Chapter 1

# Overview of Hematologic Malignancies

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## Introduction

In 1832, Thomas Hodgkin described the first hematologic malignancy. More than 30 years later, the particular type of lymphoma that he characterized was named *Hodgkin disease* in his honor. The published descriptions of other hematologic malignancies, such as leukemia and multiple myeloma, soon followed. Since that time, these malignancies have been further described and attempts made to categorize various subtypes. With the assistance of immunophenotyping and cytogenetic and molecular genetic testing, it is now understood that hematologic malignancies include a very large number of genetically diverse diseases (Lichtman, 2008). To provide specialized care for patients with hematologic malignancies, nurses must keep pace with advances in medicine and science. The purpose of this book is to provide a detailed review of these complex malignancies. The context for the review is the *World Health Organization (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues, A Consensus Classification of Hematologic Malignancies* (Swerdlow et al., 2008). The WHO classification applied the principles of the Revised European-American Lymphoma (REAL) classification from the International Lymphoma Study Group to all hematologic malignancies, incorporating morphology, immunophenotype, genetic features, and clinical features to define distinct types (Harris et al., 1999). Selected myeloid and lymphoid diseases covered in this publication are illustrated in Figures 1-1 and 1-2.

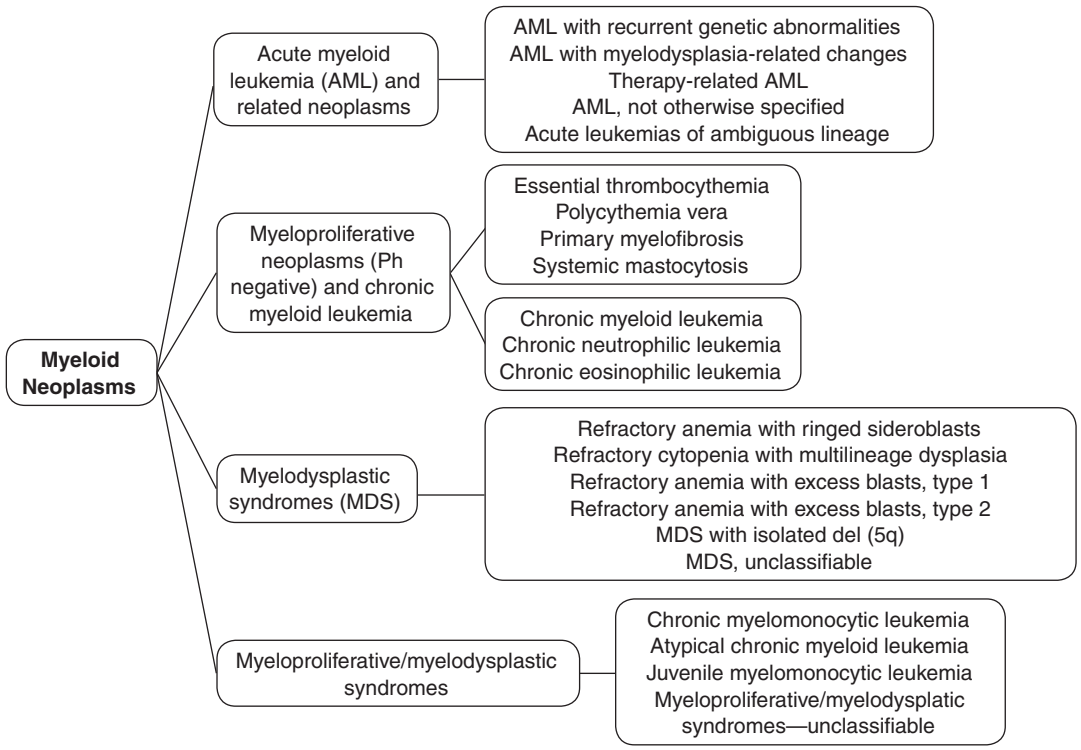
## History of Hematologic Malignancies

### Lymphoma

The first type of lymphoma was described in "On Some Morbid Appearances of the Absorbent Glands and Spleen," a paper published in 1832 by Thomas Hodgkin. In 1898, Carl Sternberg provided the first description of these malignant cells using a recently discovered staining technique. He referred to them as *giant cells* (Aisenberg, 2000). Just four years later, Dorothy Reed fully described the cells, which were termed *Reed-Sternberg* cells (Reed, 1902). For the next 60 years, more detailed clinical and pathologic descriptions of many different types of lymphoma emerged (Aisenberg, 2000).

In 1942, Gall and Mallory developed the first lymphoma classification to categorize the other lymphomas that were not characterized by the Reed-Sternberg cells (Gall & Mallory, 1942).

**Figure 1-1. World Health Organization Classification of Myeloid Neoplasms**




*Note.* Based on information from Swerdlow et al., 2008.

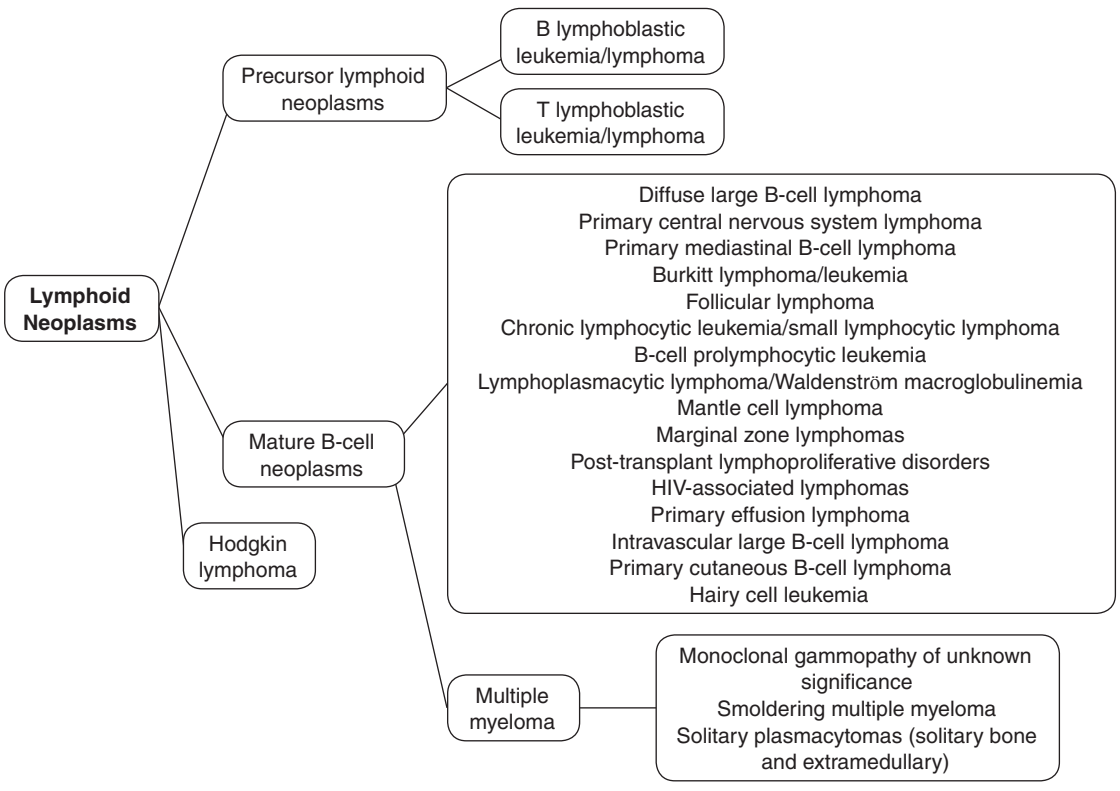
This classification system was quickly followed by the Rappaport Classification in 1956, which was based on cytology and the presence or absence of follicular structure (Rappaport, Winter, & Hicks, 1956). Almost two decades later, the International Working Formulation was introduced, and lymphoma types were classified based on cell size, cell differentiation, and whether or not the cell was cleaved. This led to a classification scheme that distinguished lymphomas with low-grade clinical behavior (nodal follicular architecture maintained) from lymphomas with high-grade or aggressive behavior (nodal architecture replaced by a diffuse pattern of tumor involvement) (Non-Hodgkin's Lymphoma Pathologic Classification Project, 1982). In 1994, the REAL classification, defining immunophenotype and molecular genotype with morphology and clinical features, was developed for non-Hodgkin lymphoma (NHL) (Harris et al., 1994). In 1965, Hodgkin lymphoma was classified into four staging categories at the Rye conference (Lukes & Butler, 1966). Prior to the development of these classifications, more than 50 different terms had been used in the literature to describe lymphoma (Lukes & Butler, 1966).

The foundations of the treatment of lymphoma, in particular Hodgkin lymphoma, began in the early 1900s with the use of radiation therapy. Responses were observed; however, patients were not cured with irradiation until the use of high-dose, extended-field radiation therapy was

developed by Henry Kaplan in the 1960s (Kaplan, 1962). In 1946, nitrogen mustard was used to treat Hodgkin lymphoma; however, patients had short remissions without cure (Goodman & Wintrobe, 1946). Another important milestone in the treatment of Hodgkin lymphoma was in 1970 when DeVita and colleagues developed the MOPP regimen (mechlorethamine, vincristine, prednisone, and procarbazine) (DeVita, Serpick, & Carbone, 1970). This four-drug chemotherapy regimen dramatically changed survival outcomes in the Hodgkin disease patient population. Bonadonna and Santoro (1982) developed the current standard of care—doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)—in the 1970s. The ABVD regimen was less leukemogenic and better tolerated by patients and was adopted as the standard of care in the 1980s. Despite the successful cures achieved in patients with Hodgkin lymphoma, treatment toxicities remain a significant source of morbidity and mortality for survivors of this disease (Hoppe, 1997). The most commonly noted causes of mortality are second malignant neoplasms and cardiovascular disease (Hoppe, 1997).

While mortality from Hodgkin lymphoma began to decline, patients with NHL were not as

**Figure 1-2. World Health Organization Classification of Lymphoid Neoplasms**




*Note.* Based on information from Swerdlow et al., 2008.

fortunate. However, in 1976, McKelvey and colleagues reported efficacy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with advanced NHL. They reported that 71% of patients treated achieved complete remissions, and 92% achieved overall responses (McKelvey et al., 1976).

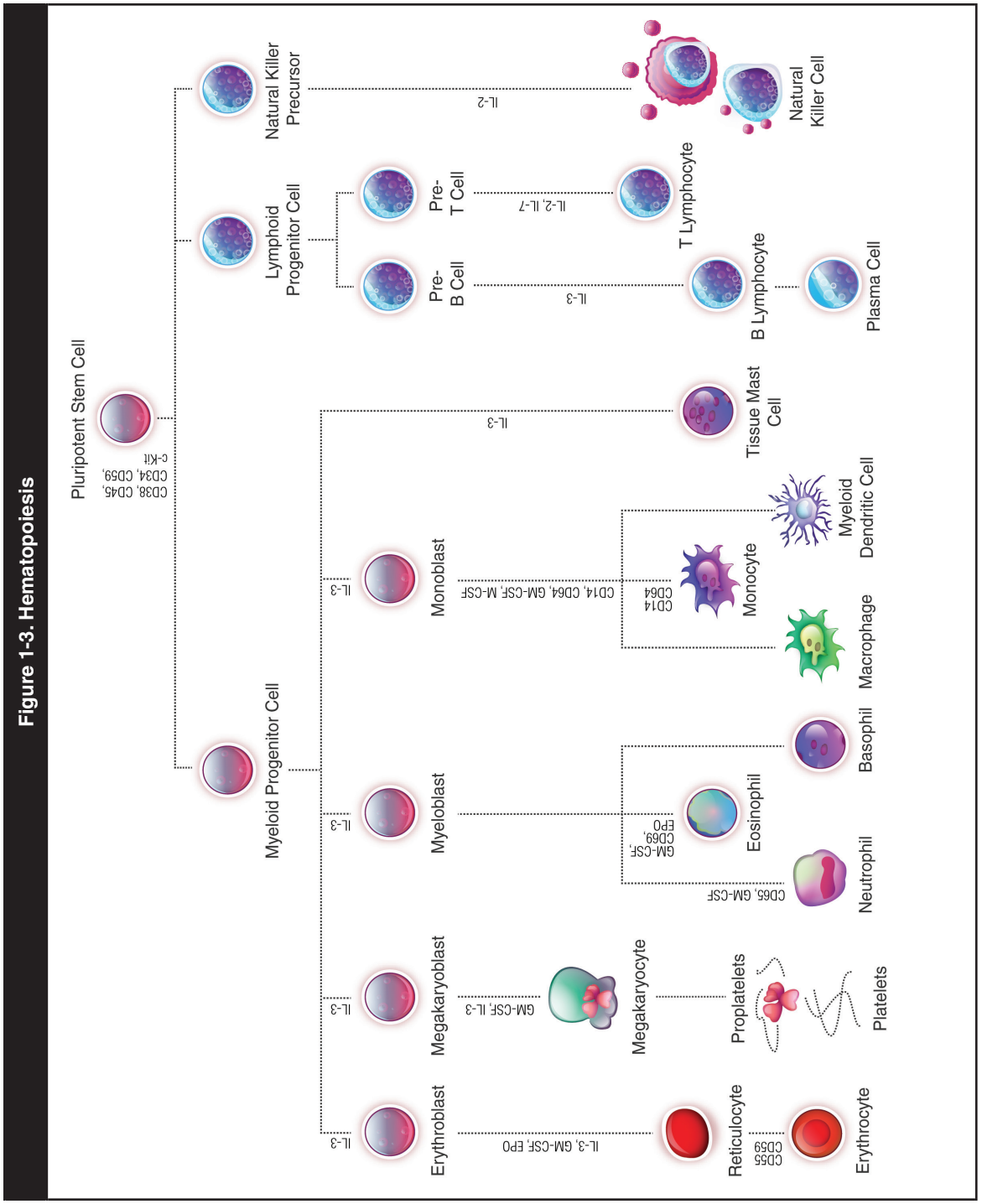
Flow cytometry, developed in the 1970s, can distinguish various types of hematopoietic cells and their specific antigens. Leukemia and lymphoma cells often express antigens or specific products on their surfaces, making them ideal diseases for therapeutic targets. Hybridoma technology, used to produce monoclonal antibodies to target these antigens, was developed in the mid-1970s and led to the discovery of the first monoclonal antibody, anti-CD20 antibody rituximab (Rituxan®). The manufacture of humanized monoclonal antibodies has allowed for a decrease in immunogenicity, improved pharmacokinetics, and enhanced antibody-dependent cytotoxicity (Kampen, 2012). The discovery of monoclonal antibodies was important for patients with NHL, and the addition of rituximab to CHOP (R-CHOP) resulted in higher complete response (76% vs. 63%) and overall survival rates (62% vs. 51%) (Coiffier et al., 2002). R-CHOP continues to be a standard regimen for patients with B-cell NHL (National Comprehensive Cancer Network, 2013). Currently, more than 40 different types of lymphoma have been identified, and as our understanding of these diseases rapidly grows, further improvements in survival will occur as novel therapies are developed.

## Leukemia

In 2011, an estimated 44,600 patients were diagnosed with leukemia in the United States, and 21,780 men and women died of the disease (National Cancer Institute, 2011). The term *leukemia* is derived from Greek words "leukos" and "heima," which refer to excess white blood cells in the body. Leukemia, once considered a single disease, was first recognized as a blood disease around the fourth or fifth century BC. The first case was officially diagnosed by John Hughes Bennett and published in 1845 in the *Edinburgh Medical and Surgical Journal* (Bennett, 1845). Alfred Donné pioneered the use of microscopy to study blood diseases in the early to mid-1800s, and this coincided with the discovery of leukemia as a blood cancer (Kampen, 2012). Then, in 1868, Ernst Neumann, a professor of pathologic anatomy, discovered a link between the source of blood and the bone marrow. This led to the knowledge that all blood cells derive from the bone marrow through hematopoiesis (Piller, 2001) (see Figure 1-3). In 1877, Paul Ehrlich invented a stain that could aid in the distinction of blood cells, which led to the subsequent classification of leukemia (Piller, 2001).

At the end of the 19th century, leukemia was no longer considered a single disease and was classified into subtypes: chronic lymphocytic leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, and acute myeloid leukemia. These four subtypes continue to be used as the basis for our understanding of these diseases. However, it is now known that leukemia comprises a variety of hematopoietic neoplasms that are both complex and unique. Each subtype can be further distinguished by morphologic differences, cytogenetic abnormalities, immunophenotype, and clinical features.

The discovery of the molecular structure of DNA by James Watson and Francis Crick in 1953 allowed us to understand the mechanisms of cancer and the potential causes (Watson & Crick, 1953). It was not until 1960 that the significance of chromosomal abnormalities in leukemia was recognized. Peter Nowell, a pathologist at the University of Pennsylvania, and his colleague David Hungerford discovered that missing chromosomes existed in cancerous white blood cells of patients with chronic myeloid leukemia (Patlak, 2002). In the 1980s, laboratory research demonstrated that this chromosom-



al translocation, t(9;22), known as the Philadelphia (Ph) chromosome, resulted in fused genes, which produced a protein called *BCR-ABL*, and was responsible for the development of chronic myeloid leukemia. The *BCR-ABL* protein was found to be an enzyme called a *tyrosine kinase*, and became an important target for the development of new drugs for leukemia (Druker, 2002). Another translocation, t(15;17), was later discovered in patients with acute promyelocytic leukemia. This translocation alters the normal functioning of a receptor for retinoic acid, rendering the leukemia cells unable to mature. The administration of retinoic acid enables the cells to differentiate and ultimately die. These are just a few examples of the complexity of the various types of leukemia and the promises that these discoveries yield.

One of the oldest forms of treatment for leukemia is arsenic. Thomas Fowler created a solution (Fowler's solution) in the 18th century, which was a mixture of arsenic and potassium bicarbonate. This became a treatment for many ailments and was later used for patients with Hodgkin lymphoma and leukemia (Doyle, 2009). Prior to the 1960s, the treatment of leukemia consisted of blood-letting, iron supplementation, and radioactive phosphorus. Electromagnetic radiation therapy was also used in the early part of the 20th century to treat patients with leukemia, and although some patients received short-term palliation of symptoms, it was not considered a successful or viable treatment option (Kampen, 2012). In 1945, a complete exchange blood transfusion was performed on a patient with leukemia, which resulted in a remission lasting a few months (Kampen, 2012).

The successful treatment of patients with leukemia continued to elude physicians until World War II, when nitrogen mustard, a form of chemical warfare, was found to cause myelosuppression in those exposed to it (Piller, 2001). Nitrogen mustard is an alkylating agent, which causes breakage of DNA strands. Clinical trials using this chemotherapy drug began in the United States in the mid-1940s in patients with lymphoma and leukemia. Subsequently, a number of other alkylating agents were discovered and used for the treatment of leukemia; busulfan and hydroxyurea were the most notable. In the 1950s, a four-drug regimen was employed that used vincristine, amethopterin (now commonly known as methotrexate), 6-mercaptopurine, and prednisone, which resulted in the first cures in patients with leukemia (Patlak, 2002). Central nervous system involvement of leukemic cells presented a difficult challenge in which IV chemotherapy was unsuccessful. The first doses of chemotherapy administered via the intrathecal route were used with success in the 1960s to treat patients with leukemia (Hardisty & Norman, 1967).

Today, numerous therapies exist for the treatment of leukemia. Responses vary based on the type of leukemia, cytogenetic abnormalities present, and individual response to therapy. With an improved understanding of the various types of leukemia, very specific treatments have emerged. It is now clear that every type of leukemia is complex and unique, requiring a specialized approach to ensure an optimal outcome.

## Multiple Myeloma

The first known case of a patient with multiple myeloma was documented by Solly in 1844; the patient was treated with a rhubarb pill and orange peel (Solly, 1844). Solly described the bones of a patient with multiple myeloma as soft and discolored. After the death of a 47-year-old man who presumably had multiple myeloma, Dr. Henry Bence Jones was asked to study the patient's urine and noted the presence of an abnormal protein. This protein was later called *Bence-Jones protein* (Kyle & Steensma, 2011). Interestingly, this 47-year-old man was initially treated with phlebotomy, leeches, steel, and quinine, and he lived for approximately two years (Kyle & Steensma, 2011). In the early 1900s, multi-

ple myeloma was further characterized by pathologic fractures, proteinuria, anemia, and chronic renal disease; however, sedimentation rate and blood protein abnormalities were not described at that time (Kyle & Steensma, 2011). Between 1922 and 1953, the discovery of two classes of Bence-Jones proteins, kappa and lambda, and serum monoclonal protein using electrophoresis and immunofixation led to further understanding of this hematologic malignancy (Kyle & Steensma, 2011). The standard therapy from 1947 to 1966 was urethane, or ethyl carbamate; however, a randomized trial comparing urethane with placebo found no benefit and significantly more deaths in the urethane arm (Holland et al., 1966). In 1958, melphalan was first used and was later successfully combined with prednisone (Alexanian et al., 1969), and melphalan and prednisone (MP) became the standard of care.

Beginning in the 1990s, the treatment of patients with multiple myeloma was transformed as the understanding of the pathobiology of the disease led to the discovery of a number of new therapies. Thalidomide, an immunomodulatory drug with antiangiogenic activity, demonstrated single-agent activity in a trial published in 1999, and in 2006, lenalidomide received U.S. Food and Drug Administration approval. Hematopoietic cell transplantation (HCT) using high-dose melphalan has been employed in patients with multiple myeloma since the 1980s and continues to be a treatment option to enhance overall survival (Bayraktar, Bashir, Qazilbash, Champlin, & Ciurea, 2012). The discovery of new drugs such as thalidomide, lenalidomide, and bortezomib for treatment of multiple myeloma has led to significant benefits, including increased overall survival and quality of life.

## Hematopoietic Cell Transplantation

HCT has evolved over the past 50 years from experimental bone marrow transplantation for patients with incurable leukemia to standard treatment for a broad range of patients with both myeloid and lymphoid neoplasms. For many of these diseases, HCT is the only curative option. Today, 45,000–50,000 HCTs are performed annually in the world (Horowitz, 2004). In 1957, the first allogeneic marrow transplantations in humans were performed following delivery of high doses of radiation; severe organ toxicity was observed, which precluded its use (Thomas, 2005). In the late 1960s and early 1970s, George Santos (1989) studied the use of busulfan and cyclophosphamide for bone marrow ablation in lieu of high-dose radiation. E. Donnall Thomas and Joseph Ferrebee applied this approach to allogeneic marrow transplantation (Appelbaum, 2007). Knowledge of histocompatibility was limited, and it was not until the 1960s that human leukocyte antigen (HLA) typing methods were developed. Thomas began allogeneic marrow transplantation clinical trials in 1969 using matched siblings. In order to support these patients, Thomas worked with Robert Hickman to develop a central line catheter for infusions and blood draws during the transplantation process. Many patients who underwent transplantation died of their diseases or from the associated treatment-related toxicities. However, a few entered complete remission, prompting excitement for this treatment of patients with advanced leukemia (Appelbaum, 2007).

In 1979, Thomas and colleagues reported a 50% cure rate using allogeneic bone marrow transplantation in patients with acute myeloid leukemia in remission at the time of transplant (Thomas et al., 1979). Also during this time, the first autologous transplants were performed after high-dose chemotherapy in patients with NHL (Appelbaum, 2007). Hansen performed a successful matched unrelated donor transplant in a patient with acute lymphoblastic leukemia in second remission (Hansen et al., 1980); the donor and patient were unrelated but phenotypically HLA-A, HLA-B, HLA-D, and HLA-DR

identical (Hansen et al., 1980). These advances led to an expansion of transplantation as a treatment option for patients who do not have a matched sibling.

The focus of the next decade included supportive care improvements to decrease morbidity and mortality related to infection, organ toxicity, and graft-versus-host disease (GVHD). In 1979, the graft-versus-leukemia effect was identified as an important factor in the prevention of leukemia recurrence (Appelbaum, 2007). Thomas demonstrated that relapse rates were lower in those patients who developed GVHD, and thus, syngeneic transplant recipients had the highest rate of relapse because of the lack of GVHD (Appelbaum, 2007). This discovery led to the successful use of donor lymphocytes in patients who relapsed following marrow transplantation (Appelbaum, 2007).

Transplantation using other sources of stem cells besides the bone marrow became an area of intense research in the 1970s and '80s. Today, more than 70% of all allogeneic transplantations in adults are performed using peripheral blood stem cells after mobilization with growth factors (Center for International Blood and Marrow Transplant Research, 2012; Thomas, 2005). Umbilical cord blood is another source of stem cells being used throughout the world, mostly in children. The first umbilical cord blood transplantation was performed in 1989 by Gluckman and colleagues on a five-year-old with Fanconi anemia (Gluckman et al., 1989).

The most recent major advancement in transplantation has been the reduced-intensity conditioning approach using HLA-matched or HLA-mismatched donors. This has allowed older patients and those without an HLA-matched sibling to undergo HCT (Pollack, O'Connor, Hashash, & Tabbara, 2009). Ongoing research will lead to further developments in HCT. Today, many patients with hematologic malignancies will be treated and potentially cured with HCT.

## Summary

This book will assist nurses and other healthcare professionals in understanding the complex diseases, treatments, complications, and toxicity management of patients with hematologic malignancies. Nurses play an essential role in providing care for patients with hematologic malignancies. Each chapter details select disease types using the *WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues* (Swerdlow et al., 2008). A substantial portion of the book will focus on the management of the disease-related manifestations and the treatment-related side effects and toxicities. The management of patients with myeloid and lymphoid neoplasms is unique, complex, and vital to ensuring successful outcomes and improved quality of life. Table 1-1 includes a list of drugs used in the treatment of hematologic malignancies.

With the help of molecular diagnostics, the past few decades have brought exciting discoveries, such as the t(9;22) *BCR-ABL* translocation in chronic myeloid leukemia; the t(15;17)(q22;q12) translocation (PML/RAR-alpha) in acute promyelocytic leukemia, which is both diagnostic for the disease and indicated for the use of all-trans-retinoic acid; and the use of microarray analysis to define new subsets of diffuse large B-cell lymphoma (Wang, 2012). With these discoveries, new treatments have transformed the care of patients with hematologic malignancies. As our knowledge of molecular biology expands, so will our ability to confirm or establish a new diagnosis or recurrence, follow patients for response to therapy, predict prognosis and response to therapy, and tailor treatments to patients based on gene expression profiling. Table 1-2 contains a description of diagnostic tests used in patients with hematologic malignancies, and Table 1-3 contains a list of markers in hematologic malignancies.

**Table 1-1. Drugs Used in the Treatment of Hematologic Malignancies***

| Classification | Mechanism of Action | Examples |
|---|---|---|
| Antitumor antibiotics | Interact directly with DNA in the nucleus of cells, interfering with cell survival | • Bleomycin sulfate (Blenoxane®)<br>• Daunorubicin (Cerubidine®)<br>• Idarubicin (Idamycin®)<br>• Doxorubicin (Adriamycin®)<br>• Mitoxantrone (Novantrone®) |
| Antimetabolites | Block cells' ability to form RNA or DNA, preventing cell growth and accelerating cell death | • Cladribine (Leustatin®, 2-CdA)<br>• Cytarabine (cytosine arabinoside, ARA-C, Cytosar-U®)<br>• Fludarabine (Fludara®)<br>• Hydroxyurea (Hydrea®, Droxia®)<br>• 6-Mercaptopurine (Purinethol®)<br>• Methotrexate<br>• 6-Thioguanine (Thioguanine®, Tabloid®)<br>• Azacitidine (Vidaza®)<br>• Decitabine (Dacogen®)<br>• Clofarabine (Clolar®) |
| Immunomodulators | Exact mechanism of action is unclear; immune, cytotoxic, and antiangiogenic effects | • Interferon (Roferon® A, Intron® A)<br>• Pegylated interferon (PEG IFN)<br>• Thalidomide (Thalomid®)<br>• Lenalidomide (Revlimid®) |
| Histone deacetylase inhibitors | Modulate chromatin structure and gene expression; induce cell growth arrest, cell differentiation, and death of leukemia cells | • Vorinostat (Zolinza®) |
| Corticosteroids | Cytotoxic activity against lymphoma and leukemia cells | • Dexamethasone (Decadron®)<br>• Methylprednisolone (Medrol®)<br>• Prednisone (Deltasone®) |
| Bisphosphonates | Block the reabsorption of bone in myeloma and have direct effects on myeloma cells | • Pamidronate (Aredia®)<br>• Zoledronic acid (Zometa®) |
| Plant alkaloids | Act on certain proteins (enzymes) in the cell nucleus that normally repair injury to DNA *(DNA-repair enzyme inhibitors)* | • Etoposide (VP-16, VePesid®, Etopophos®, Toposar®)<br>• Teniposide (VM-26, Vumon®)<br>• Topotecan (Hycamtin®) |
| | Impair structures in the cell that are required for cells to divide into two daughter cells *(block mitosis)* | • Vinblastine (Velban®)<br>• Vincristine (Oncovin®)<br>• Paclitaxel (Taxol®) |
| Alkylating agents | Alter DNA and enhance cell death | • Bendamustine (Treanda®)<br>• Busulfan (Myleran®, Busulfex®)<br>• Carboplatin (Paraplatin®) |

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**Table 1-1. Drugs Used in the Treatment of Hematologic Malignancies* *(Continued)***

| Classification | Mechanism of Action | Examples |
|---|---|---|
| Alkylating agents *(cont.)* | Alter DNA and enhance cell death | • Carmustine (BCNU, BiCNU®)<br>• Chlorambucil (Leukeran®)<br>• Cisplatin (Platinol®)<br>• Cyclophosphamide (Cytoxan®, Neosar®)<br>• Dacarbazine (DTIC-Dome®)<br>• Ifosfamide (Ifex®)<br>• Lomustine (CCNU®, CeeNU®)<br>• Mechlorethamine (nitrogen mustard, Mustargen®)<br>• Melphalan (Alkeran®)<br>• Procarbazine (Matulane®) |
| Proteasome inhibitors | Act on the breakdown of proteins in the proteasome, a key cell function; used for multiple myeloma | • Bortezomib (Velcade®) |
| Monoclonal antibodies | Target specific antigens on cancer cells | • Rituximab (Rituxan®)<br>• Yttrium-90-ibritumomab tiuxetan (Zevalin®)<br>• Tositumomab (Bexxar®)<br>• Ofatumumab (Arzerra®) |
| Tyrosine kinase inhibitors | Block specific mutant proteins that initiate malignant cell transformation | • Imatinib mesylate (Gleevec®)<br>• Dasatinib (Sprycel®)<br>• Nilotinib (Tasigna®) |
| Cell-maturing agents | Induce maturation of leukemia cells | • Tretinoin (all-trans-retinoic acid [ATRA], Vesanoid®)<br>• Arsenic trioxide (Trisenox®) |
| Janus kinase inhibitor | Janus kinase inhibitor (*JAK1* and *JAK2*) | • Ruxolitinib (Jakafi®) |
| Phototherapy | Activated by ultraviolet light to kill skin lymphoma cells | • Psoralen |

*Combinations of these drugs and drug groups are used to treat hematologic malignancies. This table does not include every approved drug or drug under study in clinical trials.

*Note.* Based on information from Lichtman, 2008.

**Table 1-2. Diagnostic Tests Used in Hematologic Malignancies**

| Diagnostic Test | Description |
|---|---|
| Microscopy | Microscopy allows for the visualization of cells to determine morphology and staining characteristics.<br>• Oldest diagnostic technique used in hematologic malignancies<br>• Limitation includes inability to distinguish cells that are morphologically the same but molecularly distinct. |
| Immunohistochemistry | Immunohistochemistry is a technique used to identify specific molecules in different kinds of tissue. The tissue is treated with antibodies that bind to the specific molecule. These are made visible under a microscope by using a color reaction, a radioisotope, or a fluorescent dye.<br>• Used to help diagnose cancer and to detect the presence of microorganisms<br>• Assists in determining whether tumors will be responsive to therapies based on the detection of elevated levels of the molecular target |
| Flow cytometry | Flow cytometry is the measurement of cellular properties as they are moving in a fluid stream past a detector. Cells of different subtypes can be sorted and collected for further analysis. It is capable of rapid, quantitative, multiparameter analysis of heterogeneous cell populations on a cell-by-cell basis, providing single-cell analysis.<br>• Characterizes the hematopoietic stem cell to establish lineage markers, state of maturation, or differentiation<br>• Detects presence of intracellular proteins or proteins expressed on the cell surface when used with monoclonal antibodies<br>• Qualitative and quantitative analysis of cells<br>• Used to monitor reconstitution of the immune system after hematopoietic cell transplantation (HCT)-donor engraftment, vaccine therapy, or donor lymphocyte infusion |
| Immunophenotyping | Immunophenotyping uses fluorochrome-tagged monoclonal antibodies to analyze heterogeneous populations of cells.<br>• Antibodies are used to detect specific antigens (markers) that are expressed on cells.<br>• Used with flow cytometry, it is the method of choice for identifying and sorting cells within complex populations. |
| Fluorescence in situ hybridization (FISH) | FISH combines standard microscopic cytogenetic analysis with molecular methods and is also known as *interphase cytogenetics*. DNA probes are hybridized to metaphase spreads or interphase nuclei, typically one color for each gene involved in a translocation. When the genes are on separate chromosomes (i.e., there is no translocation), the color signals will be separated in space. When a translocation is present, the two probes are brought into proximity, resulting in generation of a fusion signal of a new color. Actively dividing cells are not required.<br>• Characterizes structural chromosomal abnormalities and identifies chromosomes of uncertain origin<br>• Useful in monitoring minimal residual disease<br>• Can identify donor versus recipient origin of blood post-HCT |

*(Continued on next page)*

**Table 1-2. Diagnostic Tests Used in Hematologic Malignancies *(Continued)***

| Diagnostic Test | Description |
|---|---|
| Cytogenetics | Cytogenetics is the analysis of chromosomes during metaphase. Using a staining technique that produces specific banding patterns, chromosomes are analyzed under a microscope. Generally, 20 cells are analyzed. Cytogenetics is also known as *conventional cytogenetics*, *chromosome analysis*, or *karyotyping*.<br>• Describes the number of chromosomes and their appearance<br>• Identifies chromosomal abnormalities, such as translocations, inversions, deletions, and extra copies of chromosomes |
| Polymerase chain reaction (PCR) | PCR can be performed with DNA or RNA. Amplification of DNA sequences and copies are made to produce enough DNA to be tested (DNA-PCR). For RNA, a DNA copy of the RNA target is synthesized using the enzyme reverse transcriptase. The resulting DNA copy (cDNA) is then amplified as in conventional DNA-PCR. This technique is known as the reverse-transcription PCR.<br>• Used to detect chromosomal translocations, deletions, and duplications<br>• Can identify disease-causing bacteria or viruses<br>• Detects small numbers of neoplastic cells; useful in detection of minimal residual disease<br>• Identifies genes that are different and unique to that organism<br>• Reveals specific genetic flaws on cells and is highly sensitive and specific |
| Gene expression profiling | Gene expression profiling uses DNA microarrays to measure activity of genes. Distinguishes between cells that are activity dividing. This technique can be used to identify targets for future diagnostic testing, treatment, and evaluation of prognosis. |

*Note.* Based on information from Craig & Foon, 2008; Cumpston & Craig, 2010; Koca & Qazilbash, 2010; Monga & Devetten, 2010; Sabath, 2004; Staudt, 2003; Tay et al., 2010.

**Table 1-3. Markers in Hematologic Malignancies**

| Name | Normal Expression | Comments |
|---|---|---|
| CD1a | Immature T cells; Langerhans cells | Associated with ALL |
| CD2 | T cells and NK cells | May be aberrantly expressed in AML and systemic mastocytosis |
| CD3 | T cells | Indicates T-cell lineage |
| CD4 | T-cell subset, monocytes, histiocytes | Associated with mature T-cell lymphoid neoplasms and monocytic AML |
| CD5 | T cells and B-cell subset | Indicates T-cell lineage; may be expressed aberrantly on B cells, such as CLL and MCL |
| CD7 | T cells and NK cells | Indicator of T-cell lineage; may be aberrantly expressed in AML, MDS, and MPN |

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**Table 1-3. Markers in Hematologic Malignancies *(Continued)***

| Name | Normal Expression | Comments |
|---|---|---|
| CD8 | T-cell subset and some NK cells | Associated with some mature T-cell lymphoid neoplasms |
| CD9 | Precursor B cells, activated T cells, and platelets | Associated with precursor B-cell ALL |
| CD10 | Immature T cells and B cells, subset of mature T cells and B cells, and neutrophils | Associated with ALL, some mature T-cell neoplasms, and some mature B-cell neoplasms. In mature B-cell neoplasms, it is associated with a germinal center phenotype of FL and DLBCL. |
| CD11b | Maturing neutrophilic and monocytic cells and some lymphoid cells | Aberrantly expressed in AML, MDS, and MPN |
| CD11c | Subset of B cells and subset of T cells | Associated with HCL; occasionally with CLL and MCL |
| CD13 | Myeloid and monocytic cells | Indicates neutrophilic and monocytic lineage. Associated with myeloid neoplasms; may be aberrantly expressed in B-cell neoplasms, MDS, and MPN. |
| CD14 | Monocytes | Associated with monocytic AML |
| CD15 | Myeloid and monocytic cells | May be aberrantly expressed in AML, MDS, and MPD |
| CD16 | NK cells, NK/T cells, monocytes, and maturing neutrophilic cells | Indicates NK differentiation; may be aberrantly expressed in AML, MDS, and MPN |
| CD19 | All B cells including lymphoblasts, mature B cells, and most plasma cells | Indicates B-cell lineage |
| CD20 | Mature B cells (except plasma cells) and small subset of T cells | Indicates B-cell lineage; aberrant expression in ALL |
| CD22 | Cytoplasmic expression in early B cells and surface expression acquired during maturation of precursor B cells | Indicates B-cell lineage in ALL and mature B-cell neoplasms |
| CD23 | Weak expression on resting B cells; intensity increases with activation | Distinguishes between CD5+ mature B-lymphoid neoplasms (e.g., CLL is CD5+/CD23+ and MCL is CD5+/CD23–) |
| CD25 | Activated B cells and activated T cells | Associated with ATLL and HCL; variable expression in other mature T-cell neoplasms and systemic mastocytosis |
| CD26 | Immature T cells, NK cells, and activated T cells | Associated with CTCL/Sézary syndrome |
| CD30 | Activated T cells and B cells, and monocytes | Associated with HL and ALCL |

*(Continued on next page)*

**Table 1-3. Markers in Hematologic Malignancies *(Continued)***

| Name | Normal Expression | Comments |
|---|---|---|
| CD33 | Myeloid and monocytic cells | Associated with AML; may be aberrantly expressed in B-cell neoplasms, MDS, and MPNs |
| CD34 | Hematopoietic precursors, B-cell and T-cell precursors and myeloblasts | Associated with AML and ALL blasts and one of the stem cell markers |
| CD36 | Monocytes, erythroid cells, megakaryocytes, and platelets | When used in combination with CD64, is a more sensitive marker of monocytic differentiation than CD14 |
| CD38 | Precursor B cells (hematogones), normal follicle center B cells, immature and activated T cells, plasma cells (bright intensity), myeloid and monocytic cells, and erythroid precursors | Associated with plasmacytic differentiation and multiple myeloma; poor prognostic marker in CLL/SLL |
| CD41 | Megakaryocytes and platelets | Associated with megakaryocytic differentiation |
| CD43 | T cells, myeloid, monocytes, and small B-cell subset | Aberrant expression in CLL, MCL, and some MZL |
| CD45 | All B cells and T cells; weaker intensity on precursors and plasma cells | Useful to distinguish between precursor lymphoid neoplasms from mature lymphoid neoplasms; identifies blasts in acute leukemia |
| CD45RA | B-cell subsets, T-cell subsets, including mostly naïve T cells | – |
| CD45RO | B-cell subsets, T-cell subsets, including mostly memory T cells | – |
| CD52 | Thymocytes, T and B cells (not plasma cells), monocytes, macrophages | – |
| CD56 | NK cells and NK/T cells | Indicates NK differentiation; aberrant expression in AML, MM, MDS, and MPN |
| CD58 | Leukocytes including bright-intensity staining of precursors; intensity decreases with maturation | Distinguishes ALL from normal precursor B-cell (hematogones) including detection of MRD |
| CD61 | Megakaryocytes and platelets | Associated with megakaryocytic differentiation |
| CD64 | Monocytes and intermediate neutrophilic precursors | Associated with monocytic differentiation; may be aberrantly expressed in AML, MDS, and MPN; expressed on neutrophils during sepsis |
| CD71 | Erythroid precursors, myeloid, activated lymphoid, and proliferating cells | Identification of immature erythroid cells; possibly expressed in MDS |

*(Continued on next page)*

**Table 1-3. Markers in Hematologic Malignancies *(Continued)***

| Name | Normal Expression | Comments |
|---|---|---|
| CD79a and CD79b | Precursor B cells, plasma cells positive, variable expression mature B cells | Indicates B-cell lineage in ALL and mature lymphoid neoplasms; intensity often differs between subtypes of mature B-cell neoplasm; may be seen in some T-cell lymphoid neoplasms |
| CD103 | B-cell subset and intramucosal T cells | Associated with HCL, EATL, and some MZL |
| CD117 | Immature myeloid cells and mast cells | Associated with myeloblasts; may be aberrantly expressed MM and MGUS |
| CD123 | Monocytes, neutrophils, basophils, megakaryocytes, and plasmacytoid dendritic cells | May be expressed with monocytic AML |
| CD138 | Plasma cells | Associated with MM |
| CD163 | Monocytes and macrophages | Indicates monocytic differentiation |
| FMC-7 | B cells | Distinguishes CD5+ lymphoid neoplasm: CLL is FMC-7 negative, and MCL is FMC-7 positive. Associated with HCL. |
| Bcl-2 | T cells and some B cells; absent on normal germinal center cells | Distinguishes CD10+ lymphoid neoplasms: FL is usually positive, BL negative, variable in DLBCL. |
| HLA-DR | Myeloblasts, monocytes, promyelocytes, all B cells, and activated T cells | Associated with APL; may be aberrantly expressed in AML, MDS, and MPN |
| Kappa and lambda | Mature B cells | Immunoglobulin light chain restriction in B cells |
| MPO | Neutrophilic and monocytic cells | Indicates myeloid differentiation; in contrast to cytochemical stain, measures the presence of antigen, not enzyme activity |
| TCR | T-cell receptor on mature T cells | Used in classification of mature T-cell neoplasms |
| TdT | B-cell and T-cell precursors | Associated with ALL and some AML |
| ZAP-70 | T cells, NK cells, precursor B cells | Poor prognostic marker in CLL/SLL |

ALCL—anaplastic large cell lymphoma; ALL—acute lymphoblastic leukemia; AML—acute myeloid leukemia; APL—acute promyelocytic leukemia; ATLL—adult T-cell lymphoma; BL—Burkitt lymphoma; CD—cluster designation; CLL—chronic lymphocytic leukemia; CTCL—cutaneous T-cell lymphoma; DLBCL—diffuse large B-cell lymphoma; EATL—enteropathy-associated T-cell lymphoma; FL—follicular lymphoma; HCL—hairy cell leukemia; HL—Hodgkin lymphoma; HLA-DR—human leukocyte antigen D-region; MCL—mantle cell lymphoma; MDS—myelodysplastic syndromes; MGUS—monoclonal gammopathy of undetermined significance; MM—multiple myeloma; MPN—myeloproliferative neoplasm; MPO—myeloperoxidase; MZL—marginal zone lymphoma; NK—natural killer; SLL—small lymphocytic lymphoma; TCR—T-cell receptor; TdT—terminal deoxynucleotidyl transferase; ZAP-70—zeta chain associated protein 70

*Note.* Based on information from Craig & Foon, 2008.

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