table 4.1 Biological Activities of Interleukins *(cont.)*

Interleukin	Biological Activities
Interleukin-3	Supports the growth of pluripotent bone marrow stem cells
	Acts as a growth factor for mast cells
	Stimulates histamine secretion
Interleukin-4	Acts as a growth factor for activated B cells
	Induces MHC class II antigens on B cells
	Acts as a growth factor for resting T cells and mast cells
	Enhances cytolytic activity of cytotoxic T cells
	Promotes growth of TIL in combination with IL-2
	Induces class switch to IgE and IgG
	Increases phagocytic activity of macrophages
Interleukin-5	Induces B-cell growth and differentiation
	Induces eosinophil growth and differentiation
	Stimulates secretion of IgA and IgM
Interleukin-6	Increases secretion of antibodies by plasma cells
	Costimulates T-cell activation with IL-1
	Aids in differentiation of myeloid stem cells
	Induces B-cell differentiation into plasma cells
	Induces megakaryocyte maturation
	Potential role in cachexia
	Induces acute-phase protein synthesis in hepatocytes
Interleukin-7	Supports the growth of B-cell precursors
	Stimulates the growth of thymocytes
	Stimulatory effect on cytotoxic T cells and LAK cells
	Induces proliferation and antitumor activity in monocytes and macrophages
Interleukin-8	Chemotactically attracts neutrophils
	Induces adherence of neutrophils to vascular endothelial cells; aids migration to tissues
	Angiogenic ability: stimulates capillary endothelial cell growth
Interleukin-9	Induces T-helper-cell growth
	Acts as a costimulator with several cytokines (e.g., supports erythroid colony formation with erythropoietin)

Table 4.1 Biological Activities of Interleukins *(cont.)*

Interleukin	Biological Activities
	Acts as a growth factor for mast cells
	Promotes production of IgE by B cells
Interleukin-10	Potent regulator of cell-mediated immunity
	Suppresses cytokine production by T-helper-cell subset
	Inhibits secretion of T-cell cytokines
	Inhibits macrophage function
	Inhibits cytokine production of NK cells
	Enhances or stimulates functions of B cells and mast cells
Interleukin-11	Enhances early hematopoietic progenitor cells
	Induces acute phase protein release from hepatic and nonhepatic cells
	Enhances megakaryocytopoiesis alone and with IL-3
Interleukin-12	Enhances survival and proliferation of stem cells
	Facilitates cytotoxic T-cell responses
	Facilitates cytotoxic activity of T lymphocytes, NK cells, LAK cells, and macrophages
	Enhances production of interferon-γ in infection
	Has a key role in the differentiation of the T-helper-cell system
Interleukin-13	Inhibits the production of macrophage-derived cytokines; end effect is anti-inflammatory effects on monocytes and macrophages
	Induces B-cell proliferation and differentiation (similar actions to IL-4)
	Decreases production of IL-1β and increases production of anti-inflammatory factor IL-1 receptor antagonist
	Inhibits the procoagulant effects of tumor necrosis factor and IL-1
	Reduces production of nitric oxide and reactive oxygen species
Interleukin-14	Induces B-cell proliferation and expands some B-cell populations
	No reported activity on T cells
	Augments proliferation of B-cell non-Hodgkin's lymphoma cell lines in vitro

continued

Table 4.1 Biological Activities of Interleukins *(cont.)*

Interleukin	Biological Activities
Interleukin-15	Stimulates proliferation of T lymphocytes
	Stimulates both CTL and LAK activity as well as NK cells
Interleukin-16	Initiates T-cell-mediated inflammatory process associated with atopic asthmatic phenotype
Interleukin-17	Induces other cytokine production including IL-6 and IL-8
	Induces protein tyrosine kinase–mediated signaling
Interleukin-18	Stimulates T cells to produce IFN-γ
	Induces protein tyrosine kinase–mediated signaling

Key abbreviations: CTL (cytotoxic T lymphocytes), Igs (immunoglobulins), NK (natural killer), LAK (lymphokine-activated killer), ACTH (adrenal corticotropic hormone), ICAM (intracellular adhesion molecule), MHC (major histocompatibility complex), TIL (tumor infiltrating lymphocytes).

Adapted with permission from Sharp, E. 1995. "The Interleukins." In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

HOW DO THE INTERLEUKINS WORK?

ILs have been likened to hormones, that is, they are the hormones of the immune response.

Interleukins bind to receptors on cell membranes. The receptors then signal the cell to alter its activation level. ILs produce the following actions:

- *Autocrine* (activating the same cell that produced the IL)
- *Paracrine* (activating nearby cells)
- *Endocrine* (activating distant cells)

Except for endocrine action, ILs mostly affect local or regional cells.

ILs control the balance between cell activation and immunoregulation. IL actions are: *redundant* (similar

effects produced by two or more ILs), *synergistic* (more than one IL is needed to produce cell activity), or *antagonistic* (IL inhibits the cell activity induced by another IL).

Of the known interleukins, only IL-2 and IL-11 have received regulatory approval. IL-11 is presented in Chapter 5, Hematopoietic Growth Factors. The interleukins remain under clinical investigation in cancer management, stimulation of hematopoiesis, and the treatment of autoimmune diseases.

WHAT IS INTERLEUKIN-2?

A T-cell growth factor produced mostly by activated T-helper cells, IL-2 is a messenger regulatory molecule with great immunomodulatory effects. IL-2 production depends on T-cell activation by antigens, which requires two signals:

1. The T-helper cell must recognize the major histocompatibility complex (MHC) antigens on an antigen-presenting cell.
2. The T-helper cell interacts with IL-1 produced by the antigen-presenting cell.
3. The T-helper cells then produce IL-2 and express IL-2 receptors.

How Does IL-2 Work?

IL-2 has the following biological actions:

- Promotes the proliferation of T-cell subpopulations
- Promotes activation of cytotoxic T cells, NK cells, and monocytes
- Induces activation of peripheral blood lymphocytes into LAK
- Supports B-cell growth and antibody production
- Induces the secretion of secondary cytokines such as interferon-gamma (IFN-gamma), granulocyte-

macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF)
- Enhances expression of the IL-2 receptor on T-cell surfaces

IL-2 binds to the IL-2 receptor (IL-2R) on target cell-surface membranes. The IL-2R is made of three subunits: an alpha, beta, and gamma chain. The affinity of the cell for binding IL-2 can be high, moderate, or low depending on how the subunits are expressed:

• High affinity:	Activated T cells, all three subunits
• Moderate affinity:	NK cells, beta and gamma subunits
• Low affinity:	Alpha subunit alone—no signal generated

Clinical Experience with IL-2

Native IL-2 alone or combined with lymphokine-activated killer (LAK) cells was found to cause tumor regression in animals. This finding led to the first clinical studies to evaluate the utility of IL-2 for the treatment of cancer. Although the recombinant form of IL-2 differs slightly from the native form, the two have similar activities. Recombinant IL-2 has been used as a single agent or combined with LAK cells, *tumor-infiltrating lymphocytes (TILs)*, other biological response modifiers (BRMs), or chemotherapy to treat human tumors. Some tumors have responded to IL-2, especially renal cell carcinoma and malignant melanoma.

IL-2 continues to be studied to define its activity at different doses, routes, schedules, and in combination regimens. IL-2 has been given by IV (bolus vs. continuous infusion), subcutaneous, intra-arterial, intralymphatic, intraperitoneal, and inhalation routes.

- Outpatient, low-dose therapy is being evaluated with increasing frequency as a means to decrease toxicity yet maintain clinical efficacy.

Interleukin-2 Alone

- Melanoma—Overall response rate of 17%, regulatory approval for high-dose therapy
- Renal cell cancer—Overall response rate of 14%, regulatory approval for high-dose therapy

Durable, long-term remissions have been achieved in a subset of patients.

- Phase II evaluation of IL-2 in other malignancies is limited (e.g., ovarian cancer, colon cancer, or breast cancer).
- Post-high-dose chemotherapy and autologous bone marrow transplant in hematologic malignancies.

  Proposed mechanism of action includes

  - Amplification of graft-versus-leukemic effect
  - Decrease graft-versus-host effect

Phase III trials are under way.

Interleukin-2 Plus Immune Effector Cells (Adoptive Cellular Immunotherapy)

LAK Cells

This approach has been evaluated primarily in patients with renal cell cancer or metastatic melanoma. At present, randomized trials do not support a major contribution of the addition of LAK cells to IL-2 in either disease.

Tumor-Infiltrating Lymphocytes

This approach has been evaluated primarily in patients with renal cell cancer or metastatic melanoma. Increased responses have been reported; however, comparative data are not yet available. The generation of TILs remains

complex, costly, and technically impossible in many patients.

Combination Therapy

- Other biological agents, primarily IFN-α
  - Renal cell cancer
  - Melanoma
  - No clearly superior clinical effect yet demonstrated
- Chemotherapy
  - Synergistic antitumor effects
  - Chemotherapy first: may prime the immune system or decrease tumor burden
  - Concurrent: chemotherapy-induced damage to the tumor cell membrane or IL-2-induced intratumor capillary leak may occur
  - Biotherapy first: immunomodulation
- Used primarily in renal cell cancer and melanoma
- Use with drugs that have known efficacy in these diseases

Ongoing investigations are exploring the safety and efficacy of various combinations of chemotherapeutic agents with rIL-2.

Biochemotherapy

- Combines IL-2, IFN-α, combination chemotherapy
- Used primarily in melanoma
  - Response rates exceeding 50% have been documented
  - Randomized phase III trials are in progress to document superiority of combinations
- Example of regimen:
  IL-2 9×10^6 IU/m^2 continuous IV infusion x 4 days
  IFN-α 5×10^6 IU/m^2 subcutaneous injection x 5 days
  Cisplatin 20 mg/m^2 daily x 4 days
  Dacarbazine 800 mg/m^2 IV day 1
  Vinblastine 1.6 mg/m^2/day x 5 days
  Repeat every 21 days

Regulatory Approval

In 1992 the FDA approved aldesleukin, a form of human IL-2, for adults with metastatic renal cell carcinoma. Because effects at this dose are serious and sometimes fatal, patients should have normal cardiac, pulmonary, hepatic, and CNS function before beginning therapy.

In January 1998 the FDA approved aldesleukin for the treatment of adults with metastatic malignant melanoma.

What Are the Side Effects of IL-2?

- In general, high doses produce severe toxic effects (see Tables 4.2 and 4.3).
- Patient performance status, organ function, age, and tumor size affect the severity of side effects.
- Protracted therapy may produce greater toxic effects.
- Side effects usually start shortly after therapy begins and intensify over time.
- Once therapy finishes, most side effects resolve.
- Irreversible effects are rare.
- The side effects of IL-2 can involve nearly every major organ system.

Table 4.2 Interleukin-2 Dosing Schedule

Interleukin-2 Dose	Administration Route	Care Setting
High Dose		
600,000 IU/kg Q 8 hours	Intravenous bolus	Inpatient unit Intensive care unit (potential)
Intermediate Dose		
18 million IU/m^2/day	Intravenous continuous infusion	Inpatient general oncology unit
Low Dose		
18 million IU/day	Subcutaneous	Outpatient/ ambulatory care

Adapted with permission from Sharp, E. 1995. "The Interleukins." In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

Table 4.3 Major Side Effects

System	Effects
General	Flulike syndrome: chills, rigors, fevers. Myalgias, arthralgias, malaise, headache, fatigue, and nasal stuffiness. Symptoms usually start 4 to 6 hours after therapy begins.
Cardiovascular	Tachycardia, hypotension, arrhythmias, edema, and weight gain. These effects result from dose-related fluid imbalances caused by a vascular leak syndrome.
Pulmonary	Dyspnea and pulmonary congestion. These effects may occur as a result of interstitial pulmonary edema related to increased vascular permeability, migration of activated T cells to the lungs, or release of secondary cytokines in the lungs. In extreme cases, patients may develop adult respiratory distress syndrome (ARDS), leading to respiratory failure.
Renal	Decreased urine output and increased serum creatinine and blood urea nitrogen levels. Contributing factors include hypoperfusion of the kidneys and direct effects of IL-2 on the kidneys.
Liver function	May be temporarily impaired. Signs include elevated liver function enzymes and jaundice. The reversible cholestasis that occurs may result from direct effects of IL-2 or indirect effects of secondary cytokines.
Skin changes	Erythematous rash, intense pruritus, dry skin with desquamation, and peeling skin on the palms and soles are common. Patients who receive subcutaneous injections may experience local inflammation at injection sites beginning 4 to 6 hours after injection and lasting up to 5 days. The site may be painful, erythematous, and indurated. Small, painless subcutaneous nodules may develop that take months to resolve.
Gastrointestinal	Nausea, vomiting, diarrhea, anorexia, mucositis. Nausea, vomiting, and diarrhea often occur within hours of intravenous bolus IL-2 or subcutaneous IL-2. With continuous-infusion IL-2, these effects may be intermittent. Anorexia may be a side effect of long-term or repeated therapy. Gastrointestinal effects resolve rapidly after therapy is completed.
Neurologic	Lethargy, confusion, sleep disturbances, decreased concentration, mood swings, depression. Severe neurologic changes may occur with high-dose therapy.

continued

Table 4.3 Major Side Effects *(cont.)*

System	Effects
Hematologic	Mild anemia, leukopenia, thrombocytopenia. With prolonged or repeated therapy, eosinophilia occurs. After therapy stops, rebound lymphocytosis occurs as activated lymphocytes circulate in the blood. Impaired neutrophil function with decreased chemotaxis occurs. Therefore, patients with infections should be treated with antibiotics before receiving IL-2 therapy. Thought should be given to using prophylactic antibiotics in patients with indwelling central lines or long-term venous access devices.
Allergic reactions	Reactions to both ionic and nonionic radiographic computed tomography contrast media may occur in patients who received IL-2 therapy. Symptoms include fever, chills, nausea, vomiting, hypotension, leukocytosis, skin rash, and elevated serum creatinine. The risk of contrast media reactions may be highest early on, so the use of contrast agents should be avoided during this time.

Future Directions

- Clinical studies will continue to evaluate the role of IL-2 in bone marrow transplantation. IL-2 produces immunologic effects and increased NK and LAK activity that may contribute to the elimination of residual disease. It is hoped that this approach may result in a reduced rate of relapse.
- IL-2 is being investigated in HIV infections and AIDS. The goal is to increase the number of lymphocytes and functional capacity. Studies have demonstrated that a temporary increase in T cells can occur with 2 to 3 weeks of low-dose therapy.
- Low doses of IL-2 given to patients with lepromatous leprosy led to a significant reduction in bacterial load.
- IL-2 may be useful for treating bacterial, fungal, viral, and parasitic infections and for preventing infections in burn patients.

- Randomized trials to determine superiority of combination therapy versus single agent therapy.
- Randomized trials to compare efficacy of high-dose versus *lower dose regimens.*
- Investigation of strategies to *minimize toxicity.* Because hemodynamic effects of IL-2 are related to induction of secondary cytokines, agents that interfere with the secretion of cytokines are being tested. Pentoxifylline reduces IL-2 toxicity in mice and preserves antitumor efficacy. It does not inhibit human LAK cytotoxicity. Other possible agents include dexamethasone, anti-TNF antibodies, soluble TNF receptors, platelet-activating factor antagonists, and IL-1-receptor antagonists.
- Combination regimens with other cytokines, activated lymphocytes, vaccines, and chemotherapeutic agents.

INTERLEUKIN-1

IL-1 is a glycoprotein, secreted primarily by macrophages, that exists in two forms: α and β. They are produced by separate genes and have different amino acid sequences, but they bind to the same cell-surface receptors and share biological activities.

How Does IL-1 Work?

Biological actions of IL-1 include:

- Immunomodulation
- Antiproliferative activity
- Promotion of hematopoiesis
- Mediation of inflammation
- Mediation of disease

Other beneficial activities include:

- Promoting bone resorption
- Stimulating fibroblasts
- Radioprotection of normal tissues

Immunomodulatory Functions

- Activating T cells, natural killer (NK) cells, polymorphonuclear cells, and monocytes
- Enhancing B-cell growth and antibody production
- Enhancing the antitumor effects of monocytes and NK cells
- Inducing the secretion of secondary cytokines

IL-1 and tumor necrosis factor (TNF) may work together to enhance TNF cytotoxicity.

Antiproliferative Activity

- Demonstrated antiproliferative activity against certain human cell lines
- Demonstrated antiproliferative activity against several murine tumors
- Enhances antitumor effects of other immune cells such as monocytes

Promotion of Hematopoiesis

- IL-1 induces the production of hematopoietic growth factors (GM-CSF, M-CSF, and IL-1).
- IL-1 promotes the growth and differentiation of hematopoietic progenitor cells in vitro.
- IL-1 accelerates the recovery of granulocytes and platelets if given after chemotherapy or radiation; it is myeloprotective if given before.

Mediation of Inflammation

- IL-1 is in the circulatory system within hours of infection or trauma.
- Biological effects include induction of fever; sleep; acute-phase protein synthesis; production of ACTH, cortisol, and insulin.
- IL-1 causes neutrophils to travel from the bone marrow to extravascular spaces and tissue sites.
- IL-1 activates neutrophils and monocytes.
- IL-1 induces liver hepatocytes to make acute-phase proteins.

Mediation of Disease

- In septic shock, IL-1 causes production of platelet-activating factor, prostaglandins, and nitric oxide.
- In animals, these mediator molecules act as vasodilators, producing hypotension and shock.
- TNF stimulates production of IL-1, which may play a role in autoimmune disorders.
- In vitro incubation of human and animal islet cells with IL-1 induces beta cell death. Therefore, IL-1 may destroy beta cells in patients with insulin-dependent diabetes.
- IL-1 is found in the synovial fluid and lining of patients with rheumatoid arthritis.
- In animals, IL-1 induces leukocyte infiltration and cartilage degeneration.
- In inflammatory bowel disease, lesions contain activated neutrophils and macrophages; concentrations of IL-1 and IL-8 are high.
- In animals, blocking IL-1 with an IL-1-receptor antagonist reduces the disease.
- IL-1β messenger RNA is found in cells of patients with acute myelogenous leukemia or chronic granulocytic leukemia cells of the juvenile type.

IL-1 may also play a role in atherosclerosis, psoriasis, asthma, osteoporosis, periodontal disease, transplant rejection, graft-versus-host disease, sleep disturbances, alcoholic hepatitis, and premature labor secondary to uterine infection.

Clinical Experience with IL-1

IL-1 may be useful in treating cancer because it activates effector cells, induces production or activity of secondary cytokines, protects cells from radiation-induced injury, restores damaged bone marrow, and confers anti-infective properties. IL-1 antagonists may reduce production or action of IL-1 in other diseases.

Phase I Trials

- Intravenous IL-1 was given for 15 minutes every day for 7 days to patients with advanced malignancies. The MTD was 0.3 mcg/kg.
- Dose-limiting effects were hypotension, confusion, renal insufficiency, myocardial infarction, and severe abdominal pain.
- Hematologic effects caused a significant increase in white blood cells. Platelet counts temporarily dropped but increased after therapy. Bone marrow cellularity increased.
- IL-1α accelerates recovery of platelets after high-dose carboplatin therapy; IL-1β has stimulatory effects in hematopoiesis. Hypotension was a dose-limiting factor.
- Investigation of the use of IL-1 following bone marrow transplant continues.

Corticosteroids, nonsteroidal anti-inflammatory drugs, and cytokines may reduce IL-1 production. Inhibition of IL-1-converting enzymes may decrease IL-1 processing and release. Strategies to counteract the biological effects of IL-1 have also been investigated for use in the treatment of diseases mediated by IL-1 production.

- One method to neutralize IL-1 is by using anti-IL-1 antibodies and soluble IL-1 receptors.
- Another method is to use IL-1-receptor antagonists (IL-1ra) that compete with and bind to IL-1 receptor sites. Administration of IL-1 receptor antagonist reduces mortality in patients with septic shock syndrome.

Regulatory Approval

As of December 1998, IL-1 has not received approval from the Food and Drug Administration (FDA) for clinical use.

What Are the Side Effects of IL-1?

The margin between clinical benefit and unacceptable toxicity in humans is exceedingly narrow. Side effects observed in clinical trials include fever, chills, headache, myalgias, nausea, and vomiting. Most patients had chills followed by monophasic temperature elevation. Chills were successfully treated with IV meperidine and warm blankets. Nausea and vomiting were not severe (grade 2 or less). Less common side effects were somnolence, abdominal pain, dyspnea, and peripheral vein phlebitis. Hypotension was dose-related and was a dose-limiting toxicity.

Future Directions

Areas of future study include IL-1's role in immunomodulation, inflammation, hematopoiesis, autoimmune disorders, wound healing, radioprotection, cancer treatment, treatment of severe burns, and treatment of those who receive toxic therapies (irradiation). Reducing the activity of IL-1 may help treat acute or chronic inflammatory or autoimmune disorders.

INTERLEUKIN-4

IL-4 is a cytokine produced mostly by activated T cells. Antigens, antigen-presenting cells, or antibodies in conjunction with T cells induce production of IL-4. It apparently exerts its biological activity through a single class of high-affinity receptors found on both hematopoietic and nonhematopoietic lineage cells. IL-4 receptor-positive cells include resting T and B cells, macrophages, myeloid progenitors, stromal cells, fibroblasts, and liver cells.

How Does IL-4 Work?

Biological Actions

IL-4 has pleiotropic functions on B cells:

- IL-4 stimulates the growth of resting B cells.
- Following antigen activation, IL-4 serves as a B-cell growth factor by stimulating the B cell to replicate its DNA.
- IL-4 promotes differentiation of antibody-stimulated B cells (it is known as a B-cell growth and differentiation factor).
- As a "switch factor," IL-4 regulates immunoglobulin (Ig) isotope expression, inducing IgE and IgG1 production.

IL-4 has pleiotropic functions on T cells:

- IL-4 induces T-cell growth and enhances production of IL-2.
- IL-4 increases expression of IL-2R to increase T-cell stimulation by IL-2.
- IL-4 enhances proliferation of cytotoxic T cells and may mediate or stimulate LAK activity.
- IL-4 promotes growth of TIL cytotoxic to human melanoma cells.
- IL-4 acts synergistically with IL-2 to enhance activation of $CD4^+$ cells while inhibiting nonspecific cytotoxicity.

- IL-2 combined with IL-4 has synergistic effects on growth and lytic activity of cytotoxic T cells.

IL-4 has pleiotropic functions on other immune cells:

- IL-4 also activates granulocytes, macrophages, megakaryocytes, thymocytes, and mast cells.
- IL-4 serves as a costimulant with G-CSF, GM-CSF, and erythropoietin for the production of progenitor cells.

Clinical Experience with IL-4

The clinical utility of IL-4 has been evaluated in both phase I and phase II trials:

- Administration is through both the subcutaneous and intravenous routes.
- Its use has been evaluated in the treatment or management of renal cancer, melanoma, hematologic malignancies (e.g., chronic lymphocytic leukemia and refractory Hodgkin's disease).
- Few responses have been documented in solid tumors.

Combination Trials

- The combination of IL-2 and IL-4 has been evaluated, and no increase in response rates was seen.
- In phase II trials using TIL (whose proliferation was increased in vitro by IL-2 and IL-4 administration), TILs were given with IL-2 to patients with metastatic renal cell carcinoma. The response rate was no greater than with IL-2 alone.

Regulatory Approval

As of December 1998, IL-4 had not received approval by the FDA.

What Are the Side Effects of IL-4?

The most common side effects in patients receiving single-agent IL-4 are fever, nasal congestion, headache, nausea/vomiting, diarrhea, anorexia, fatigue, capillary leak syndrome, weight gain, and dyspnea. Asymptomatic elevations in liver function tests occur but are transient. Gastroduodenal erosion or ulceration may occur; transfusions were required in three of these patients. No deaths occurred.

Future Directions

IL-4 shows antitumor activity in animals but has yet to produce useful antitumor responses in humans. IL-4 can induce class switch in immunoglobulin production to IgE and IgG1. Control of Ig synthesis could prevent or minimize IgE-mediated allergic conditions. Strategies to neutralize IL-4, block its production, or inhibit its activity may be explored in such diseases as asthma or other allergic diseases.

INTERLEUKIN-6

IL-6 was first discovered in 1979 and termed IFN-β2. It is a cytokine that has multiple biological effects related primarily to host defense maintenance. T lymphocytes, monocytes, fibroblasts, endothelial cells, and keratinocytes all produce IL-6.

How Does IL-6 Work?

IL-6 is an important regulatory protein for hematopoiesis; in addition, it has a wide variety of biological effects, which have led to its use in treatment of cancer.

Hematopoiesis

- Regulatory protein that stimulates hematopoiesis
- Stimulates production of platelets

Other Biological Effects

- Major inducer of the acute phase response
- Potential role in the pathogenesis of sepsis
- Effects on both the humoral and the cellular arms of the immune system

Clinical Experience with IL-6

Phase I and phase II trials have evaluated the clinical utility of IL-6 in the following areas:

- Evaluation of hematologic effects following chemotherapy and radiation therapy
- Stimulation of platelet production
- Acceleration of recovery from chemotherapy
- Evaluation in combination with other agents such as G-CSF or GM-CSF
- Antineoplastic activities in cancer
  - Role not yet fully explored
  - Few clinical responses yet seen

What Are the Side Effects of IL-6?

- Constitutional symptoms, including fever, chills, and fatigue
- Mild nausea and vomiting
- Significant increases in C-reactive protein, fibrinogen, platelet counts, and soluble lymphocyte IL-2 receptor levels (at doses greater than 3 mcg/kg)
- Thrombocytosis and anemia (likely dilutional in nature)
- Cardiovascular: hypertension, bradycardia, atrial fibrillation, dizziness, and pedal edema; generally mild to moderate
- Pulmonary: cough, dyspnea, nasal congestion, abnormal breath sounds; generally mild to moderate
- Erythema and pain at injection site

The most common route of administration is by subcutaneous injection.

In general, toxicity was moderate and reversible; it consisted mainly of fever, flulike symptoms, fatigue, and moderate hepatotoxicity. Anemia, leukocytosis, thrombocytosis, and induction of an acute phase response were observed in most patients. Prolonged subcutaneous administration of rh IL-6 on an outpatient basis is safe and feasible. Profound regulatory effects on hematopoiesis and inflammatory response of rh IL-6 are observed.

Regulatory Approval

As of December 1998, IL-6 was continuing in clinical trials and had not yet received approval by the FDA.

Future Directions

Phase II and III trials studying IL-6 alone and in combination with other growth factors continue for patients with cancer.

- Ability to reduce thrombocytopenia following chemotherapy
- Antitumor effects
- Overproduction is associated with several diseases such as multiple myeloma. Interluekin-6 (IL-6)/IL-6 receptor (IL-6R) play a major role in autocrine/paracrine growth regulation of myeloma cells and are the central mediators for bone destruction and other systemic manifestations of multiple myeloma.
  - Strategies to block effects of IL-6 through antagonist

INTERLEUKIN-10

Interleukin-10 is a relatively recently defined, important immunoregulatory cytokine whose principal biological function appears to involve the suppression of cytokine synthesis in a subset of T-helper cells. IL-10 was originally named cytokine synthesis inhibitory factor (CSIF).

How Does IL-10 Work?

- Inhibition of cytokine synthesis through T cells by increasing cytotoxic T-cell number and function
- Inhibition of the production of pro-inflammatory cytokines such as IL-1, tumor necrosis factor-alpha, IFN-γ, and IL-6 through inhibitory action on Th1 cells and macrophages
- Enhances proliferation of activated human B lymphocytes and induces them to secrete high amounts of immunoglobulins
- Produced by select T cells, B cells, keratinocytes, and monocytes and macrophages

Role in the Pathophysiology of Disease

Inflammatory Bowel Disease

Active inflammatory bowel disease is characterized by

- Increased monocyte secretion of pro-inflammatory cytokines.
- Immunoregulatory cytokines such as IL-10, IL-4, and IL-13, which are capable of inhibiting the pro-inflammatory cytokine response of activated monocytes.
- Ulcerative colitis and Crohn's disease may be associated with a decreased production of IL-10 and IL-4, which are cytokines capable of suppressing macrophage and T-cell function.
- May act as a naturally occurring damper of the acute inflammatory process of inflammatory bowel disease.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is characterized by a progressive deterioration of cell-mediated immune responses as cytokines are dysregulated.

- IL-10 is a cytokine that is overexpressed in HIV-infected individuals.
- Inhibitory effect of IL-10 on HIV replication in maturing monocytes is thought to be mediated mainly by the inhibition of cellular gene expression and the inhibition of maturation of monocytes into macrophages.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease with inflammatory manifestations in the peripheral synovial joints.

- Joints are infiltrated by activated T cells, macrophages, and plasma cells.
- IL-10 has been found to have an inhibitory effect on synovial cells and is an important immunoregulatory component of the cytokine network in rheumatoid arthritis.
- IL-10 may be responsible for regulating monocyte and in some cases T-cell cytokine production.
- IL-10 may be useful in the treatment of patients with rheumatoid arthritis.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is an autoimmune disease characterized by:

- IL-10 is produced in large amounts by B lymphocytes and monocytes and is responsible for autoantibody production. Elevations in IL-10 levels in patients with SLE correlate with disease activity.
- Potential defect in either IL-10 production or responsiveness may cause an intrinsic defect in IL-10-induced suppression of cytokine synthesis (e.g., IL-6 or IFN-α).
- Use of monoclonal antibodies to IL-10 may represent a potential therapeutic strategy in this disease.

Psoriasis

- Study of cytokine patterns of active and lesion-free skin in psoriasis patients demonstrated the following:
  - Increased expression of mRNA for IL-2, IFN-γ, and lymphotoxin in active lesions
  - Lack of IL-4, IL-5, and IL-10

Overexpression of pro-inflammatory, type 1 cytokines has been demonstrated in psoriasis and is believed to be of pathophysiologic importance. IL-10 is a type 2 cytokine with a major impact on immunoregulation, since it inhibits type 1/pro-inflammatory cytokine formation. The administration of IL-10 may represent a therapeutic approach for the treatment of psoriasis.

Multiple Sclerosis

- Low serum IL-10 levels have been found in patients with multiple sclerosis.
- IL-10 may block secretion of pro-inflammatory cytokines in vivo in patients with multiple sclerosis, and may have clinical utility in the treatment of multiple sclerosis.
- IFN-β induces the up-regulation of IL-10, which may have a therapeutic effect in relapsing-remitting multiple sclerosis.

Regulatory Approval

As of December 1998, IL-10 had not yet received approval by the FDA.

What Are the Side Effects of IL-10?

- Fever, headaches, and flulike symptoms
- Many of these side effects can be relieved with acetominophen and/or ibuprofen

Future Directions

- Many phase I and II studies have been completed with IL-10 to evaluate its use in a variety of clinical settings.
- Suppressive effects of IL-10 on cell-mediated immunity may represent a potential role in transplant rejection or the treatment of graft-versus-host disease.

INTERLEUKIN-12

IL-12 is a cytokine with potent immunoregulatory and antitumor activity. IL-12 was originally called natural killer cell stimulatory factor and cytokine lymphocyte maturation factor based on its stimulatory effects on these cytolytic lymphokine populations.

Monocytes appear to be the major source of IL-12 in activated peripheral blood mononuclear cell suspensions in vitro. B cells transformed with Epstein-Barr virus and other antigen-presenting cells also appear to produce IL-12.

How Does IL-12 Work?

- Allows continued proliferation of activated T and NK cells.
- Potent inducer of IFN-γ release from both T lymphocytes and NK cells.
- Promotes Th1 cell development while inhibiting Th2 cell development.
  - Th1 cells produce IL-2 and IFN and stimulate cell-mediated immunity.
  - Th2 cells produce IL-4, IL-5, and IL-10.
- May have a role in humoral immunity.

Clinical Experience with IL-12

- Phase I and II trials completed in solid tumors (primarily metastatic renal cancer or metastatic melanoma).
- In a phase I study administered by bolus IV injection initially as a single test dose, then daily for 5 days every 3 weeks, for a maximum of six, 5-day cycles; MTD on this regime was determined to be 500 ng/kg.
- In a phase II trial of IL-12 administration at 500 ng/kg using the same schedule as the phase I trials but *without* the single test dose:
  - Trial closed because of unexpected severe toxicity.
  - Of the 17 patients treated, 12 were hospitalized and 2 of the 12 died.
- Adverse events involved multiple organ systems and were associated with constitutional, cardiac, renal, hematopoietic, hepatic, neurologic, and gastrointestinal toxicities.
- Extensive analysis confirmed that a single injection of IL-12 1 week before starting the consecutive daily treatment with IL-12 has a profound and unexpected abrogating effect on toxicity.
- Careful attention to dose and especially schedule has been required to assure safe and effective clinical development of this highly promising cytokine.
- Additional clinical studies of IL-12 have been conducted, and several hundred subjects have been safely treated with IL-12.

Regulatory Approval

As of December 1998, IL-12 was not approved by the FDA. It remains under clinical investigation.

What Are the Side Effects of IL-12?

- Based on the phase I and II trials conducted in patients with metastatic disease, potential side effects may include:

- Flulike symptoms.
- Fever—note generally *delayed.*
- Usually occurs 8 to 12 hours after the administration of IV IL-12 and 12 to 24 hours after subcutaneous administration.
- Chills, fatigue, headache, and myalgias were universal at all dose levels.
- GI: Nausea and vomiting are rare; however, stomatitis has been reported, appears to be dose-dependent, and usually resolves within 3 days.
- Hematologic: Anemia, neutropenia, and thrombocytopenia appear to be independent of dose. Absolute neutrophil count (ANC) nadir occurs around day 5 of each cycle without cumulative toxicity, and with full recovery by day 15. Lymphocytopenia occurred in a majority of patients at all dose levels and resolved without rebound lymphocytosis.
- Liver: Hypertransaminasemia and increases in alkaline phosphatase, bilirubin, and LDH levels are dose-dependent. Hypoalbuminema has also been documented. Levels usually return to baseline in 7 to 10 days.
- Metabolic: Hyperglycemia and increases in triglyceride levels have been observed frequently.
- Skin: 10% of those who received subcutaneous IL-12 had subcutaneous induration at the site of the injection. Skin rash was rare.

Side effects are generally proportional in frequency and severity to the dose level of IL-12 administered.

Future Directions

IL-12 is an experimental agent that is continuing to be studied. It should not be considered a treatment option. Several studies in the area of oncology are ongoing in which the data have yet to be analyzed. New clinical trials are being developed as the therapeutic role of IL-12 in several diseases is determined.

QUICK SUMMARY

AGENT: Interleukin-2, aldesleukin (Proleukin®)
Manufacturer: Chiron, Emeryville, Calif.

WEBSITE: www.chiron.com

First approved by FDA in May 1992.

Aldesleukin, a human recombinant interleukin-2 (IL-2) product, is a highly purified protein produced by recombinant DNA technology. Aldesleukin possesses the biological activity of human native IL-2.

REGULATORY APPROVALS

Disease	*Dosing*
Metastatic renal cell carcinoma	Two 5-day treatment cycles separated by a rest period of 9 days: 600,000 IU/kg administered every 8 hours by a 15-minute IV infusion for a total of 14 doses. Patients treated with this schedule received a median of 20 doses because of toxicity.
Metastatic melanoma	Two 5-day treatment cycles separated by a rest period of 9 days: 600,000 IU/kg administered every 8 hours by a 15-minute IV infusion for a total of 14 doses. Patients treated with this

schedule received a median of 18 doses because of toxicity.

PHARMACOKINETICS

Elimination: Metabolized in the kidneys, with little or no bioactive protein excreted in the urine.

High plasma concentration occurs following short IV infusion, with a half-life of 13 minutes. Following subcutaneous administration, peak levels are achieved in 5 hours.

SETTING: Hospital, for regulatory approved doses

Many patients currently receive aldesleukin in the ambulatory setting when receiving treatment regimens using low to moderate dosing schedules

DIAGNOSTIC/LABORATORY TESTS

The following clinical evaluations are recommended for all patients prior to beginning treatment at regulatory approved doses and then daily during drug administration: standard hematologic tests, including CBC, differential and platelet counts; blood chemistries, including electrolytes, renal and hepatic function test; chest X rays.

All patients should have baseline pulmonary function test with arterial blood gases and evaluation of cardiac function using a stress thallium study.

Proleukin® *continued*

Daily monitoring during therapy should include vital signs, weight, and clinical pulmonary assessment.

ADMINISTRATION

Vial Sizes

22 x 10^6 IU/vial (18 million IU [1.1 mg] per mL when reconstituted)

Single-use vials, discard unused portion.

Reconstitute with 1.2 mL sterile water for injection by directing diluent against the side of the vial to avoid excess foaming.

Swirl gently to mix. Do not shake.

Dilute the reconstituted aldesleukin dose in 50 mL of 5% dextrose injection and infuse over 15 minutes. *Do not use in-line filters when administering aldesleukin.*

Caution: Avoid reconstitution or dilution with bacteriostatic water for injection or 0.9% sodium chloride injection because of increased aggregation. Dilution with albumin can alter the pharmacology of aldesleukin. *Do not mix with other drugs.*

Storage/stability: Store in a refrigerator at 2° to 8°C. Administer within 48 hours of reconstitution.

GENERAL PRECAUTIONS (see package insert for details)

- Monitor for capillary leak syndrome (CLS), which begins immediately following administration of aldesleukin. CLS results from the extravasation of plasma proteins and fluid into the extravascular space and loss of vascular tone. CLS may be associated with cardiac arrhythmias, angina, myocardial infarction,

respiratory insufficiency requiring intubation, GI bleeding or infarction, renal insufficiency, and mental status changes.

- Early administration of dopamine (1 to 5 mcg/kg/min) to patients manifesting CLS, before the onset of hypotension, can help maintain organ perfusion particularly to the kidney and thus preserve urine output.
- Aldesleukin may exacerbate autoimmune disease.
- Patients with significant cardiac, pulmonary, renal, hepatic, or CNS impairment should be excluded from therapy with high-dose aldesleukin.
- In high-dose therapy, all patients with an indwelling central line should receive prophylactic antibiotic therapy effective against *Staphylococcus aureus.*
- **Avoid concurrent use of glucocorticoids, which may reduce the antitumor effectiveness of aldesleukin.**
- Antihypertensives may potentiate the hypotension seen with aldesleukin.
- See package insert for clinical guidelines for holding or interrupting a dose or for discontinuing of therapy. Organ systems most often involved include cardiovascular, pulmonary, renal, CNS, GI, and hepatic.
- The use of premedication with acetaminophen and/or nonsteroidal anti-inflammatory agents is common to control flulike symptoms.

Proleukin® *continued*

RESOURCES FOR PATIENTS

"Interleukin-2: Information for Patients and Their Families." 1997. Write to: Attn: Interleukin-2 Therapy Medicalliance, Inc., 5565 Sterett Pl., Ste. 200, Columbia, MD 21044-9590.

Video: "Interleukin-2 Therapy. Information for Patients and Their Families." Available through: American Medical Communications, Houston, TX; (713) 590-1475.

National Kidney Association, "Interleukin-2 and Biologic Therapy."

RESOURCES FOR PROFESSIONALS

Chiron Professional Services Department

To request specific product information and educational materials

Access to Nurse Network

Open from Monday through Friday, 6:00 A.M. to 5:00 P.M. PST.

To contact, please call 1-800-CHIRON-8, selection #2 (from within the United States)

Reimbursement hotline 1-800-775-7533

Proleukin® inpatient management guidelines

Proleukin® outpatient management guidelines

Reprint: Management of patients receiving interleukin-2 therapy. *Seminars in Oncology Nursing* 9(3, suppl 1):1–35 (August 1993).

Physicians' and Nurses' Guidelines for Proleukin® (aldesleukin) therapy

Biotherapy: Considerations for Oncology Nurses

CE accredited newsletter

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Washington Crossing, PA 18977

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Monograph on IL-2 produced by Chiron: Rieger, P. T. (ed.) (1998). Interleukin-2: a paradigm for developing nursing strategies for patient management. Beachwood, OH: Pro ED Communications, Inc.

Clinical Pearls

INTERLEUKIN-2 THERAPY

1. Pretreatment assessment: Because of toxicities related to the administration of IL-2, especially capillary leak syndrome, it is important to establish baseline status/functioning of the following body systems: renal, hepatic, hematologic, cardiovascular, and pulmonary.
2. Performance status should be ECOG 0 or 1, or Karnofsky PS 70 to 100%.
3. **Concomitant use of corticosteroids may reduce the effectiveness of aldesleukin and should therefore be avoided.**
4. In-house studies at Chiron have demonstrated safety when a 5-day supply of medication is drawn into syringes in a sterile environment and stored at refrigerated temperatures. Consult package insert or manufacturer for details.
5. For subcutaneous and continuous-infusion regimens designed for the ambulatory setting, patients must have ready access to the health care team for response to questions or to manage adverse events.
6. Even in regimens designed for the ambulatory setting, adverse events stemming from capillary leak syndrome may become problematic. Patients should be monitored on a regular basis for symptomatic hypotension, tachycardia, weight gain of 5 to 10 pounds over several days, shortness of breath, and significantly decreased urine output. For high-dose inpatient regimens, patient should be monitored every 4 hours for changes in neurologic, pulmonary, cardiovascular, and renal function.

7. Patients with indwelling central lines should be placed on prophylactic antibiotic coverage to prevent infection from gram-positive organisms.
8. For patients receiving IL-2 in the ambulatory setting, education of the patient and family is vital. Self-care skills (e.g., either medication self-administration through subcutaneous injection or management of an ambulatory infusion pump), reportable signs and symptoms (see sidebar), contact numbers to call for questions or management of adverse events and when to report for laboratory and diagnostic tests and follow-up clinic visits are crucial to include in the teaching plan.
9. Aggressive management of toxicities such as flulike symptoms, nausea and vomiting, stomatitis, pruritus, and dry desquamated skin with concomitant medications and nonpharmacologic interventions must be considered and planned for at the onset of therapy. See Table 4.4.
10. Once a cycle of therapy is completed, fluid is rapidly mobilized from the periphery, and weight generally returns to pretreatment baseline. On occasion, furosemide is used to assist in the mobilization of fluid.
11. Because of skin changes resulting from IL-2 therapy, instruct patients to avoid direct sunlight and to use sun screen when outdoors.
12. Have patients keep a diary of symptoms, timing, and placement of injections to assist with monitoring the occurrence of toxicities and success of management strategies.

Table 4.4 Medications Used to Manage Il-2 Toxicity

Antipyretic analgesic agents
acetaminophen

Anti-inflammatory agents
indomethacin
naproxen
sulindac

Histamine H2 antagonist agents
cimetidine
ranitidine

Antiemetic agents
lorazepam
prochlorperzine maleate
promethazine HCL
droperidol
ondansetron
ABH (lorazepam, diphenhydramine, haloperidol)
scopolamine patches

Antidiarrheal agents
codeine phosphate
kaolin and pectin
opium tincture
diphenoxylate HCL with atropine SO_4

Antianxiety, antihallucinogen, and hypnotic agents
diphenhydramine
diazepam
fetanyl
flurazepam
haloperidol

Diuretic agents
furosemide
metolazone

Agents to control chills
meperidine HCL
indomethacin
dilaudid SL

Vasopressors and antiarrythmic agents
dopamine HCL
verapamil HCL
atropine SO_4

Antihypotensive measures
0.9% sodium chloride boluses
5% serum albumin

Antipruritic agents
hydroxyzine hydrochloride
diphenhydramine
colloidal oatmeal

Source: Adapted and reprinted with permission from Padavic-Shaller, K. 1988. Nursing applications in a developing science. Seminars in Oncology Nursing 4(2): 142

Reportable Signs and Symptoms

System	Sign or Symptom
General	Overwhelming fatigue (patient spends majority of day in bed or is unable to perform routine activities of daily living)
	Fever uncontrolled with antipyretics
Neurologic	Confusion or disorientation
	Extreme drowsiness
	Hallucinations
	Sleep disturbance
Gastrointestinal	Inability to maintain adequate hydration or food intake because of nausea and vomiting, stomatitis, or diarrhea
	Emesis uncontrolled with antiemetics
	Diarrhea (more than two to three loose stools per day or uncontrolled with antidiarrheal medication)
Cardiovascular	Weight gain > 5 to 10 pounds within a week
	Palpitations, chest pain
	Dizziness when changing position
Pulmonary	Shortness of breath, respiratory distress
	Cough with production of sputum
Renal	Voiding only small quantities of urine
	No urine output
Integument	Large, painful inflammatory reactions at the injection site
	Signs of infection (erythema, swelling)
	Severe desquamation

Adapted with permission from Hossan, E., and P. T. Rieger. 1997. Interleukin-2 therapy: Nursing management + patient education + success in the ambulatory setting. *Biotherapy: Considerations for Oncology Nurses* 2(2):1–7.

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CHAPTER 5

HEMATOPOIETIC GROWTH FACTORS

WHAT ARE THE HEMATOPOIETIC GROWTH FACTORS?

Hematopoietic growth factors (HGFs) are glycosylated proteins that regulate the reproduction, maturation, and function of blood cells. They attach to receptors on the surface membrane of a target cell, and the cell proliferates, differentiates, and matures. Some HGFs stimulate a single response, others a cascade effect.

Key characteristics of HGFs are as follows:

- They are hormone-like proteins that mediate intracellular communication.
- They may be produced by several types of cells.
- They usually have only a local effect.

Historically, HGFs were named colony-stimulating factors (CSFs) because they induced growth and maturation of colonies of cells in vitro. The four classic CSFs control formation of neutrophils and monocyte-macrophages and are part of the HGF family. They are:

1. Granulocyte colony-stimulating factor (G-CSF)
2. Granulocyte-macrophage colony-stimulating factor (GM-CSF)
3. Macrophage colony-stimulating factor (M-CSF)
4. Interleukin-3 (IL-3) (multipotential colony-stimulating factor)

See Table 5.1 for a list of FDA-approved HGFs and associated side effects.

Table 5.1 Side Effects of Approved Hematopoietic Growth Factors

HGF	Generic Name (Trade Name)	Manufacturer	Side Effects
Erythropoietin	Epoetin-alfa (Epogen®)	Amgen	Occasional headache, elevated blood pressure
	Epoetin-alfa (Procrit®)	Amgen Distributor: Ortho Biotech	Occasional headache, elevated blood pressure
G-CSF	Filgrastim (Neupogen®)	Amgen	Bone pain in areas of high bone marrow reserve. Rare allergic reactions with rash, urticaria, facial edema, dyspnea, hypotension, tachycardia
GM-CSF	Sargramostim (Leukine®)	Immunex	Fever. Dose-related fluid retention, dyspnea, myalgias, joint pain, bone pain
rhIL-11	Oprelvekin (Neumega®)	Genetics Institute	Most common: peripheral edema, dyspnea, tachycardia, conjunctival redness

Reprinted with permission from Wujcik, D. 1995. "The Hematopoietic Growth Factors." In P. Rieger (ed.), *Biotherapy: A Comprehensive Overview.* Boston: Jones and Bartlett.

HOW ARE HEMATOPOIETIC GROWTH FACTORS CLASSIFIED?

Class I HGFs are *multilineage*, acting on the pluripotent and immature progenitors. Class II HGFs act on more mature progenitor cells and are *lineage restricted* (See Table 5.2).

Lineage-Restricted HGFs

Lineage-restricted HGFs include G-CSF, M-CSF, and erythropoietin.

Granulocyte Colony-Stimulating Factor

- G-CSF stimulates neutrophil production and maturation.
- The effect occurs later in the differentiation cascade on maturing progenitor cells.
- G-CSF also enhances the function of mature neutrophils.

Erythropoietin (Epo)

- Epo is produced in response to decreased oxygen concentration in the blood.
- Epo allows a proliferating pool of committed erythroid progenitors to be maintained, permits erythroblast differentiation, and recruits immature progenitors.

Macrophage Colony-Stimulating Factor

- M-CSF activates monocytes, prompting macrophage production.
- It also stimulates enhanced cytotoxicity against fungi.

Multilineage Hematopoietic Growth Factors

The multilineage HGFs include GM-CSF, IL-3, IL-11, and SCF.

Table 5.2 Source and Function of Hematopoietic Growth Factors

HGF	Classification	Primary Source	Function
Epo	Lineage-restricted	Kidney, liver	Stimulates erythrocyte progenitors
G-CSF	Lineage-restricted	Macrophages, fibroblasts, endothelial cells	Simulates neutrophil progenitors
M-CSF	Lineage-restricted	Many cell types	Stimulates progenitors of monocytes/macrophages
GM-CSF	Multilineage	T lymphocytes, macrophages, endothelial cells, fibroblasts	Stimulates progenitors of neutrophils, eosinophils, monocytes, basophils
IL-3	Multilineage	T lymphocytes	Stimulates early progenitors for neutrophils, monocytes, platelets, eosinophils, basophils, stem cells
SCF	Multilineage	Bone marrow stroma, many cell types	Stimulates pluripotent stem cell and progenitors for all cell lines
IL-11	Multilineage	Bone marrow stromal cells	Stimulates early progenitor cells and functions as a maturation factor in megkaryocytopoiesis

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Granulocyte-Macrophage Colony-Stimulating Factor

- GM-CSF supports neutrophil, eosinophil, and macrophage development and interacts with earlier progenitors than G-CSF.
- Direct effects on mature cells are inhibition of neutrophil migration, degranulation, changes in receptor expression, and effects on cytoskeleton and cell shape.
- Indirect effects are enhanced neutrophil ability to respond to secondary triggering signals, allowing amplification of immune response; enhanced phagocytic function of neutrophils, macrophages, and eosinophils; and increased antibody-dependent cell-mediated cytotoxicity toward tumor cells.

Interleukin-3

- IL-3 causes stem cells to differentiate into granulocytes, macrophages, megakaryocytes, erythrocytes, and lymphocytes.
- It works at the earliest level and may affect the pluripotent stem cell.

Interleukin-11

- IL-11 stimulates early progenitor cells.
- It stimulates megakaryocyte progenitor cells.
- It induces megakaryocyte maturation.

Stem Cell Factor (SCF)

- SCF supports and enhances early cells in the hematopoietic hierarchy.
- It enhances activity in the presence of such other HGFs as EPO, GM-CSF, IL-3, and G-CSF.

See Figure 5.1.

Figure 5.1 Hematopoeitic Tree and Growth Factors

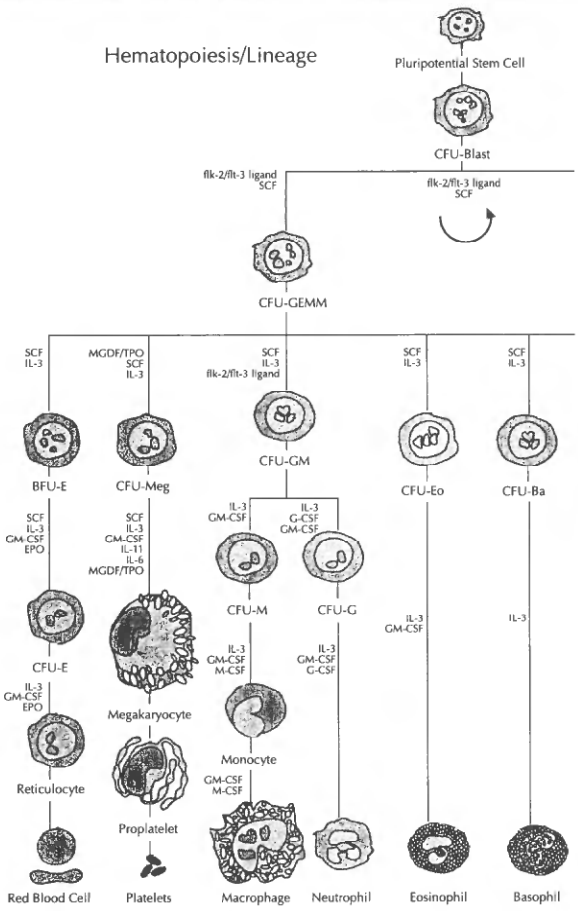
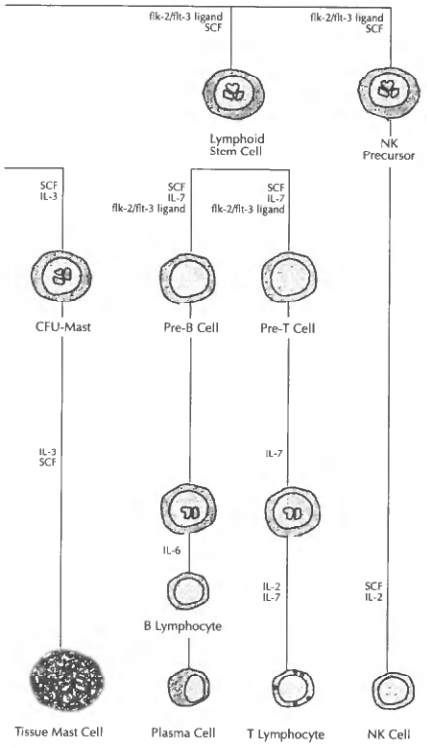


Figure 5.1 Scheme of hematopoesis including some of the growth factors that influence the production of blood cells. CFU-GEMM, multilineage colony-forming cell; BFU-E, erythroid burst-forming cell; CFU-E, erythroid colony-forming cell; CFU-GM, granulocyte-macrophage colony-forming cell; CFU-M, macrophage colony-forming cell; CFU-E, eosinophil colony-forming cell; CFU-Ba, basophil colony-forming cell; IL, interleukin; SCF, stem cell factor, G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; TPO, thrombopoietin; MGDF, megakaryocyte growth and development factor; EPO, erythropoietin. (Figure courtesy Amgen Inc., Thousand Oaks, CA.)

Figure 5.1 Hematopoeitic Tree and Growth Factors *(cont.)*



WHICH CELLS PRODUCE HEMATOPOIETIC GROWTH FACTORS?

Hematopoietic growth factors are synthesized by a wide variety of cells (see Table 5.2):

- Activated T lymphocytes produce IL-3.

- Fibroblasts, endothelial cells, and macrophages secrete G-CSF and GM-CSF.
- Activated macrophages, fibroblasts, and endothelial cells produce macrophage colony-stimulating factor.

HOW DO HEMATOPOIETIC GROWTH FACTORS WORK?

Hematopoiesis

Hematopoiesis, the process by which the formed elements of the blood are produced, is tightly regulated and critical to survival. Hematopoiesis occurs in extravascular spaces.

The process begins with the pluripotent stem cell (PPSC) and ends with the production of circulating cells (see Figure 5.1). The PPSC has the potential to become any blood cell. PPSCs account for only 0.1% of marrow cells. They produce two daughter cells: one enters a differentiation pathway; another returns to a resting pool of cells, allowing self-renewal of the stem cell pool and supplying cells to replace dying mature cells.

PPSCs develop in sinusoidal spaces surrounded by bone marrow stroma, consisting of endothelial cells, fibroblasts, adipocytes, and macrophages that produce collagen and adhesive proteins. Stress, infection, hemorrhage, or bone marrow depletion increases PPSC production.

The progenitor cells stick to the collagen and adhesive proteins, ensuring development in the presence of appropriate growth factors.

Many HGFs are produced by stromal cells.

Committed Progenitors

Once a cell leaves the stem cell pool, it commits itself. The first commitment is to the myeloid or lymphoid lineage. These precursor cells can commit to one of several cell lines. The cells become more differentiated as they change from pluripotent to unipotent cells.

The lymphoid stem cells mature into pre-B and pre-T progenitor cells, and then B and T lymphocytes. Myeloid stem cells become the multilineage colony-forming unit (CFU-GEMM) that produces granulocytes, erythrocytes, macrophages, and megakaryocytes.

Each cell line that produces a mature cell follows this process: from progenitor to precursor to mature cell. Progenitors are the earliest committed cells. *Precursors* are immature forms. As cells mature, their ability to proliferate decreases.

Types of Blood Cells Produced

Granulocytes

Granulocytes (neutrophils, eosinophils, and basophils) defend against bacteria.

Neutrophils

- Neutrophils are the most numerous granulocytes, accounting for 50–70% of the total white blood cell (WBC) count.
- They go through six stages of maturation: the first three stages (myeloblasts, promyelocytes, and myelocytes) undergo cell division over four to five days. At the metamyelocyte level, cells are no longer capable of mitosis, but maturation continues for six more days.
- Mature cells are released into the peripheral blood where half will circulate freely; the other half adhere to vessel walls.
- Neutrophils remain in the blood six to eight hours and then move into tissues for two to three days.
- Neutrophils are mature WBCs containing granules that destroy bacteria.
- They arrive first at the site of disease or injury in greater numbers than other types of white blood cells.
- Three times as many are stored in the bone marrow as are circulating.
- In times of serious injury, the life span of a neutrophil decreases to several hours.

Eosinophils

- Eosinophils comprise up to 4% of the WBC.
- There are three immature forms (eosinophilic myeloblast, promyelocyte, myelocyte) and the mature eosinophil.
- Eosinophils circulate for eight hours, then migrate into the tissues.
- Eosinophils ingest bacteria and release factors that alter inflammation.
- Eosinophil levels are increased in parasitic infections and allergic responses.

Basophils

- Basophils account for up to 0.05% of the WBC and may be higher in patients with asthma, allergies, and some cancers.
- Basophils differentiate like eosinophils: basophilic myeloblast, promyelocyte, myelocyte, metamyelocyte, and the mature basophil.
- Basophils do not phagocytize bacteria. They release substances following stimulation, contributing to hypersensitivity reactions.

Monocytes/Macrophages

Monocytes and neutrophils share a common progenitor cell, colony-forming unit-granulocyte-macrophage (CFU-GM).

- Upon stimulation by HGFs, the CFU-GM produces monoblasts, which ultimately mature into promonocytes and monocytes.
- Mature monocytes are released into the blood, where they circulate for one to three days.
- After entering tissue, the monocyte matures into a macrophage, which provides nonspecific immunity against parasitic, protozoan, and fungal infections.
- Normal monocyte levels are 6–8% of the WBC.

Erythrocytes

- Erythrocyte development begins with the burst forming unit-erythroid (BFU-E).
- The immature forms are proerythroblast and erythroblast.
- The reticulocyte is released into the blood, where it circulates for one to two days until fully matured.
- The erythrocyte transports oxygen to the tissues and carries carbon dioxide from tissues to the lungs.

Thrombocytes (Platelets)

- The committed megakaryocyte progenitor cell is the colony-forming unit-megakaryocyte (CFU-Meg).
- The earliest thrombocyte progenitor in bone marrow is the megakaryoblast. The next level is the megakaryocyte, which releases platelets.
- Platelets form hemostatic plugs at sites of injured blood vessels and release clotting factors.
- Thrombocytes survive seven to eight days.

Lymphocytes

Lymphocytes make up 30–35% of WBCs.

- The lymphoid stem cell arises from the PPSC and differentiates into B or T lymphocytes.
- Pre-T lymphocytes mature in the thymus into prothymocytes, lymphoblasts, and T lymphocytes.
  - T lymphocytes mediate cell immunity, circulating between tissue and blood. When stimulated, T lymphocytes produce cytokines that regulate the immune response.
- Pre-B lymphocytes migrate to lymph tissue to mature.
  - The B lymphoblast matures into the B lymphocyte. This cell matures into a plasma cell capable of secreting antibodies (i.e., immunoglobulins).
  - B lymphocytes make up 20–25% of the lymphocytes.

HGFs in Hematopoiesis

The HGFs regulate hematopoiesis by stimulating cells to divide and mature. Some HGFs influence precursor and mature cells; others affect cell differentiation and proliferation.

In infections, HGF levels increase to stimulate neutrophil production. When T-cell receptors are activated, multiple cytokines are produced. Monocytes and macrophages respond to bacteria, bacterial cell wall products, and cytokines by releasing other cytokines. As infection resolves, HGF levels return to normal.

Endogenous levels of G-CSF are high in those with chemotherapy-induced neutropenia and decline as neutrophil counts recover. M-CSF and IL-6 are elevated in febrile, neutropenic patients.

Cell Surface Receptors

Hematopoietic growth factors bind to cell surface membrane receptors.

- Each receptor receives a single type of HGF, but receptors for more than growth factor may be found on a cell.
- There are few receptors on each cell.
- Biological effects occur with only about 10% receptor occupancy.
- Receptors are on both mature and immature cells.

Direct actions are initiated by HGFs binding to cell surface receptors.

- After binding, the protein and receptor are internalized into the cell; the cell divides or matures.
- The remaining HGF cell surface receptors are internalized or inactivated.

HGF also can act indirectly on cells.

- A protein product released from an initial action can bind to a different cell and stimulate it, initiating a secondary cytokine cascade.
- GM-CSF can stimulate the release of macrophages, and the production of TNF, and IFN-γ. These cytokines cause fever and chills.

CLINICAL EXPERIENCE WITH HEMATOPOIETIC GROWTH FACTORS

Table 5.3 summarizes potential clinical uses for HGFs.

Table 5.3 Potential Clinical Applications for Hematopoietic Growth Factors

Decrease chemotherapy-induced myelosuppression
Stimulate hematopoiesis in marrow failure
Promote cellular differentiation
Support peripheral stem cell harvesting
Decrease the length of antibiotic therapy

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Erythropoietin

Because the kidneys produce 90% of endogenous erythropoietin, patients with renal failure have low levels of erythropoietin and chronic anemia.

- Administration of Epo stimulated erythropoiesis in these patients, usually increasing the reticulocyte count within 10 days and increasing the hematocrit two to six weeks after therapy.
- Patients with renal failure typically became independent of transfusions on Epo dosages of 50 to 300 units/kg 3 times weekly.

Patients with *HIV* may respond to Epo.

- Patients with erythropoietin levels less than or equal to 500 mUnits/ml generally responded to Epo therapy.
- Those patients with levels greater than 500 mUnits/mL did not respond.

In patients with cancer, anemia may be related to the disease or to chemotherapy administration.

- Patients with lower endogenous erythropoietin levels responded to Epo therapy.

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

Initial studies were conducted in patients with AIDS, myelodysplastic syndromes (MDS), and those receiving myelosuppressive chemotherapy.

In patients with AIDS

- The use of GM-CSF allowed some patients to receive myelosuppressive drugs.
- Increased WBC counts were documented along with side effects such as edema, weight gain, and myalgias.
- An increased number of circulating neutrophils and increased function of neutrophils occurred when GM-CSF was given intravenously.

When GM-CSF was given to patients with MDS

- Neutrophil levels increased.
- Infections and transfusions decreased.
- No significant risk of HGF-induced transformation to acute leukemias was documented in the initial clinical trials.

In clinical trials evaluating GM-CSF, a dose-response leukocytosis occurred with continuous intravenous infu-

sion, bolus intravenous infusion, and subcutaneous injection. In patients receiving myelosuppressive chemotherapy, neutropenic fever, antibiotic treatment, and hospitalization were reduced.

After high-dose chemotherapy followed by autologous bone marrow transplant, neutropenia was reduced from 18 to 12 days; platelet recovery did not occur any earlier. Patients receiving GM-CSF had shorter fevers, decreased transfusions, and fewer days of hospitalization.

GM-CSF used in allogeneic BMT is well tolerated and does not increase graft-versus-host disease (GVHD). GM-CSF is more effective in patients who receive GVHD prophylaxis with cyclosporine (CSA) and prednisone rather than CSA and methotrexate.

Both G-CSF and GM-CSF are effective in promoting neutrophil recovery after chemotherapy for acute myelogenous leukemia (AML), with no evidence of CSF-induced blast cell acceleration. GM-CSF was given to high-risk elderly patients newly diagnosed with AML. Growth factors have been used to recruit AML blast cells into the S phase of the cell cycle, followed immediately by high-dose chemotherapy. This therapy significantly increased cell kill.

Granulocyte Colony-Stimulating Factor (G-CSF)

Patients with MDS treated with intravenous G-CSF:

- Had rapid increases in peripheral leukocyte and marrow granulocyte precursor levels, with no increase in blast cell level.
- When subcutaneous G-CSF was used, 10 of 12 patients had 5- to 40-fold increases in neutrophils.

Patients who received G-CSF after chemotherapy:

- Experienced a lower incidence of febrile neutropenia.
- Had a significant reduction in days on antibiotics and days of hospitalization.

Patients with advanced cancer who received a continuous subcutaneous infusion of G-CSF or GM-CSF experienced less myelosuppression than control patients. The subcutaneous route was more effective than intravenous bolus infusion.

A dose-response leukocytosis is achieved with continuous intravenous infusion, bolus intravenous infusion, and subcutaneous infusion of G-CSF. In studies of patients who received myelosuppressive chemotherapy, the days of neutropenic fever, treatment with antibiotics, and hospitalization were reduced.

G-CSF increases levels of circulating peripheral blood stem cells (PBSC). These cells are harvested by leukopheresis and used as an alternative to bone marrow for hematopoietic rescue after high-dose chemotherapy. Hematopoietic growth factors can increase the number of progenitor cells for harvesting. One study demonstrated that the PBSCs collected increased by 83 times.

Several studies have shown the impact of G-CSF on chemotherapy dose intensification. With increased dose and frequency of doxorubicin to two to three times the normal levels in patients with advanced breast or ovarian cancer, G-CSF allowed the cytotoxic drugs to be given at 14-day intervals. Dose-limiting effects were mucositis and skin toxicity.

Interleukin-11 (IL-11)

In patients with cancer who received IL-11 after chemotherapy, the following clinical effects were seen:

- Reduction of the incidence of severe chemotherapy-induced platelet depletion
- Reduction of the need for platelet transfusion
- Reduction in the number of platelet transfusions

REGULATORY APPROVALS

Approved Agents

Granulocyte Colony-Stimulating Factor

G-CSF (filgrastim, Neupogen®) first received regulatory approval by the FDA in 1991 to decrease infections in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. Additional approvals are for post-BMT use in nonmyeloid malignancies, for mobilization of hematopoietic progenitor cells in peripheral blood stem cells (PBSC) transplantation, to support the treatment of patients with acute myeloid leukemia, and in the treatment of severe chronic neutropenia.

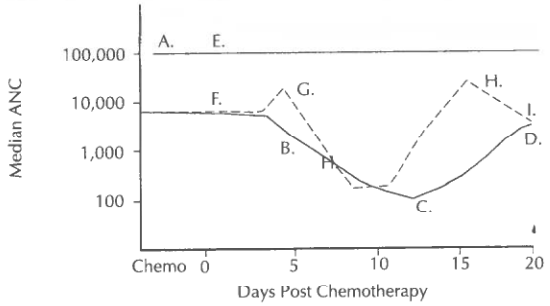
Filgrastim may be given intravenously over at least 30 minutes diluted to less than 2 mcg/mL. Filgrastim is diluted with 5% dextrose and is not compatible with saline. Because the levels of neutrophils decrease by about 50% in the first 24 hours after G-CSF is discontinued, it must be given past the expected nadir (see Figure 5.2) for up to two weeks or until the neutrophil counts exceed 10,000 cells/mm^3.

Granulocyte-Macrophage Colony-Stimulating Factor

GM-CSF (sargramostim, Leukine®) first received approval by the FDA to accelerate myeloid recovery in patients undergoing autologous bone marrow transplant. Additional approvals now include the following:

- For treatment of bone marrow engraftment failure or delay
- After induction chemotherapy in older adults with acute mylogenous leukemia
- Myeloid reconstitution following autologous peripheral blood progenitor transplant
- Mobilization of autologous peripheral blood progenitor cells
- Acceleration of myeloid recovery in patients undergoing allogeneic bone marrow transplant from HLA-matched related donors

Figure 5-2 Effect of HGF on Neutrophil Recovery Following Chemotherapy



Infection risk and prophylaxis in a patient who was receiving myelosuppressive chemotherapy. (A) Chemotherapy is administered with varying numbers and combinations of drugs. (B) In response to interrupted blood cell production, the absolute neutrophil count (ANC) begins to decrease (solid line). (C) The nadir, or lowest ANC, usually occurs 10 to 14 days after chemotherapy begins. (D) Recovery of ANC is seen three to four weeks after chemotherapy begins. (E) Prophylactic antibiotics may be given to protect the patient throughout the period of neutropenia. (F) Colony-stimulating factors (CSFs) may be administered daily beginning 24 hours after therapy ends. (G) A rise in the ANC was due to the release of reserve cells from the marrow (broken line). (H) The nadir occurs earlier than expected, is of a shorter duration and is less severe, and the ANC recovers rapidly. The CSF therapy is discontinued when the ANC exceeds 10,000/ mm^3. (I) The ANC decreases by half in 24 hours after discontinuation; the patient continues to produce neutrophils at normal levels.
Source: Reprinted with permission from: Wujcik, D. 1993. Infection control in oncology patients. *Nursing Clinics of North America* 28(3): 639–50.

Erythropoietin

Erythropoietin (epoetin alfa) is marketed under two trade names: Epogen® and ProCrit®. Epogen® is approved by the FDA for the treatment of chronic renal failure requiring dialysis. ProCrit® has regulatory approval for use in chronic renal failure, the treatment of patients with HIV infection requiring myelosuppressive therapy (e.g., therapy with AZT), and the treatment of anemia resulting from the administration of cancer chemotherapy. The most recent indication is to reduce the need for transfusion in anemic patients scheduled to undergo elective noncardiac, nonvascular surgery.

Interleukin-11

Interleukin-11 (oprelvekin, Neumega®) received regulatory approval in November 1997 to promote the production of the body's supply of platelets in patients with cancer (either solid tumors or lymphoma) who are undergoing chemotherapy.

WHAT ARE THE SIDE EFFECTS OF HGFs?

In general, HGFs are well tolerated and have few side effects.

For a complete review, see Table 5.1.

CLINICAL ISSUES

Timing and Length of Therapy

In general, HGFs should be given no sooner than 24 to 72 hours after chemotherapy. The optimal length of HGF therapy remains unclear. Guidelines published by the American Society of Clinical Oncology (ASCO) recommend continuing until the absolute neutrophil count (ANC) is greater than 10,000/mm^3.

Dose Intensification

HGFs have the ability to reduce morbidity and make chemotherapy regimens more tolerable. The use of HGFs may allow for dose-intensification of therapy that could translate into improved survival. Currently, results are far from definitive. ASCO guidelines do not recommend HGFs to augment dose intensification.

INVESTIGATIONAL AGENTS

Stem Cell Factor

Stem cell factor (SCF) acts on the earliest progenitors and

possibly on the PPSC. It is also known as steel factor, kit ligand, and mast cell growth factor.

SCF interacts with the primitive cells and supports growth of colonies when used with other HGFs. Compared with GM-CSF and IL-3, SCF produces a greater number of and larger cell colonies. However, exposure of bone marrow cultures to SCF alone does not result in significant colony formation. When SCF is given with G-CSF, GM-CSF, or IL-3, both colony size and number increase.

SCF has a number of potential applications. Expansion of a progenitor population responsive to a later, more lineage-restricted hematopoietin seems possible. In addition, SCF may decrease the dose of a second growth factor needed to stimulate colonies. Another potential is to accelerate marrow regeneration in bone marrow transplantation.

Current studies are evaluating its use with other cytokines in mobilization of PBSC for transplantation.

STEMGEN® (Ancestim), a major regulator of stem cells, is produced by Amgen. Amgen filed a U.S. license application for STEMGEN® in April 1997. A phase III clinical trial demonstrated that the combination of STEMGEN® and NEUPOGEN® reduced the number of collection procedures required to collect an optimal target of stem cells for breast cancer patients preparing to receive high-dose chemotherapy.

In July 1998, the Biological Response Modifier's Advisory Committee (BRMAC) to the Food and Drug Administration (FDA) voted 10 to 1 to recommend the approval of STEMGEN®. It is currently under review for approval for licensure by the Food and Drug Administration.

Macrophage Colony-Stimulating Factor

M-CSF is lineage-specific and supports the activation of monocytes and progenitors. Monocytes stimulated by M-CSF have greater cytotoxicity in fungal infections than normal monocytes. M-CSF may be useful in treating fungal infections refractory to amphotericin B therapy.

Interleukin-3

IL-3 is a multilineage HGF and acts on early progenitor cells. Alone it is the most effective cytokine in supporting CFU-GEMM colony formation in humans and is a more potent stimulator of megakaryocytopoiesis than other HGFs. IL-3 also increases the number of leukocytes, platelets, and reticulocytes.

IL-3 continues to be evaluated in clinical trials.

Platelet Growth Factors

A number of HGFs, including IL-1, IL-3, GM-CSF, IL-6, PIXY 321, and SCF, have been studied in the hope of lessening chemotherapy-induced thrombocytopenia. Each of these has demonstrated minimal efficacy and moderate to excessive toxicity. Preclinical trials with two new growth factors, thrombopoietin (TPO) and megakaryocyte growth and development factor (MGDF), have demonstrated a dose response in platelets similar to the response of neutrophils to G-CSF or GM-CSF.

Thromobopoietin (TPO)

The term *thromobopoeitin* was first used in 1958 to describe the humoral substance responsible for the rebound thrombocytosis (increased platelet count) that follows states of thrombocytopenia. Since then, belief in the existence of a distinct regulator of platelet production varied as the purification and cloning of this protein remained elusive. The cloning of TPO was first reported in June 1994. Clinical trials began in mid-1995.

Thrombopoietin is a naturally occurring glycosylated polypeptide that

- Stimulates proliferation and differentiation of bone marrow stem cells
- Stimulates megakaryocytic progenitor cells into mature megakaryocytes, resulting in an increased number of platelets

Preclinical testing with full-length recombinant thrombopoietin produced impressive results. Administration increased platelet production 10-fold in normal mice and monkeys.

Phase I/II trials evaluating the clinical efficacy of thrombopoietin indicate the following:

- Increased platelet count over baseline when TPO was given after chemotherapy
- Long half-life, often dosing only once per week
- Delayed response
- Well tolerated, mild transient headache
- Dosing by IV or SC routes

Phase III trials are currently in progress.

Proposed clinical uses include accelerating platelet recovery after myelosuppressive therapy. The rationale for this is as follows:

- Endogenous thrombopoietin levels do not increase immediately after chemotherapy. This provides a window during which the exogenous hormone could immediately begin the process of megakaryocyte recovery before the patient mounts his or her own response.
- Platelet transfusions suppress blood levels of the hormone. Administered thrombopoietin could overcome this suppressive effect.
- Preclinical trials using several different myelosuppressive protocols were uniformly successful in ameliorating thrombocytopenia. Nadir platelet counts improved, and the duration of thrombocytopenia decreased substantially.

Megakaryocyte Growth Development Factor (MGDF)

Megakaryocyte growth and development factor (MGDF) is a truncated, pegylated derivative molecule of thrombopoietin. Preclinical studies in monkeys demonstrated significant increases in platelet counts.

Phase I/II trials indicate

- Dose-related increase in platelet counts
- Platelet recovery enhanced over placebo
- Decreased duration and severity of thrombocytopenia
- The drug is well tolerated
- Dosing used the SC route

MGDF was also found to boost platelet production in healthy donors.

Phase III trials are in progress.

COMBINATIONS OF HEMATOPOIETIC GROWTH FACTORS

G-CSF and Epo prevented anemia and neutropenia in AIDS patients receiving zidovudine. Other combinations of HGFs, such as IL-3 and GM-CSF, indicate that sequential administration produces better results than simultaneous administration.

Fusion Molecules

One approach has been to try to genetically engineer molecules that are composed of two growth factors fused together. IL-3 and GM-CSF have been combined into a molecule, named PIXY 321, with 10 to 20 times greater bioactivity than either growth factor alone. This molecule was administered in clinical trials by either the subcutaneous route once or twice daily or intravenously over two hours.

Patients with sarcoma treated with cyclophosphamide, doxorubicin, and dacarbazine received PIXY 321 subcutaneously twice daily before the first doses of chemotherapy and after the second cycle of chemotherapy. A dosage of 750 mcg/m^2 was optimal for decreasing myelosuppression and reducing cumulative thrombocytopenia. Local skin reactions and mild constitutional symptoms were the only side effects. Randomized trials have not proven superiority of PIXY 321 to current standard therapy.

FUTURE DIRECTIONS

- Continued development of clinical guidelines that will assist in optimizing the use of HGFs
- Investigation of second-generation molecules that demonstrate improved activity over the natural molecules. Examples include:
  - Filgrastim SD-01: Currently in phase II studies to evaluate the safety and preliminary efficacy, Filgrastim SD-01 is a second-generation molecule composed of the protein Filgrastim to which a polyethylene glycol (PEG) has been bound. Pegylated proteins have increased plasma half-life and, as a result, circulate longer in the body. Therefore, patients generally require fewer injections.
  - Novel erythropoiesis stimulating protein (NESP): NESP, a non-naturally occurring recombinant protein, is being evaluated for its potential to stimulate the production of red blood cells. It has an increased serum half-life compared with Epo and may offer a clinical advantage by allowing less frequent dosing.
  - Continued evaluation of combinations of HGFs that will optimize patient care.
  - The use of HGFs in primary and secondary bone marrow failure states.

QUICK SUMMARY

AGENT: Oprelvekin (Neumega®)
Manufacturer: Genetics Institute, Inc., Cambridge, Mass.,
Subsidiary of American Home Products

First received regulatory approval November 1997

WEBSITES:
www.genetics.com/genetics/genetics/index.htm
www.neumega.com

Oprelvekin, the active ingredient in Neumega®, is produced in *Escherichia coli* by recombinant DNA methods. The protein is nonglycosylated. Oprelvekin (interleukin-11) is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and includes megakaryocyte maturation, resulting in increased platelet production.

REGULATORY APPROVALS

Disease	*Dosing*
Neumega® is indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive	50mcg/kg once daily started by subcutaneous injection 6 to 24 hours following chemotherapy

(continued)

Neumega® *continued*

chemotherapy in patients with non-myeloid malignancies who are at high risk of severe thrombocytopenia.

PHARMACOKINETICS

Peak serum levels following subcutaneous injection of 50 mcg/kg occurred at 3.2 hours postinjection. Terminal half-life was approximately seven hours.

Elimination: Primarily in the kidney, molecule is metabolized prior to excretion.

WHAT SIDE EFFECTS ARE SEEN WITH NEUMEGA®?

Adverse events associated with Neumega® were mild to moderate in severity, associated with fluid retention, and were reversible after discontinuation of dosing. The most common adverse events associated with Neumega® treatment included

- Peripheral edema
- Dyspnea
- Tachycardia
- Conjunctival redness

SETTING: Ambulatory

DIAGNOSTIC/LABORATORY TESTS

Complete blood count, including platelet count, prior to chemotherapy and at regular intervals during oprelvekin therapy. Monitor platelet counts during the time of the expected nadir and until adequate recovery has occurred.

MONITORING

- Monitor fluid balance and institute appropriate medical management as required
- Continue dosing until postnadir platelet count is ≥ 50,000 cells/mcl

ADMINISTRATION

Vial Sizes

Neumega® is available for subcutaneous administration in single-use vials containing 5 mg of oprelvekin (specific activity approximately 8 x 10^6 Units/mg) as a sterile, lyophilized powder with 23 mg Glycine, USP, 1.6 mg dibasic sodium phosphate heptahydrate, USP, and 0.55 mg monobasic sodium phosphate monohydrate, USP.

When reconstituted with 1 mL of sterile water for injection, USP, the resulting solution has a pH of 7.0 and a concentration of 5 mg/mL.

Reconstitution: Direct diluent against the side of the vial and swirl contents gently. Avoid excessive or vigorous agitations. Use within three hours of reconstitution. *Do not reenter or reuse the single-use vials. Discard any unused portion.*

Neumega® *continued*

Storage/stability: Store in a refrigerator at 2° to 8° C.

Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Hypersensitivity to oprelvekin or any component of the product.
- Oprelvekin is known to cause fluid retention; use with caution in patients with clinically evident congestive heart failure (CHF) and in patients who may be susceptible to developing CHF.
- Monitor preexisting fluid collections, such as pleural effusions or pericardial effusions or ascites. Consider drainage if medically indicated.
- *Capillary leak syndrome has not been observed.*

RESOURCES FOR PATIENTS

Neumega® Access Program, a program available to uninsured and underinsured patients based on financial status.

A Patient Information Booklet is under development.

RESOURCES FOR PROFESSIONALS

See Website: www.neumega.com

Complete prescribing information

Product press release

Request for further information

Coming: online discussion event

QUICK SUMMARY

AGENT: Filgrastim (Neupogen®)
Manufacturer: Amgen, Inc., Thousand Oaks, Calif.

First received regulatory approval February 1991.

WEBSITE: www.amgen.com

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Filgrastim is produced by *Eschericia coli* bacteria inserted with the human G-CSF gene. As a natural body protein, G-CSF regulates the production of neutrophils within the bone marrow.

REGULATORY APPROVALS

Disease	*Dosing*
In patients with cancer, following myeloablative chemotherapy to reduce the incidence of infection in patients with non-myeloid malignancies.	5 mcg/kg/day given daily by either SC injection, IV bolus infusion, or continuous SC or IV infusion. Administer no earlier than 24 hours following chemotherapy.

Bone marrow transplant: To reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by BMT.	10mcg/kg/day given as an IV infusion of 4 or 24 hours or as a continuous 24-hour SC infusion. Administer at least 24-hours following chemotherapy or BMT infusion. Titrate dose by response.
Peripheral blood progenitor cell (PBPC) collection: For the mobilization of hematopoietic progenitor cells into the peripheral blood for leukapheresis collection.	10mcg/kg/day SC, as a bolus or continuous infusion. It is recommended that Filgrastim be given for at least four days before the first leukapheresis.
Severe chronic neutropenia (SCN): To reduce the incidence and duration of sequelae of neutropenia.	Congenital: 6mcg/kg twice daily SC every day. Idiopathic or cyclic: 5 mcg/kg as a single injection daily. Adjust dose based on patient's clinical course as well as ANC.

PHARMACOKINETICS

Peak serum levels following subcutaneous injection occurred within two to eight hours following dosing, with longer time corresponding with higher doses. The elimination half-life is approximately 3.5 hours.

Neupogen® *continued*

WHAT SIDE EFFECTS ARE SEEN WITH NEUPOGEN®?

Adverse events associated with Neupogen® were mild. The majority of adverse experiences in clinical trials were associated with the underlying malignancy or cytotoxic chemotherapy. The most common adverse event associated with Neupogen® treatment was medullary bone pain.

Other effects include decreased platelet count, but counts will generally remain within normal limits.

SETTING: Ambulatory

DIAGNOSTIC/LABORATORY TESTS

Complete blood count, including differential, and platelet count prior to chemotherapy and at regular intervals (twice per week following chemotherapy; three times per week following BMT) during filgrastim therapy. Monitoring during the time of recovery of neutrophils is important to avoid leukocytosis.

MONITORING

An initial rise in the neutrophil count is expected. It is important to continue dosing until the postnadir absolute neutrophil count is ≥ 10,000 cells/mm^3.

ADMINISTRATION

Vial Sizes

Neupogen® is available for subcutaneous administration in single-use vials containing 300 mcg/mL or 480 mcg/1.6mL of liquid.

The vials are preservative-free; do not reenter or reuse the vials. Discard any unused portion.

Neupogen® may be diluted in 5% dextrose solution for IV administration. *Do not dilute with saline at any time; product may precipitate.*

At concentrations between 5 and 15 mcg/mL, filgrastim should be protected from absorption to plastic materials by the addition of albumin (human) to a final concentration of 2 mg/mL.

Admixture incompatibilities: Amphotericin B; cefonicid; cefoperazone; cefotaxime; cefoxtin; ceftizoxime; ceftriaxone; cefuroxime; clindamycin; dactinomycin; etoposide; fluorouracil; furosemide; heparin; mannitol; metronidazole; methylprednisolone; mezlocillin; mitomycin; prochlorperazine; piperacillin; thiotepa.

Storage/stability: Store in a refrigerator at 2° to 8°C.
Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

Hypersensitivity to filgrastim or any component of the product.

Neupogen® *continued*

RESOURCES FOR PATIENTS

Patient Information Brochures (available in printed format and online through the Amgen Website).

"NEUPOGEN® (Filgrastim) Part of the Good News About Today's Chemotherapy," information about a particular side effect of chemotherapy, a low white blood cell count, and how one drug, NEUPOGEN® (Filgrastim), helps manage it.

"The Most Important Part of Your Treatment Is You." The more you know about cancer, the more you can participate in its treatment. Learn about where to find sources of information and what questions to ask of your doctor.

"The First Step in Chemotherapy Is Overcoming Your Fear," information about medicines that are available to manage side effects of chemotherapy and help you lead a more active life.

"What I Wish I Knew," a brief description of a free informative video that presents six women who offer hope and help in dealing with breast cancer. Six women give different, yet similar, perspectives on dealing with breast cancer. To order, go online or call 1-888-268-1191.

Consumer information line: 1-888-508-8088.

RESOURCES FOR PROFESSIONALS

See website: www.amgen.com

Professional Services Department
1-800-772-6436 (1-800-77-AMGEN)

Filgrastim Slide Program (order online or through product sales representative)

Amgen Clinical Support Specialist —Available for consultation or to provide programs related to the use of hematopoietic growth factors and patient management. Access by contacting Amgen product sales representative.

Professional Speakers Bureau

QUICK SUMMARY

AGENT: Epoetin alfa (ProCrit®)
Manufacturer: Amgen Inc., Thousand Oaks, Calif.
Distributed by: Ortho Biotech, Raritan, N. J.

WEBSITE: www.procrit.com

PROCRIT® is a genetically engineered version of the body's natural hormone erythropoietin. Produced primarily in the kidneys, erythropoietin stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Epoetin alfa is manufactured by recombinant DNA technology; the gene for human erythropoietin is inserted into mammalian cells. The recombinant product contains the identical amino acid sequence of natural erythropoietin.

Through a product licensing agreement, Johnson & Johnson acquired the rights to develop and market recombinant human erythropoietin. In the United States, Ortho Biotech (Ortho Biotech was established in 1990 by Johnson & Johnson as the first biotechnology subsidiary of a major health care company) markets recombinant human erythropoietin, manufactured by Amgen, Inc., under the trade name PROCRIT® (Epoetin alfa) for the anemias associated with cancer chemotherapy for nonmyeloid malignancies, HIV-infected AZT-treated patients, and chronic renal failure (CRF) patients not yet on dialysis. In December 1996, PROCRIT® gained FDA clearance for another indication. It now is also indicated for the treatment of anemic patients scheduled to undergo elective, noncardiac, nonvascular surgery. Janssen/Cilag, a Johnson & Johnson compa-

ny, markets this product internationally under the trade name EPREX® for a variety of indications, including CRF patients receiving dialysis treatment.

REGULATORY APPROVALS

Disease	*Dosing*
Approved for the treatment of anemia in patients with chronic renal failure	50 to100 U/kg 3x/week by intravenous infusion or SC until target hemoglobin is reached
Approved for the treatment of anemia in AZT-treated HIV-infected patients (Epo level ≤ 500 mU/mL)	100 U/kg 3x/week SC injection or by intravenous infusion for eight weeks—starting dose
Approved for the treatment of anemia in cancer patients on chemotherapy	150 U/kg 3x/week SC until target hemoglobin is reached. Alternate schedule: Some institutions have tried an alternate schedule of 40,000 U SC q week. If after four weeks Hgb level has not increased more than 1 g/dl from baseline, dose may be increased to 60,000 U weekly.

ProCrit® *continued*

Reduction of allogeneic blood transfusions in surgery patients (elective, nonvascular, noncardiac surgery)	300 U/kg/day SC for 10 days prior to surgery, the day of surgery, and four days after surgery. Alternate schedule: 600 U/kg SC q week (21, 14, and 7 days before surgery and on day of surgery).

PHARMACOKINETICS

Circulating half-life is 4 to 13 hours in patients with CRF following IV administration. Peak serum levels are achieved from 5 to 24 hours after SC administration in patients with CRF and decline slowly thereafter.

WHAT SIDE EFFECTS ARE SEEN WITH PROCRIT®?

In general, epoetin alfa is well tolerated. In the CRF population, the most common side effects observed were hypertension and headache.

Monitor blood pressure at baseline and at regular intervals.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

At baseline perform CBC with differential and platelet count and repeat at regular intervals as clinically determined.

Determine hematocrit twice weekly (CRF) and once weekly (HIV-infected patients and patients with cancer) until stabilized, then at regular intervals.

- Because of the time required for erythropoiesis and the red cell half-life, allow a minimum of four weeks to determine initial responsiveness. Following a dosage adjustment, allow two to six weeks to determine effectiveness.
- See package insert for full instructions for dosage adjustments.

Suggested target hematocrit range is 30 to 36%.

If hematocrit increases too rapidly (> 4 points in a two-week period), dosage should be decreased.

Prior to and during therapy, monitor patient's iron status by measurement of serum ferritin (should be at least 100 ng/mL) and transferrin saturation (should be at least 20%). Patients may require supplementation with ferrous sulfate to achieve full therapeutic benefit of epoetin alfa.

In HIV-infected patients and patients with cancer on chemotherapy, at baseline an erythopoietin (Epo) level will assist in identifying those patients who are most likely to respond to therapy. In HIV-infected patients, those with an initial Epo level ≥500 mU/mL are less likely to respond. In patients with cancer, those with an initial Epo level ≥200 mU/mL are generally not recommended to receive therapy.

Reasons to consider for delayed or diminished response: functional iron deficiency; underlying infectious, inflammatory, or malignant processes; occult blood loss; underlying hematologic diseases; vitamin deficiencies (folic acid or B_{12}); hemolysis; aluminum intoxication; osteitis fibrosa cysitca; and increased zidovudine dosage.

ProCrit® *continued*

ADMINISTRATION

Vial Sizes

Single-use vials of injectable solution with no preservative: 2000 U/mL; 3000 U/mL; 4000 U/mL; 10,000 U/mL

Multidose vials of injectable solution with preservative: 10,000 U/mL in 2-mL vials; 20,000 U/mL in 1-mL vials; 40,000 U/mL (available February 1999)

Do not shake vials as prolonged shaking may denature the glycoprotein, rendering it inactive.

Do not reuse or reenter single-use vials. Discard unused portion.

Multidose vials: Discard 21 days after initial entry.

Compatibility: Do not give in conjunction with other drug solutions.

Storage/stability: Store in a refrigerator at 2° to 8°C.

Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice as it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- The use of epoetin alfa is contraindicated in patients with uncontrolled hypertension or with hypersensitivity to mammalian cell–derived products or the human albumin.
- Not intended as a substitute for emergency transfusion in severe anemia.

RESOURCES FOR PATIENTS

Dimensions of Caring Program

Fatigue booklet

Fatigue video

www.procrit.com/oncology/index.html

"Coping with Cancer"

"Understanding Your Blood Counts"

"Fatigue and Cancer"

RESOURCES FOR PROFESSIONALS

WEBSITE: www.procrit.com

www.thebody.com/ortho/procrit/treatment.html
(An AIDS and HIV information resource)

ProCrit® *continued*

Customer Service: 1-800-325-7504
Reimbursement Hotline: 1-800-553-3851
Fax: 1-908-526-6457

Professional Speakers Bureau (contact product representative): 1-800-2BIOTECH

Peer-to-Peer Network (professional support for questions related to ProCrit® administration) 1-800-984-PEER

Dimensions of Caring Program
8:30 A.M.–5 P.M. EST
1-800-984-PEER

Oncology Nurse Educators
Available for consultation and programs

Check with product sales representative for availability of monographs on anemia and treatment of cancer-related anemia.

QUICK SUMMARY

AGENT: Epoetin alfa (Epogen®)
Manufacturer and distributor:
Amgen, Inc., Thousand Oaks, Calif.

WEBSITE: www.amgen.com

Epogen® is a genetically engineered version of the body's natural hormone erythropoietin. Produced primarily in the kidneys, erythropoietin stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Epoetin alfa is manufactured by recombinant DNA technology; the gene for human erythropoietin is inserted into mammalian cells. The recombinant product contains the identical amino acid sequence of natural erythropoietin.

REGULATORY APPROVALS

Disease	*Dosing*
Approved for the treatment of anemia in patients with chronic renal failure	50 to 100 U/kg 3x/week by intravenous infusion until target hemoglobin is reached

PHARMACOKINETICS

Circulating half-life is 4 to 13 hours in patients with CRF following IV administration. Peak serum levels are achieved from 5 to 24 hours after SC administration in patients with CRF and decline slowly thereafter.

Epogen® *continued*

WHAT SIDE EFFECTS ARE SEEN WITH EPOGEN®?

In general, epoetin alfa is well tolerated. In the CRF population, the most common side effects observed were hypertension and headache.

Monitor blood pressure at baseline and at regular intervals.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

At baseline perform CBC with differential and platelet count and repeat at regular intervals as clinically determined.

Determine hematocrit twice weekly (CRF), then at regular intervals.

- Because of the time required for erythropoiesis and the red cell half-life, allow a minimum of four weeks to determine initial responsiveness. Following a dosage adjustment, allow two to six weeks to determine effectiveness.
- See package insert for full instructions for dosage adjustments.

Suggested target hematocrit range is 30 to 36%. If hematocrit increases too rapidly (> 4 points in a two-week period), dosage should be decreased.

Prior to and during therapy, monitor patient's iron status by measurement of serum ferritin (should be at least 100 ng/mL) and transferrin saturation (should be at least 20%). Patients may require supplementation with ferrous sulfate to achieve full therapeutic benefit of epoetin alfa.

Reasons to consider for delayed or diminished response: functional iron deficiency; underlying infectious, inflammatory, or malignant processes; occult blood loss; underlying hematologic diseases; vitamin deficiencies (folic acid or B_{12}); hemolysis; aluminum intoxication; osteitis fibrosa cystica; and increased zidovudine dosage.

ADMINISTRATION

Vial Sizes

Single-use vials of injectable solution with no preservative: 2000 U/mL; 3000 U/mL; 4000 U/mL; 10,000 U/mL

Multidose vials of injectable solution with preservative: 10,000 U/mL in 2mL vials; 20,000 U/mL in 1 mL vials

Do not shake vials as prolonged shaking may denature the glycoprotein, rendering it inactive.

Do not reuse or reenter single-use vials. Discard unused portion.

Multidose vials: Discard 21 days after initial entry.

Compatibility: Do not give in conjunction with other drug solutions.

Storage/stability: Store in a refrigerator at 2° to 8°C.

Do not freeze.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

Epogen® *continued*

RESOURCES FOR PATIENTS

Online: About Epogen® (epoetin alfa)

Patient Assistance Program

RESOURCES FOR PROFESSIONALS

Online: Epogen® FAQ (most frequently asked questions)

Epogen® backgrounder

Epogen® prescribing information

Epogen® News

Patient Assistance Program

Kidney Disease Resources

QUICK SUMMARY

AGENT: Sargramostim (recombinant human granulocyte-macrophage colony-stimulating factor [GM-CSF]) (Leukine®)
Manufacturer: Immunex, Seattle, Washington

WEBSITE: www.immunex.com

Sargramostim is a recombinant human granulocyte-macrophage colony-stimulating factor produced by recombinant DNA technology in a yeast *(S. cerevisiae)* expression system.

American Home Products (AHP) owns a majority interest in Immunex.

REGULATORY APPROVALS

Disease	*Dosing*
Neutrophil recovery following chemotherapy in acute myelogenous leukemia	The recommended dose is 250 mcg/m^2/day administered intravenously over a four-hour period starting approximately on day 11 or 4 days following the completion of induction chemo-therapy, if the day 10 bone marrow is hypo-plastic with <5% blasts. If a second cycle of induction chemotherapy is necessary,

Leukine® *continued*

	Leukine® should be administered approximately four days after the completion of chemotherapy if the bone marrow is hypoplastic with <5% blasts. Leukine® should be continued until an ANC >1500/mm^3 for three consecutive days or a maximum of 42 days. Leukine® should be discontinued immediately if leukemic regrowth occurs. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates.
Mobilization of peripheral blood progenitor cells	The recommended dose is 250 mcg/m^2/day administered IV over 24 hours or SC once daily. Dosing should continue at the same dose through the period of PBPC collection. The optimal schedule for PBPC collection has not been established.

	If WBC > 50,000 cells/mm^3, the Leukine® dose should be reduced by 50%. If adequate numbers of progenitor cells are not collected, other mobilization therapy should be considered.
Post peripheral blood progenitor cell transplantation	The recommended dose is 250 mcg/m^2/day administered IV over 24 hours or SC once daily beginning immediately following infusion of progenitor cells and continuing until an ANC >1500/mm^3 for three consecutive days is attained.
Myeloid reconstitution after autologous or allogeneic bone marrow transplantation	The recommended dose is 250 mcg/m^2/day for 21 days administered IV over a two-hour period beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or

Leukine® *continued*

	radiotherapy. Patients should not receive Leukine® until the postmarrow infusion ANC is less than 500 cells/mm^3. Leukine® should be continued until an ANC >1500/mm^3 for three consecutive days is attained. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates. Leukine® should be discontinued immediately if blast cells appear or disease progression occurs.
Bone marrow transplantation failure or engraftment delay	The recommended dose is 250 mcg/m^2/day for 14 days as a two-hour IV infusion. The dose can be repeated after seven days off therapy if engraftment has not occurred. If engraftment still has not occurred, a third course of 500 mcg/m^2/day for 14

days may be tried after another seven days off therapy. If there is still no improvement, it is unlikely that further dose escalation will be beneficial. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates. Leukine® should be discontinued immediately if blast cells appear or disease progression occurs.

PHARMACOKINETICS

At doses of 250 mcg/m^2 given by SC injection, serum levels peaked in approximately three hours.

Metabolism of sargramostim has not been well established.

WHAT SIDE EFFECTS ARE SEEN WITH LEUKINE®?

The most common adverse events were fever, asthenia, headache, bone pain, chills, and myalgia. These systemic events were generally mild or

(continued)

Leukine® *continued*

moderate and were usually prevented or reversed by the administration of analgesics and antipyretics such as acetaminophen.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

In order to avoid potential complications of excessive leukocytosis (WBC > 50,000 cells/mm^3 or ANC > 20,000 cells/mm^3), a CBC with differential is recommended twice per week during Leukine® therapy. Leukine® treatment should be interrupted or the dose reduced by 50% if the ANC exceeds 20,000 cells/mm^3.

Biweekly monitoring of renal and hepatic function in patients with renal or hepatic dysfunction prior to initiation of treatment is recommended.

Carefully monitor body weight and hydration status during administration.

ADMINISTRATION

Vial Sizes

Leukine® liquid is a preserved (1.1% benzyl alcohol), sterile, injectable solution: 500 mcg/mL

Cartons of five multiple-dose vials of liquid 500 mcg/mL Leukine®

Lyophilized Leukine® is a sterile, white, preservative-free, lyophilized powder: 250-mcg or 500-mcg vials

Cartons of five vials of lyophilized 250 mcg Leukine®

Cartons of five vials of lyophilized 500 mcg Leukine®

Both Leukine® liquid and reconstituted lyophilized Leukine® are suitable for SC injection and IV infusion.

Preparation of Leukine®

Lyophilized Leukine® requires reconstitution with 1 mL sterile water for injection, USP or 1 mL bacteriostatic water for injection, USP. The Leukine® liquid injectable and the reconstituted lyophilized Leukine® solutions are clear, colorless, isotonic solutions. The contents of vials reconstituted with different diluents should not be mixed together.

Sterile water for injection, USP (without preservative): Leukine® vials contain no antibacterial preservative, and therefore solutions prepared with sterile water for injection, USP should be administered as soon as possible, and within six hours following reconstitution and/or dilution for IV infusion. The vial should not be reentered or reused. Do not save any unused portion for administration more than six hours following reconstitution.

Leukine® *continued*

Bacteriostatic water for injection, USP (0.9% benzyl alcohol): Reconstituted solutions prepared with bacteriostatic water for Injection, USP (0.9% benzyl alcohol) may be stored for up to 20 days at 2° to 8° C prior to use. Discard reconstituted solution after 20 days. Previously reconstituted solutions mixed with freshly reconstituted solutions must be administered within six hours following mixing. Preparations containing benzyl alcohol (including Leukine® liquid and lyophilized Leukine® reconstituted with bacteriostatic water for injection) should not be used in neonates (see warnings).

Once the vial has been entered, Leukine® liquid may be stored for up to 20 days at 2° to 8° C. Discard any remaining solution after 20 days.

During reconstitution the diluent should be directed at the side of the vial and the contents gently swirled to avoid foaming during dissolution. Avoid excessive or vigorous agitation; do not shake.

Leukine® should be used for SC injection without further dilution.

Dilution for IV infusion should be performed in 0.9% sodium chloride injection, USP. If the final concentration of Leukine® is below 10 mcg/mL, albumin (human) at a final concentration of 0.1% should be added to the saline prior to addition of Leukine® to prevent adsorption to the components of the drug delivery system. To obtain a final concentration of 0.1% albumin (human), add 1 mg albumin (human) per 1 mL 0.9% sodium chloride injection, USP (e.g., use 1 mL 5% albumin [human] in 50 mL 0.9% sodium chloride injection, USP).

An in-line membrane filter should not be used for intravenous infusion of Leukine®.

Storage/stability: Store Leukine® liquid and reconstituted lyophilized Leukine® solutions under refrigeration at 2° to 8° C (36 °–46° F).

Do not freeze.

In the absence of compatibility and stability information, no other medication should be added to infusion solutions containing Leukine®. Use only 0.9% sodium chloride injection, USP to prepare IV infusion solutions.

GENERAL PRECAUTIONS (see package insert for details)

- Do not use in patients with excessive leukemic myeloid blast in the bone marrow or peripheral blood (≥ 10%); known hypersensitivity to GM-CSF, yeast-derived products, or any component of the product; simultaneous administration with cytotoxic chemotherapy or radiotherapy, or administration 24 hours preceding or following chemotherapy or radiotherapy.

- Use with caution in patients with preexisting cardiac disease as occasional transient supraventricular arrhythmias have occurred.

- Occasional sequestration of granulocytes in the pulmonary circulation has occurred following sargramostim infusion, resulting in dyspnea. Monitor patients for any respiratory distress during infusion, especially those patients with preexisting lung disease.

Leukine® *continued*

- In patients with preexisting pleural and pericardial effusions, administration of sargramostim may aggravate fluid retention; use with caution in preexisting fluid retention, pulmonary infiltrates, or congestive heart failure.

- Benzyl alcohol as a preservative has been associated with a fatal "gasping syndrome" in premature infants.

- First dose effects: A syndrome with respiratory distress, hypoxia, flushing, hypotension, syncope, or tachycardia has occurred rarely following the first use. These signs have resolved with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

RESOURCES FOR PATIENTS

Patient Information Leukine® (sargramostim)

Available on Web at:
www.immunex.com/PRODUCTS/HTML/leudefault.html

RESOURCES FOR PROFESSIONALS

www.immunex.com/

Customer Service and Professional Services
1-800-IMMUNEX (1-800-466-8639)

Leukine® slide curriculum

Hematopoiesis chart

Professional Speakers Bureau

Reimbursement Hotline
1-800-321-4669

Video: "Expanding Role of the Community Care Oncology Nurse in the Transplant Setting," CEU credit available

Clinical Pearls

HEMATOPOEITIC GROWTH FACTORS

1. Currently, the majority of hematopoietic growth factors (HGFs) are used as supportive therapy in the oncology setting—to decrease sequelae of hematopoietic toxicity following chemotherapy or bone marrow transplantation or to enhance yield during pheresis for stem cells to be used in peripheral blood stem cell transplantation.
2. The majority of HGFs are well tolerated with minimal side effects. In general, multilineage growth factors such as Interleukin-11 or granulocyte-macrophage colony-stimulating factor tend to have more toxicity, perhaps related to the induction of other cytokines in the body.
3. In the majority of cases, HGFs are given by the subcutaneous route in the ambulatory setting. Patients and/or family members must therefore learn medication self-administration and subcutaneous injection skills. Reimbursement for the drug may be problematic, especially for those patients on Medicare, in the ambulatory setting.
4. In general, with white blood cell growth factors, an increase in white blood cells is seen very quickly following administration. It is important, therefore, to administer the HGF through the expected nadir. For example, an initial rise in WBCs will be seen, followed by a drop, then recovery.
5. With HGFs for other cell lines, such as red blood cells, it may take more time for the clinical effect to be seen. Epoetin alfa often requires four to eight weeks before clinical

results are seen. Therefore, when possible, it is wise to proactively plan for the need for epoetin alfa to avoid severe anemia in patients.

6. Determine whether the institution or clinical setting has guidelines in place for the use of HGF in patients with cancer. Many institutions have adopted guidelines set forth by the American Society of Clinical Oncology.
7. Patients should be educated concerning reportable signs and symptoms such as fever (what temperature is the threshold for reporting fever to the health care team?) and signs/symptoms of infection.

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CHAPTER 6

MONOCLONAL ANTIBODIES

WHAT ARE MONOCLONAL ANTIBODIES?

Antibodies, or *immunoglobulins*, are proteins secreted by the immune system, each in response to a specific foreign antigen. *Monoclonal antibodies (MABs)* are produced from a single clone of cells. MABs generally are artificially produced antibodies that are used in the diagnosis, detection, or treatment of cancer and other diseases.

HOW DO MONOCLONAL ANTIBODIES WORK?

To fully understand how MABs work, it is important to review antibody structure and function.

Antibody Structure

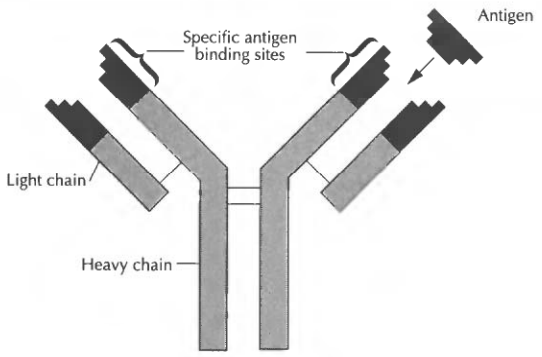
Antibodies are composed of four polypeptide chains, two heavy and two light. Each chain is made up of a constant region and a variable region (see Figure 6.1). The variable region binds to antigen and gives the antibody its potential to react with an infinite number of antigens.

An antibody structure can be separated into three fragments:

Fab (fragment antigen binding): Two antibody fragments that retain the antibody's ability to bind antigen.

Fc (fragment crystallization): Third antibody fragment, can be crystallized out of solution. Fc cannot bind antigens, but it is responsible for the biological functions of the molecule once the antigen binds to the Fab region of the antibody. For example, the Fc fragment can bind with other immune cells and initiate destruction of the bound antigen.

Figure 6.1 Immunoglobulin



Source: From Chiras, D.D. 1995. *Human Biology: Health, Homeostasis, and the Environment.* 3d ed. Boston: Jones and Bartlett.

Mechanisms That Trigger Tumor Cell Destruction

1. Activation of the complement cascade: Certain classes of antibody bind to the complement subcomponent C1q. This complex may trigger phagocytosis of tumor cells. A bond between the antibody and C1q induces the remaining steps in the complement cascade, which lyses cells by disrupting their membranes.
2. Antibody-dependent cell-mediated cytotoxicity: This process occurs when the Fc portion of antibody-coated cells joins by specific receptors with the host's effector cells. The cellular components include natural killer cells, killer T cells, and macrophages. Antibody-coated cells are engulfed by the phagocytic cells in the reticuloendothelial system.

Criteria for Tumor Destruction

Several factors are important to the antibody's ability to locate and destroy the tumor:

- Antibody must not have cross-reactivity with normal tissue.
- Surface membrane antigens on the tumor must be dense.
- Antibody should possess a high affinity for the antigen target.
- Antigen should remain on the tumor surface providing a target. There should be little circulating antigen to react with the antibody before it reaches the tumor.
- Tumor vascularization is also important so that the MAB may be delivered to the tumor site.

MABs may also be conjugated to other substances to increase their effectiveness. MABs have been conjugated with low-dose radioisotopes for use in detection of tumors, or to high-dose radioisotopes for treatment. These are known as *radioimmunoconjugates.* Other conjugates include *chemoimmunoconjugates* (MABs conjugated to chemotherapy) and *protein toxin-antibody conjugates* (e.g., MAB conjugated to diphtheria toxin).

HOW ARE MONOCLONAL ANTIBODIES MADE?

Hybridoma technology was discovered by Köhler and Milstein in 1975 as a methodology to produce a large amount of pure antibody. They capitalized on the properties of two types of cells: antibody-forming B lymphocytes (chosen for their production of antibodies targeted toward a chosen antigen) and malignant plasma cells (chosen for their immortality, or the ability to be main-

tained in cell culture for long periods of time). Köhler and Milstein were awarded the Nobel Prize for their discovery.

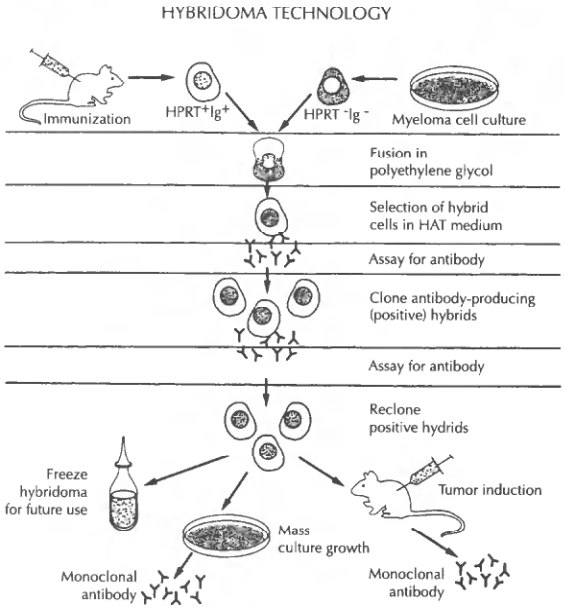
The *hybridoma technique* produces unlimited amounts of pure MAB that vary little from batch to batch and are highly specific for a single *antigenic determinant.* They are usually targeted to oncofetal or differentiation antigens, proteins that are found on all cells but in higher concentrations on malignant cells.

Hybridoma Technology

1. A mouse is immunized with the desired antigen, and an antibody response is allowed to develop.
2. The mouse's spleen is harvested, and the lymphocytes from the spleen are placed in solution with myeloma cells from a culture deficient in the enzyme hypoxanthine phosphoribosyl transferase (HPRT). The myeloma cells are also incapable of antibody production.
3. Only the fused cells (myeloma lymphocytes) will survive.
4. Assay for antibody production is done, and those cells producing the desired antibody are cloned.
5. The hybridoma may be frozen for future use, may be grown in mass culture, or may be used to induce a tumor in the mouse that results in antibody production.

Hybridoma technology results in the production of murine (i.e., mouse) MABs (see Figure 6.2). In recent years, molecular techniques have been used both to speed up antibody production and to produce antibodies composed primarily of human antibody fragments rather than murine antibodies.

Figure 6.2 Hybridoma Technology



Source: Reprinted with permission from DiJulio, J. 1988. Treatment of B-cell and T-cell lymphomas with monoclonal antibodies. *Seminars in Oncology Nursing,* 4:103.

Production of Chimeric Antibodies

Currently humanized antibodies (i.e., chimeric murine/human monoclonal antibody) are produced through genetic engineering. A chimeric antibody may, for example, contain a murine light- and heavy-chain variable region sequence and a human constant region sequence. The gene segments coding for each of these regions are spliced together and inserted into an expression system for production, e.g., mammalian cells (Chinese hamster ovary). Once produced by the expression system, the

antibody goes through a purification process. Many investigators and companies have developed humanized or chimeric antibodies. Both rituximab and trastuzumab are chimeric murine/human monoclonal antibodies.

CLINICAL STUDIES

Monoclonal antibodies have been used in a variety of ways in the management of cancer.

Unconjugated MABs

Native (or unconjugated) MABs—those not bound to drugs, toxins, or isotopes—have been used to treat cancers such as B-cell lymphomas, chronic lymphocytic leukemia, cutaneous T-cell lymphoma, acute lymphocytic leukemia, neuroblastoma, lung malignancies, gastrointestinal malignancies (including colon), breast cancer, and melanoma.

Unconjugated Antibodies and Hematologic Malignancies

Target Antigen CD-5

Patients with T-cell lymphoma, T-cell leukemia, and chronic lymphocytic leukemia have received antibodies directed against the surface antigen CD5.

Results: Transient clearing of cells in patients with chronic B-cell lymphocytic leukemia occurred. Observable tumor responses occurred in patients with T-cell lymphoma. Responses lasted from 1.4 to 4 months, but many were interrupted by development of human antimouse antibodies (HAMA). The HAMA response, which may develop in individuals who are immunocompetent (since MAB is derived from mice), negates the antitumor response.

Differentiation Antigens

Monoclonal antibodies against differentiation antigens have been used to treat patients with non-Hodgkin's lymphoma, as well as both acute and chronic leukemias. Administration of a chimeric anti-CD20 antibody produced significant response rates in patients with relapsed non-Hodgkin's lymphoma. This antibody, Rituximab, has now received regulatory approval for the treatment of lymphoma. The use of MABs targeted toward other differentiation antigens remains under study.

Anti-idiotype MAB Therapy

In B-cell malignancies, the immunoglobulin produced by the tumor provides an ideal tumor marker. The antibody binding site, also known as the *idiotype*, serves as a tumor-specific marker on the surface of the B cell. MABs have been produced against idiotypes and have been studied in clinical trials. Clinical studies have shown that anti-idiotype antibodies are active therapeutic agents in both heavily treated patients and patients who have progressed to higher grade lymphomas. In some centers these anti-idiotype MABs are "tailor-made" for each patient. The practical limitations of existing technology make widespread use of this approach difficult and not cost effective.

Shared Anti-Idiotype Antibodies (SIDs)

Less costly and time-consuming than custom-made anti-idiotypes MABs, SIDs are reactive to lymphoma cells from more than one patient. For example, IDEC Pharmaceutical Corporation has produced 15 anti-idiotype antibodies that react with tumors of 20% of patients with B-cell lymphoma. SIDs are more readily available and may be used for many patients, however their use remains under clinical investigation.

Remission Duration

Delayed onset of response with MAB therapy in the B-cell lymphoma trials, 1 to 2 months following therapy, suggests that the treatment induced an immune response against the tumor. It appears that if patients can enter a complete remission, they will remain disease-free for an extended time.

Solid Tumors

Monoclonal antibodies have been used to treat solid tumors such as colorectal carcinoma, malignant melanoma, and breast cancer. Although treatments are generally well tolerated, HAMA responses were frequent in early trials and tumor-cell kill was limited. When responses were obtained, they generally did not last long.

More than 100 patients with colorectal carcinoma have been treated with the MAB 17-1A, targeted toward a surface antigen in gastrointestinal and other adenocarcinomas. Overall response rate is less than 5%. Current trials are evaluating this antibody in the adjuvant setting and in combination with biological agents such as interferon.

Therapy for malignant melanoma has been attempted with a variety of antibodies. Partial responses have been reported with MABs R24, Me36.1, 3F8, 14G2a, and human L7.

Antibodies that react with the epidermal growth factor receptor (EGFR) have demonstrated the ability to inhibit the growth of tumor cells ex vivo in the absence of complement components or host effector cells. Clinical trials are in progress in such tumors as breast cancer, lung cancer, and head and neck cancers to evaluate the efficacy of anti-EGFR MABs. Antibodies that block the binding of epidermal growth factor to the EGFR affect growth more readily than do antibodies that bind to other sites on the receptor.

Antibodies that react with the extracellular domain of the c-erbB2 (HER2/neu) proto-oncogene product also inhibit tumor cell growth in the absence of complement or immune effector cells. Two recent phase III trials of

recombinant human anti-HER2 monoclonal antibody (trastuzumab), used alone and in combination with chemotherapy, produced significant objective responses in patients with stage IV breast cancer. In September 1998 trastuzumab received regulatory approval for use in patients with metastatic breast cancer who have tumors that overexpress the human epidermal growth factor receptor2 (HER2) protein. It is indicated for treatment both as first-line therapy in combinations with paclitaxel and as a single agent in second- and third-line therapy.

Diagnostic Tool

MABs are used ex vivo to diagnose autoimmune disease, cancer, and myocardial infarction. For example, MABs are used to classify leukemias and lymphomas.

Bone Marrow Purging

MABs have been used to perform immunologic purging of bone marrow after high-dose ablative therapy. MABs are used to purge the bone marrow of residual tumor cells. Once purged, the marrow is used for bone marrow transplantation. This approach has been investigated primarily with leukemias and lymphomas. The use of bone marrow purging has been debated and remains investigational.

Combination Therapy

MABs have been combined with chemotherapy and biological agents in solid tumors. For example, in the treatment of melanoma interleukin-2 has been combined with MABs to augment antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by antibodies. Interferon-α can modulate the expression of cell-surface antigens, thus enhancing tumor targeting by the MAB.

Conjugated MABs

Now undergoing clinical trials are agents formed by coupling antibodies with alpha-, beta-, and gamma-emitting radionuclides; or with protein toxins, such as ricin, pseu-

domonas, and diphtheria; or with chemotherapeutic drugs, such as doxorubicin and methotrexate.

Disadvantages: Instability of the binding between the conjugate and the antibody. Damage to normal tissue can occur if the toxin is freed before reaching the tumor. Both toxins and drugs must be internalized by the cell to cause cell death. This approach remains under clinical investigation.

Radioimmunodetection (RAID)

Conjugates of monoclonal antibodies with isotopes have been developed as a treatment and as a method of imaging tumors. These antibodies are useful in imaging solid tumors such as melanoma; lymphomas; and tumors of the lung, ovaries, and breast.

Optimal radioisotopes: Have high photon energy, 100 to 200 keV; minimal particulate radiation; adequate half-life; low expense; and availability.

FDA-approved agents: Two radiolabeled imaging agents have been approved by the FDA: OncoScint® CR/Ov-In, or indium 111–labeled satumomab pendetide, and ProstaScint®, or indium 111–labeled capromab pendetide.

Radiotherapy

The lymphomas are radiosensitive, and MABs with relative specificity for these tumors already exist. Non-Hodgkin's lymphomas and Hodgkin's disease tumors respond to radioimmunoconjugates, however, bone marrow toxicity remains a major problem.

Iodine 131: Most frequently used radioisotope. Antitumor activity demonstrated in lymphoma and ovarian tumors.

Yttrium 90: In patients with refractory Hodgkin's disease, complete remissions were observed in 30% of evaluable patients treated with yttrium 90–labeled polyclonal antiferritin immunoglobulin.

The use of MABs for radioimmunotherapy remains investigational.

Problems with Using Radioimmunoconjugates

- Since the antibody is usually cleared by the liver, dose may cause liver toxicity.
- Occasionally, the MAB and the radionuclide separate before reaching the intended target.
- Only a fraction of the radiolabeled antibody reaches the tumor.
- Because the antibody must be freshly labeled and exposure to radiation controlled, its use is inconvenient in an outpatient setting.

Chemoimmunoconjugates

No significant responses have yet been seen in clinical trials. Instability of the conjugate of agents such as doxorubicin, methotrexate, chlorambucil, vinca alkaloids, or mitomycin conjugated with MABs appears to be the greatest obstacle.

Protein Toxin-Antibody Conjugates

The usefulness of linking a plant or a bacterial toxin to a tumor-specific MAB has been investigated in solid tumors and hematologic malignancies. Toxins most commonly conjugated with MABs are ricin-A chain, diphtheria toxin, and the genetically modified *Pseudomonas* exotoxin *(PE4O)*.

Mechanism: Immunotoxins are transported to the tumor cell surface by the MAB. After binding to the antigen, the complex is internalized. Toxin escapes to the cytosol, crosses the cell membrane, and inhibits protein synthesis, leading to cell kill. Toxins kill not only dividing cells but also resting cells.

Clinical Trials: Trials have been limited by toxicity, immunogenicity of the murine antibody and the immunotoxin, and low response rates with short durations. This approach has been used in patients with both solid tumors (e.g., melanoma and colorectal cancers) and leukemias and lymphomas.

REGULATORY APPROVAL

Two MABs have received regulatory approval for the detection of cancer: OncoScint® CR/Ov-In, or indium 111–labeled satumomab pendetide, is used for determining the extent and location of extrahepatic malignant disease in patients with colon or ovarian cancer. ProstaScint®, or indium 111–labeled capromab pendetide, is an imaging agent that targets prostate-specific membrane antigen (PSMA), a glycoprotein expressed by prostatic epithelium. ProstaScint® can provide additional information about disease spread for both newly diagnosed prostate cancer patients and post-prostatectomy patients who return with rising serum PSA levels.

Two MABs have been approved for the treatment of cancer: Rituxan™ (rituximab) is used for the treatment of patients with relapsed or refractory low-grade or follicullar, CD20-positive, B-cell non-Hodgkin's lymphoma. Herceptin® (trastuzumab) is used for the treatment of metastatic breast cancer in patients who have tumors that overexpress the HER2 protein. It is indicated for treatment of patients both as first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy.

WHAT ARE THE SIDE EFFECTS OF MAB THERAPY?

Most toxic effects are transient and respond to standard interventions. In general, the major toxicities are a result of allergic reactions against murine antibodies, reactions of administered MAB with circulating cells, or the result of conjugates fused with the antibody (e.g., immunotoxins or radioisotopes).

Anti-idiotype Antibodies

Anti-idiotype antibodies used for the treatment of non-Hodgkin's B-cell lymphomas cause the following:

Infusion-related toxic effects

Fever (T > 38° C)
Chills
Rigor
Urticaria
Mucosal congestion
Nausea
Diarrhea myalgia/arthralgia

More severe toxic effects

Bronchospasm
Increased respiratory secretions
Hypotension

Thrombocytopenia

Thrombocytopenia occurred in patients with baseline platelet counts less than 100,000/mm^3. The cause is unclear. The reduction in platelets may result from small amounts of antibody being absorbed by the Fc receptors. Transient granulocytopenia also occurred in patients with baseline white blood cell counts less than 1000 cells/mm^3.

Tumor Flare

Swelling, tenderness, and warmth in lymph nodes occurred in anti-idiotype MAB studies, typically 7 to 14 days after treatment, but they resolve 2 to 7 days later.

High Idiotype Levels

Toxic reactions are generally associated with high levels of circulating tumor cells and high idiotype levels and occur within one to three treatments. Side effects usually resolve once the free idiotype protein or idiotype-positive cells have been cleared from the serum and an excess of antibody can be achieved.

Preventing Allergic Reaction

Slow infusion (rather than bolus infusion) of nonspecific antibodies for treatment of lymphoid malignancies prevents acute allergic reaction and anaphylaxis.

Reducing Toxic Effects

Tailoring antibodies to the specific antigenic binding site of the tumor cell reduces the frequency of toxic effects. Most significant toxic effects developed in patients with prolymphocytic leukemia, chronic lymphocytic lymphoma, or a high level of circulating idiotype.

Side Effects of MAB Treatment of Solid Tumors

Side effects are generally categorized as allergic or nonallergic.

Patients experience allergic symptoms, anaphylaxis, urticaria, nausea, vomiting, diarrhea, and mild constitutional symptoms. If a HAMA reaction occurs, it is usually manifested by fever, rigors, rash, and neutropenia. Allergic reactions are less common in patients receiving chimeric MABs, and similar to those seen with anti-idiotype MABs.

Hematologic Effects of Radiolabeled Antibodies

Bone Marrow Toxicity

Bone marrow toxicity occurs as a result of prolonged circulating antibody-isotope conjugates or free radiolabel released from the conjugate.

Nonhematologic Toxic Effects of Radiolabeled Antibodies

Mild: fever, urticaria, pruritus, malaise, asymptomatic hypothyroidism. Nausea is thought to be due to gastric irradiation caused by the excretion of free iodine 131 by the stomach.

Chemoimmunoconjugates

The usual toxic effects related to antibody occur; if circulating free drug is present, all of the usual side effects of the drug occur. Unusual toxic effects resulting from nonspecific binding of the chemoimmunoconjugate to normal tissues may occur. Myelosuppression is usually the dose-limiting toxic effect.

Immunotoxins

The most severe toxic effects have been attributed to protein toxin-antibody conjugates.

Reversible effects: Noted even at doses too low to yield detectable binding of the immunoconjugate to the target antigen were vascular leak syndrome characterized by weight gain, edema, dyspnea, decreased albumin levels, and hypotension.

Unacceptable effects: Central nervous system toxic effects with *Pseudomonas* exotoxin (PE4O) and ricin A in some trials have included delayed debilitating neuropathy 2 to 3 months after treatment, residual paresthesias lasting 6 months, axonal loss, segmental demyelination, pulmonary edema, weight gain, dyspnea on exertion, arthralgias, fever, and mild elevations in liver enzymes. Because of these toxic effects, further entry of patients into the study was halted.

Hepatotoxicity: SGOT and SGPT levels rose as high as 10 times the upper limit of normal as an effect of treatment with ricin and similarly with diphtheria toxin. Tolerable toxic effects such as fevers, malaise, fatigue, nausea, hypoalbuminemia, and thrombocytopenia were noted.

WHAT ARE OBSTACLES TO TREATMENT WITH MABS?

Antigenic Modulation

This is one of tumor cells' defense mechanisms, in which the antigen is internalized into the cell. Modulation occurs more often with hematopoietic cells than in solid tumor cells. If therapeutic antibody is administered during this modulation, there may not be sufficient binding to cell surfaces to eliminate the target cell.

Importance of Dose Scheduling

Careful scheduling of the antibody doses may circumvent modulation effects, since the modulation reverses itself and the antigen is reexpressed on the cell surface once the antibody disappears. Using biological response modifiers such as interferon-α to upregulate tumor-associated antigens on the cell surface may lead to better binding.

HAMA Response

The development of HAMA was often problematic in early trials with MABs. The development of host antibodies against the protein has a neutralizing effect and inhibits antibody binding. A HAMA response has been observed in patients with hematologic malignancies.

There are three techniques for overcoming HAMA response:

1. Modification of MAB: Researchers are studying ways to overcome the HAMA response. One suggestion is to use immunosuppressive therapy before antibody treatment. The most prevalent method, however, is modification of the antibody. Using a human antibody instead of a mouse antibody is one approach. Manufacture of human monoclonal antibodies involves immortalizing immune B cells with Epstein-Barr virus. The immune B cell is fused with a

human myeloma cell line or a human lymphoblastoid cell line.

2. Chimeric MAB: A second method of antibody modification is to reduce the mouse protein in the antibody by inserting a human gene that codes for the constant region. The human antibody that results is called a *chimeric antibody.* Patients with melanoma, colon cancer, cutaneous T-cell lymphoma, and non-Hodgkin's lymphoma have been treated with chimeric MABs.
3. "Humanized" MAB: A third technique is to include even more human portions in the engineered antibody. MABs thus adapted are "humanized." They are differentiated from chimeric antibodies in that they contain a human constant region and a variable region consisting of both the murine complementarity-determining regions and the human V-region framework determinants. Therefore, only a small portion of the humanized MAB contains mouse genetic material.

Antigen Blockade

Most tumors shed antigen into the serum. When circulating antigen is freely secreted, it prevents administered antibody from reaching the tumor cell and binding. Infusing large amounts of MAB clears excess antigen but poses a risk of toxic effects. Clinical trials using plasmapheresis before and during therapy to clear free idiotype from the serum have not yielded a significant response until excess serum idiotype was depleted and free antibody could persist.

Tumor Heterogeneity

Tumor cells secrete mutant forms of surface immunoglobulin that elude the antibody and allow tumor growth. Somatic mutation in the variable region of the active immunoglobulin genes results in amino acid changes in the immunoglobulin molecule and alteration in the idiotype. Following treatment with anti-idiotype therapy,

these variant cells become the prominent population. Tumor heterogeneity is also a problem when treating solid tumors. For example, because melanomas can express a variety of associated antigens, administration of a single MAB would not allow for detection of tumors expressing a different melanoma-associated antigen.

ARE MABS USED IN OTHER DISEASES BESIDES CANCER?

Preventing Transplant Rejection

The MAB Orthoclone OKT 3 (muromonab-CD3) has been used to treat acute cell-mediated rejection in organ transplants. The antibody reacts with the surface antigen T3 of human T cells and removes the antigen-bearing T cells from circulation, rendering them ineffective in mounting an immune response.

Side Effects

Side effects include fever, chills, nausea, vomiting, and diarrhea. Pulmonary edema was observed in early trials. Generalized aches and malaise are common. Because MAB suppresses the immune system, patients are at risk for bacterial, fungal, and viral infections. Fevers may herald an infection.

Other Uses of MAB

Multidrug resistance in normal and malignant cells has been studied by using MABs targeted toward P-glycoprotein. Future applications of this antibody may include conjugation to biological toxins or cytotoxic drugs.

Studies evaluating the use of MABs to reduce the early morbidity and mortality in seriously ill patients with gram-negative sepsis have demonstrated positive results.

Several MABs have enhanced the ability to diagnose tumors and subsets of tumors. For example, lymphocytes look the same under a microscope, but when they are stained with antibodies that have an affinity to certain surface markers, it is easy to identify T and B cells at different stages of differentiation.

QUICK SUMMARY

AGENT: Rituximab (Rituxan™)
Manufacturer: IDEC/Genentech, South San Francisco, Calif.

WEBSITE: www.gene.com

First received FDA approval November 1997.

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. This antigen is expressed on more than 90% of B-cell non-Hodgkin's lymphomas (NHLs) but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues. The constant portion (Fc) of rituximab recruits immune effector functions to mediate B-cell lysis.

REGULATORY APPROVALS

Disease	*Dosing*
Non-Hodgkin's lymphoma: Treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma	375 mg/m^2 given as an IV infusion weekly for 4 doses

PHARMACOKINETICS

Administration of rituximab results in a rapid and sustained depletion of circulating and tissue-based B cells. Mean serum half-life was 59.8 hours after the first infusion and 174 hours after the fourth infusion. The wide range seen in half-lives may reflect variable tumor burden among patients because peak and trough serum levels are inversely correlated with baseline values for the number of circulating CD20-positive B cells and measures of disease burden.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

Obtain complete blood counts and platelet counts at regular intervals during rituximab therapy and more frequently in patients who develop cytopenias.

ADMINISTRATION

Vial Sizes

10 mg/mL, preservative-free, in 10- and 50-mL single-unit vials.

Storage/stability: Vials are stable at 2 to 8°C. Protect vials from direct sunlight. Stable at room temperature for 12 hours.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler,

Rituxan™ *continued*

near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product may occur.

- For severe allergic reactions (e.g., bronchospasm, hypotension, and angioedema), the infusion should be interrupted and resumed at a 50% reduction in rate once symptoms have completely resolved. Treatment of symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated.

- Emergency drugs (e.g., epinephrine, antihistamines, corticosteroids) should be readily available at the bedside for immediate use in the event of a reaction during administration.

- Infusion-related complex symptom consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other infusion-related symptoms included nausea, urticaria, fatigue, headache, pruritus, bronchospasm, dyspnea, a sensation of tongue or throat swelling, rhinitis, vomiting, hypotension, flushing, and pain at the disease sites. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and they resolved with slowing or interruption of the infusion and with supportive care (IV saline, diphenhydramine, and acetaminophen).

- Rituximab-induced B-cell depletion occurred in 70 to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients. The incidence of infection does not appear to be increased.

- **Do not administer by IV push or as an IV bolus. Hypersensitivity reactions may occur.**

- Consider premedication with acetaminophen and diphenhydramine before each infusion of rituximab. This may attenuate the infusion-related events. Because of the potential for hypotension, consideration should be given to holding hypertensive medication 12 hours prior to the infusion.

- Administer infusion at a rate of 50 mg/hour. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50-mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

- Subsequent infusion can be initiated at a rate of 100 mg/hour and increased by 100 mg/hour to a maximum of 400 mg/hour.

- **Do not mix or dilute rituximab with other drugs. May be mixed for infusion with either 0.9% sodium chloride or 5% dextrose in water.**

RESOURCES FOR PATIENTS

Genentech Assistance Program provides medication for medically indigent patients.

1-800-879-4747

Rituxan™ *continued*

RESOURCES FOR PROFESSIONALS

Full Prescribing Information and On-line Resources currently under development.

Medical Information Line
1-800-821-8590

EDUCATIONAL MATERIALS
Rituxan™ Administration Video
Rituxan™ Administration Resource Kit (Includes dosing, mixing, and administration guidelines and charts, Q&A pamphlet and tearout Patient Information Sheet)

Non-Hodgkin's Lymphoma Classification Wall Chart

Non-Hodgkin's Lymphoma Classification Pocket Pamphlet

QUICK SUMMARY

AGENT: Trastuzumab (Herceptin®)
Manufacturer: Genentech, Inc., South San Francisco, Calif.

Herceptin® (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) [CHO] suspension.

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration.

Approved September 1998.

WEBSITE: www.gene.com

REGULATORY APPROVALS

Disease	*Dosing*
Herceptin® (Trastuzumab) as a single agent is indicated for the treatment of patients with	Initial loading dose 4mg/kg administered as a 90-minute infusion.

(continued)

Herceptin® *continued*

metastatic breast cancer whose tumors overexpress the HER2 (human epidermal growth factor receptor2) protein and who have received one or more chemotherapy regimens for their metastatic disease. Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. Herceptin should only be used in patients whose tumors have HER2 protein overexpression.	Weekly maintenance does of 2mg/kg administered as a 30-minute infusion.

In 25–30% of women with metastatic breast cancer, there is a genetic alteration in the HER2 gene which produces an increased amount of the growth factor receptor protein on the tumor cell surface. This HER2 protein overexpression is associated with more aggressive disease. HER2 protein overexpression is determined by immunohistochemical testing. Patients should contact their physician to discuss testing for HER2 overexpression.

PHARMACOKINETICS

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range = 1 to 32 days) was observed. Between weeks 16 and 32, Trastuzumab serum concentrations reached a steady-state with a mean trough and peak concentrations of approximately 79 microgram/mL and 123 microgram/mL, respectively.

SETTING: May be given in the ambulatory setting

DIAGNOSTIC/LABORATORY TESTS

As clinically indicated.

ADMINISTRATION

Vial Size

Each vial contains 440 mg of Herceptin® as a lyophilized, sterile powder. Each carton contains one vial of 440 mg of Herceptin®; one 30 mL vial of bacteriostatic water for injection, USP, 1.1% benzyl alcohol.

Each vial should be reconstituted with the diluent supplied to yield a multi-dose solution containing 21 mg/mL Trastuzumab. May be used for

Herceptin® *continued*

28 days following reconstitution when stored properly. The Trastuzumab solution should be added to a 250 mL bag of 0.9% sodium chloride, USP. **Dextrose (5%) solution should not be used.** Gently invert the bag to mix the solution.

Storage/stability: Vials of Herceptin® are stable at 2 to 8°C (36 to 46°F) prior to reconstitution.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

No known contraindications.

- **Warning Cardiomyopathy:** Herceptin® administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with Herceptin®. Discontinuation of Herceptin® treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who

received Herceptin® in combination with anthracyclines and cyclophosphamide.

- Candidates for treatment with Herceptin® should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: EKG, echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

- General: Herceptin® (Trastuzumab) therapy should be used with caution in patients with known hypersensitivity to Trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

- Drug Interactions: There have been no formal drug interaction studies performed with Herceptin® in humans.

- Infusion-Associated Symptoms: During the first infusion with Herceptin®, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin® infusion). Herceptin® discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. The symptoms occurred infrequently with subsequent Herceptin® infusions.

Herceptin® *continued*

- **Do not administer as an IV push or bolus.**
- It is advisable to keep emergency drugs (e.g., epinephrine, antihistamines, corticosteroids) readily available at the bedside for immediate use in the event of a reaction during administration.

RESOURCES FOR PROFESSIONALS

On-line product prescribing information

Medical Information Line
1-800-821-8590

QUICK SUMMARY

AGENT: Daclizumab (Zenapax)
Manufacturer: Roche Laboratories, Nutley, N.J.

Approved December 11, 1997.

Daclizumab is an immunosuppressive, humanized IgG MAB produced by recombinant DNA technology that binds specifically to the alpha subunit (Tac subunit) of the human high-affinity interleukin-2 receptor that is expressed on the surface of activated lymphocytes. Daclizumab is a composite of human (90%) and murine (10%) antibody sequences. It functions as an IL-2 receptor antagonist by inhibiting the binding of IL-2 to its receptor. Daclizumab inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

REGULATORY APPROVALS

Disease	*Dosing*
Organ rejection, prophylaxis: Prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.	1 mg/kg IV as a bolus infusion over 15 minutes. The standard course of therapy is for five doses. The first dose should be given ≤24 hours prior to transplantation. Give the four remaining doses at intervals of 14 days.

Zenapax *continued*

PHARMACOKINETICS

In vitro and in vivo data suggest that serum levels of 5 to 10 mcg/mL are necessary for saturation of the Tac subunit of the IL-2 receptors to block the responses of activated T lymphocytes.

WHAT ARE THE SIDE EFFECTS OF ZENAPAX?

The incidence and types of adverse events were similar in both placebo-treated patients and the daclizumab-treated patients (all received cyclosporine and corticosteroids) in preliminary clinical trials. Gastrointestinal disorders were the most commonly reported effects.

SETTING: Ambulatory or inpatient

DIAGNOSTIC/LABORATORY TESTS

As clinically indicated.

ADMINISTRATION

Vial Sizes

25 mg/5 ml, preservative-free, in single-unit vials.

Preparation: Mix the calculated volume of daclizumab with 50 mL of sterile 0.9% sodium chloride solution and administer via a peripheral or central vein over a 15-minute period. When mixing the solution, gently invert the bag to prevent foaming; do not shake.

The product contains no antimicrobial preservative or bacteriostatic agents. Once the solution is prepared, administer IV within 4 hours. May be held longer, refrigerated at 2 to 8°C for 24 hours. If not used within 24 hours, discard.

Storage/stability: Vials are stable at 2 to 8°C. Protect vials from direct sunlight. Stable at room temperature for 4 hours.

GENERAL PRECAUTIONS (see package insert for details)

- Emergency drugs (e.g., epinephrine, antihistamines, corticosteroids) should be readily available at the bedside for immediate use in the event of an allergic reaction during administration. Reactions have not been observed but may occur during the administration of proteins.

- **Do not infuse or add any other drug substances simultaneously through the same IV line.**

QUICK SUMMARY

AGENT: Muromonab-CD3 (Orthoclone OKT3)
Manufacturer: Ortho Biotech, Raritan, N. J.

Muromonab-CD3 is a murine monoclonal antibody to the T3 (CD3) antigen of human T cell which functions as an immunosuppressant. Muromonab-CD3 is for IV use only. The antibody is a biochemically purified IgG2a immunoglobulin. It reverses graft rejection, probably by blocking the T-cell function, which plays a major role in acute allograft rejection.

REGULATORY APPROVALS

Disease	*Dosing*
Organ rejection: Treatment of acute organ rejection in patients receiving renal transplants.	5 mg/day for 10 to 14 days. Begin treatment once acute renal rejection is diagnosed.
Cardiac/hepatic allograft rejection: Treatment of steroid-resistant acute allograft rejection.	5 mg/day for 10 to 14 days. Begin treatment when it is determined that a rejection has not been reversed by an adequate course of corticosteroid therapy.

PHARMACOKINETICS

In vitro and in vivo data suggest that serum levels > 0.8 mcg/mL block the function of cytotoxic T cells.

SETTING: Hospital or ambulatory treatment center

WHAT ARE THE SIDE EFFECTS OF ORTHOCLONE OKT3?

Cytokine-release syndrome: The majority of patients experience pyrexia and chills, headache, tremor, nausea and vomiting, diarrhea, abdominal pain, malaise, muscle/joint ache and pains, and generalized weakness with the first few doses. This is attributed to the release of cytokines by activated lymphocytes or monocytes. The syndrome typically begins 30 to 60 minutes after the administration of a dose and may persist for several hours.

Serious and occasionally fatal, immediate (usually within 10 minutes) hypersensitivity (anaphylactic) reactions have occurred. Manifestations of anaphylaxis may appear similar to manifestations of the CRS.

DIAGNOSTIC/LABORATORY TESTS

Monitor the following tests prior to and during therapy: BUN, serum creatinine; hepatic transaminases, alkaline phosphatase, bilirubin; CBC with differential and platelets.

Chest X ray within 24 hours before initiating treatment, which should be free of any evidence of heart failure or fluid overload.

Quantitative T-lymphocyte surface phenotyping.

Testing for human-mouse antibody titers is strongly recommended; a titer ≥1:1,000 is a contraindication for use.

Orthoclone OKT3 *continued*

ADMINISTRATION

Vial Sizes

5 mg/5mL with 1 mg polysorbate 80.

Administer as an IV bolus in < 1 minute.

Do not give by IV infusion or in conjunction with other drug solutions.

Preparation: Draw solution into a syringe through a low-protein-binding 0.2- or 0.22-micrometer filter.

Do not add or infuse with other drugs simultaneously through the same IV line. If the same IV line is used for sequential infusion of several different drugs, flush with saline before and after infusion of muromonab-CD3.

Cytokine-release syndrome may be prevented or minimized by pretreatment with 8 mg/kg of methylprednisolone given 1 to 4 hours prior to administration of the first dose of muromonab-CD3 and by closely following recommendations for dosage and treatment duration.

If hypersensitivity reaction is suspected, discontinue the drug immediately and do not resume therapy or reexpose the patient to muromonab-CD3. Serious acute hypersensitivity reactions may require emergency treatment with epinephrine and other resuscitative measures.

Storage/stability: Refrigerate at 2 to 8°C.

Do not freeze or shake.

GENERAL PRECAUTIONS (see package insert for details)

- Patients at higher risk for serious complications from CRS may include those with unstable angina; recent myocardial infarction or symptomatic ischemic heart disease; heart failure of any etiology; pulmonary edema of any etiology; any form of chronic obstructive pulmonary disease; intravascular volume overload or depletion of any etiology; cerebrovascular disease; advanced symptomatic vascular disease or neuropathy; history of seizures; or septic shock.

- **Make efforts to correct or stabilize background conditions prior to the initiation of therapy.**

- Emergency drugs (e.g., epinephrine, antihistamines, corticosteroids) should be readily available at the bedside for immediate use in the event of an allergic reaction during administration. Reactions have not been observed but may occur during the administration of proteins.

- Patients should be monitored closely at the initiation of the infusion.

- **Drug interactions:** Do not use with indomethacin because encephalopathy and other CNS effects have occurred with concurrent use.

Use the ampule immediately once opened, since there is no bacteriostatic agent present, and discard any unused portion.

Orthoclone OKT3 *continued*

RESOURCES FOR PATIENTS

Advise patients to seek medical attention at the first sign of skin rash, urticaria, rapid heartbeat, difficulty in swallowing and breathing, or any swelling that may suggest angioedema or other allergic reaction.

Clinical Pearls

1. It is important to determine the origin of the MAB being administered (i.e., murine [derived solely from mouse immunoglobulin] or chimeric [part human, part mouse]). Newer generation chimeric antibodies will have less tendency to cause allergic reaction due to the decreased portion of the antibody that is of murine origin.
2. Emergency drugs should be kept at the bedside (e.g., epinephrine, corticosteroids, and diphenhydramine) for the treatment of a potential allergic reaction. Although extremely rare, the potential for an anaphylactic reaction to occur is ever present.
3. If an anaphylactic reaction occurs, the infusion should be stopped immediately, fluids started, the physician paged, and emergency drugs administered as ordered.
4. Patients should be monitored closely at the onset of infusion for the potential of an allergic reaction or infusion-related symptom complex.
5. The occurrence of infusion-related symptom complex is believed to be related to the interaction of the MAB with circulating white blood cells and the subsequent release of cytokines. It is more commonly seen with MABs targeted toward white blood cells. Concomitant administration of diphenhydramine or acetaminnophen is useful in the management of these symptoms.
6. In general, with most MABs used in the oncology setting, the MAB is administered as a controlled infusion, not as a bolus infusion. The use of an infusion pump for administration is recommended.

7. Antibodies conjugated to other substances such as chemotherapy or radioisotopes will require additional precautions and handling procedures appropriate for the conjugate. For example, a MAB conjugated to iodine 131 requires appropriate precautions and handling for the radioactive isotope iodine 131.
8. MABs given as anti-idiotypic vaccines may produce local reactions and a flu-like syndrome, especially when given in conjunction with adjuvants.
9. It is important to determine whether the antibody is being given for a diagnostic/detection purpose (e.g., OncoScint®) or for a therapuetic reason (e.g., Rituxan®). This will assist in educating the patient concerning the goals of therapy.

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CHAPTER 7

IMMUNOMODULATORS, DIFFERENTIATION AGENTS, AND VACCINES

BACILLUS OF CALMETTE AND GUÉRIN

In 1908, Leon Calmette and Alphonse Guérin discovered that adding beef bile to bovine tubercle bacillus made it lose its pathogenicity. In 1921, the first human was vaccinated with an attenuated strain of bacillus Calmette-Guérin (BCG), as the isolated vaccine was designated.

Early immunotherapy trials found that BCG prevented or delayed development of sarcomas, carcinomas, and ascitic tumors in mice. This preliminary work in animals led to the use of BCG in cancer treatment in humans. Mathé first used BCG in the treatment of childhood acute lymphoblastic leukemia. The positive results from his trial served as a catalyst for several hundred clinical trials using BCG for the treatment of a variety of cancers, such as melanoma, lymphoma, bladder cancer, and head and neck cancers.

WHAT IS BCG?

Bacillus Calmette-Guérin is made from an attenuated strain of a live virus, *Mycobacterium bovis,* and has been used for many years for immunization against tuberculosis and as an immunopotentiating agent in cancer.

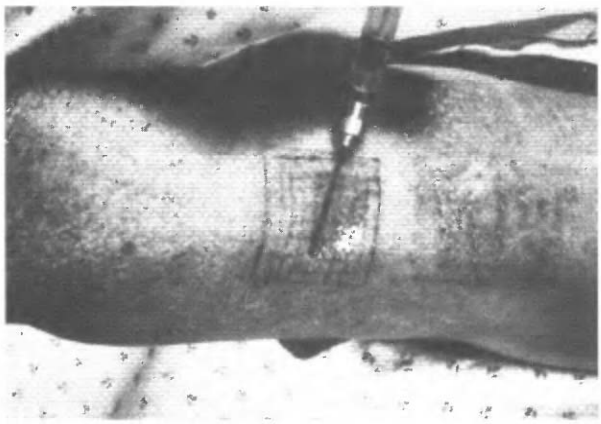
HOW DOES BCG WORK?

BCG is a nonspecific immunostimulatory agent.

- When administered, it starts a cascade of immunologic events involving humoral and cellular immunity.

- T cells, B cells, macrophages, and natural killer cells are potentiated by lymphokines and cytokines induced when BCG is given.
- The mechanism by which BCG works is unknown.
- It is important to have an immunocompetent host; this treatment is generally effective only in patients with a small tumor burden.
- Weekly multisite scarifications with BCG formed the basis of many of the early clinical trials (see Figure 7.1). Patients experienced generalized fever and flu-like symptoms and, often, local inflammatory reactions at the site of scarification.

Figure 7.1 Scarification Technique of BCG Administration



Source: Courtesy of the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REGULATORY APPROVAL

The FDA approved BCG for intravesical treatment of carcinoma in situ of the bladder in 1990.

- Treatment: induction—1 ampule of BCG suspended in 50 mL of saline administered once per week for at least six weeks.

- Maintenance—periodic treatments for up to 24 months.
- Effectiveness is evaluated every three months by cystoscopy and urine cytology tests.

WHAT SIDE EFFECTS ARE SEEN WITH BCG?

When BCG is given intravesically, more than half of recipients report bladder dysuria, frequency, and hematuria. In addition, fever, chills, malaise, and myalgias occur in one-third, but fewer than 10% of these are severe.

- Complications: hypersensitivity reactions or a disseminated BCG infection.
- Immediate hypersensitivity reactions can lead to death. Symptoms: fever, chills, hypotension, oliguria. Emergency equipment should be available.
- Symptoms of disseminated BCG infection: persistent fever, nausea, vomiting, fatigue, weight loss. Antimicrobial treatment is needed; many clinicians recommend isoniazid.

QUICK SUMMARY

AGENT: ImmuCyst®/TheraCys® (Bacillus of Calmette and Guérin [BCG])
Manufacturer: Pasteur Merieux Connaught
Rhône-Poulenc Group,
Toronto, Canada

WEBSITE: www.connaught.com

AGENT: TICE BCG (BCG vaccine) (OncoTICE®)
Manufacturer: Organon,
West Orange, N. J.

WEBSITE: www.organoteknica.com/

BCG is a freeze-dried suspension of an attenuated strain of *Mycobacterium bovis* (Bacillus Calmette and Guérin) used in the nonspecific active therapy of carcinoma in situ of the urinary bladder. TheraCys® is BCG live and comes from a strain developed at the Pasteur Institute.

REGULATORY APPROVAL

Disease	*Dosing*
ImmuCyst®/TheraCys® Primary and relapsed carcinoma in situ of the urinary bladder with or without papillary tumors and following failure to respond to other treatment regimens. Drug is used to eliminate residual tumor cells and to reduce	Induction 81 mg intravesically under aseptic conditions once weekly for six weeks beginning 7 to 14 days after biopsy or transurethral resection if this procedure is done. Maintenance Therapy One treatment given

the frequency of tumor recurrence.	3, 6, 12, 18, and 24 months following the initial treatment.
TICE BCG Primary treatment of carcinoma in situ of the bladder in the absence of an associated invasive cancer without papillary tumors or with papillary tumors after transurethral resection and as primary or secondary treatment for patients with medical contraindications to radical surgery.	One vial (50 mg) given intravesically per catheter once a week for six weeks. Schedule may be repeated if tumor remission is not achieved or if deemed clinically necessary. Thereafter, administer one dose at approximately monthly intervals at least 6 to 12 months.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS

Urinalysis

ADMINISTRATION

Vial Sizes

TheraCys: 81 mg (1.05 billion ±0.87 billion colony-forming units after reconstitution) 5% MSG. Preservative-free, in single-dose vials with two vials of diluent (3 mL and 50 mL).

TICE BCG: 50 mg (1 to 8 x 10^8 CFU) lactose, preservative-free in 2 mL ampules

BCG is instilled directly into the bladder.

TheraCys® *continued*

Keep BCG and any accompanying diluent refrigerated between 2° and 8°C. At no time should the freeze-dried or reconstituted BCG be exposed to sunlight, direct or indirect. Keep exposure to artificial light to a minimum.

INDUCTION THERAPY

- Insert a urethral catheter into the bladder aseptically, drain bladder, and then instill 53 mL of suspension slowly by gravity; withdraw catheter.
- Patient should lie for 15 minutes each in prone and supine positions and on each side.
- The patient is then allowed to be up but retains suspension for another 60 minutes, for a total of two hours.
- All patients may not be able to retain suspension for two hours. Patients may void in less time, if needed.
- At the end of two hours, patient should void in a seated position for safety reasons. Disinfect urine voided for six hours after instillation with an equal volume of undiluted household bleach and allow to stand for 15 minutes before flushing.

Most local reactions occur following the third intravesicular administration; symptoms usually begin two to four hours after instillation and persist for 24 to 72 hours. Systemic reactions usually last for one to three days after each intravesicular instillation. Irritative bladder symptoms can be managed symptomatically with phenazopyridine, propantheline, and acetaminophen.

- If bladder catheterization has been associated with bleeding or possible false passage, do not administer drug and delay retreatment by at least one week. Thereafter, resume treatment as if no interruption has occurred.

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- Persons handling BCG should be masked, gloved, and gowned and should have no immunological deficiencies. *BCG should be treated as infectious material.*

- Carefully monitor urinary status for evidence of hematuria, urinary frequency, dysuria, and bacterial urinary tract infection. If there is an increase in patient's existing symptoms, if symptoms persist, or if any symptoms develop, evaluate patient and manage for urinary tract infection or BCG toxicity.

- Instruct patient to maintain adequate hydration.

- Treatment is contraindicated in patients on immunosuppressive therapy or with compromised immune systems.

TheraCys® *continued*

- Treatment is contraindicated in presence of urinary tract infection; use may result in risk of disseminated BCG infection or an increased severity of bladder irritation.

- Monitor closely for signs of systemic BCG infection. If systemic BCG infection is suspected (fever is greater than 39°C or persistent fever is greater than 38°C, severe malaise), consult an infectious disease specialist and initiate fast-acting antituberculous therapy (BCG systemic infections are rarely evidenced by positive cultures).

- Intravesicular treatment with BCG could complicate future interpretations of skin test reactions to tuberculin in diagnosis of suspected mycobacterial infections; determine patient's reactivity to tuberculin before administration of BCG.

- Instruct patients to report blood in urine, fever and chills, frequent urge to urinate, increased frequency of urination, increased tiredness or fatigue, joint pain, nausea and vomiting, painful urination, cough (rare), and skin rash (rare) to the health care team.

RETINOIDS

The retinoids have been recognized for over 50 years for their profound impact on biological functions. Dramatic results following treatment of acute promyelocytic leukemia, metastatic squamous cell cancer of the skin, and squamous cell carcinoma of the cervix led cancer specialists to obtain investigational new drug status for the therapeutic use of retinoids in early 1990.

WHAT ARE THE RETINOIDS?

The retinoids consist of vitamin A (retinol) and related derivatives. Retinoids play significant roles in vision, growth, reproduction, epithelial cell differentiation, and immune function. Retinol is found in foods such as liver, meat, eggs, milk products, and carotenoids in fruits and cruciferous vegetables. Retinol is stored in the liver and released constantly into the blood.

Retinoids used in clinical trials include

- All-trans-retinoic acid (tRA, tretinoin)
- 4-hydroxyphenyl all-trans-retinoic acid amide (4-HPR, fenretinide)
- 13-cis-retinoic acid (cRA, isotretinoin)
- 9-cis-retinoic acid

HOW DO THE RETINOIDS WORK?

The mechanism of action of retinoic acid in cancer treatment is elusive.

- Intracellular receptors for the retinoids, vitamin D, and thyroid hormone, as well as those for the classic steroids such as estrogens, progestogens, androgens, and glucocorticoids, all belong to a superfamily (steroid receptor superfamily) involved in the selective regulation of transcription of specific genes that control cell differentiation and proliferation.

- Specific binding proteins may transport retinol into the cell, where it binds to nuclear retinoic acid receptors and mediates gene expression.
- There are six known retinoic acid receptors (RAR) that mediate the actions of the four above-mentioned retinoids. These receptors are DNA-binding transcription factors that can activate or suppress the expression of many genes.
- The first receptors to be cloned, RAR-α, RAR-β, and RAR-γ, bind all-trans-retinoic acid and 9-cis-retinoic acid with high affinity.
- Recently three new retinoid receptors, known as RXR-α, RXR-β, and RXR-γ, have been cloned. These RXRs bind only 9-cis-retinoic acid.
- Retinoic acid may direct differentiation, growth inhibition, paracrine-mediated growth inhibition or differentiation, and apoptosis.
- Retinoids enhance humoral- and cell-mediated immune responses and phagocytosis by macrophages and induce prostaglandin synthesis. Interleukin-2 production is also augmented.
- Their use in chemoprevention is based on their action in the postcarcinogen (postinitiation) phases of promotion and progression.

WHICH DISEASES ARE TREATED WITH THE RETINOIDS?

The retinoids have been investigated extensively for such uses as

- Chemoprevention of oral leukoplakia
- Prevention of second primary tumors in head and neck cancers
- Improving bronchial metaplasia
- Achieving regression of actinic keratoses
- Prevention of recurrence in bladder cancer
- Chemoprevention of breast cancer
- Treatment of cervical dysplasia

Currently, a number of large, randomized trials are evaluating the use of the retinoids for chemoprevention.

Combination trials have been conducted for treatment of advanced squamous cell carcinoma of the skin and locally advanced squamous cell carcinoma of the cervix. IFN-α and cRA have been used in combination, with some patients achieving a complete response. The regimen was well tolerated.

REGULATORY APPROVALS

Currently, there are few indications for the retinoids in the treatment of cancer.

- Vitamin A capsules are approved for vitamin A deficiency.
- Retin A® cream is approved for acne vulgaris.
- Accutane® is approved for cystic acne.
- Vesanoid (tretinoin) is indicated for induction of remission in patients with acute promyelocytic leukemia, French-American-British classification M3 (including the M3 variant), characterized by the presence of t(15;17) translocation and/or presence of PML/RAR-alpha gene, who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated.

WHAT SIDE EFFECTS ARE SEEN WITH THE RETINOIDS?

- Acute hypervitaminosis A toxicity causes drowsiness, irritability, headache, vomiting.
- Dermatologic changes include desquamation, pruritus, alopecia, increased pigmentation, and drying and cracking of the lips, mucous membranes, and skin.
- Common side effects are fatigue, anorexia, arthralgias, hepatosplenomegaly, eye irritation.

- Serious effects are rare.
- Symptoms usually disappear one to four weeks after treatment stops.
- Headaches, visual disturbances, dizziness, and lethargy may occur more often in patients receiving tRA.
- Both tRA and cRA can produce spontaneous abortions and craniofacial, cardiac, thymic, and CNS malformations in fetuses. Women of childbearing age must understand the serious risks if they become pregnant while undergoing treatment.
- Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia, which were reversible upon completion of therapy.
- A hyperleukocytosis syndrome unique to tRA may cause fatal pulmonary complications in patients with acute promyelocytic leukemia within the first two to three weeks. Symptoms include fever, dyspnea, and pleural effusions.
  - Treatment: leukapheresis and/or high-dose steroids given at first suspicion appear to reduce morbidity and mortality. At first sign or symptom, immediately give high-dose steroids (10 mg of dexamethasone IV q12h for three days or until resolution of symptoms), irrespective of WBC count. Most patients do not require discontinuation.

QUICK SUMMARY

AGENT: Tretinoin, (Vesanoid®)
Manufacturer: Roche Laboratories, Nutley, N.J.

WEBSITE: www.roche.com

First received FDA approval November 1995. Tretinoin is all-trans-retinoic acid, a derivative of vitamin A.

REGULATORY APPROVALS

Disease	*Dosing*
Induction of remission in patients with acute promyelocytic leukemia	45 mg/m^2/day P.O. in two evenly divided doses until complete remission is documented

All patients should receive standard consolidation and/or maintenance chemotherapy for acute promyelocytic leukemia after completion of induction therapy with tretinoin, unless otherwise contraindicated. Maintain supportive care appropriate for acute promyelocytic leukemia patients during tretinoin therapy.

PHARMACOKINETICS

Following oral administration, peak concentration occurs in one to two hours.

- *Metabolism:* Cytochrome p450 (CYP) enzymes have been implicated in the oxidative metabolism of tretinoin.

Vesanoid® *continued*

- *Excretion:* Tretinoin is excreted in the urine and the feces.

- *Interactions:* As tretinoin is metabolized by the hepatic CYP system, there is potential for alteration of pharmacokinetics in patients administered concomitant medications that are also inducers or inhibitors of this system.

SETTING: Primarily ambulatory

DIAGNOSTIC/LABORATORY TESTS/ MONITORING

- Blood: Frequently monitor patient's hematologic profile, coagulation profile, and triglyceride and cholesterol levels. Closely observe patient for signs of leukocytosis.

- Liver function: Carefully and frequently monitor liver function test results during therapy.

- Respiratory function: Closely observe patient for signs of respiratory compromise.

- Pregnancy test: Within one week before start of therapy, collect blood or urine for a pregnancy test with a sensitivity of at least 50 mIU/L. Delay therapy, if possible, until a negative result from test is obtained. When a delay is not possible, place patient on two reliable forms of contraception. Repeat pregnancy testing monthly throughout therapy.

Absorption of retinoids shown to be enhanced when taken with food.

Drug should be given under supervision of a physician experienced in management of acute

leukemia and in a facility with laboratory and supportive services sufficient to monitor drug tolerance and protect and maintain a patient compromised by side effects related to administration of the drug, including respiratory compromise.

ADMINISTRATION

Capsules, 10 mg

STORAGE DURING TRAVEL

Protect from extremes in temperature. Do not leave medication in the car or trunk. When traveling by airplane, take vials on board in passenger cabin so that medication will not be exposed to temperature extremes in the baggage compartment. Vials should be transported in a cooler, near but not touching ice packs. Do not use dry ice because it may freeze the vials.

GENERAL PRECAUTIONS (see package insert for details)

- ***Advise patient to avoid pregnancy.***
- Instruct patient to use two reliable contraceptive methods simultaneously during therapy and for one month following discontinuation.
- Contraception must be used even when there is a history of infertility or menopause, unless a hysterectomy has been performed.
- Confirm diagnosis by detection of t(15;17) genetic marker by cytogenetic studies or other molecular diagnostic techniques. Efficacy of other disease subtypes to tretinoin has not been demonstrated.

Vesanoid® *continued*

- Drug is contraindicated in patients with a known hypersensitivity to retinoids.

- Approximately 25% of APL patients treated with tretinoin have experienced the retinoic acid-APL (RA-APL) syndrome characterized by fever, dyspnea, weight gain, radiographic pulmonary infiltrates, and pleural or pericardial effusions. This generally occurs during the first month of treatment.

TUMOR VACCINES: ACTIVE SPECIFIC IMMUNOTHERAPY

The use of active specific immunotherapy (ASI) to treat patients with cancers, which dates to the early 1900s, was prompted by the success of vaccines against infectious disease. Current technological advances and improved understanding of the immune system and its response to cancer has fueled a rebirth of interest in the use of vaccines in cancer therapy. ASI is a means to reintroduce (the host already has the tumor) tumor-associated antigens in a way that will be more *immunogenic* in the host. The specific goals of active immunotherapy with cancer vaccines are

- To overcome the immunosuppression produced by tumor-derived factors
- To stimulate specific immunity that will destroy tumor cells
- To enhance the immunogenicity of tumor-associated antigens (TAA)

Nonspecific active immunotherapy (adjuvants) is used in conjunction with ASI to further augment immune responses.

Assumptions

- Tumor cells encode antigens that are different enough from self-antigen that an immune response is generated that will eradicate the tumor.
- The target tumor used in the vaccine must have some level of immunogenicity.
- The immunogenicity can be inherent or induced.
- Adjuvants induce or enhance immunogenicity.
- Tumor vaccines induce a cellular immune response.

Types of Tumor-Associated Antigens

Tumor cells express potentially immunogenic molecules commonly referred to as *tumor-associated antigens* (TAA). There are essentially four categories of TAA:

1. Neoantigens—antigens not expressed by the normal cells from which cancer cells are derived but found in other normal tissues
2. Oncofetal antigens—antigens not expressed by any normal tissues but expressed on fetal tissues
3. Tumor-specific antigens—antigens not found in normal adult or fetal tissues
4. Peptide antigen systems—tumor antigens recognized by T cells that may also be found in normal progenitors

WHAT TYPES OF VACCINES ARE USED?

- Whole-cell autologous vaccines—This type of vaccine is made from the patient's tumor cells. Tumor cells are irradiated, and must come from fresh tumor. Many investigators have used this method to treat patients with advanced melanoma, renal cell carcinoma, or microscopic residual colon cancer. With autologous vaccination, treatment is limited to patients with advanced disease with enough cells to enable vaccine preparations. The cells are obtained through surgery and stored for future use.
- Whole cell allogeneic vaccines—This type of vaccine is made from cells from more than one patient. The cells are irradiated and either lysed or their antigens shed into a supernatant fluid. This method has the potential for a standard (generic) product, enabling treatment of many patients and prevention of recurrence in those with microscopic residual disease.
- Purified tumor associated antigen—These may include fully or partially purified TAA. The process of purification eliminates HLA antigens. Included in

this type of vaccine are recombinant protein vaccines, anti-idiotypic monoclonal antibody vaccines (which mimic TAA), and polyvalent shed antigen vaccines. Anti-idiotypic monoclonal antibodies may possess mirror images of tumor-associated antigens and may enhance anti-tumor–associated antigen immune responses. Polyvalent vaccines contain cell surface macromolecules and antigens in a fairly purified form that are shed from the cell surface when tumor cells are grown in culture. The polyvalent nature of the vaccine increases its chances of stimulating protective immunity. Purified TAA vaccines are reasonably well characterized and reproducible, and they do not induce anti-HLA class I and II antibodies, which may confound measurement of cellular immune functions involved in vaccine responses.

WHAT STRATEGIES ARE USED TO INCREASE IMMUNOGENICITY?

- Modify the composition of allogeneic tumor cell vaccines by exposing the patient's immune system to a variety of TAA from different tumor cell lines.
- Diminish immunosuppressive cells; for example, use cytoxan to reduce suppressor cell functions.
- Combining adjuvants with tumor cells vaccines to nonspecifically stimulate the immune system.
- BCG; *Corynebacterium parvum;* DETOX™, a detoxified endotoxin; infecting viruses (Newcastle disease virus and vaccinia vaccine virus); and *Freund's adjuvant* are a few adjuvants used with ASI.

  C. parvum, a gram-positive formalin-killed bacterium, is a strong stimulator of the reticuloendothelial system. It also activates macrophages that stimulate B lymphocytes to proliferate and produce antibody.

DETOX™, a pyrogen-free preparation, is formulated from *Salmonella minnesota* and cell wall skeletons of *Mycobacterium phlei.* A nonspecific stimulator, DETOX™ triggers antibody and cell-mediated immunity.

Vaccinia (smallpox) vaccine virus is a model for viral oncolysis because of experiments by Cassal. In these experiments, animals were treated with tumor cells infected with vaccinia virus. When exposed to uninfected tumor cells, the animals were completely resistant to further tumor cell growth; untreated controls developed tumors. Newcastle disease virus is a mouse-adapted neurotropic virus for the immunization of patients with certain cancers and is a viral oncolysate.

Freund's complete adjuvant consists of heat-killed mycobacteria in mineral oil.

- Chemical adjuvants, such as enzymes, may be used to modify TAA.
- Genetically altered tumor cells obtained during resection or biopsy are grown in tissue culture. A viral vector, usually a retroviral vector, is used to insert the gene for an immunostimulatory cytokine such as tumor necrosis factor (TNF) into the tumor cells. The vaccine thus consists of genetically altered tumor cells that secrete a cytokine such as TNF.

Helper T lymphocytes (specifically, CD4+) may be the keys that unlock the cascade of events critical to rejection of the tumor by the host. Once a TAA is presented to the CD4+ cell, it activates other helper T cells and macrophages; both proliferate and release cytokines. Ultimately, killer T cells and macrophages kill the tumor.

HOW ARE VACCINES USED CLINICALLY?

Despite many years of study to perfect effective active specific immunotherapy, there is no cancer for which the use of vaccines can be considered standard therapy. Many reports from phase I or II trials indicate that partial and complete responses are observed, with little or no toxicity. These responses have been observed primarily in patients with metastatic melanoma or renal cell cancer. The striking aspect of such responses is that they are often durable and may continue for many years. Thus, the underlying concept of clinically useful responses is no longer in question. All of these trials must be interpreted according to the source of vaccine, its method of preparation and schedule of administration, and the patient's tumor burden prior to therapy.

HOW ARE VACCINES ADMINISTERED?

Vaccines are generally administered in the ambulatory setting as an intradermal or subcutaneous injection. When the intradermal route is used, several injections may be required due to the small volume required (generally a maximum of 0.5 mL).

Patients may also require premedication with prophylactic analgesia for multiple intradermal injections. EMLA cream, a topical anesthetic, is generally effective when applied an hour before the injection.

WHAT SIDE EFFECTS ARE SEEN WITH VACCINES?

Side effects seem to be determined by the adjuvant, which is either virus- or bacteria-based. Fatigue, nausea and vomiting (if a cytotoxic agent is added), mild flulike symptoms, and local reactions—such as pain, itching, granuloma, and ulceration—are common.

HOW SHOULD PATIENTS BE MANAGED?

Patient evaluation and documentation after vaccine injection should include the following:

- Timing of the assessment (i.e., the number of hours postinjection)
- Measurement of induration, erythema, or edema at the vaccination site
- Assessment for site-specific symptoms or systemic symptoms such as fever
- Determination of the effectiveness of symptom-control measures
- Assessment for lymphadenopathy in draining lymph node regions in the limb where the injection was placed

An acute reaction within the first 15 minutes (local or systemic)—versus the expected cellular inflammatory response—may suggest an allergic reaction.

Before the use of vaccines, the patient's cellular immunity is often assessed with the use of delayed type hypersensitivity (DTH) skin testing.

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CHAPTER 8

PATIENT MANAGEMENT

The management of patients receiving biological agents includes the following:

- Assessment and planning of therapy
- Administration and handling of the agent
- Management of side effects
- Patient education
- Understanding reimbursement issues
- Documentation

The Nursing Process

"Standards of care" describe a competent level of nursing care: assessment, diagnosis, outcome identification, planning, implementation, and evaluation. The American Nurses' Association's *Standards of Clinical Nursing Practice* (ANA, 1991) defines the scope of a nurse's duties and describes the minimum care patients should receive. *Standards of Oncology Nursing Practice* (ANA & ONS, 1996) is a guide for implementing the standards described above and for caring for patients with cancer. These standards are the cornerstone for managing patients receiving biotherapy.

HOW SHOULD PATIENTS BE ASSESSED?

Nurses have a major responsibility in the multidisciplinary management of patients who are receiving biological agents. The collection and examination of health data is used to develop nursing diagnoses and the plan of care.

Pretherapy Assessment

Before therapy, the nurse should use a body systems approach to perform a baseline physical assessment.

Assessment includes prior treatment history and response; current disease symptoms; history of chronic illnesses; allergies; functional status; psychosocial concerns; and hopes, fears, and expectations of therapy.
Factors that may place the patient at a higher risk for developing side effects include

- Preexisting cardiac or pulmonary problems
- History of psychiatric problems
- History of autoimmune disease
- Poor functioning, poor nutrition, or old age

Geriatric patients require special attention. Factors that may affect dose and tolerance include

- Alterations in hepatic and renal function
- Decreased cardiovascular function
- Alterations in vision
- Decreased integrity of tissue, skin, and mucous membranes

Examination of the medication profile is of special importance to assess for medications that may be contraindicated or that may exacerbate side effects seen with biological agents. Some medications (such as steroids, aspirin, or sedatives) may be contraindicated.

Baseline physiologic measurements include height, weight, temperature, pulse, blood pressure (including orthostatic measures for patients receiving agents causing hypotension), and respiratory rate.

Results of baseline chest X ray, electrocardiogram, and hematologic, renal, metabolic, and hepatic functions should be reviewed or measured.

Baseline laboratory profile may include the following:

- Complete blood count, differential count, platelet and reticulocyte count, prothrombin time, and partial thromboplastin time
- Blood urea nitrogen, creatinine, urinalysis
- Electrolytes, calcium, magnesium, and phosphorus

- Serum albumin, liver function tests
- TSH, T3, T4 (with IL-2 or IFN therapy)

Patients should be able to explain the rationale for and the nature of therapy. The goal of chemotherapy is generally treatment of disease. However, when biotherapy is used, the goals may be

- Investigational (e.g., for a phase I trial determination of the maximum tolerated dose and optimal biological dose)
- Therapeutic (treatment of disease)
- Diagnostic (detection of disease with monoclonal antibodies or classification of leukemias through flow cytometry using antibodies)
- Supportive (the use of hematopoietic growth factors following chemotherapy)

The therapeutic plan should be evaluated before treatment begins so that the oncology nurse can develop a care plan and intervene appropriately. Special areas to consider include the following:

Setting:	Where will the patient receive therapy—the hospital, ambulatory clinic, both, or at home?
Diagnostic tests required:	Routine lab work, special lab work, pharmacology studies, diagnostic procedures
Toxicity:	What agent(s) will the patient receive; what are the side effects?
Nature of therapy:	Is the therapy approved by the FDA or investigational? Has consent been secured if investigational?

Monitoring:	Will special monitoring (orthostatic blood pressure, special vital signs, central venous pressure, intake and output measurements) be needed?

The initial assessment should include evaluation of the patient's coping patterns, support systems, financial status, and related concerns. Cultural factors such as race, religion, and belief systems should be considered in formulating the plan of care in partnership with the patient and family. The high percentage of biotherapy given to outpatients requires assessing the home and the patient's ability to travel to and from the treatment center. Allowing patients to voice their concerns about therapy and helping them resolve problems is important. Appropriate referrals such as for home health care, or the services of a social worker, can then be instituted as required.

Table 8.1 lists potential nursing diagnoses for patients receiving biotherapy.

Table 8.1 Nursing Diagnoses

Prevention and Detection

Health-seeking behaviors

Information and Education

Knowledge deficit

Management of therapeutic regimen (individual), ineffective

Coping

Anxiety

Coping, ineffective individual

Spiritual distress

Body image disturbance

Social interaction, impaired

Role performance, altered

Discomfort

Pain

Nutrition

Nutrition, altered: less than body requirements

continued

Table 8.1 Nursing Diagnoses *(cont.)*

Protective Mechanisms
Infection, high risk for
Oral mucous membrane, altered
Sensory/perceptual alterations
Skin integrity, impaired
Skin integrity, impaired, high risk for
Body temperature, altered, high risk for
Thought processes, altered
Protection, altered
Sleep pattern disturbance
Mobility and Activity
Fatigue
Activity intolerance
Elimination
Diarrhea
Urinary elimination, altered
Sexuality
Sexuality patterns, altered
Ventilation
Gas exchange, impaired
Circulation
Fluid volume deficit, high risk for tissue perfusion, altered (specify)

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Assessment During Therapy

During therapy the nurse performs an important role in monitoring a patient's adherence to and tolerance of therapy. Information gained by the nurse during assessment can help delineate the spectrum of side effects, especially with investigational biological agents.

Nurses should regularly and systematically monitor vital signs and review body systems and pertinent laboratory values every shift or every clinic visit.

Onset, duration, and frequency of symptoms should be noted, as well as location, setting, quality, quantity, aggravating and alleviating factors, and associated symp-

toms. Even though few scales exist that reliably quantify common symptoms associated with biotherapy, it is useful to do so. Examples of approaches include

- Verbal reports of mild, moderate, or severe
- Numerical scales (e.g., 0 to 10)
- Clinical trial toxicity scales (e.g., National Cancer Institute Scale)

A symptom report form for self-reporting or a nursing care flow sheet can be designed to quantify and record the side effects. This approach can be very helpful in determining patterns of side effects. These forms can be placed in the patient's record to track side effects and effectiveness of management strategies over time.

Posttherapy Assessment

Once patients have completed therapy, routine follow-ups should continue. Side effects should be reassessed to assure resolution, as many biotherapy-related side effects such as fatigue and mental status changes may continue for up to several months.

Psychosocial Concerns

Stopping therapy due to progression of disease is often a time of crisis for patients, and emotions may be intense. It is critical that a patient not feel abandoned. The simplest measures, such as touch or active listening, can reassure patients. Even if cure is not possible, symptoms can be managed and hope fostered.

Support groups, lay volunteers, or cancer survivors trained to provide support may be helpful.

WHAT ARE IMPORTANT CONSIDERATIONS FOR ADMINISTRATION OF BIOTHERAPY?

Biological agents are administered in a variety of routes and dosing schedules. The schedule may even differ for the same agent when used in different diseases. For exam-

ple, the dose of interferon-alfa will be different for hepatitis treatment than when used as adjuvant therapy for malignant melanoma.

The most common routes are subcutaneous (SC), intramuscular (IM), or intravenous (IV) by single bolus, intermittent or continuous infusions. The oral route is seldom used. Other routes such as intraperitoneal (IP), intraarterial (IA), intrathecal (IT), intravesical, intralesional, or scarification may be used.

Dosage is usually calculated by body surface area (per m^2), per kilogram (kg), or a predetermined standard dosage. Increasingly, clinical guidelines are adhering to dosages that more closely match vial sizes to minimize waste of drug.

Use the following safety measures when administering biological agents:

- Proper aseptic technique
  The nurse should be aware that patients receiving IL-2 are often at higher risk for catheter-related infections. Strict aseptic technique should be used. In addition, many institutions use prophylactic antibiotics to prevent infection.
- Appropriate institutional procedures for investigational agents.
- Identify availability of emergency equipment and supplies (especially important for administration with monoclonal antibodies).
- Administer premedication as ordered.
- Educate patients on side effects and symptoms that should be reported.
- Determine special handling precautions or special equipment or supplies.
- Verify monitoring of special vital signs (e.g., every 15 minutes for one hour), orthostatic blood pressures, or assessment of injection sites.
- Use appropriate storage requirements. Many biological agents should be refrigerated at 36°–46°F (2° to 8°C).

Some biological agents, such as interferons, are produced by several companies. Characteristics of the drug to be used, such as available vial size, solubility, stability, compatibility, filterability, and storage requirements, should be determined. Special considerations, such as mixing with albumin, must be assessed.

See the section on individual agents for considerations for common biological agents. Pharmacy personnel and package inserts can provide specific information on each biological agent.

Handling Biological Agents

There has been little if any formal research to date regarding the safest way to handle biological agents. Although the majority of biological agents do not directly affect DNA and are therefore not considered genotoxic substances, some institutions do place them under cytotoxic handling procedures. Nurses should check on their institution's policy.

It is wise to avoid direct contact with skin and to avoid generating aerosols. The addition of chemotherapeutic agents or toxins to biological agents necessitates special handling; the addition of radioisotopes requires using radiation safety precautions.

Proper disposal of used vials and equipment, especially at home, is important. Institutional and community policies should be researched. Many institutions allow patients to return used sharps in appropriate containers for disposal at the clinical facility.

The United States Environmental Protection Agency (1993) provides an educational card for disposal of equipment at home. In general, used vials, needles, and syringes should be disposed of in a sealed, puncture-resistant container. Patients should not recap needles. Needle recapping devices are available that can be used at home or in the clinical setting if required.

Disposal Tips for Home Health Care
(Professional Brochure)

IDENTIFICATION NUMBER

EPA530-F-93-027a
Brochure encouraging health care professionals to educate patients and clients on safely practicing home health care by disposing of "sharps" (lancets, needles, and syringes) in hard plastic or metal containers with screw-on or tightly secured lids. Includes detachable order form for professional brochure and patient flyer.

ORIGINATOR

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HOW SHOULD SIDE EFFECTS BE MANAGED?

Side effects commonly associated with biotherapy include flulike symptoms, fatigue, anorexia, weight changes, mental status changes, skin changes, hypotension, and hematologic changes. The pathophysiology underlying many biotherapy-related side effects remains unknown. By utilizing existing expertise in the care of cancer patients, the nurse has a foundation for managing side effects unique and specific to biotherapy. See Table 8.2 for an overview of biotherapy-related side effects.

Characteristics of Biotherapy-Related Side Effects

Most biotherapy toxicity is dose related; the higher the dose and/or the more intensive the regimen, the more side effects can be anticipated.

Toxic effects are often noncumulative (i.e., there is no dose beyond which a patient can receive no further therapy).

Most biotherapy-related side effects, myelosuppression included, are reversible when therapy stops.

Certain side effects may occur early and are termed acute, such as flulike symptoms in interferon therapy. Others occur late and tend to persist throughout therapy, such as fatigue.

Most side effects are not life-threatening; however, they tend to affect quality of life (e.g., fatigue, anorexia, mental status changes).

See Table 8.3 for a list of critical indicators that should be reported to the health-care team. See Appendix A for care plans for different side effects experienced by patients receiving biological agents.

Table 8.2 Side Effects of Biological Agents

System	Interferons	Interleukin-2	Hematopoietic Growth Factors	Monoclonal Antibodies	Tumor Necrosis Factor	Retinoids
Central Nervous System	Impaired concentration, headache, lethargy, confusion, depression	Impaired concentration, headache, lethargy, confusion, anxiety, psychoses, depression	Rare	Rare	Confusion, rare seizures	Headache*,visual disturbances, changed visual acuity, anxiety, insomnia, depression
General	Constitutional symptoms*, fatigue*	Constitutional symptoms*, fatigue* weight gain during therapy, followed by weight loss*	Mild constitutional symptoms, fatigue (mostly with GM-CSF)	Constitutional symptoms, allergic reactions, rare anaphylaxis	Constitutional symptoms*, rigors*, fatigue*	Fever*, malaise
Cardiovascular	Hypotension, tachycardia, arrhythmias, rare myocardial ischemia	Hypotension* edema*, ascites, arrhythmias, decreased systemic vascular resistance*	Rare hypertension with epoetin alfa	Hypotension, chest pain	Hypotension*, arrhythmias	Hypotension, hypertension, flushing

continued

* Denotes common side effects.

Table 8.2 Side Effects of Biological Agents *(cont.)*

System	Interferons	Interleukin-2	Hematopoietic Growth Factors	Monoclonal Antibodies	Tumor Necrosis Factor	Retinoids
Pulmonary	Rare	Dyspnea, pulmonary edema	Rare occurrence of dyspnea with first dose of GM-CSF	Dyspnea, wheezing	Dyspnea	Dyspnea, pleural effusion in patients with APL experiencing RA-APL syndrome
Renal/Hepatic	Proteinuria, elevated liver enzymes*	Oliguria* increased BUN, creatinine* proteinuria, azotemia, increased bilirubin, SGOT, SGPT, LDH	Rare elevation of LDH, alkaline phosphatase with G-CSF	Rare	Increased bilirubin, liver enzymes	Elevation of triglycerides and cholesterol, elevation of liver function tests.
Gastrointestinal	Nausea/vomiting, diarrhea, anorexia*	Nausea/vomiting* diarrhea*, anorexia* mucositis	Rare	Nausea/vomiting	Nausea, vomiting, anorexia, diarrhea	Nausea and vomiting, mucositis, diarrhea
Genitourinary	Impotence, decreased libido	Decreased libido	Rare	Rare	Decreased libido	Rare

(cont.)

Integument	Alopecia, rash	Rash*, dry desquamation*, erythema*, pruritus*, inflammatory reaction at injection sites*	GM-CSF/G-CSF: Inflammation at injection site, rare occurrence of rash	Urticaria, rash, pruritus	Inflammatory reaction at injection sites	Dryness of skin and mucous membranes*, pruritis, increased sweating
Hematologic	Leukopenia*, anemia, thrombocytopenia	Anemia*, thrombocytopenia, lymphopenia*, eosinophilia*	Leukocytosis*, eosinophilia (GM-CSF) *Note: expected biologic effect of HGF used	In hematologic malignancies, leukopenia	Thrombocytopenia, granulocytopenia	Leukocytosis in patients with APL
Musculoskeletal	Myalgias*, arthralgias*	Myalgias, arthralgias	Bone pain* with GM- and G-CSF	Rare arthralgias	Myalgias, arthralgias	Bone pain*, myalgias*, arthralgias*

* Denotes common side effects

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Table 8.3 Critical Indicators in Biotherapy

Excessive fatigue
Severe mental status changes
Excessive somnolence
Confusion
Psychosis
Cardiac symptoms
Chest pain
Arrhythmias
Symptomatic hypotension
Weight changes
Losses greater than 10 pounds
Gains greater than 10 pounds
Allergic reactions
Anaphylaxis
Hives and itching
Dyspnea
Oliguria
Severe local inflammatory reactions
Fever
Uncontrolled with antipyretics
Unrelated to normal patterns of response

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General

Flu-like Symptoms (FLS)

Defined as a cluster of constitutional signs and symptoms that may include fever, chills, rigors, myalgias, headache, malaise, upper respiratory symptoms (e.g., nasal congestion), and gastrointestinal symptoms (e.g., diarrhea, nausea).

Significant side effect for several reasons:

- Common to most biological agents
- Can cause further debilitation to patients who are already compromised
- Has a substantial impact upon quality of life

Presentation by Agent Category

The pattern and severity of FLS will vary with agents. Through clinical experience with patients receiving biological agents, the nurse will become familiar with the expected pattern of FLS associated with a given agent, e.g., IFN versus a hematopoietic growth factor. The nurse can then distinguish between FLS as an expected side effect of therapy or related to an infectious process.

Interferons: Chills often precede fever, which begins about two to four hours after injection and peaks at about six hours. Duration of fever is four to eight hours. High fevers are expected when therapy is initiated, but tolerance tends to develop over time with daily doses. With IFN-gamma, fevers tends to last longer and no tolerance is seen.

Interleukin-2: Onset is generally two to four hours following administration. With continuous IV infusions, fever tends to remain elevated throughout and will require around-the-clock administration of antipyretics.

Hematopoietic growth factors: Generally not a prominent side effect, especially with single lineage growth factors. With multilineage growth factors, low-grade fevers may be seen and are thought to result from the stimulation of additional cytokines.

Monoclonal antibodies: Fever is a common side effect and is usually seen either during the first hour of infusion or one to two hours following the infusion.

Pathophysiology

Many of the cytokines used therapeutically for the treatment of cancer are key components in the causation of fever and its accompanying signs and symptoms during illness and infection. Or, the administration of cytokines may cause the production of other cytokines directly involved in the pathogenesis of fever.

Fever is defined as a condition where the thermoregulatory "set point" governing the temperature of the body is raised above the normal level. Warming mechanisms are

then initiated to raise the body temperature to the higher "set point." Chills and rigors are thus physiologic mechanisms for generating heat.

Management

Assessment: Assess (onset, duration, associated symptoms, aggravating, or alleviating factors) and potential risk for infection. Even though FLS are a common side effect of biological agents, never assume that all fevers are non-infectious in nature. Careful assessment of the patient and knowledge of the expected pattern of toxicity will assist the nurse in this determination.

Manipulation of the treatment schedule: Within the latitude allowed by the treatment protocol, adjustment of dose, schedule, route, and rate of administration may assist in diminishing FLS.

Prophylactic medications: Premedication and prn administration of antipyretics, such as acetaminophen or nonsteroidal anti-inflammatory drugs. Meperidine and other narcotics may be used to relieve chills but are generally not given on a routine basis.

Nursing measures: Comfort measures such as extremity wraps, bundling, increasing the ambient temperature, hydration, relaxation and guided imagery, and patient and family education are useful strategies.

Fatigue

Fatigue is one of the most commonly experienced side effects in patients receiving biotherapy. As a symptom it has a significant impact upon quality of life, and in some cases has been the dose-limiting toxicity in clinical trials.

Presentation by Agent Category

Interferons: Often profound at doses equal to or greater than 20 MIU daily. Those patients with poor performance status are generally more severely affected. Tends to be a chronic side effect that does not diminish in intensity over time.

Interleukin-2: A prevalent side effect with therapy that is more intense in regimens using higher doses or where therapy is given for a more prolonged period. Many IL-2-related side effects such as nausea and vomiting, diarrhea, or hypotension will impact fatigue, as will medications used to control IL-2-related side effects. With higher doses of IL-2, patients may tend to spend the majority of their day lying down or in bed.

Hematopoietic growth factors: Generally not a significant side effect. When seen, it tends to be mild and readily reversible with the cessation of therapy.

Monoclonal antibodies: Fatigue is not commonly associated with the administration of MABs.

Management

Assessment: Pretherapy assessment is important to provide baseline information and functional status. Determination of patients at risk for developing fatigue (patients with poor performance status, or cofactors such as anemia that will predispose for the development of fatigue or influence the severity of fatigue) is important. Knowledge of biological agents known to cause high levels of fatigue, such as IFN or IL-2, should result in preplanning strategies to manage fatigue proactively. At periodic intervals during therapy, the patient should be assessed for the presence of fatigue and, when present, its severity and the effectiveness of management strategies. Choose a clinical tool to "measure" fatigue such as numerical scales or toxicity grading scales.

Education: Provide anticipatory guidance regarding the likelihood of experiencing fatigue and strategies for managing its occurrence.

Strategies: Maintain adequate hydration and nutrition. Balance activity and rest.

Help patients to prioritize activities so that they have energy available for activities that are most important to them.

Delegate activities that can be performed by others.

Promote strategies that replenish energy stores, such as normal nighttime sleep patterns, mild to moderate exercise within the patient's physiologic capabilities, relaxation or diversional activities, management of correlates of fatigue such as anemia, nausea, and pain.

Promote strategies that effectively use existing energy stores, such as modification of the environment and activities. A physical therapy consult may be very helpful for identifying these types of strategies. Schedule diagnostic tests and clinic visits so that patient energy stores are not depleted by repeated trips to the clinical facility.

Stress reduction: Teach and reinforce effective coping strategies. Assess for the presence of depression and anxiety. Depression can be either a cause or a result of fatigue. It is often a clinical challenge to differentiate between the two. Patients should be assessed for the presence of clinical depression and treated accordingly.

Fatigue is recognized as a significant symptom in patients receiving biotherapy. At times, it may be so severe as to become the dose-limiting side effect. Patients may request to stop effective therapy due to the negative impact of fatigue on quality of life. Nurses are key to managing this challenging side effect and should work with patients and families to initiate effective strategies for its management.

Gastrointestinal System

Baseline weight, nutritional status, and dietary intake should be assessed and documented prior to initiation of therapy.

Anorexia

Patients often complain of a decreased desire for food or lack of motivation to eat. Taste changes are commonly reported. Measures used with other oncology patients—such as small, frequent meals and caloric supplements—are appropriate. Emphasize foods the patient tolerates well rather than foods the patient no longer finds appealing. Educate the family not to expect the patient to eat three meals daily. Encourage socialization with meals. A dietary consult should be used if needed; if weight loss becomes significant (5 to 10% of body weight), tube feedings or total parenteral nutrition may be considered.

Nausea and Vomiting

Nausea and vomiting are uncommon with biological agents, except for IL-2. Prophylactic, scheduled administration of antiemetics is often necessary to control this side effect in patients receiving IL-2 therapy. With interferon therapy, nausea and vomiting usually occur with FLS and are seen more commonly at higher doses. Prophylactic administration of antiemetics may be helpful. See Table 4.4 for useful antiemetic medications used with IL-2 therapy. Relaxation therapy and guided imagery may be helpful. An odor-free environment and cold foods are also practical.

Mucositis

Mucositis—a dry, inflamed oral mucosa without ulceration—occurs most commonly with IL-2 therapy. The oral cavity should be assessed and its condition documented at regular intervals. A pretreatment oral assessment by the dental oncologist may be recommended. Patients should have meticulous oral hygiene with saline and baking soda rinses and soft toothbrushes. Diet may be modified for comfort and to avoid injuring the oral mucosa. Avoid commercial mouthwashes that can exacerbate oral dryness. Artificial saliva and food with sauces may be helpful.

Diarrhea

Severe diarrhea may occur with IL-2. Antidiarrheal medications are generally effective in its control. Assessing hydration and electrolyte balance is important. Fluid replacement and dietary modifications, such as avoiding roughage, are helpful suggestions. It is also important that skin in the perianal area be assessed. Hygienic measures and the use of prophylactic barrier creams to protect both damaged and intact skin are indicated.

Cardiovascular/Pulmonary Systems

Standard nursing measures include monitoring heart rate and blood pressure (including orthostatic checks for agents known to cause hypertension such as IL-2).

Capillary Leak Syndrome

The assessment of cardiovascular parameters is extremely important in IL-2 therapy due to capillary leak syndrome. In addition to standard monitoring measures, central venous pressure and other cardiac indices may be used for hospitalized patients on high-dose regimens.

Accurate daily weights and strict fluid intake and output measures are important for evaluating fluid shifts, as is evaluation for edema and ascites.

Daily measurement of abdominal girth may help determine fluid retention.

Teach patients to rise slowly from a lying to a sitting or standing position to avoid dizziness. Bed rest may be needed if systolic blood pressure consistently runs less than 80 mm Hg and the patient is symptomatic.

Medical management includes the use of vasopressors to maintain blood pressure, judicious use of fluid boluses, and, if cardiovascular parameters are unstable, transfer to the intensive care unit.

At low- to moderate-dose regimens in the ambulatory setting, capillary leak syndrome is generally manageable.

Pulmonary Complications

Pulmonary complications are most commonly associated with IL-2 therapy or allergic reactions to a monoclonal antibody.

Assessment includes auscultation of breath sounds, monitoring oxygenation, and evaluating shortness of breath or altered breathing patterns.

Nursing measures include positioning patients for minimal effort during respiration, adjusting the patient's physical activities, and reporting significant changes to the physician.

Medical management includes administering oxygen or diuretics or interrupting therapy. In extreme cases intubation and mechanical ventilation may be required with IL-2 high-dose therapy.

Mental Status Changes

Although neurotoxic effects are rare after treatment with monoclonal antibodies and hematopoietic growth factors; interferon-alfa and interleukin-2 have significant acute, subacute, and chronic toxic effects, which may have a considerable impact on patients' quality of life.

Presentation by Agent Category

Interferons: Neurologic side effects seen most frequently include depression, difficulty concentrating, memory problems, slowed thinking, impaired motor coordination, and impaired frontal lobe functioning. These changes in mental status may be subtle and are often more readily noticed by family members or others who know the patient well.

Interleukin-2: Neurologic side effects seen most frequently include hypersomnolence, difficulty concentrating, irritability, and confusion. Patients may also have a tendency to withdraw from social contact, and in extreme cases, may experience bizarre dreams, delusions, and hallucinations.

Management

Assessment: A baseline assessment is crucial to determine pretherapy functional status. Identification of risk factors that may predispose to problems—such as preexisting neurobehavioral difficulties, history of psychological illnesses such as depression, or the use of medication that can affect mental status—is important.

Education: Patient education regarding the potential occurrence of neurologic side effects cannot be stressed enough. This is an area that is often overlooked. When changes in mental status occur, patients may inadvertently attribute their occurrence to a more serious cause such as brain metastases or will fear they are "going crazy."

Assess, at intervals, for the occurrence of neurologic side effects, the need for implementation of safety measure and compensation techniques, and effectiveness of management strategies.

In cooperation with the patient, develop strategies to address alterations in mental status. Examples include the use of calculators for patients experiencing trouble with calculations and the use of lists for memory problems. Patients may at times require an adjustment of work or home responsibilities.

The use of medications to manage neurotoxic symptoms is new. The use of tricyclic antidepressants or opiate antagonist is currently under evaluation.

Renal System

Renal toxicity is most frequently seen with IL-2 therapy, although changes in renal function may be seen with interferon therapy.

Assessment for elevations in BUN and creatinine, decreased urine output, and significant weight gains should be made. With IL-2, fluid shifts will cause urine output to decrease. Intake and output will not balance;

therefore, it is helpful if the physician defines a minimum urinary output (10 to 30 mL/hr, for example) to be used as a guideline for reporting changes.

Hospitalized patients may be placed on infusion of vasopressors to improve renal perfusion and urine output. *Pharmacy resource personnel can provide charts to determine the infusion rate required to achieve the desired mcg/kg dosage of vasopressors such as dopamine.*

Hematologic

Hematologic changes are not typically problematic in patients receiving biotherapy. White blood cell count with differential, coagulation profile, and reticulocyte count should be monitored to detect significant lowering. Changes in blood cell counts are an expected clinical effect with the administration of hematopoietic growth factors.

Should myelosuppression or thrombocytopenia develop, stopping therapy will generally lead to rapid recovery. The patient should be taught the symptoms and precautions for thrombocytopenia, neutropenia, and anemia should they occur.

Hepatic Function

Changes in hepatic function are common in patients receiving interferon or interleukin-2. Assess patients for changes in liver function tests, hyperbilirubinemia, jaundice, or hepatomegaly, and report significant changes. Dosage adjustment may be required.

Metabolism

Hypothyroidism, hypomagnesemia, hypophosphatemia, and hypocalcemia may occur, most commonly in treatment with interferon or interleukin-2. Lab values should be monitored and significant changes reported and treated.

Integument

Rash

Rashes may occur with interferon and GM-CSF. Baseline assessment should include evaluating for a history of underlying skin conditions. Patients with a history of psoriasis may experience an exacerbation of their disease during interferon therapy. Rashes are common with IL-2, in association with dry, desquamated, pruritic skin. Patients who receive IL-2 should not use topical steroids.

Skin should be inspected for signs of breakdown or infection. Therapeutic measures for dry, pruritic skin include applying water-based lotions several times daily. Cleansing should be gentle, bath water should be tepid, and clothing should be soft cotton. Perfumed lotions are to be avoided.

Additional measures include aggressive use of antipruritic medications such as diphenhydramine or hydroxyzine hydrochloride and colloidal oatmeal baths. For some patients room humidifiers relieve pruritic skin conditions.

Changes in body image can cause significant distress for patients. Encourage patients to express their feelings and reassure them that these changes will go away when therapy is completed.

Inflammatory Reactions at Injection Sites

Most commonly seen with hematopoietic growth factors such as GM-CSF and IL-2, inflammation generally resolves within 24 to 48 hours. Further injections at inflamed sites must be avoided until healing is complete.

If pruritus occurs at the injection site, premedication with diphenhydramine may help. Occasionally patients complain of pain associated with subcutaneous injections. Topical applications of cream containing 50% lidocaine and 50% prilocaine may be useful.

With IL-2 injections, patients may experience subcutaneous nodules at the injection site that persist for several months. There is no known treatment that will eliminate the nodules. The area should be avoided for further injection as possible until the nodules resolve.

Applications of cold or heat have also been tried to eliminate local symptoms. Their use should be verified with the physician because medication absorption patterns may potentially be altered.

Hair Thinning

Alopecia may occasionally be experienced, most commonly with interferon therapy. Use of wigs, scarves, and headwraps is appropriate. Patients may be reassured that hair will regrow when therapy is complete.

Allergic Reactions

Allergic reactions are most commonly seen in association with the administration of monoclonal antibodies, especially those of murine (mouse) origin. Symptoms include fever, chills, hives, pruritus, shortness of breath, and hypotension.

Allergic reactions can range from mild—such as hives or itching—to the more rare occurrence of anaphylaxis. Patients should be monitored regularly and observed closely when MAB therapy begins.

Emergency drugs such as epinephrine, hydrocortisone, and diphenhydramine should be kept at the bedside. MAB should be administered via a side port so that if a severe allergic reaction occurs, the infusion can be stopped and intravenous fluids initiated immediately. An infusion pump should be used for administration to avoid inadvertent bolus infusions. An injection port should be available for the administration of emergency drugs.

To prevent or alleviate chills, fever, or urticaria, medication may be administered before or during therapy.

RADIATION PRECAUTIONS

Appropriate radiation safety precautions should be observed in patients receiving MABs conjugated with radioisotopes. Appropriate precautions are determined by the isotope used and the dose. Special precautions, such as using disposable food trays, flushing the toilet

three times after voiding, sitting while urinating (men), and avoiding bathing for 24 hours after administration of the isotope, should be reviewed.

Patients should be educated about the need for isolation with high doses of radionuclides.

Patients are often fearful of radiotherapy. Appropriate discharge precautions and issues related to sexuality should be discussed before discharge.

SEXUALITY

Patients receiving biotherapy may experience changes in sexuality. These changes may commonly be seen in patients receiving interferon therapy or interleukin-2.

The PLISSIT model is frequently used for sexuality counseling or nursing interventions. The success of each step depends on the nurse's knowledge and comfort level.

- P = *permission.* Discussion of patient concerns is promoted; the couple is encouraged to continue in its present pattern of sexual activity.
- LI = *limited information.* New information is included to address sexual concerns.
- SS = *specific suggestions.* New activities or techniques for the couple may be included.
- IT = *intensive therapy.* If necessary, the couple is referred to a therapist or counselor for more intensive treatment.

The American Cancer Society's books on sexuality for men and women with cancer provide excellent resources.

AMBULATORY CARE

The majority of biotherapy is administered in the ambulatory setting; thus patients will be responsible for administering therapy at home.

Major areas that need to be addressed include monitoring the patient's reaction to the initial treatment, assessing tolerance to and compliance with therapy, patient education, support systems and referrals, and financial concerns.

When therapy is initiated in the outpatient or home setting, patients should be monitored for tolerance to the first dose. The agent(s) administered and the dose will determine the time patients need to be monitored and how often vital signs should be checked.

Patients generally require regular follow-up visits or home visits to assess tolerance. Use symptom flow sheets to facilitate assessment and management of outpatients. Patient diaries or logbooks of symptoms can be useful. Toxic effects should be quantified and documented and patient response to interventions assessed.

Schedule follow-up visits to determine patient adherence to the regimen. Address misunderstandings or problems.

Evaluate patient or caregiver support systems. Lack of financial resources or social support will need to be addressed to ensure successful therapy.

WHAT ARE IMPORTANT CONSIDERATIONS IN PATIENT EDUCATION?

The goal of patient education is to assist patients and their families to develop the skills and knowledge to adapt to alterations in their health and lifestyle. Educated patients are better able to participate in their care and facilitate early discharge.

Assessment

Assessing patients' needs and learning styles helps the nurse provide individual instruction, promote effective use of resources, identify information important to patients, and save time.

Ability to Learn

Patients should be assessed for visual or auditory impairment or impaired motor ability. Assessing a patient's ability to communicate in English is important.

Literacy level should be assessed. Patient education literature has an average reading level of 11th grade. Experts recommend that most patient education materials be targeted to a 5th grade reading level. It is imperative that nurses recognize nonverbal cues to poor reading skills, such as poor attention span, little or no interest in the topic, frustration, and slow reading speed. Patients may be unable to answer questions about the literature or may ask that someone else read the literature. Nurses should use simple vocabulary and lay terminology when talking to patients.

The nurse must assess whether patients are visual learners (who like to read or watch videos), auditory learners (who like to listen to tapes, lectures, or videos), or tactile learners (who like to handle equipment or demonstrate procedures). Most people prefer a combination. To assess learning style, nurses can ask patients how they best learn.

Readiness to Learn

Several factors influence patients' readiness to learn, including cultural background, emotional state, and goals. Anxiety is normal and can increase patients' receptiveness to learning. Too much anxiety, however, can be overwhelming.

Knowledge Deficits

It is vital to assess previous knowledge and experience. For example, a mother who has been administering insulin subcutaneously to her child should be able to give herself subcutaneous interferon.

It is important to note topics that patients are most concerned about. If patients are nervous about administering a subcutaneous injection, the nurse may want to plan a demonstration/return demonstration before teaching reconstitution and drawing up medication.

Planning

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2. The past experiences of adults serve as a resource.
3. Readiness to learn emerges from the need to cope with a task or social role.
4. Adults need to see immediate benefits.

The chosen teaching strategies should not only reflect the learning needs assessment, goals and objectives, and content to be presented, but also should be based on these principles of adult learning while corresponding to the learning style of the patient or family members.

Teaching techniques include lecture, demonstration/return demonstration, and role playing.

Demonstration/return demonstration must be done when teaching a psychomotor skill, such as self-injection.

Role playing provides a nonthreatening way for a patient to act out new behaviors. For example, a nurse may have patients act out a telephone call in which they report signs and symptoms.

Teaching aids (printed material, posters and flip charts, videotapes, and physical models) increase interest and reinforce learning.

Implementation

A frequent obstacle to teaching is time. One strategy is to trade time with another nurse so that other patients will be cared for during a scheduled teaching time or by incorporating teaching time with patient care. Some ambulatory clinics may assign a nurse to do teaching each day, or allot a specific time of the day for teaching.

If the teaching plan is mutually agreed upon, compliance is more likely. It is important to limit the amount of new knowledge at each session. Positive feedback enhances self-esteem and motivates patients to continue.

Evaluation

Evaluation should be ongoing. It should occur at the time of teaching and later as well. In today's climate of liability, accountability, and quality assurance, evaluation and documentation are crucial.

Evaluation should relate to the original written goals. For example, a patient should respond verbally if the goal required the patient to describe the treatment protocol. A return demonstration without coaching may be required for a psychomotor skill. After evaluation, the nurse might have to revise the teaching plan and begin again.

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The JCAHO requires that nursing care data related to patient assessments, nursing diagnoses or patient needs, nursing interventions, and patient outcomes are permanently integrated into the medical record. Besides proving that the requirement for patient education has been met, documentation communicates teaching and progress to others and provides a legal record.

Documentation of teaching should list all learning needs with a target date for completion. It should tell whether the patient learned alone or with family members. Standardized teaching plans or standards of care should be specified. Teaching aids should be listed. The outcome of the teaching should be documented. Any unresolved goals must be documented with a follow-up plan. Nurses should have the learner sign to show that the goal was accomplished. Many institutions or clinics use a specific form for documentation of teaching.

ARE REIMBURSEMENT ISSUES IMPORTANT?

Economic considerations have become an integral part of health care planning, research, and patient care. Reimbursement denials for oncology treatment have been growing for three reasons: (1) state-of-the-art biological

cancer therapy often involves an investigational agent or is often combined with an investigational technology; (2) much of standard oncology practice includes the use of approved drugs in unapproved treatments or patients; and (3) biological therapies are costly.

Investigational Biological Therapy

Clinical investigation constitutes a significant component of cancer treatment; investigational therapy represents the best care in patients for whom no standard therapy exists. Investigational biological therapy offers patients access to the newest and most promising therapy. A drug or biological agent is investigational when it has not been approved by the FDA. The data developed from clinical trials provide information about the benefits of a new therapy before FDA approval. Because of this continuum, the distinction between when a drug should be investigational and when it becomes standard therapy is often blurred.

Despite the fact that cancer treatment given in a scientifically valid, peer-reviewed clinical trial represents the best available care, many insurers do not cover such therapy. The National Cancer Institute (NCI) along with other professional oncology organizations is working to ensure patient access to clinical trials.

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Prescribing cancer drugs to be used in unapproved ways is called off-label use. The FDA cannot restrict a physician's use of an oncology drug once it has been approved. Off-label drug use may be appropriate in certain circumstances. Medicare guidelines also permit wider use of oncology drugs than the uses described in the labeling, provided the therapy is "medically reasonable and necessary."

Third-party payers often deny reimbursement for the cost of a drug when it was used for an off-label indication.

Many states have passed legislation addressing this issue. For example, California and Illinois have passed

laws to mandate coverage of therapy when it is included in one of the three drug compendia: *The American Medical Association Drug Evaluation; American Hospital Formulary Service Drug Information;* and *The United States Pharmacopeia Dispensing Information.*

Costs

Biological agents face reimbursement obstacles because of their high cost. Insurers are reluctant to approve such great expenditures because they might become standard. Thus, significant focus has been directed toward including cost-effectiveness analysis when considering an expensive biological agent such as hematopoietic growth factors. Many clinical trials currently include economic end points along with an evaluation of effectiveness. Many institutions also employ guidelines, such as those developed by the American Society of Clinical Oncology, for the use of such biological agents as hematopoietic growth factors.

Nursing Strategies for Reimbursement

It is important for a nurse to have accurate information about the reimbursement potential of therapy and how to work with insurers.

Nurses should educate patients about financial issues of treatment. In some clinical trials, insurance coverage is an eligibility requirement. Patients often assume their insurance covers such therapy and are shocked when this is not the case. Many pharmaceutical companies that manufacture biological agents have national reimbursement programs to assist patients in obtaining reimbursement.

Patients on Medicare are often unable to receive biological agents at home because of coverage constraints. It is often necessary for these patients to come to the clinical site (office or ambulatory clinic) to receive their injection.

Nursing Strategies for Reimbursement

1. Be informed.
   - Have accurate information regarding the therapy, including knowledge of supportive literature.
   - Be familiar with information sources.
2. Know the process of working with insurers.
   - Develop working relationships with third-party payers (case managers, medical directors).
   - Document the benefits and scientific basis for the treatment planned.
3. Assist patients with financial issues as part of the informed consent process.
   - Educate patients about financial responsibility for specific aspects of treatment.
   - Inform patients of reimbursement issues involving off-label use and investigational therapy when relevant.
   - Facilitate and promote strategies for reimbursement.
   - Access pharmaceutical company reimbursement information services and indigent patient programs.
4. Develop financially efficient plans of care.
   - Include economic considerations in clinical decision making for equipment and treatment strategies.
   - Develop an institutional model that balances cost and quality in clinical care.
5. Become involved.
   - Participate in professional organizations that are involved in setting national reimbursement standards in oncology.

Applications of cold or heat have also been tried to eliminate local symptoms. Their use should be verified with the physician because medication absorption patterns may potentially be altered.

Hair Thinning

Alopecia may occasionally be experienced, most commonly with interferon therapy. Use of wigs, scarves, and headwraps is appropriate. Patients may be reassured that hair will regrow when therapy is complete.

Allergic Reactions

Allergic reactions are most commonly seen in association with the administration of monoclonal antibodies, especially those of murine (mouse) origin. Symptoms include fever, chills, hives, pruritus, shortness of breath, and hypotension.

Allergic reactions can range from mild—such as hives or itching—to the more rare occurrence of anaphylaxis. Patients should be monitored regularly and observed closely when MAB therapy begins.

Emergency drugs such as epinephrine, hydrocortisone, and diphenhydramine should be kept at the bedside. MAB should be administered via a side port so that if a severe allergic reaction occurs, the infusion can be stopped and intravenous fluids initiated immediately. An infusion pump should be used for administration to avoid inadvertent bolus infusions. An injection port should be available for the administration of emergency drugs.

To prevent or alleviate chills, fever, or urticaria, medication may be administered before or during therapy.

RADIATION PRECAUTIONS

Appropriate radiation safety precautions should be observed in patients receiving MABs conjugated with radioisotopes. Appropriate precautions are determined by the isotope used and the dose. Special precautions, such as using disposable food trays, flushing the toilet

three times after voiding, sitting while urinating (men), and avoiding bathing for 24 hours after administration of the isotope, should be reviewed.

Patients should be educated about the need for isolation with high doses of radionuclides.

Patients are often fearful of radiotherapy. Appropriate discharge precautions and issues related to sexuality should be discussed before discharge.

SEXUALITY

Patients receiving biotherapy may experience changes in sexuality. These changes may commonly be seen in patients receiving interferon therapy or interleukin-2.

The PLISSIT model is frequently used for sexuality counseling or nursing interventions. The success of each step depends on the nurse's knowledge and comfort level.

- P = *permission.* Discussion of patient concerns is promoted; the couple is encouraged to continue in its present pattern of sexual activity.
- LI = *limited information.* New information is included to address sexual concerns.
- SS = *specific suggestions.* New activities or techniques for the couple may be included.
- IT = *intensive therapy.* If necessary, the couple is referred to a therapist or counselor for more intensive treatment.

The American Cancer Society's books on sexuality for men and women with cancer provide excellent resources.

AMBULATORY CARE

The majority of biotherapy is administered in the ambulatory setting; thus patients will be responsible for administering therapy at home.

Major areas that need to be addressed include monitoring the patient's reaction to the initial treatment, assessing tolerance to and compliance with therapy, patient education, support systems and referrals, and financial concerns.

When therapy is initiated in the outpatient or home setting, patients should be monitored for tolerance to the first dose. The agent(s) administered and the dose will determine the time patients need to be monitored and how often vital signs should be checked.

Patients generally require regular follow-up visits or home visits to assess tolerance. Use symptom flow sheets to facilitate assessment and management of outpatients. Patient diaries or logbooks of symptoms can be useful. Toxic effects should be quantified and documented and patient response to interventions assessed.

Schedule follow-up visits to determine patient adherence to the regimen. Address misunderstandings or problems.

Evaluate patient or caregiver support systems. Lack of financial resources or social support will need to be addressed to ensure successful therapy.

WHAT ARE IMPORTANT CONSIDERATIONS IN PATIENT EDUCATION?

The goal of patient education is to assist patients and their families to develop the skills and knowledge to adapt to alterations in their health and lifestyle. Educated patients are better able to participate in their care and facilitate early discharge.

Assessment

Assessing patients' needs and learning styles helps the nurse provide individual instruction, promote effective use of resources, identify information important to patients, and save time.

Ability to Learn

Patients should be assessed for visual or auditory impairment or impaired motor ability. Assessing a patient's ability to communicate in English is important.

Literacy level should be assessed. Patient education literature has an average reading level of 11th grade. Experts recommend that most patient education materials be targeted to a 5th grade reading level. It is imperative that nurses recognize nonverbal cues to poor reading skills, such as poor attention span, little or no interest in the topic, frustration, and slow reading speed. Patients may be unable to answer questions about the literature or may ask that someone else read the literature. Nurses should use simple vocabulary and lay terminology when talking to patients.

The nurse must assess whether patients are visual learners (who like to read or watch videos), auditory learners (who like to listen to tapes, lectures, or videos), or tactile learners (who like to handle equipment or demonstrate procedures). Most people prefer a combination. To assess learning style, nurses can ask patients how they best learn.

Readiness to Learn

Several factors influence patients' readiness to learn, including cultural background, emotional state, and goals. Anxiety is normal and can increase patients' receptiveness to learning. Too much anxiety, however, can be overwhelming.

Knowledge Deficits

It is vital to assess previous knowledge and experience. For example, a mother who has been administering insulin subcutaneously to her child should be able to give herself subcutaneous interferon.

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SUMMARY

Biotherapy is now accepted as the fourth modality of cancer care. The rapid introduction of novel agents, approaches, and combination therapies into standard oncology care mandates that oncology nurses be knowledgeable about this newest therapeutic modality.

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Yarbro, C., ed. 1993. Management of patients receiving interleukin-2 therapy. *Seminars in Oncology Nursing* 9(3)(Suppl 1):1–35.

RESOURCES

North American Nursing Diagnosis Association (NANDA)
Website: www.nanda.org (Under development)
Telephone 1-800-647-9002

Oncology Nursing Society
Website: www.ons.org

Discussion forum for biotherapy
Biotherapy Special Interest Group
Biotherapy ONCBIO (newsletter for SIG members)
Telephone 1-412-921-7373

The Cancer Survival Toolbox™
A set of self-help audio tapes that teaches survivors skills they need to advocate for themselves when it comes to treatment, insurance, and employment issues.
Call 1-877-TOOLS-4-U (1-877-866-5448)
Website: www.cansearch.org/programs/toolbosx.htm

Additional Websites:

National Cancer Institute
www.nci.nih.gov
Cancer Trials
www.cancertrials.nci.nih.gov

Pharmaceutical Websites:

Pharmaceutical Information Network
www.pharminfo.com
Pharmaceutical companies on the Web
www.pharminfo.com/phrmlink.html#pharmco
Cancer Information Network
www.cancernetwork.com

CHAPTER 9

DISEASES TREATED WITH BIOTHERAPY

AIDS-RELATED KAPOSI'S SARCOMA

Incidence

Traditionally, Kaposi's sarcoma (KS) was seen only in selected populations such as elderly men of Jewish or Mediterranean descent and severely immunocompromised persons such as organ transplant recipients. The disease was very rare, with the incidence in the general population estimated to be only two to six cases per 100 million persons. Fewer than 40 cases were reported to the Centers for Disease Control (CDC) between 1976 and 1980.

Since the 1980s and the recognition of acquired immune deficiency syndrome (AIDS), a form of KS that mimics the more invasive form previously seen in a central African population has appeared. Approximately 20% of bisexual and homosexual men with AIDS present with KS. Statistics for AIDS-related KS are kept only for initial diagnosis of AIDS.

Currently, four types of KS are recognized: endemic, classic, transplantation-induced, and epidemic.

Etiology and Pathogenesis

There is a distinct relationship between immunosuppression and KS, although the degree of immunosuppression provides no predictive ability in AIDS. It is hypothesized that a sexually transmitted agent may in fact be responsible for the development of KS in patients with AIDS because KS is more frequently seen in homosexual and bisexual men with AIDS than in hemophiliacs or IV drug abusers.

Lesions are described by pathologists as interlacing bands of spindle cells, with vascular structures in a network of reticular and collagen fibers. Lymphatic and blood vessels are present throughout the lesion and on its periphery. An inflammatory response involving histiocytes, plasma cells, and lymphocytes may also be seen.

All forms are rarely curable, but they are generally not life-threatening. In patients with AIDS the cause of death is usually related to concomitant opportunistic infections or the pathologic effects of HIV itself.

Clinical Presentation

- Multicentric skin lesions on any part of body.
- Pigmentation ranges from brown, brown-red, and purple to dark red and violet.
- Lesions may be raised nodules or flat and painless.
- Visceral and lymphatic involvement.
- Progressive disease can result in enlarging lesions.
- Severe edema results from compromised lymphatic drainage and blood circulation.
- Protein-losing enteropathy is caused by gastrointestinal involvement.
- Respiratory distress often occurs because of lung involvement.

The classical form of KS appears as dark blue to reddish purple spots or nodules on the arms (25%) or legs (75%). Patients exhibit edema and may have involved lymph nodes or viscera.

In those who are HIV-positive, epidemic KS is the most common malignancy and is characterized by smaller pink to purple lesions on the trunk, head, and neck. Most patients have multiple lesions and edema secondary to lymph node blockage. Visceral lesions can occur on the gastrointestional (GI) tract, lungs, liver, pancreas, gingiva, pharynx, tongue, soft palate, adrenal glands, spleen, testes, and larynx.

KS involvement of the lymph nodes, GI tract, and lungs can cause significant morbidity. GI lesions result in

diarrhea. Pulmonary lesions cause dyspnea, orthopnea, and cough, which may be incorrectly attributed to *Pneumocystis carinii* pneumonia. Many patients have additional symptoms that may be related to immunodeficiency and infection, such as fever, weight loss, malaise, and anorexia.

Diagnosis and Staging

- Self-observation of cutaneous lesions.
- Biopsy suspicious lesions.
- Histologic examination confirms diagnosis.

A staging system has been proposed, although prognostic indicators have not yet been well delineated. Initially AIDS-related KS was staged as localized cutaneous (stage I), disseminated cutaneous (stage II), visceral only (stage III), or both cutaneous and visceral (stage IV) (Mitsuyasu staging). Patients may be subtyped according to the presence of "B" symptoms. A consensus conference in 1989 proposed a staging system similar to TNM that utilized the extent of tumor, degree of immunosuppression, and other systemic illnesses. Patients are assigned to either a good-risk or a poor-risk category.

Treatment

- Classic KS generally requires little or no treatment.
- AIDS-related KS: goal is to lessen morbidity.
- Surgery: minimal role, with exception of biopsy.
- Need to control tumor without exacerbating immunodeficiency.
- Radiation therapy for local control of lesions and cosmetic effect.
- Chemotherapeutic agents, alone or in combination, may be beneficial. Agents commonly used include doxorubicin, vincristine, etoposide, and vinblastine. Guidelines are in use for the initiation of chemotherapy and biological therapy in patients with AIDS-related KS.

- Responders to interferon include patients with CD4 cell counts higher than 200/mm^3, no "B" symptoms (fever, night sweats, weight loss), and no prior AIDS defining diagnosis. Responses range from approximately 40 to 80%.

Suggested Reading: AIDS-Related Kaposi's Sarcoma

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WEBSITES

www.nci.nih.gov

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) is one of a group of diseases known as the myeloproliferative disorders. CML is characterized by three phases and is not currently curable with conventional chemotherapy.

Incidence

The annual incidence of CML is estimated at approximately 10 cases per million. The disease accounts for approximately 15% of all patients with leukemia. Unlike chronic lymphocytic leukemia, it can occur in children and younger adults.

The median age of patients with Ph+ CML is 40 to 45 years. Median survival is 3 to 4 years, with a range of less than 1 year to more than 10 years. Survival after development of an accelerated phase is usually less than 1 year and after blastic transformation is only a few months.

Median age for patients who are Ph– is 60 to 65 years, and median survival is about 18 months.

Etiology and Pathogenesis

In the majority of patients with CML, a causative factor cannot be identified. It is well known, however, that ionizing radiation is a causative factor in leukemias. Although CML has been observed, the most common type of leukemia following radiation has been acute myeloid leukemia.

CML is a clonal disorder of a myeloid stem cell that is usually easily recognized because the leukemic cells of more than 95% of patients have a distinctive cytogenetic abnormality, the Philadelphia (Ph) chromosome.

- The Ph chromosome results from a reciprocal translocation between the long arms of chromosomes 9 and 22.
- This translocation is demonstrable in all hematopoietic precursors.

- At the molecular level, this translocation results in the transfer of the Abelson (abl) oncogene to an area of chromosome 22 termed the *breakpoint cluster region (bcr).*
- The result is a new fusion product, the bcr-abl gene, which produces an abnormal tyrosine kinase protein.
- This aberrant protein may be related to the disordered myelopoiesis found in CML.
- Molecular techniques can now be used to supplement cytogenetic studies to detect the presence of the 9;22 translocation in patients without a visible Ph chromosome (Ph–).
- Ph– CML is a poorly defined entity that is less clearly distinguished from other myeloproliferative syndromes. Patients with Ph– CML generally have a poorer response to treatment and shorter survival than Ph+ patients.
- However, Ph– patients who have bcr-abl gene rearrangement detectable by Southern blot analysis have prognoses equivalent to those of Ph+ patients.
- A small subset of patients have bcr-abl detectable only by reverse transcription–polymerase chain reaction (RT-PCR), which is the most sensitive technique currently available. Patients with RT-PCR evidence of the bcr-abl fusion gene appear clinically and prognostically identical to patients with a classic Ph chromosome.

CML results in an increase in the myeloid component of the bone marrow and peripheral blood cells. The total granulocyte pool is from 10 to 150 times normal. It is hypothesized that the primary biological defect in CML is not unregulated proliferation of leukemic stem cells, but rather a change in maturation. A slight delay in cell maturation within the myeloid compartment results in increased myeloid mass. In contrast to the normal state, in which the primitive progenitors have a large proliferative potential and produce the majority of cells, in CML early progenitors have reduced proliferative capacity as the leukemic population expands.

Clinical Presentation

Symptoms and signs usually develop insidiously and include the following:

- Fatigue.
- Anemia.
- Progressive splenomegaly.
- Leukocytosis.
- CBC shows a white blood cell count of approximately 200,000/mL in the chronic phase. Myeloid cells in the peripheral blood show all stages of differentiation, but the myelocyte predominates. Basophils and eosinophils are prominent, and more than half of patients experience platelet counts above 1,000,000/mL. Fortunately, thrombotic phenomena are unusual.
- Bone marrow: Hypercellular and devoid of fat. Bone marrow aspirate demonstrates a shift in the myeloid series to immature forms that increase in number as patients progress to the blastic phase of the disease. As the disease evolves, varying degrees of fibrosis occur. The cause of this is unknown, but presumably the fibroblasts are not part of the malignant clone. Evidence suggests that the marrow fibrosis may be a secondary phenomenon resulting from an abnormal interaction between the proliferative clone of hematopoietic cells and elements that regulate marrow fibrosis and collagen. Factors that may be involved include platelet-derived growth factor, transforming growth factor–beta, basic fibroblastic growth factor, and other factors not completely described as yet.
- The leukocyte alkaline phosphatase enzyme is either absent or markedly reduced in the neutrophils of patients with chronic myelogenous leukemia.
- The myeloid/erythroid ratio in the marrow is usually greatly elevated.

Transition from the chronic phase to the accelerated and later the blastic phase may occur gradually over a period of

1 year or more, or it may appear abruptly ("blast crisis"). Signs and symptoms commonly heralding such a change are:

- Progressive leukocytosis
- Thrombocytosis or thrombocytopenia
- Anemia
- Increasing and painful splenomegaly or hepatomegaly
- Fever
- Bone pain and/or development of destructive bone lesions
- Thrombotic or bleeding complications

In the accelerated phase, differentiated cells persist, although they often show increasing morphologic abnormalities, and increasing anemia and thrombocytopenia and marrow fibrosis are apparent.

Studies have suggested that certain presenting features have prognostic significance and may help in identifying patients in whom bone marrow transplantation should be considered earlier in the course of the disease. Predictive models using multivariate analysis have been derived. Sex, spleen size, hematocrit, platelet count, and percentage of circulating blasts have been identified as significant prognostic indicators. Poor prognostic indicators include:

- Increased splenomegaly
- Male sex
- Elevated serum lactate dehydrogenase
- Cytogenetic abnormalities in addition to the Ph chromosome
- High proportion of blasts in the peripheral blood or marrow and/or
- Increased Basophils, and anemia which predict for a shorter chronic phase

Diagnosis and Staging

- Physical exam
- Complete blood count with differential
- Bone marrow aspiration and biopsy with cytogenetic analysis to assess cellularity, degree of fibrosis, and cytogenetics
- Molecular studies

Chronic Phase

Bone marrow and cytogenetic findings as described previously with less than 5% blasts and promyelocytes in the peripheral blood and bone marrow.

Accelerated Phase

Greater than 5% in either the peripheral blood or bone marrow but less than 30% blasts in both the peripheral blood and bone marrow.

Blastic Phase

Greater than 30% blasts in the peripheral blood or bone marrow. When greater than 30% blasts are present in the face of fever, malaise, and progressive splenomegaly, the patient has entered blast crisis, and survival is on the order of a few months.

Treatment

Treatment of CML is usually initiated once the diagnosis is established. At initial diagnosis, consideration should be given to referral of patients younger than age 60 years to centers exploring potentially curative therapy with bone marrow transplantation when appropriate donors are available. Allogeneic bone marrow transplantation in the chronic phase is the only therapy known to cure CML.

Other state-of-the-art treatment of CML does not cure the disease, prevent blast crisis, or prolong the average survival time. Thus, all newly diagnosed patients should

be considered appropriate candidates for clinical trials exploring new therapeutic approaches, including bone marrow transplantation, biological response modifiers, and combination chemotherapy.

The treatment of chronic-phase CML is aimed at decreasing granulocytic hyperplasia, hyperleukocytosis, thrombocytosis, and splenomegaly and reducing the degree of anemia. Approaches include:

- Hydroxyurea (Hydrea): This agent is S phase and cell-cycle specific, and is thought to function as an antimetabolite. It has well-documented efficacy in CML.
- Busulfan (Myleran): This is an alkylating agent, also used in CML.
- Interferon-alfa: Of 190 patients treated with partially purified IFN-α and recombinant interferons (IFN-alfa 2a and IFN-alfa 2b) at M. D. Anderson the complete hematologic response rate was 74%. The cytogenetic response rate was 53%. Forty-nine patients (26%) had complete cytogenetic remissions, 14 (7%) had partial remissions, and 38 (20%) had minor remissions. Approximately 30% of the total population, or about half of the cytogenetic responders, achieved durable remissions. The durability of remission was directly related to the degree of cytogenetic remission. In addition, there was a correlation between dose and response. Patients treated early in the course of the disease tended to have a better cytogenetic response than did those treated later.
- The question of whether interferon improves survival as compared with conventional therapy was investigated by the Italian Study Group on Chronic Myeloid Leukemia. A total of 322 patients were randomized to receive IFN-alfa 2a or hydroxyurea. Patients were also stratified according to risk factors, including risk of disease progression, spleen size, platelet count, and percent blasts in the peripheral blood.

- Treatment was started at 3×10^6 units for 2 weeks and was escalated to a final dose of 9×10^6 units daily thereafter. Those patients on the interferon arm were allowed to receive hydroxyurea if the response was considered sluggish. This occurred in one-third of the patients. After a median follow-up of 68 months, the frequency of clinical (hematologic) remission was the same in both arms. However, in the interferon arm, a complete cytogenetic response was seen in 8% of the complete responders and a major response (67 to 99% Ph–) was seen in 11%. This compares with 0% and 1%, respectively, for the conventionally treated group. The time to progression from the chronic phase of leukemia to an accelerated or blastic phase was 72 months in the interferon group as compared with 45 months in the conventionally treated group ($P<.001$), as was survival (median 72 versus 52 months, respectively).

Dose intensity is of extreme importance in the treatment of CML with IFN-alfa. Leukopenia of 2,000 to 3,000/dL is necessary to obtain a response. Patient education and coaching are important in CML to help patients anticipate and tolerate the effects of rIFN-alfa.

- Some studies are beginning to demonstrate an advantage with the use of low-dose ara-C and biological response modifiers such as IFN-alfa for the treatment of CML.
- Leukapheresis and platelet pheresis are used occasionally to rapidly lower white blood count or platelet count, respectively. This is of only temporary benefit and is rarely required in adults in chronic phase.

Treatment for Blast Crisis

When blast crisis occurs, minimally satisfactory remission-induction treatment appears to be available only to a group of patients whose cells are positive for the enzyme terminal deoxynucleotidyl transferase (TdT). In these patients survival can be extended 4 to 8 months using simple treatment with combinations of drugs including vincristine and prednisone, usually given in the treatment of acute lymphocytic leukemia.

In addition, intensive chemotherapy/radiation therapy followed by reinfusion of marrow or peripheral blood or both collected and frozen during the chronic phase has also been used regardless of TdT status. However, in most patients early relapse of blast crisis has developed. Unfortunately, the treatment of blast-phase chronic myeloid leukemia remains unsatisfactory.

Suggested Reading: Chronic Myelonenous Leukemia

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www.nci.nih.gov

Website for the Leukemia Newsletter:
www.mdacc.tmc.edu/~leukemia/insights.html

eGroups—Website Support Groups:
www.egroups.com/list/cml

HAIRY CELL LEUKEMIA

Incidence

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder of B-cell origin. Immunophenotyping suggests that the hairy cell is a relatively mature cell, perhaps at a pre-plasma cell stage of development. The disease is characterized by splenomegaly and pancytopenia without lymphadenopathy. The peripheral blood smear shows a small percentage of abnormal, mononuclear cells with irregular, cytoplasmic projections; hence the name "hairy cell leukemia."

The disease is relatively rare and accounts for about 2% of adult leukemias. There are an estimated 400 to 800 new cases diagnosed per year in the United States. The clinical course of HCL is variable, but most often it is chronic. Median survival has now improved owing to the introduction of effective systemic therapy. A small percentage of patients, up to 10%, have mild disease, require no treatment, and have prolonged survival.

Etiology and Pathogenesis

The cause of HCL remains unknown. It is seen more often in men by a ratio of 4 : 1. An association with radiation exposure has been suggested but studies have failed to verify this relationship.

Clinical Presentation

The most common symptoms at presentation are those related to cytopenia and include

- Fatigue
- Easy bruising
- Infection

Cytopenias result from a combination of splenic sequestration and bone marrow underproduction owing to

leukemic infiltration. Recurrent or severe infections, often with opportunistic organisms, are a significant cause of morbidity and the most common cause of death in HCL.

Symptoms related to splenomegaly occur in about 20% of patients.

Autoimmune syndromes characterized most often by vasculitic skin lesions, arthritis, and polyarteritis have also been observed in approximately 25% of patients.

Up to 20% of new patients are asymptomatic and come to attention when abnormalities are noted on routine blood tests.

Physical examination reveals palpable splenomegaly in the majority of patients at presentation. The enlarged spleen is due primarily to diffuse infiltration of the splenic red pulp cords and sinuses by hairy cells. Peripheral adenopathy is uncommon.

Diagnosis and Staging

A marrow biopsy specimen is the most reliable means to confirm the diagnosis of HCL. The bone marrow is usually fibrotic and often is not aspirable. In virtually all patients, the marrow biopsy demonstrates a diffuse or patchy infiltrate of leukemic cells. The bone marrow is most frequently hypercellular.

There is no generally accepted staging system that is useful both for prognosis and therapy. For the purpose of treatment decisions, it is best to consider this disease in two broad categories:

1. Untreated hairy cell leukemia
2. Progressive hairy cell leukemia, either post-splenectomy or post-systemic therapy

Progressive hairy cell leukemia, post-splenectomy (or following any systemic therapy) is characterized by progressive bone marrow replacement by hairy cells, with pancytopenia refractory to treatment.

Treatment

Survival

For patients with advanced hairy cell leukemia treated with 2 chlorodeoxyadenosine (2-CdA), pentostatin, or interferon alfa, the survival rate appears to be greater than 85% at 5 years after the initiation of any one of these therapies.

It is reasonable to offer no therapy if the patient is asymptomatic and blood counts are maintained at an acceptable range.

Treatment indications for HCL include

- Severe anemia (HCT below 25%)
- Thrombocytopenia (below 50,000 cells per microliter)
- Marked granulocytopenia (fewer than 1,000 neutrophils per microliter)
- Splenic pain or rupture
- Recurrent infections
- Bone involvement
- Vasculitis
- Bulky retroperitoneal disease

Surgery

Splenectomy was the indicated treatment in the 1970s and early 1980s and was used to correct the effects of hypersplenism. Currently, it is still considered for a few patients, such as those with severe thrombocytopenia.

The pattern of hematologic response to splenectomy has been well characterized. The platelet count is the most likely to respond, often rising within days after surgery. Several weeks to months may be required to see improvment in the anemia and granulocytopenia.

Chemotherapy

In the early 1980s, recombinant interferon-alpha (IFN-α) was shown to be effective in the treatment of HCL by Quesada and colleagues at The University of Texas M. D.

Anderson Cancer Center. IFN-α was given regulatory approval for the treatment of HCL in 1986.

Since then two other drugs, the adenosine deaminase inhibitor deoxycoformycin (pentostatin) and a deoxyadenosine analogue, 2-chlorodeoxyadenosine (cladribine) have induced a higher percentage of complete responses than did interferon.

These drugs have comparable response rates but have not been compared in phase III trials. 2-CdA is administered as a one-time continuous infusion or series of subcutaneous injections and is associated with a high rate of febrile neutropenia. Pentostatin is administered intermittently for a longer treatment duration but may result in a lower incidence of febrile complications. Both nucleoside analogues cause profound suppression of CD4 (helper T-cells) counts which may last for a year.

In summary, the initial therapies of choice are either 2-chlorodeoxyadenosine (2-CdA) or pentostatin. 2-CDA is often favored as a high CR rate can be obtained with a single 7-day course. Therapy with interferon-alfa is another treatment option if 2-CDA or pentostatin are not available. The disease now has an extremely favorable prognosis with various intermittent therapies. It is well-controlled, however few patients have yet to be followed long enough to assess cure.

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WEBSITE

www.nci.nih.gov

MALIGNANT MELANOMA

Incidence

Melanoma currently accounts for approximately 3% of all cancers diagnosed in the United States and is rapidly increasing in incidence. At present, the incidence increases by 5 to 7% yearly, doubling the population risk every 10 to 15 years. The age-adjusted annual incidence in the United States is approximately 10 per 100,000, although there tends to be a greater incidence in the Sun Belt. Australia has the highest incidence of melanoma in the world: approximately 17 per 100,000 per year. According to the American Cancer Society, 41,600 new cases of melanoma were diagnosed in the United States in 1998, and there were approximately 7,300 deaths from the disease. At the current rate of increase, it is anticipated that by the year 2000, 1 in 90 individuals will develop cutaneous melanoma.

Etiology and Pathogenesis

Currently, the etiology of melanoma is unknown. However, the mechanism underlying UV-mediated skin cancers, and melanoma in particular, is believed to result from damage to the DNA of cutaneous cells. Familial human melanoma is characterized by an increased risk of developing primary melanoma, a higher incidence of multiple primary melanomas, and an earlier age at onset. Germline mutations have been discovered that are related to familial melanoma.

Risk factors include excessive exposure to UV radiation; fair complexion; occupational exposure to coal tar, pitch, creosote, arsenic compounds, or radium; family history; multiple nevi or atypical nevi.

Malignant melanoma originates in proliferative, single melanocytes in the lower epidermis. Lesions can arise on any epithelial surface (e.g., gallbladder, esophagus, meninges, vagina, or upper respiratory tract), but they usually occur on the skin. Growth can proceed radially or vertically.

Melanomas are found predominantly on the trunk, head, and neck of males and on the lower and upper extremities of females. When African-Americans develop melanomas, they are commonly located on less pigmented skin areas, such as the palms of the hands and the soles of the feet, and on subungual areas.

Clinical Presentation

Early detection is critical. Recognition of changes in skin growths or the appearance of new growths is the best way to detect melanoma early. Adults should practice skin self-exam regularly. A sudden or progressive change in a mole's appearance should be checked by a physician.

Melanoma often starts as small, molelike growths that increase in size and change color.

A simple ABCD rule outlines the warning signals of melanoma:

- A is for asymmetry. One half of the mole does not match the other half.
- B is for border irregularity. The edges are ragged, notched, or blurred.
- C is for color. The pigmentation is not uniform or intensely black.
- D is for diameter greater than 6 millimeters. Any sudden or progressive increase in size should be of particular concern.

Patients should be evaluated for precursor lesions such as the following:

Dysplastic Nevi (DN)

- May occur in familial and nonfamilial settings
- Risk of melanoma is high in members of families with familial DN
- Normal nevi appear between ages of 5 and 8 years, with dysplastic changes after puberty
- Patient with "classic" DN has more than 100 moles

- One mole larger than 8 mm
- DN appear on face, trunk, arms, buttocks, groin, scalp, and breast
- Pigmentation is irregular, with mixtures of tan, brown and black, or red and pink

Congenital Nevi

- Present at birth or shortly thereafter
- Range in size from large to small, covering arms, hand, or trunk
- Colors range from brown to black
- Lesions may have irregular surface
- Lifetime risk of malignant transformation is 6 to 7%

Lentigo Maligna

- Large lesions
- Tan with shades of brown
- 10 to 25 years before malignant transformation

The American Joint Committee on Cancer (AJCC) identifies five forms of extraocular melanoma that occur in humans: lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma, and mucosal lentiginous melanoma.

Lentigo Maligna Melanoma (LMM)

- 4 to 10% of melanomas
- Least serious type
- Common sites are areas exposed to sun (face, neck, back of hands)
- Clinically, the lesions are generally large (3 to 4 cm in diameter) and flat with irregular borders, in variable shades of tan to dark brown

Superficial Spreading Melanoma (SSM)

- Accounts for 70% of melanomas
- Generally arises in a preexisting lesion and is the lesion most commonly associated with pigmented DNS
- Seen on head and neck, trunk and back in men
- Seen on legs in women
- Aggressive

Nodular Malignant Melanoma (NM)

- Accounts for 15 to 30% of melanomas
- Common sites are head, neck, and trunk
- NM does not have a radial growth phase and is associated with rapid evolution to vertical growth and invasion of the dermis
- NMs tend to be thicker, more high-risk lesions

Acral Lentiginous Melanoma (ALM)

- Found in 35 to 60% of dark-skinned persons, primarily African-Americans, Asians, and Hispanics
- Occurs on palms, soles, nailbeds, mucous membranes
- Biologically more aggressive than LMM

Mucosal Lentiginous Melanoma (MLM)

- Similar in appearance to ALM, this lesion occurs in a variety of mucosal sites
- Most common sites include the oral cavity, esophagus, anus, vagina, and conjunctiva

Diagnosis and Staging

Definitive diagnosis is obtained by performing pathologic examination of lesions removed by an excisional biopsy. **To microstage the lesion accurately, all layers of the skin must be included in the sample. For this reason, shave biopsy or curetting is contraindicated.**

Clark's microstaging	Based on levels of penetration through the dermis to the subcutaneous fat. Success is directly related to the experience of the examining dermatopathologist and the ability to recognize the microscopic anatomy of the skin accurately. The deeper the level of penetration, the poorer the prognosis. This observation has been repeatedly confirmed when primary lesions are microstaged by experienced dermatopathologists.
Breslow's microstaging	Based on the use of an ocular micrometer to measure the vertical thickness of the primary tumor from the granular layer of the epidermis, or the base of an ulcer, to the deepest identifiable contiguous melanoma cell. Technique has wide acceptance and is a more easily reproducible and accurate prognostic parameter than Clark's level of invasion. The thicker the melanoma, the greater the risk for developing metastatic disease.
Clinical staging system	Involves three stages: I, localized melanoma; II, regional metastatic melanoma; and III, disseminated melanoma. This original

three-stage system offers the advantage of simplicity but does not account for the important prognostic indicator of depth of invasion.

Prognosis

The 5-year survival rate is 93% for localized disease and 57% for regional disease; distant metastatic disease survival is only 15%. About 82% of melanomas are localized at the time of diagnosis. Melanoma metastasizes to lymph nodes, skin, lung, brain, liver, and bone. The single most important prognostic indicator is tumor thickness.

Researchers have examined the relationship between melanoma development and menstruation, pregnancy, and exogenous hormones. Studies have noted that women diagnosed during pregnancy have shorter disease-free survival time and greater likelihood of lymph node metastases. Long-term survival rates, however, are the same as for women not diagnosed while pregnant. Additional studies have been unable to link melanoma developments to menstrual or exogenous hormone factors.

Treatment

Surgical intervention is used as follows in the diagnosis and treatment of melanoma.

Surgery

- Biopsy for suspected melanoma
- Wide excision for stage I melanoma
- Excision of primary lesions and surgical dissection of involved nodes for clinical stage II
  Appropriate width of primary excision remains controversial. In general, optimal therapeutic effects will be achieved by excisions of at least 1 cm for melanomas thinner than 1 mm, and at least 2 cm for

melanomas thicker than 1 mm. Larger margins are generally used for thicker lesions (e.g., 3- to 5-cm margins for lesions thicker than 4 mm).

- Elective lymph node dissection is controversial. Intraoperative lymphatic mapping is a newer approach to determining lymph node status. It is based on the premise that a primary melanoma drains initially to one or more "sentinel" lymph nodes, which therefore should be the first nodes at risk for harboring occult metastatic disease. Mapping involves the intradermal injection of a vital dye that readily enters the subdermal lymphatics and passes through the lymphatic channels to the regional nodal basin/station draining that particular skin site. This permits identification of the sentinel lymph node, which is selectively excised and examined by frozen section. If metastatic melanoma is identified, a complete lymphadenectomy is performed; if not, the procedure is terminated.

Chemotherapy

In general, metastatic melanoma is resistant to most chemotherapeutic agents. Dacarbazine (DTIC) is currently considered the single most active agent in disseminated melanoma. Unfortunately, adjuvant trials with DTIC, either alone or in combination with immunotherapy or other chemotherapeutic agents, have demonstrated no better survival than that associated with surgery alone.

Radiotherapy

- Most effective when tumor volume is low.
- Often used for palliation.
- The role of radiotherapy as adjuvant therapy for melanoma remains controversial.

Biological Therapy

Several agents (interferons, interleukins, tumor necrosis factors, monoclonal antibodies) are under investigation

for the treatment of melanoma. The results of treatment with the two subspecies of recombinant IFN-alfa are comparable in 11 published studies, achieving an overall objective clinical response rate of 17.5%. Generally, smaller tumor masses respond more frequently to IFN alfa than do larger masses. Some responses have been observed after protracted periods of treatment. The optimal dosage for therapy, however, has not been rigorously determined.

IFN alfa-2b has regulatory approval as a postsurgical adjuvant in AJCC stage III melanoma.

High doses of IL-2 (600,000 IU/kg), Chiron Corp., administered daily for up to 5 days by IV bolus every 8 hours, and repeated after 7 to 10 days has regulatory approval for the treatment of metastatic melanoma. Clinical trials resulted in partial responses (approximately 24% of evaluable melanoma patients treated).

Melanoma vaccines: The use of vaccines as a form of active specific immunotherapy for the adjuvant treatment of melanoma is an active area of research. Trials have demonstrated that some patients appear to have improved survival.

Combination chemotherapy/biotherapy: The use of interferon-alfa, IL-2, and combination chemotherapy has resulted in a dramatic response rate (>50%) in several studies. Some patients have achieved long-standing, complete remissions.

Patient Education

Prevention:	The sun's UV rays are strongest between 10 A.M. and 4 P.M.; exposure at these times should be limited or avoided. When outdoors, cover as much skin as possible with a hat that shades the face, neck, and ears, and a long-sleeved shirt and long pants. Sunscreen comes in various strengths, graded by the solar protection factor (SPF). Use a sunscreen with an SPF of 15 or higher. Because of the possible link between severe sunburns in childhood and greatly increased risk of melanoma in later life, children, in particular, should be protected from the sun.

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www.cancernews.com/skin

Website for Academy of Dermatology:
www.aad.org

Website for the American Cancer Society:
www.cancer.org

Schering Website:
www.skin-cancer.com/Schering

MULTIPLE SCLEROSIS

Incidence

Multiple sclerosis (MS) is a progressive neurologic disease characterized by demyelination of nerve fibers of the brain and spinal cord. It is the most common chronic disease of the central nervous system (CNS) among young adults in North America, with an incidence of 40 to 60 per 10,000 persons. The majority of cases occur between the ages of 20 and 40 years. The mean age at onset is 30 years, with the peak being 23 to 24 years in women and 25 years in men. Onset in persons younger than age 14 and older than age 60 is rare. The sex ratio is 1.8:1, with females affected more often than males. With onset before the age of 30, the disease is usually relapsing and remitting; after age 40, it is often progressive.

Interestingly, several studies have confirmed an association between the incidence of MS and distance from the equator (i.e., the farther from the equator, the more prevalent the disease). MS is a major cause of disability, with a societal cost in the billions of dollars.

Etiology and Pathogenesis

The cause of MS is unknown. It is important to note that it is not a contagious disease. Evidence points to the interaction of genetic, virologic, environmental, and immunologic factors that ultimately lead to myelin-specific autoimmunity.

Genetic features	First-degree relatives of a person with MS have over a 15-fold increase in incidence over that of the general population.
Virologic features	Individuals with MS have an increased titer of antiviral antibodies.

Environmental features	Prevalence of the disease is increased in colder and temperate climates.
Immunologic features	A majority of individuals with MS have abnormalities such as increased level of IgG present in the cerebrospinal fluid (CSF). Suppressor lymphocyte function is altered, and immunoregulation appears to be defective.

The fundamental lesion (plaque) is seen predominantly in the white matter of the CNS, although gray matter involvement also occurs. Distribution of the lesions is random. It is characterized by focal demyelination, relative axonal sparing, and variable inflammation with infiltration by lymphocytes, macrophages, and plasma cells.

Acute lesions	Associated with blood-brain barrier breakdown, focal edema, and the presence of macrophages engulfing degenerating myelin lamellae. The lesion may be initiated by T cells. Plaques are commonly perivenular and especially found in the optic nerves, spinal cord, brain stem, cerebellum, and periventricular regions. Recovery from an attack generally leads to resolution of edema, limited remyelination, and physiologic CNS adaptation.
Chronic lesions	Result in a gliotic scar. Partially demyelinated

fibers are susceptible to blocking of neural conduction, which may be precipitated by slight rises in body temperature. Demyelinated fibers result in several significant problems: a decrease in nerve conduction velocity; nerve conduction block; differential rates of impulse transmission; and a complete failure of impulse transmission.

Clinical Presentation

Sensory symptoms	Numbness and tingling of extremities or the face; loss of joint sensation; or loss of sense of position and vibration.
Ocular symptoms	Optic neuritis; nystagmus; diplopia; dilation of affected pupil when light is shone into the eye (known as the Marcus Gunn phenomenon); and dilation of the affected pupil when light is moved from the unaffected eye to the affected eye (known as the "swinging flashlight" sign).
Motor symptoms	Weakness in lower extremities, facial palsy, decline in motor function after a hot bath or shower, inability to coordinate movements,

	intentional tremors of upper extremities, staggering gait, spastic weakness of speech muscles.
Vestibular/auditory	Vertigo
Mental/behavioral	Emotional lability, mild depression, changes in judgment, irritability, with ultimate memory deficits, confusion, and disorientation.

Diagnosis and Staging

Clinical diagnosis made by demonstration of lesions in white matter tract in noncontiguous areas that are best explained by a diagnosis of MS. Recent criteria allow for the inclusion of lesions detected by imaging and evoked potentials and of analysis of the CSF results.

Examination of CSF	Elevated gamma globulin levels, normal to low CSF protein levels, increased white blood cell (WBC) counts, presence of myelin basic pattern.
Computed tomography	Areas of low attenuation around cerebral ventricles. With long-term disease, may see cerebral atrophy.
Magnetic resonance imaging	More sensitive than computed tomography and shows multiple white matter abnormalities in well over 90% of patients with clinically definite MS.

Evoked response (measurement of time needed to transmit electrical impulses)	Visual responses are impaired in more than 80% of patients; abnormal responses may also be detected in the brain stem and somatosensory pathways.

No laboratory test is diagnostic of MS.

Treatment

No treatment is known that alters the long-term natural history. Even patients starting out with infrequent relapses often develop a slow progressive course later in their disease. In general, after 15 years of disease, approximately 30% of patients are still working and 50% are still walking.

Surgical	Contralateral thalamotomy Rhizotomy
Chemotherapuetic	Acute exacerbations usually improve spontaneously but do so more rapidly with high doses of oral corticosteroids (e.g., prednisone). More aggressive attempts at immunosuppression are in progress, such as oral administration of azathioprine, which appears to have modest effect. Interferon-β has received approval for the treatment of exacerbations and remissions of MS. A variety of drugs are used to treat symptoms, such as carbamazepine for paroxysmal symptoms, tricyclic

antidepressants for emotional lability, anticonvulsants for seizures, and muscle relaxants such as baclofen (Lioresal) for spasticity.

Nursing and supportive care is crucial to the management of patients with MS. Nutritional consultation, physiotherapy, occupational therapy, speech therapy, home health care services, and evaluation of the need for extended care facilities are all important measures. Key problems that require management include respiratory dysfunction, bowel incontinence, fatigue, and impaired communication.

Suggested Reading: Multiple Sclerosis

Frozena, C. 1997. Clinical snapshot: Multiple sclerosis. *American Journal of Nursing* 97(11):48–49.

Halper, J., and N. Holland. 1998. Meeting the challenge of multiple sclerosis. *American Journal of Nursing* 98:26–31.

Keating, M. M., and P. L. Ostby. 1996. Education and self-management of interferon beta 1b therapy for multiple sclerosis. *Journal of Neuroscience Nursing* 28:350–352, 357–358.

Kelley, C. L. 1996. Pharmacology update: The role of interferons in the treatment of multiple sclerosis. *Journal of Neuroscience Nursing* 28:114–120.

Reder, A. T., ed. 1997. *Interferon therapy of multiple sclerosis.* New York: M. Dekker.

Stuifbergen, A. K., and S. Rogers. 1997. The experience of fatigue and strategies of self-care among persons with multiple sclerosis. *Applied Nursing Research* 10(1):2–10.

Swain, S. E. 1996. Multiple sclerosis: Primary health care implications. *Nurse Practitioner* 21(7): 40, 43, 47–50, 53–54.

WEB SITES

www.ninds.nih.gov

www.infosci.org/MS-Internat

Website for the National Multiple Sclerosis Association: www.nmss.org

Website for the Multiple Sclerosis Foundation: www.msfacts.org

NON-HODGKIN'S LYMPHOMA

Incidence

The malignant lymphomas comprise a group of diseases characterized by neoplastic transformation of cells that reside predominantly within lymphoid tissues. Hodgkin's and non-Hodgkin's lymphomas (NHLs) differ in the neoplastic cell of origin, the site of disease, and the presence of systemic symptoms, and in their response to treatment. Hodgkin's disease can be cured in nearly 75% of all patients by employing both conventional and salvage treatment strategies; NHLs are cured in less than 25% of patients.

NHL is seven times more common than Hodgkin's disease, with an estimated 52,700 new cases diagnosed annually. As many as 23,300 patients each year will succumb to the disease. Over the past 25 years, the incidence of NHL has increased by over 65%. Overall survival at 5 years with optimum treatment for all patients with NHL is approximately 50 to 60%. NHL can occur in any age group, but an increase in incidence is seen beginning in the fourth decade. Males are more often affected than females.

Etiology and Pathogenesis

NHL is a malignancy of subpopulations of B and T lymphocytes. Clones of the malignant cells may infiltrate the lymph nodes, bone marrow, peripheral blood, or other organs.

Viral etiology	Implicated in animals more strongly than in humans. Epstein-Barr virus (EBV) has a strong association with the development of Burkitt's lymphoma and human immunodeficiency virus (HIV)–1 related

	lymphoma, while the human T-cell leukemia virus–1 appears to be a causative agent of the adult T-cell leukemia/lymphoma.
Immunosuppression	Individuals with congenital or acquired immunodeficiencies, including individuals with AIDS, those undergoing organ transplantation and receiving immunosuppressive drugs, and those with autoimmune diseases, are at increased risk for developing NHL.
Drug or chemical exposure	Diphenylhydantoin (Dilantin); dioxin, radiation, prior chemotherapy and radiotherapy. More controversial is whether certain chemical exposures, including phenoxyherbicides, pesticides, and hair dyes, are involved in the development of NHL. Additional potential environmental associations are exposure to arsenic, phenoxyacetic acids, chlorophenols, and organic solvents.

Clinical Presentation

- Localized or generalized painless lymphadenopathy, which may have waxed and waned over a period of several months.

- Early involvement of the oropharyngeal lymphoid tissue or infiltration of the bone marrow is common.
- Patients may also exhibit systemic "B" symptoms, including night sweats, fever, and/or weight loss.
- Systemic complaints such as fatigue, malaise, and pruritus, occur in less than 10% of patients.
- Approximately one-third of patients will have splenomegaly or hepatomegaly.
- CNS involvement in immunocompetent individuals is uncommon at diagnosis.

Diagnosis and Staging

- Differential diagnosis of generalized lymphadenopathy first necessitates the exclusion of infectious etiologies, such as bacterial, viral, or parasitic infections.
- A firm lymph node of larger than 1 cm that is not associated with a documentable infection and that persists longer than 4 to 6 weeks should be considered for biopsy.
- Advances in both immunology and molecular biology have refined the ability to diagnose and detect NHL. Identification of the cell-surface molecules that are involved in the regulation of cellular growth as well as microenvironmental localization form the basis of characterizing NHL.
- Historically, the Rappaport classification subdivided NHLs into two major subtypes: diffuse and follicular (nodular). Nodular lymphomas tend to be more indolent, whereas the diffuse lymphomas tend to be more aggressive. The pattern of spread is less predictable with NHL than with Hodgkin's disease, and disease is frequently disseminated at the time of diagnosis. The importance of the Rappaport classification was that each histologically defined subtype of NHL exhibited a unique natural history and response to therapy. The use of modern human immunologic studies has allowed for better characterization of the cells involved. Over time it became clear that the Rappaport classification needed modification. Today,

the "Working Formulation" is used. It incorporates the best characteristics of earlier classification systems and also maintains clinical relevance. Over 90% of cases of NHL are of B-cell derivation.

- The Ann Arbor staging system, developed in 1971 for Hodgkin's lymphoma, has been adapted for staging NHLs. This system focuses on the number of tumor sites (nodal and extranodal), location, and presence or absence of systemic symptoms.
- In addition to careful examination of all lymph node regions and biopsy, a complete blood count (CBC), and bone marrow biopsy are utilized to diagnose NHL.
- Serum chemistry may reflect alterations in liver function and elevated uric acid and calcium levels.
- Radiologic tests such as chest X ray, chest computed tomography, lymphangiography, or other diagnostic tests such as lumbar puncture are performed as required by presenting signs and symptoms.
- The histology of the tumor is more important to prognosis than the extent of disease and is secondarily influenced by clinical parameters, including age, tumor bulk, extranodal disease, and performance status.

Treatment

Surgery	The primary role of surgery is to establish diagnosis and to assist with staging. Rarely, surgery is utilized to resect areas of the gastrointestinal tract to prevent bowel obstruction, or for splenectomy in patients who exhibit hypersplenism.
Radiotherapy	Used frequently in low-grade disease because of high radioresponsiveness of the tumor.

Single-agent chemotherapy	Alkylating agents are used in low-grade lymphomas.
Combination chemotherapy	A variety of regimens have been explored that commonly include the incorporation of prednisone, alkylating agents, and doxorubicin.
Biological agents	Interferon-α (IFN-α) is an active agent in relapsed low-grade NHL. Two prospective, randomized trials have examined the role of interferon when added to combination chemotherapy in patients with advanced-stage disease. Both studies found significant prolongation of remission duration; however, only the trial that involved maintenance IFN-α found a significant prolongation of survival and higher rate of overall response. Monoclonal antibodies (MAB) are also used in the treatment of lymphoma; anti-B-cell (anti-CD20) MABs have been particularly effective. MABs continue to be investigated in unconjugated and conjugated form (e.g., attached to toxins or radioisotopes).

Although tremendous progress has been made in the treatment of NHL with conventional, salvage, and high-dose ablative chemotherapy, the majority of patients do not achieve a cure. With the advent of hematopoietic growth factors, conventional-dose therapy can be escalated to near-ablative doses and is under continuing evaluation. The incorporation of biological agents into more traditional therapy and the investigation of new biological agents and approaches will continue.

Suggested Reading: Lymphoma

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McLaughlin, P., A. J. Grillo-López, B. K. Link, R. Levy, M. S. Czuczman, M. E. Williams, M. R. Heyman, I. Bence-Bruckler, C. A. White, F. Cabanillas, V. Jain, A. D. Ho, J. Lister, K. Wey, D. Shen, and B. K. Dallaire. 1998. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *Journal of Clinical Oncology* 16:8, 2825–2833.

Vose, J. M. 1998. Current approaches to the management of non-Hodgkin's lymphoma. *Seminars in Oncology* 25:4, 483–491.

WEBSITES

www.nci.nih.gov

www.lymphoma.org

RENAL CELL CARCINOMA

Incidence

Approximately 29,900 patients in the United States are expected to be diagnosed with renal cell carcinoma in 1998, with an estimated 12,000 deaths. The male-to-female ratio is traditionally 2:1; however, 1998 estimates show approximately 18,000 cases for men and 12,000 for women. Renal cell carcinoma is more common among Scandinavians and North Americans, whereas the incidence is lower among Asians and Africans. Most cases occur in persons between 50 and 70 years of age, but the disease has been observed even in newborns.

Cancers involving the kidney may be primary or secondary, with the kidney being a relatively common site of metastasis. The frequency of different types of neoplastic lesions in the kidney is as follows:

- Renal cell carcinoma (mostly adenocarcinoma): approximately 85% of all renal neoplasms
- Nephroblastoma (i.e., Wilms' tumor): approximately 5 to 6%
- Transitional cell neoplasms of the renal pelvis: approximately 7 to 8%
- Sarcomas of renal origin: rare

More and more renal cancers are now being discovered incidentally during radiographic procedures such as ultrasonography or computed tomography (CT) for nonurologic problems.

Etiology and Pathogenesis

A number of chemical and biological agents have been cited as possible causal factors in the development of renal cell cancer. The following is a short list of proposed casual factors:

- Cigarette smoking
- Obesity
- Lead phosphate exposure
- Dimethyl nitrosamine

Von Hippel–Lindau disease (VHL) is a hereditary cancer syndrome where the mutated VHL gene (on chromosome 3) is transmitted in an autosomal dominant manner. It is associated with retinal angiomas, hemangioblastomas of the CNS, and RCC. Over two-thirds of patients with phakomatosis develop renal cell carcinoma, which often is bilateral.

Approximately 30 to 50% of patients on long-term dialysis develop acquired cystic disease in their native kidney. Up to 6% of these patients with acquired cystic disease develop renal cancer.

Clinical Presentation

Renal cell carcinoma can present with a variety of clinical manifestations that range from the classic triad to less frequently seen symptoms such as those of paraneoplastic syndromes. More commonly, renal tumors are discovered incidentally during the course of various diagnostic studies.

The classic triad usually indicates patients with far-advanced disease; it is seen in less than 10% of patients at presentation:

- Hematuria
- Pain
- Palpable renal mass

Hematuria, the most common presenting symptom, is seen in over 50% of patients with renal cell cancer. It is generally observed only if the tumor has invaded the collecting system. Studies have shown microscopic hematuria to be present in 63% of patients with proven renal cell carcinoma. Patients may present with pain if they have clot formation with associated colic. The mass generally is firm and nontender, and it moves with respiration.

A considerable number of patients with renal cell carcinoma present with systemic symptoms. The diagnosis of renal cancer may be difficult because the disease may masquerade in a variety of symptom patterns that are suggestive of other illnesses. Vague problems such as fever of unknown origin, polycythemia, weight loss, or anemia may occur. The numerous systemic and humoral manifestations of renal cell carcinoma have been known as the *paraneoplastic syndromes.*

- Fever: seen in up to 20% patients
  - Caused by the production of endogenous pyrogens
  - Usually intermittent
  - Often ceases once the primary tumor is removed
- Anemia: seen in up to 40% of patients
  - Generally not explained by blood loss
  - Tends to be normochromic, normocytic anemia of chronic disease
- Erythrocytosis: seen in almost 5% of patients
  - Associated with a hemoglobin greater than 15 g/dL
  - Tumor cells may produce erythropoietin
- Abnormal liver function tests (LFTs): seen in up to 15% of patients
  - Etiology is unknown
  - May revert to normal after nephrectomy
  - Ominous prognostic sign if LFTs remain elevated after nephrectomy
- Hypercalcemia: seen in up to 15% of patients
  - May be secondary to osseous metastases or ectopic production of parathyroid-like hormone

A small number of patients may present with secondary amyloidosis, which may be responsible for renal failure. Prognosis of these patients is poor. Renin levels often are elevated in patients with renal cell cancer. Patients may present with a polyneuromyopathy manifested by neurologic complaints. Elevation of serum human chorionic gonadotropin (HCG) has been seen in patients with

renal cell cancer and the clinical picture of gynecomastia and diminished libido.

Diagnosis and Staging

A variety of imaging studies are currently used to determine whether a space-occupying renal mass is benign or malignant. It is important to separate benign renal cysts from solid neoplasms, most of which are malignant.

Selective renal arteriography via percutaneous femoral artery catheterization	Mainstay of diagnosis and staging for renal carcinoma Tumors are generally well vascularized Accuracy rate of 95 to 98% in differentiating renal cell carcinoma from a benign cyst
CT scan	Demonstrates relationship of mass to surrounding structures Imaging procedure of choice for diagnosis and staging of renal cell cancer
Inferior vena cavography	Provides preoperative knowledge regarding the extent of renal vein or inferior vena caval involvement Essential for the proper planning of surgical removal of the tumor
MRI	Procedure of the choice for staging renal vein and/or vena caval involvement

Staging determines the extent of involvement in both regional and distant sites. Metastases most commonly occur to regional lymph nodes, lung, skeleton, liver, the ipsilateral adrenal gland, and the contralateral kidney.

The single most important determinant of prognosis for a patient with renal cell carcinoma is the pathologic stage when the tumor is initially diagnosed and treated. Accurate staging primarily depends on histologic evaluation of the resected tumor.

Treatment

Survival Rates

Five-year survival rates after radical nephrectomy for stage I renal cell carcinoma is approximately 94%; patients with stage II lesions have a survival rate of 79%. Patients with renal vein or inferior vena caval involvement have a survival rate of 25 to 50%, and those with regional lymph node involvement or extracapsular extension have a survival rate of 12 to 25%. Five-year survival rates for patients with stage IV (metastatic) disease are less than 5%.

Surgery

The treatment of choice for renal cell carcinoma is surgical removal (radical nephrectomy). Involvement of the regional lymphatics and periaortic lymph nodes has been noted in almost 25% of patients with renal cell carcinoma; thus, a rationale exists for performing regional lymphadenectomy in conjunction with radical nephrectomy. The primary value of identifying regional lymph node involvement would seem to be for determination of prognosis.

Therapy: Adjuvant or Metastatic Disease

Surgery	Removal of distant metastases
Radiation	Tumor tends to be radio-resistant
Hormonal	Poor response rates (<5–10%)
Chemotherapy (floxuridine [FUDR]) Vinblastine)	Response rates generally less than 15%
Interferon-α	Overall response rate <15%

Generally comparable to and probably superior to chemotherapy

Interleukin-2	Regulatory approval for the treatment of renal cell cancer

Future directions in research include the continued study of the combination of adoptive immunotherapy (LAK cells or TILs) with chemotherapy or biological agents (e.g., IFN, IL-2) through randomized trials. Clinical trials with new cytokines such as IL-12, IL-6, or IL-4 are under way. The genes for IL-2, IFN, and GM-CSF may be transduced into human renal cell carcinoma cell lines by using retroviral vectors. Such cytokine-secreting cells may serve as autologous tumor vaccines.

Suggested Reading: Renal Cell Cancer

Godley, P. A., and M.A. Escobar. 1998. Renal cell carcinoma. *Current Opinion in Oncology* 10(3):261–265.

McKinney, B. 1996. When this rare cancer strikes. *RN* 59(12):36–41.

Motzer, R. J., N. H. Bander, and D. M. Nanus. 1996. Renal-cell carcinoma. *New England Journal of Medicine* 335(12): 865–875.

WEBSITES

www.nci.nih.gov

Website for the National Kidney Cancer Association (free publication "Interleukin-2 and Biologic Therapy"): www.nkca.org

Website for the University of Pennsylvania Oncolink® (visit disease-oriented menus): www.cancer.med.upenn.edu

VIRAL HEPATITIS

Hepatitis is an inflammatory process in the liver that can ultimately lead to cirrhosis and hepatocellular carcinoma. It is typically categorized by its cause: viral, alcohol or drug abuse, or autoimmune disorder. To date, six viruses (A, B, C, D, E, and G) have been identified that account for most cases of viral hepatitis, although the most is known about hepatitis viruses A, B, and C. Although the agent, mode of transmission, and course of the disease may vary with each type of virus, the pathophysiology is the same.

Incidence

Viral hepatitis is a common infectious disease and a major public health problem. More than 5 million people in the United States have chronic viral hepatitis, and 8,000 to 12,000 died as a result of the condition in 1998. Also in 1998, more than $1 billion was spent on associated medical costs. Experts project that over the next 10 years, the number of deaths from chronic hepatitis infections, as well as associated health care expenses, will triple.

Approximately 150,000 acute hepatitis B infections occur every year in the United States. Between 5 and 10% of acute hepatitis B infections become chronic. Each year, an estimated 30,000 new cases of acute hepatitis C occur. Unfortunately, only 25 to 30% are diagnosed. More than 85% of acute hepatitis C infections become chronic. Liver failure due to chronic hepatitis C infection is the leading cause of liver transplants in the United States.

Etiology and Pathogenesis

Hepatitis A virus (HAV)	Transmitted person-to-person by the fecal-oral route; contaminated food, water, and shellfish.

Hepatitis B virus (HBV)	Transmitted by direct and indirect contact with blood, saliva, and semen, sexual contact, perinatal. A carrier state may persist for years. High-risk behaviors include exposure to infected blood or body fluids through tattooing, body piercing, or sharing razors or toothbrushes. Unprotected sex with many partners or experimentation with illicit IV drugs and use of contaminated needles are also high-risk behaviors that may result in infection with the hepatitis virus.
Hepatitis C virus (HCV)	Transmitted similarly to HBV. Once known as "non-A, non-B" hepatitis. Both HBV and HCV are more infectious than HIV.

Those persons most at risk of being infected with hepatitis B or C include health care workers, people with multiple sex partners, intravenous drug users, and hemophiliacs. Anyone who has had a tattoo, body piercing, or blood transfusion (prior to routine screening of donated blood that began in 1972 for hepatitis B and 1990 for hepatitis C) and those who are in close household contact with an infected person are also at higher risk of being infected. Hepatitis B or C can even be transmitted by sharing toothbrushes or nail files contaminated with infected blood, although these forms of transmission rarely occur.

The hepatitis virus invades, replicates, and produces damage in liver cells. Inflammatory changes and mononuclear cell infiltrations in the liver parenchyma

and portal ducts result in necrosis of hepatic cells and the accumulation of necrotic debris in the lobules and portal ducts. The end result is disturbance in bilirubin excretion. Failure of the liver cells to regenerate while the necrotic process is ongoing may result in a severe, fulminant, and frequently fatal hepatitis. This is most commonly seen in hepatitis B.

Clinical Presentation

Many people who get hepatitis B or C have no recognizable signs or symptoms. A person may feel and appear perfectly healthy yet still be infected with the disease and capable of infecting others.

- Common symptoms include flulike symptoms, such as loss of appetite, nausea and vomiting, fever, weakness, or tiredness, as well as mild abdominal pain in the right upper quadrant. The onset of symptoms is acute for hepatitis A, and patients generally experience fever up to 40°C.
- Less common symptoms are dark urine and yellowing of the skin and eyes (jaundice).
- The only way these diseases can be positively identified is through blood tests.
- Acute versus chronic: Infections that last less than 6 months are considered acute, while those that last longer than 6 months are labeled chronic. An acute infection of hepatitis B or hepatitis C has the potential to become chronic, but hepatitis A is always limited to an acute infection.
- Hepatitis infection in the chronic state is an unpredictable disease. Patients with chronic infections have the potential to develop a multitude of problems, including fibrosis, cirrhosis, hepatic failure and hepatocellular carcinoma (HCC). Of the 85% of patients whose infections become chronic, at least 20% develop cirrhosis about 20 years after infection. Additionally, 20% develop HCC leading to liver failure and liver transplantation. Chronic hepatitis C (HCV) is the

leading cause of liver transplantation in the United States.

Many of the patients diagnosed with chronic hepatitis B and C are asymptomatic. Fatigue may be present and may be described in a subtle way, such as with references to increased sleep, decreased activity level, or decreased libido. In addition to the fatigue, hepatitis C patients sometimes note an intermittent discomfort in the right upper quadrant. The typical HCV patient presents with an asymptomatic elevation of liver enzymes. Most patients with chronic viral hepatitis exhibit only a mild elevation in enzymes, so any degree of abnormality should be considered a potential indication of viral hepatitis.

Screening and Diagnosis

A timely diagnosis of asymptomatic chronic viral hepatitis is important to prevent progression to severe liver damage.

- Screen patients for at-risk behavior. Activities that expose a patient to viral hepatitis, such as using IV drugs or being tattooed, need not be recent. Patients can be diagnosed a long time (>20 years) after exposure. Patients with a history of risk factors that might have a negative connotation (such as drug use or multiple sexual partners) are often hesitant to admit to such activities.
- Diagnostic studies:

Hepatitis A test	Positive, indicates a recent infection or immunity to the virus due to a prior infection. Radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) test is used to detect anti-HAV antibodies.

Hepatitis B	Identifies (1) infected individuals, (2) those recovering from the disease, (3) chronic infection, or (4) immunity to hepatitis B. May use tests to detect serum antigen (radioimmunoassay) or serum antibody tests. Hepatitis B surface antigen (HBsAg) is present in acute and chronic infections. Anti-HBc (IgM) will be present if the infection is acute hepatitis B. Anti-HBc (IgG) is a lifelong marker of past or chronic hepatitis B infection. Anti-HBs antibody will be positive in patients vaccinated against hepatitis B and following infection. Hepatitis Be antigen (HBeAg) is detectable during active viral replication and indicates high infectivity.
Hepatitis C	Enzyme immunoassay (EIA) testing is used to identify infection with the hepatitis C (HCV) virus or past infection. This test is used to detect antibody against HCV, which cannot be detected until about 12 weeks after exposure. HCV-RNA tests for the presence of the virus itself, not antibodies directed against the HCV. This is

the most sensitive test for HCV infection and is considered the gold standard if performed accurately.

- Liver function studies: Evaluation of serum alanine aminotransferase (ALT) level should be part of the comprehensive health care of every adult patient. Patients with even mild elevations in ALT should be further evaluated with hepatitis serology. Studies have documented that ALTs can be intermittently elevated or within normal limits in patients with hepatitis B or C. There is a poor correlation between the magnitude of enzyme elevations and the degree of liver injury. Elevated levels of ALT and aspartate aminotransferase (AST) may indicate the presence of liver disease, but they cannot be used to estimate the degree of liver damage or the type of liver disease.

Treatment

Interferon alfa-2b (Intron® A) is the standard therapy for hepatitis B. Patients receive 30 to 35 million units, administered subcutaneously or intramuscularly for 16 weeks. The dosage can be divided into 5 million units daily or 10 million units three times a week. Patients treated in this fashion have a 39 to 48% virologic response rate. The use of Rebetron™ in conjunction with Intron® A also has regulatory approval.

Several interferons have been used to treat hepatitis C, including interferon alfa-2b, interferon alfa-2a (Roferon®), and consensus interferon (Infergen). In March 1997 the National Institutes of Health sponsored a meeting that brought together experts in the field of hepatitis. The outcome of that meeting is reported in the conference statement "Management of Hepatitis C." The panel agreed that although there are several different forms of interferon, the bulk of the available evidence reflects study of the alpha interferons. The panel recom-

mended interferon alfa (or its equivalent) for initial treatment of hepatitis C, at a dose of 3 million units three times a week, administered subcutaneously for 12 months. Patients should no longer receive only a 6-month course of therapy with interferon alfa, since 12-month regimens are more successful in achieving sustained responses. The use of other antiviral drugs in the management of hepatitis is under investigation.

Suggested Reading: Hepatitis

Herreid, J. A. 1995. Hepatitis C: Past, present, and future. *Medsurg Nursing* 4:179–187.

Takahashi Memorial Forum. Yamanaka, M., K. Okabe, and G. Toda, eds. 1995. *Interferon therapy on chronic hepatitis C: Proceedings of the "Takahashi Memorial Forum."* Amsterdam and New York: Elsevier.

WEBSITES

www.niaid.nih.gov

www.hep-help.com

Website for the American Liver Foundation:
sadieo.ucsf.edu/alf/alffinal/homepagealf.html

PLANS OF CARE FOR PATIENTS RECEIVING BIOLOGICAL AGENTS

Outcome	Interventions: Assessment	Interventions: Therapeutic	Interventions: Educational
Diagnosis: Knowledge deficit related to treatment with a biological agent*			
• Patient/significant other will verbalize expected side effects of agent and reportable signs and symptoms • Patient/significant other will demonstrate self-administration of agent if indicated •	• Assess knowledge of side effects • Assess ability of patient/significant other to be responsible for self-administration		• Instruct patient/significant other of expected side effects and reportable signs and symptoms • Instruct patient/significant other in reconstitution of agent • Instruct patient/significant other in I.M. or SQ injection technique • Instruct patient/significant other in management of portable infusion pump
Diagnosis: Altered comfort related to chills (commonly occurs prior to fever)			
• Patient/significant other will demonstrate self-care behaviors for management of chills • Patient reports acceptable control of chills	• Assess severity and duration of chills and document • Monitor vital signs frequently and report changes to physician	• Keep patient warm • Avoid icy fluids • Medicate with meperidine 25 to 50 mg I.V.P.B. or sublingual dilaudid as ordered • Antipyretics as ordered	• Instruct patient/significant other in self-management of chills • Instruct patient regarding duration (generally 30 to 60[m])

*See complete patient teaching plan in Appendix B.

(continued)

PLANS OF CARE FOR PATIENTS RECEIVING BIOLOGICAL AGENTS *(cont.)*

Outcome	Interventions: Assessment	Interventions: Therapeutic	Interventions: Educational
Diagnosis: Fever 101° to 104° (38.4°–40.0°C)			
• Patient/significant other will demonstrate self-care behaviors for management of fever • Patient reports acceptable control of temperature	• Monitor temperature frequently every one to four hours for hospitalized patients or with first course of therapy to establish patterns • Assess for complaints of tachycardia, chest pain, or shortness of breath and report to physician • Assess need for work up of potentially infectious episode for fevers unrelated to expected patterns or in neutropenic patients • Report to physician fevers > 104°F despite antipyretics or other control measures	• Encourage p.o. fluids • Medicate with antipyretic as ordered • For temps >103° despite antipyretic, consider —tepid sponge bath or shower —ice packs to temperature-control area —hypothermia blanket, if indicated	• Instruct patient/significant other to monitor temperature • As therapy continues, teach family to monitor temperature pattern in response to medication. Report unusual spikes to health-care team. • Instruct patient/significant other in self-management of fever • Instruct patient/significant other to report to physician if fever does not resolve after therapeutic measures

Diagnosis: Fatigue related to treatment with biologicals

• Patient maintains independence in activities of daily living and/or uses measures to prevent further immobility	• Assess effect of fatigue on activities of daily living • Assess usual pattern of sleep and rest • Assess for signs and symptoms associated with fatigue • Assess for cofactors that may influence fatigue (anemia, poor nutritional intake, etc.)	• Encourage patient to arrange most strenuous activities according to peak energy levels • Encourage patient to seek assistance with activities of daily living as necessary • Encourage patient to maintain mobility —ambulatory patient: mild exercise; e.g., walking as tolerated —bedridden patient: turn every two hours; active/ passive range of motion • Encourage patient to take short naps as required to increase energy levels • Treat cofactors that may contribute to fatigue as appropriate —use epoetin alfa for anemia —institute pain control measures • Evaluate need for use of assistive devices (e.g., walker, cane) to conserve energy stores • Institute measures to assure adequate intake of calories, proteins, and fluids	• Teach patient/significant other about expected side effect of biotherapy and self-management measures to prevent sequelae • Consider energy as a finite resource. How does patient want to "spend" it?

(continued)

PLANS OF CARE FOR PATIENTS RECEIVING BIOLOGICAL AGENTS *(cont.)*

Outcome	Interventions		
	Assessment	Therapeutic	Educational
Diagnosis: Potential for injury related to allergic reaction (primarily seen with murine monoclonal antibodies)			
• Patient will immediately report signs and symptoms of anaphylaxis, hives, or itching	• Prior to administration, review prior allergic episodes to include —agent thought to be responsible —description of the episode (reaction to agent) • During administration, assess for —shortness of breath, wheezing —sneezing, coughing —local or generalized urticaria and/or erythema, itching —hypotension —tachycardia —cyanosis —unconsciousness —emesis and/or diarrhea	• Administer test dose if ordered • Ensure that emergency equipment is available • Ensure that emergency drugs (epinephrine, diphenhydramine, hydrocortisone) are available • Stop infusion immediately for signs of severe allergic reactions (e.g., hypotension, angioedema, shortness of breath) —increase IV fluids —notify physician —institute orders as received	• Teach patient to report: —pain or tightness in chest; dyspnea —inability to speak —generalized itching —symptoms of uneasiness, agitation, warmth, dizziness —desire to urinate or defecate

Diagnosis: Pain related to myalgias, arthralgias, headaches			
• Patient/significant other will demonstrate self-care behaviors for the management of myalgias and headaches • Patient reports acceptable control of pain	• Assess need for analgesia —onset/duration —intensity of pain	• Acetaminophen 650 mg p.o. q. three to four hours as ordered • Apply moist heat to aching areas, cool for headache • Consider use of NSAIDs or stronger analgesics as required • For headache: adjust environment (quiet, dark room) • Consider use of massage, reflexology by trained personnel	• Instruct patient/significant other in self-management of myalgias and headaches
Diagnosis: Pruritis (primarily seen with IL-2)			
• Patient identifies/demonstrates measures to control pruritus • Patient reports acceptable control of pruritus	• Assess pruritis —onset/duration —characteristics —factors that relieve/aggravate the condition —treatment used previously • Assess for signs of skin breakdown	• Water-based lotion and/or cream to affected area p.r.n. • Use colloidal oatmeal baths in bathwater (tepid water instead of hot) • Consider use of room humidifier • Administer medications (e.g., antihistamines) as ordered; may need aggressive around-the-clock administration • Encourage use of distraction (relaxation techniques, reading, needlework, etc.) • Soft, cotton clothing	• Teach signs/symptoms of skin changes to report • Discuss measures to promote skin hydration • Teach measures to prevent further skin irritation • Teach relaxation techniques as necessary • Teach patient to substitute rub, pressure, or vibration for scratching (e.g., rub arms with lotion)

(continued)

PLANS OF CARE FOR PATIENTS RECEIVING BIOLOGICAL AGENTS *(cont.)*

Outcome	Interventions: Assessment	Interventions: Therapeutic	Interventions: Educational
Diagnosis: Altered skin integrity related to treatment with biological agents (Patients on IL-2 may experience dry desquamation)			
• Patient/significant other will verbalize understanding of factors that may cause alteration in skin integrity • Skin integrity will be maintained • Patient/significant other will demonstrate behaviors to maintain skin integrity	• Observe skin daily for any breaks, discoloration, redness • Observe injection sites for any changes • Observe I.V. sites for phlebitis, signs of infection (especially in patients on IL-2)	• Turn bedfast patient every two hours • Rotate injection sites for I.M./SQ agents • Apply moist heat to any inflamed areas • Apply water-based lotion and/or cream to entire body two to three times a day for dry desquamation • Consider use of room humidifier for dryness	• Instruct patient/significant other in individual measures for maintenance of skin integrity • Instruct patient/significant other in causative factors
Diagnosis: Altered thought processes related to treatment with biologicals (e.g., confusion, slowed mentation, somnolence)			
• Patient/significant other will verbalize understanding of factors that may cause alteration in thought processes • Patient/significant other will recognize changes in thinking or behavior • Patient will maintain reality orientation	• Assess mental status prior to therapy • Assess mental status each shift or clinic visit and when indicated • Assess amount of pre-medication and/or analgesics patient is receiving	• Orient to time and place if necessary • Allow verbalization of feelings • Refer to mental health professional if indicated • Report changes in mental status to physician • Initiate safety measures if indicated • Evaluate need for instituting therapy with antidepressants	• Instruct patient/significant other how biological response modifier may cause alteration in thought process • Inform patient/significant other that this side effect is temporary and generally resolves when therapy is stopped

		• Work with patient/family to develop strategies to compensate for deficit (e.g., lists for memory problems, alarms as reminders)	
Diagnosis: Altered nutritional status, less than body requirements related to anorexia, mucositis, nausea, vomiting			
• Patient will maintain adequate nutritional status • Patient/significant other will verbalize understanding of nutritional needs • Patient/significant other will demonstrate measures to increase nutritional intake	• Weigh patient regularly and record • Initiate a calorie count if indicated to assess intake • Assess biochemical measures of nutrition —albumin —transferrin —nitrogen balance	• Provide appetizing food consistent with patient preference • Provide high-calorie, low-bulk foods • Use nutritional supplements • Refer to dietition for consultation • Try small, frequent meals • Try cold foods if patient is sensitive to food odors • Give antiemetics as ordered. In some cases, around-the-clock administration may be necessary • Discuss with health-care team the need for tube feedings, I.V.H. if nutritional status becomes severely compromised • Consider use of appetite stimulants (e.g., megestrol acetate) if no contraindication • Institute oral hygiene measures	• Instruct patient/significant other in measures to provide adequate nutrition

(continued)

PLANS OF CARE FOR PATIENTS RECEIVING BIOLOGICAL AGENTS *(cont.)*

Outcome	Interventions		
	Assessment	Therapeutic	Educational
Diagnosis: Altered oral mucous membranes related to treatment with biologicals			
• Patient recognizes and reports changes in mucous membranes • Patient demonstrates knowledge of oral hygiene protocol	• Perform oral exam to include: —palate —gingiva —dorsum of tongue —undersurface of tongue —floor of mouth —buccal mucosa —oral pharynx —inner surface of lips • Assess normal oral hygiene routine	• Encourage patient to perform oral hygiene after meals and at bedtime • Begin use of salt and soda mouth rinses every two hours and p.r.n. • Provide lubricant for lips • Encourage use of soft tooth brush • Consider oral irrigations p.r.n. to hydrate mouth and for comfort • Avoid use of agents that further dry the oral mucosa • Alter diet (e.g., avoid foods such as potato chips) if oral mucosa is inflamed	• Explain rationale for prophylactic oral hygiene protocol • Teach proper oral hygiene protocol • Teach signs and symptoms to report to nurse/physician

Diagnosis: Diarrhea related to treatment with biological agents			
• Patient/significant other identifies measures to correct or control diarrhea	• Abdominal assessment every eight hours and p.r.n.* • Monitor intake and output every eight hours* • Monitor stools for frequency, volume, consistency and document • Assess perineal/perianal region for skin status • Assess electrolyte balance as indicated, signs of dehydration	• Administer I.V. fluid as ordered • Encourage adequate p.o. fluid intake • Administer medications that control diarrhea as ordered • Encourage hygiene measures. May consider use of sitz bath and/or barrier creams • Suggest low-residue dietary modifications	• Teach complications of diarrhea (e.g., fluid electrolyte imbalance, skin breakdown) and prevention measures • Teach signs and symptoms to report
Diagnosis: Altered tissue perfusion related to treatment with biological agents (primarily seen with IL–2)			
• Patients will maintain adequate blood pressure	• Assess —orthostatic vital signs every one to four hours —daily weights —intake and output every eight hours**	• Administer I.V. fluids, colloids, and vasopressor as ordered • Institute comfort measures as necessary • Institute safety measures: —ambulate with assistance —rise from lying to sitting position slowly • Encourage p.o. fluid intake	• Teach patient/significant other about expected side effect of biotherapy and temporary nature of side effect • Teach patient/significant other to monitor for side effects while at home (daily weight, temperature t.i.d., etc.) and notify physician of any changes or problems

*for hospitalized patients
**for hospitalized patient; for ambulatory patients, assess for oliguria

(continued)

PLANS OF CARE FOR PATIENTS RECEIVING BIOLOGICAL AGENTS *(cont.)*

Outcome	Interventions		
	Assessment	Therapeutic	Educational
	• Assess respiratory and cardiovascular system every eight hours or clinic visit for —increased heart rate —decreased blood pressure —complaints of dizziness —complaints of shortness of breath —rales • Assess for fluid shifts as evidenced by —peripheral edema —ascites —rales —weight gain —decreased urine output • Assess renal function (e.g., BUN, creatinine)		• Teach patient/significant other to recognize these signs and symptoms: —peripheral edema —shortness of breath —decreased urinary output —weight gain ≥5 pounds • Teach patient to rise from lying position slowly

Diagnosis: Altered coping related to changes in disease status and/or new therapy			
• Patient recognizes potential/ actual stressors and facilitates own coping strategies	• Assess patient's perception of stressors and beliefs about the causes • Assess patient's past use of coping strategies • Evaluate patient's ability to problem solve	• Encourage patient to verbalize thoughts and feelings about changes in disease status and new therapy • Identify available resources for support and encourage participation (e.g., American Cancer Society, support groups, chaplain, etc.)	• Teach relaxation techniques • Teach problem-solving techniques

Adapted and reprinted with permission from Rumsey, K. A. and P. T. Rieger (eds.). *Bilogical Response Modifiers: A self-instructional manual for health professionals.* 1992. Chicago: Precept Press.

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THE UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER —BIOTHERAPY PATIENT TEACHING PLAN

Objective/Expected Outcome	Content	Teaching Method
Team Member: **MD/Fellow/RN**		
I. Patients will be able to explain, in their own words, basic immune function, as evidenced by: • Expressing comprehension of their immune system, how it functions and the role it plays in their treatment. Ia. Patients will be able to explain, in their own words, their treatment plan (including frequency of administration and duration) and its rationale, as evidenced by: • Expressing understanding of what type of treatment they will have, for how long, and why it is necessary.	I. Immune function Ia. BIOTHERAPY A. Definition B. Goals of Therapy 1. diagnostic 2. therapeutic 3. supportive C. Commercial vs. investigative use 1. purpose of treatment 2. informed consent D. Treatment regimen 1. Route of administration a. Frequency of administration b. Duration of therapy 2. Location a. Clinic b. Station 19 c. Inpatient d. Hometown—referring MD	Individual instruction: • *Understanding the Immune System,* NCI booklet • *Biotherapy: A Patient Guide* • Injection Series Videotapes MDA-TV, x27287; IM #82–1–92 SC #80–1–92 Mixing Meds #81–1–92 • *What are Clinical Trials All About?* NCI booklet • Treatment-specific patient information drug card(s) • Other applicable print material (refer to Patient Education Clearinghouse listing and Patient/Family Learning Center) and videotapes (refer to Patient Guide for listings and numbers)

(continued)

THE UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER —BIOTHERAPY PATIENT TEACHING PLAN

(cont.)

Objective/Expected Outcome	Content	Teaching Method
Team Member: **MD/Fellow/RN**		
	3. Timeframes a. scheduled appointments b. Follow-up/evaluation E. Laboratory and diagnostic tests F. Special requirements (Example: extended hospital admission or need to remain in vicinity for extended period of time.)	• Printed calendar • Question/answer period
II. Patients will be able to identify potential side effects and appropriate self-management, as evidenced by: • Verbalizing understanding of [potential] side effects of their treatment.	II. Side Effects A. Key Areas 1. Incidence 2. Severity 3. Self-management B. Potential Side Effects 1. Constitutional symptoms a. fever b. chills c. arthralgia d. malaise e. flushing 2. Neurological side effects 3. Renal toxicity	Individual instruction: • Treatment-specific patient information drug card(s) • Video (MDA-TV x27287): Intro to Interferon #832–1–87 (Spanish) #956–1–90 • *Eating Hints,* NCI Booklet • *Nausea & Vomiting: What You Can Do* (if applicable, e.g., treatment with IL-2)

4. Hematologic side effects
5. Hepatic side effects
6. Dermatologic side effects
   a. erythema at injection site(s)
   b. itching
   c. rash
   d. dryness
   e. desquamation (dry or wet)
7. GI side effects*
   a. anorexia
   b. weight loss
   c. nausea/vomiting
   d. diarrhea
   e. mucositis
8. Cardiovascular/pulmonary side effects
   a. capillary leak syndrome
9. Allergic reactions

- Other applicable print material (refer to Patient Education Clearinghouse listing) and videos (refer to Patient Education and Guide for listing and numbers)

- Describing in their own words the appropriate management of those side effects.
- Identifying who/where to contact for reportable side effects.

IIa. Reporting of signs and symptoms
   A. Reportable signs and symptoms
      1 Continuing fever of 40°C
      2. Weight gain of 5–10 kg over 1 week

Clinic handout

*Dietary consult for nutritional problems

(continued)

THE UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER —BIOTHERAPY PATIENT TEACHING PLAN

(cont.)

Objective/Expected Outcome	Content	Teaching Method
	3. Weight loss of 5–10 kg over several weeks 4. Shortness of breath 5. Dizziness 6. Inability to perform ADL 2° fatigue 7. Alteration in mental status 8. Inflammation at injection site 9. Any other unusual signs/symptoms B. Who to contact 1. MDACC a. Clinic staff b. RN/fellow/attending MD c. Station 19—after 5 pm, weekends, holidays 2. Outside MDACC a. Local MD b. Local hospital	

Team Member: **RN/Pharmacist**

III. Patients will be able to self-administer IM/SC injection, as evidenced by: • Accurate return demonstration of drug reconstitution. • Accurate return demonstration of technique for self-administration of IM/SC injection. • Describing in their own words the proper storage and disposal of the medication and equipment.	III. Self-administration A. Types of equipment 1. Medication 2. Diluent 3. Alcohol swabs 4. Syringes 5. Needles B. Aseptic technique 1. Definition 2. Parts of equipment that may be handled C. Method of reconstitution D. Withdrawing liquid from the vial 1. Proper dose E. Site selection and rotation F. Injection techniques G. Storage of the medication 1. Stability of medication (single/multiple dose vial) H. Disposal of equipment at home	Individual instruction: Demonstration/return demonstration Injection series videotapes MDA-TV, x27287: IM #82–1–92 SC #80–1–92 Mixing Meds #81–1–92 Patient information cards: • Subcutaneous injection • Intramuscular injection • Drawing up a Liquid Medication Dose Preparation Instruction Sheet

(Continued)

THE UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER —BIOTHERAPY PATIENT TEACHING PLAN

(cont.)

Objective/Expected Outcome	Content	Teaching Method
Team Member: **RN/Social Worker**		
IV. Patients will adjust to their altered lifestyle and cope effectively with psychosocial issues related to their diagnosis and treatment, as evidenced by: • Identifying problems/issues in need of follow-up • Identifying appropriate strategies and resources for coping with their diagnosis and/or treatment. • Seeking information and assistance. • Taking actions to promote coping (i.e., participating in discussion/support group)	IV. Psychosocial Issues A. Common problems 1. Depression 2. Hopelessness 3. Decisional conflict 4. Financial concerns 5. Housing 6. Transportation B. Support Services 1. Social Work 2. Discussion/Support groups—hospital & community 3. Referrals C. How to access community resources	One-on-One Discussion Referral/Assistance Applicable print material (refer to Patient Education Clearinghouse Listing, Patient/Family Learning Center) and videos (refer to Patient Guide for listing and numbers)

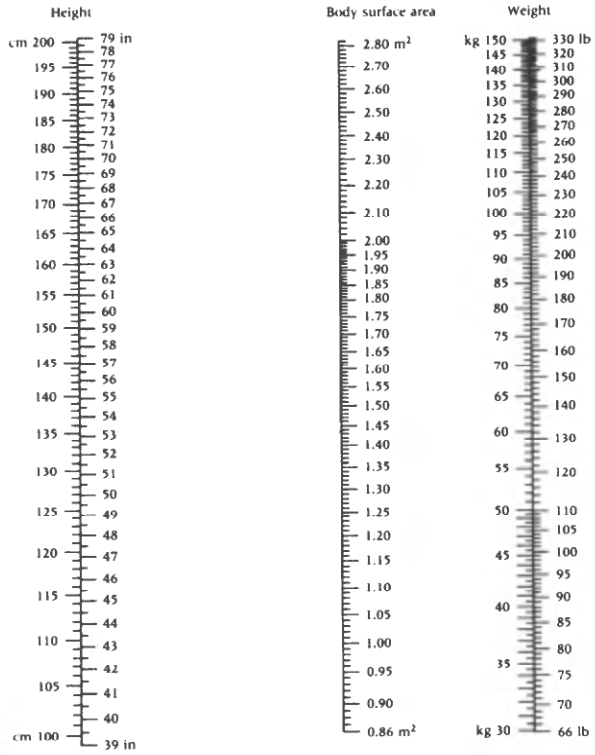
Team Member: MD/fellow/RN/Pharmacist

V. Patients will be aware of reimbursement issues common to the biotherapy patient, as evidenced by: • Verbalizing an understanding of common problems related to reimbursement. • Having and referring to written material as needed. • Identifying available resources (educational, financial, etc.) as they relate to biotherapy patients.	V. Reimbursement Issues A. Common problems 1. Investigational therapy 2. Off-label use 3. Cost of therapy 4. Lack of insurance coverage for self-administered medications B. Support Services 1. Hospital pharmacy 2. Pharmaceutical company 3. Reimbursement programs	One-on-One Discussion Referral/Assistance Applicable print material

Source: Reprinted with permission from the University of Texas M.D. Anderson Cancer Center, Department of Patient Education, Houston, Texas.

APPENDIX C

NORMOGRAMS FOR DETERMINATION OF BODY SURFACE AREA FROM HEIGHT AND WEIGHT (ADULTS)*



* From the formula of DuBois and DuBois. *Arch. micrn. Med.* 17.863 (1916): $S = W^{0.696} \times H^{0.726} \times 71.84$, or $\log S = \log W \times 0.425 + \log H \times 0.725 + 1.8564$ (S= body surface in square centimeters; W= weight in kilograms; H= height in centimeters). The body surface area is the point of intersection on the middle scale when a straight line joins the height and weight scales (e.g., Patient A weighs 109 kg and is 171 cm tall; the patient's BSA [m^2] is 2.2).

Source: Hubbard, S.M., and C.A. Seipp. 1982. Administration of cancer treatments: Practical guide for physicians and oncology nurses. In Devita, V.J. Jr., S. Hellman, and S.A. Rosenberg, eds., *Cancer Principles and Practices of Oncology.* Philadelphia: Lippincott, 1985.

GLOSSARY

Adaptive immunity Immunity generated in response to a specific antigen. Hallmarks are memory and specificity.

Adoptive cellular therapy Therapy that involves the transfer to the tumor-bearing host of immune cells with antitumor activity.

Antagonistic A substance that neutralizes or impedes the action or effect of another.

Antibody A protein whose function is to bind antigen.

Antibody dependent cell-mediated cytotoxicity (ADCC) A phenomenon in which target cells, coated with antibody, are destroyed by specialized killer cells which bear receptors for the Fc portion of the coating antibody. These receptors allow the killer cells to bind to the antibody-coated target.

Antigen Any substance that, as a result of coming in contact with appropriate tissues, induces a state of sensitivity. Traditionally, an antigen is thought of as something foreign that will generate an immune response when introduced to the immune system. Antigens are also molecules that react with antibodies or primed T-cells regardless of their ability to generate a response (e.g., histocompatibility antigens, differentiation antigens).

Antigen processing cells Non-lymphocyte cells that carry antigen and present it to lymphocytes, resulting in induction of an immune response.

Antigenic determinant The particular chemical group of a molecule that determines immunological specificity (dominant epitope clusters). This is the part that binds directly with the immunoglobulin or T-cell receptor.

Anti-idiotype An antibody targeted to the idiotype found on antibodies.

Apoptosis Programmed cell death.

Arthralgias Joint pain.

Autoimmunity A state in which the immune system reacts against self-antigens.

B lymphocyte Lymphocytes derived from the bone marrow that develop into plasma cells and are responsible for the production of antibodies.

Biological agents Agents derived from biological sources or affecting biological responses.

Biotherapy The use of agents derived from biological sources or of agents that affect biological responses.

Biological response modifiers (BRMs) Agents or approaches that modify the relationship between tumor and host by modifying the host's biologic response to tumor cells with a resultant therapeutic effect.

Chemoimmunoconjugate Linking of a drug to an antibody; usually an antineoplastic drug such as doxorubicin or methotrexate.

Chills A sensation of cold.

Chimeric Composed of parts of different origin.

Clonal anergy A theory for immunological unresponsiveness (tolerance) in which antigen-reactive lymphocytes are present but are functionally inactive.

Conjugate The process of attaching a drug, toxin, or radioactive substance to a biological molecule such as an antibody.

Cytokines A generic term for proteins released by cells on contact with a specific antigen that affect the functions of other cells. Cytokines affect the growth and differentiation of white blood cells and regulate immune and inflammatory responses.

Cytokine cascade Network of interactions that occur through mutual cytokine induction, through transmodulation of cell surface receptors, and by synergistic, additive, or antagonistic interactions that affect the function of a target cell.

Cytotoxic T-cell Effector T lymphocyte subset which directly lyses target cells.

Delirium A type of organic mental disturbance characterized by confusion, decreased ability to attend and process information, and occasionally hallucinations or delusions. Agitation is a common feature. This state generally develops over a short period of time, fluctuates during the day, and is usually reversible when

the underlying etiology is corrected. Delirium is often caused by metabolic disturbance or medication effects. This disturbance is also referred to as an acute confusional state and is one of the conditions included under the term encephalopathy.

Deoxyribonucleic acid (DNA) The type of nucleic acid found principally in the nucleus of animal and vegetable cells. The repository of hereditary characteristics (genetic information).

Differentiation antigens Antigens (proteins) expressed during different stages of development. For example, different cell surface antigens are expressed on T-cells as they mature.

Encephalopathy A term used to describe a number of organic mental disturbances including delirium, post-traumatic confusional states, etc. These are distinguished from more gradual, progressive dementias by their relatively abrupt onset. Depending upon the specific entity, an encephalopathy may be reversible (i.e., toxic-metabolic encephalopathy) or permanent (i.e., severe anoxia).

Endogenous Originating or produced within an organism.

Erythropoietin (Epo) Hematopoietic growth factor produced in response to decreased oxygen saturation in the blood circulating through the kidneys; stimulates erythroblast differentiation and recruits immature progenitors.

FAB Fragment of antibody containing the antigen-binding site, generated by cleavage of the antibody with the enzyme papain, which cuts at the hinge region.

Fc Fragment of antibody without antigen-binding sites, generated by cleavage with papain. The Fc fragment contains the C terminal domains of the heavy immunoglobulin chains.

FDA Food and Drug Administration.

Freund's complete adjuvant A vehicle used to increase antigenicity. A water-in-oil emulsion of antigen, to which killed mycobacterium are added.

Gene therapy The use of therapy in which a gene is inserted into a patient's cells to reverse an acquired gene defect or to add a new function to the cell.

Genetics The branch of science concerned with heredity.

Glycosylated A molecule with a sugar attached.

Granulocyte colony-stimulating factor (G-CSF) Hematopoietic growth factor that stimulates neutrophil production and maturation and enhances the function of mature neutrophils.

Granulocyte-macrophage colony stimulating factor (GM-CSF) Hematopoietic growth factor that preferentially supports neutrophil, eosinophil, and macrophage development and interacts with early progenitors; inhibits neutrophil migration.

Human anti-mouse antibody (HAMA) The immune response generated by the infusion of a murine antibody into an immunocompetent individual.

Helper/inducer T-cell A subset of T lymphocytes (CD4) whose presence is required by B cells for normal antibody production. CD4+ helper cells can be further divided into subsets (TH0, TH1, TH2) based on their ability to produce specific cytokines. For example, TH1 cells produce IL-2, IFN-8, and TNF-β, whereas TH2 cells produce IL-4, IL-5, IL-10, and IL-13.

Hematopoietic growth factors (HGFs) A family of glycosylated proteins that interact with specific cell surface receptors to regulate the reproduction, maturation, and functional activity of blood cells.

Hybridoma A hybrid cell that results from the fusion of an antibody-secreting cell with a malignant cell; the progeny secrete antibody without stimulation and proliferate continuously both *in vivo* and *in vitro*.

Immune surveillance The concept that immunological mechanisms "recognize" and remove malignant cells as they arise.

Immunogenic "Antigenic," having the properties of an antigen. An immunogen is a molecule capable of inducing an immune response.

Immunoglobulin Protein molecules composed of four polypeptide chains that function as antibodies. There are five classes of immunoglobulins: IgG, M, A, D, and E.

Immunomodulation Alteration of immune responses through inhibition or stimulation.

Immunophenotyping The observed immunological characteristics of an organ or cell.

Immunoregulation Having the biological property of regulating immune responses.

Immunotherapy The use of agents that modulate the immune system for the treatment of cancer or other diseases.

Innate immunity Nonspecific immunity that does not involve the specific recognition of antigen.

Interleukin Literally, "between leukocytes." This term refers to the protein molecules responsible for the signaling and communication that occur between cells in the immune system.

Interleukin–3 (IL–3) Hematopoietic growth factor that causes stem cells to differentiate into granulocytes, macrophages, megakaryocytes, erythrocytes, and lymphocytes.

Lineage restricted Affecting primarily a single hematopoietic cell type (e.g., neutrophils).

Lymphokines Protein molecules secreted by lymphocytes that serve as messengers between cells of the immune system.

Lymphokine-activated killer (LAK) cells Peripheral blood lymphocytes capable of lysing a variety of tumor cell lines after exposure to IL–2.

Macrophage An immune cell that serves as a phagocyte, an antigen-presenting cell, and an important source of immune secretions. Macrophages are fully mature monocytes found in the tissues.

Macrophage colony-stimulating factor (M-CSF) Hematopoietic growth factor that activates monocytes, prompting macrophage production and stimulates enhanced cytotoxicity against fungi.

Malaise A feeling of general discomfort, often the first indication of infection or disease.

Memory response The capacity of the immune system to respond much faster and more powerfully to subsequent antigen exposure than the first time.

Mitogen A molecule that can induce nonspecific division and activation of lymphocytes.

Molecular biology Knowledge of how the cell expresses its information from DNA to RNA to protein.

Monoclonal antibody Literally, an antibody from a single clone. A clone is the progeny of a single cell. The antibody is homogeneous.

Monokines Regulatory proteins produced by monocytes.

Multilineage Affecting more than one hematopoietic cell type.

Myalgias Muscle aches.

Natural killer cells Lymphocytes (non-B or T) which kill a range of tumor cell targets without antigen specificity; sometimes known as "large granular lymphocytes."

NDA New drug application.

Null cells Lymphocytes that lack both T- or B-cell markers.

Optimal biological dose (OBD) The minimum dose at which biological activity is maximally stimulated.

Oncofetal antigens Antigens not expressed on normal tissue, but expressed on fetal tissue.

Passive antibody therapy Administration of serum containing antibody.

Phagocytosis The process of ingestion of microbes, other cells, and foreign particles by phagocytes. Neutrophils and macrophages function as phagocytes.

Pleiotropic Characterized by the production of multiple effects.

Pluripotent stem cells (PPSC) An uncommitted cell that produces two daughter cells. One enters a differentiation pathway and the other returns to a resting pool of cells.

Precursors Immature forms of blood cells.

Progenitors Earliest committed cells in each lineage.

Pyrogens An agent that causes a rise in temperature.

Radioimmunodetection (RAID) External imaging to disclose foci of increased radioactivity after injection of radioactive antibodies.

Redundant Repetitive.

Reticulocyte Immature red blood cell, larger than mature erythrocytes yet nonnucleated. They circulate in the blood for one to two days while maturing.

Rigors A feeling of cold with severe shivering and pallor, accompanied by an elevation of temperature.

Stem cell factor (SCF) Hematopoietic growth factor that works at the earliest level of commitment and possibly affects the PPSC.

Synergistic The coordinated action of two or more substances such that the combined action is greater than that of each acting separately.

Suppressor T cell A subset of T lymphocytes responsible for suppression of the immune response.

Tachyphylaxis A progressive decrease in response following repetitive administration of a physiologically or pharmacologically active substance.

Tumor-associated antigens Antigens expressed to a greater degree on tumor cells than on normal cells. There are four basic types: oncofetal, unique, antigens from unrelated tissue, antigens from the same tissue.

Tumor-infiltrating lymphocytes (TIL) Lymphocytes obtained from tumor specimens.

White blood cells (leukocytes) There are two types of cells: granulocytes (cells with granules, primarily phagocytes) and agranulocytes (those without granules, lymphocytes, and monocytes).