

Leukemia and Myelodysplastic Syndromes

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INTRODUCTION

The leukemias represent a group of heterogeneous clonal myeloid and lymphoid malignancies that originate in the bone marrow due to a stem cell defect with variable clinical presentations, pathological characteristics, prognosis and recommended treatment. The diseases arise from either B or T lymphocytes or myeloid progenitor cells at different stages of maturation. Each is categorized based on the lineage (lymphoid or myeloid), the specific stage of maturation, and the disease trajectory (chronic vs acute). Robust scientific discovery over the last decade has improved selection of therapies based on specific disease attributes, prognostic variables, and individual patient characteristics. Further refinement of morphological, immunophenotypic, cytogenetic, and molecular analysis has established a separate classification system for the myelodysplastic syndromes (MDS), previously included as a myeloid leukemia and now categorized as a distinct disease with specific diagnostic, prognostic, and treatment guidelines.

This chapter will provide an overview of the epidemiology, etiology, pathobiology, classification, clinical presentation, risk stratification, treatment and nursing management of patients with acute leukemia, chronic leukemia, or MDS, including: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), MDS, acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL). Most of these diseases are considered incurable, but most are highly treatable. Understanding the unique attributes of each disease, available treatment options, and strategies for clinical management of the patient using a life-span approach is critical to achieving optimal outcomes for the patient.

EPIDEMIOLOGY

Worldwide there were 330,963 new cases of leukemia with 279,658 deaths reported in 2007.¹ These hematological diseases are not the most common malignancies and no 1 subtype exceeded an incidence rate of 20,000 in the US in 2009. Collectively, the incidence of leukemia in 2009 in the US for both sexes was 44,790 new cases, with CLL being the most common (15,490) and CML being the least common (5050)² (Table 57-1^{3,4}). All subtypes were found to be slightly more common in men, and most were diagnosed 10 times more frequently in adults than children. The median age at diagnosis varies, with peak incidence in patients over the age of 60 with the exception of ALL, which is more common in children with only 16.2% of cases diagnosed over the age of 45.⁵

Epidemiologic data specific to MDS has only been collected in the US since 2001,⁴ thus comparative trends are not available. Prior to 1973, only 143 cases of MDS were reported. Today, there are 10,000 to 15,000 new cases of MDS annually in the US and the prevalence is estimated to

be 35,000 to 55,000 cases based on typical life expectancy. There is an increase in the incidence of MDS with advancing age, highest at ages 80 to 84, then decreasing dramatically at age 85.

Clinical advances in the treatment of leukemia and available supportive care measures have improved survival rates for these diseases. Death rates have decreased by approximately 0.8% per year since 1995.⁵ The mortality rate for CML in particular has declined significantly due to characterization of the *BCR-ABL* fusion gene and development of therapies that target this specific molecular abnormality. The annual mortality rate for CML has been reduced from 15% to 20% to 2% and the median survival is expected to exceed 15 to 20 years based on the current rates.⁵

ETIOLOGY

Many potential risk factors have been identified for each disease, including antecedent hematological disorders (AHD), genetic predisposition, prior treatment for malignancy, chemical exposures, ionizing radiation, and concomitant autoimmune diseases. In most cases no clear etiology is identified, however, there are distinct differences in suspected risk factors for each disorder. There are no known hereditary, familial, geographic, ethnic, infectious, or economic associations identified with the risk of developing CML, therefore CML does not appear to be preventable.⁶ CLL has not been associated with ionizing radiation, chemical exposure, viruses, or prior chemotherapy, but does appear to have some familial trends in 5% to 10% of patients, suggesting an underlying genetic predisposition.⁷ Older age is a predisposing risk factor for MDS and is thought to be a result of hematopoietic senescence.⁸ Secondary MDS may develop after exposure to high doses of radiation, chemotherapy, or industrial toxins such as benzene. Benzene is the best studied and most widely used potentially leukemogenic agent. Inherited genetic predisposition for developing MDS and congenital abnormalities are rare. Chemotherapeutic agents, such as alkylating agents and topoisomerase II inhibitors, have been reported to increase the incidence of AML.⁹ Persons exposed to embalming fluids, ethylene oxides, and herbicides also appear to be at increased risk. Tobacco use has been associated with an increased risk of developing AML (particularly of French American British [FAB] subtype M2), especially in those persons aged 60 to 75.¹⁰

In both ALL and AML specific genetic abnormalities thought to have underlying chromosomal fragility have been associated with development of disease.^{11,12} Patients with chromosomal abnormalities including Klinefelter's syndrome (XXY), Fanconi anemia, trisomy 21 (Down syndrome), Bloom syndrome, and ataxia telangiectasia have a higher risk of developing ALL. Similarly, AML has been associated with these same disorders as well as

TABLE 57-1

Recent Epidemiological Trends for Leukemia in the US

Disease	New Cases (US, 2009)	Deaths (US, 2009)	Median Age at Diagnosis (years)	5-Year Relative Survival Rates 1996–2004 (%) ^a
All leukemias	44,790 ^b	21,870		50
Acute myelogenous leukemia	12,810	9000	67	21.9
Chronic myelogenous leukemia	5050	470	66	50.2
Acute lymphocytic leukemia	5760	1400	13	64.7
Chronic lymphocytic leukemia	15,490	4390	72	75.9
Myelodysplastic syndrome	9730	NA	70	45 (3 year survival rate)

^aExcludes myelodysplastic syndrome.^bIncidence rate and 3-year survival rates based on data obtained from 2001–2004.Source: Data from SEER³; and Rollison et al.⁴

Wiskott-Aldrich syndrome, Kostmann syndrome, and Patau (trisomy of chromosome 13).¹³ Given the relatively small numbers of patients diagnosed with each disease, further characterization of specific genetic risk factors has been limited. Similar to other lymphoid malignancies, infectious etiologies have been described as possible predisposing factors for the development of ALL including Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and human T-cell lymphotropic virus type 1 (HTLV1).¹²

Perhaps the greatest challenge is the clear association between chemical exposure and the development of AML and MDS. Alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors, anthracyclines, mitoxantrone, and radiotherapy have all been associated with treatment-related AML and MDS.¹³ Specific agents are associated with either early or late onset of secondary AML and MDS. The peak onset of treatment related AML or MDS is 5 to 10 years after therapy. Given the incurable nature of these disorders, particular attention must be placed on a life span approach to therapy with attention to potential secondary effects and quality of life.

PREVENTION, SCREENING, AND EARLY DETECTION

Prevention of leukemia and MDS is difficult outside of avoidance of known chemical and environmental exposures. Radiation safety programs, guidelines set by the Occupational Safety and Health Administration (OSHA), and regulation of pesticide use may provide some protection from possible exposures. Smoking cessation programs may also provide benefit as there is growing evidence that tobacco exposure is associated with bone marrow disorders.¹⁰ As the ability to control a variety of cancers over

an extended period using continuous and/or intermittent therapies has grown, there has also been an increase in the number of treatment-related bone marrow disorders including AML and MDS. Long-term follow up of patients using epidemiological approaches will be necessary to better characterize any common agents, dosing parameters, and time of onset for these secondary diseases.

There are no proven screening or early detection programs to date. These diseases are often diagnosed incidentally on a general physical exam or emergency room visit. Increasing provider awareness of the presenting symptoms may facilitate diagnosis, which is often critical to initiating therapy early and achieving optimal clinical outcomes. Encouraging regular health maintenance and screening visits will provide the best opportunity for early detection of subtle changes in blood work and physical findings such as cytopenias, adenopathy, or organomegaly. This will also provide useful analysis of trends over time, which is particularly useful in estimating the onset of disease and characterizing the disease trajectory.

PATHOBIOLOGY

The leukemias represent a group of heterogeneous clonal myeloid and lymphoid malignancies that originate in the bone marrow due to a stem cell defect. The underlying pathobiology for each disease includes abnormalities in the malignant clone itself (intrinsic abnormalities) and in the tumor microenvironment (extrinsic abnormalities). With the exception of CML where there is a distinct clonal abnormality called the Abelson-breakpoint cluster region or *BCR-ABL* fusion gene, much of the pathobiology of these diseases has yet to be fully characterized. There are several morphological, immunophenotypic, cytogenetic,

molecular, and physiological attributes that are known to be associated with each disease. Characterization of these attributes is necessary for classification, staging, and risk stratification. This in turn is used to guide treatment decisions and to estimate prognosis.

Diagnosis of each of these hematological disorders is guided by careful analysis of tissue specimens, most often a bone marrow biopsy and aspirate and/or lymphoid specimens (lymph nodes, spleen, or other extramedullary sites of disease). These specimens allow hematopathologists to apply a series of diagnostic criteria that differentiate the disease as being either myeloid or lymphoid in origin and then within each cell line indicate a specific disease entity. Understanding the key principles of pathobiology including intrinsic and extrinsic abnormalities of each disease will assist the oncology nurse in understanding the variability in clinical presentation, diagnostic criteria, treatment selection, evaluation of response, and estimation of prognosis for each disease.

There are many similarities in the pathobiology of leukemia and MDS but there are key differences that define each disease, and in some cases determine specific treatment selection. Leukemia and MDS are thought to originate as a result of complex interactions between malignant progenitor cells (malignant clone), the bone marrow stroma and microenvironment. There are both intrinsic (within the malignant clone itself) and extrinsic factors (bone marrow microenvironment and stroma) thought to play a role in the pathogenesis of each disease.¹⁴ Intrinsic factors include cytogenetic abnormalities, epigenetic DNA changes and gene mutations or disordered gene expression. Cytogenetic abnormalities are common in hematological malignancies and have long been identified as key elements of the diagnostic process for AML and CML.^{15–17} More recently, cytogenetic abnormalities have been elucidated as key diagnostic and prognostic elements of the lymphoid leukemias and MDS. Chromosomes can be considered the “blueprint” for production of each cell line. Cytogenetic abnormalities are in effect, a faulty instruction manual for the production of cells. More complex defects imply a decreased probability of normal cell production. Cytogenetic abnormalities are now considered one of the most critical independent risk factors for prognosis in the hematological malignancies.¹⁸ There are rare inherited cytogenetic predispositions to some of these diseases, however in most cases chromosomal abnormalities are a result of acquired insults to the clone. Hematopoietic senescence as a result of aging and mutagenic and genotoxic stresses, including prior chemotherapy or radiation exposure, environmental and occupational exposures to solvents, and tobacco abuse, have been associated with the development of cytogenetic abnormalities.¹⁸

Epigenetic DNA changes, unlike genetic changes such as mutations or deletions, which are irreversible (with the exception of treatment with an allogeneic stem cell transplant); represent potentially reversible modifications to

DNA and chromatin. The interactions between DNA and chromatin contribute to the regulation of transcription, chromosome stability, DNA repair and replication independent of the genetic code.¹⁹ The best known epigenetic marker is DNA methylation. DNA methylation plays critical roles in the control of gene expression and the architecture of the nucleus of the cell. Patients with AML and MDS have CpG islands that are often hypermethylated, resulting in silencing of critical regulatory or suppressor functions (signal transduction pathways) necessary for normal hematopoiesis (differentiation and apoptosis).²⁰ Of particular interest is the role of DNA hypermethylation in leukemogenesis. Aberrant DNA methylation is suggested as a primary mechanism for progression of MDS to AML.²¹ Drugs that inhibit DNA methylation promote expression of previously silenced genes. Gene expression may also be blocked by changes in chromatin structure caused by histone deacetylation. Chromatin is comprised of DNA, RNA, and proteins that collectively make up chromosomes. Histone deacetylase inhibitors remodel the chromatin structure to enable transcription of previously blocked genes. Because the process of hypomethylation can occur only when cells are actively dividing, treatment must be administered for an extended period of time before results may be achieved and prolonged treatment may be necessary because gene expression typically reverses when treatment ceases.²²

More recent investigations have identified key molecular aberrations that are associated with disease development, prognosis, and in some cases specific targets for therapy. Application of these principles to specific disease types illustrates the evolving science of the hematological malignancies. The most notable molecular fusion gene is *BCR-ABL*, which is found in all patients with CML. The *BCR-ABL* fusion gene represents a reciprocal translocation of the distal material of chromosome 22 (Ph) and chromosome 9 at specific break points (t (9;22)(q34;q11). Fusion of the Abelson (*ABL*) proto-oncogene from chromosome 9 to the breakpoint cluster region (*BCR*) of chromosome 22 results in the *BCR-ABL* fusion gene. This is a tyrosine kinase protein (oncoprotein) thought to trigger intracellular signal transduction pathways resulting in disordered myelopoiesis with accelerated cell growth, decreased apoptosis, and weakening of cellular adhesion.²³ These changes result in the characteristic clinical findings of leukocytosis, thrombocytosis, splenomegaly, and anemia seen in CML. They are also thought to contribute to the development of the more aggressive blast phase of the disease. *BCR-ABL* is present in approximately 30% of adult ALL cases and is associated with a poor prognosis.²⁴ The administration of tyrosine kinase inhibitors (TKI) targeting the *BCR-ABL* fusion gene, such as imatinib, dasatinib, and nilotinib, has provided significant improvement in the treatment of these disorders, in particular CML.

Additional molecular attributes have been identified in the other hematological malignancies. Acute promyelocytic

leukemia (APL) is characterized by the balanced reciprocal translocation between chromosome 15 and 17 (t15;17) that results in the fusion of the promyelocytic gene (*PML*) and the retinoic acid receptor α (*RAR* α) resulting in the *PML-RAR* α oncogene. This fusion gene is associated with transcriptional repression and inhibition of differentiation of promyelocytic blasts. The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) that reverse the transcriptional repression and allow normal differentiation of promyelocytes through chromatin modifying proteins has reduced the morbidity associated with APL due to bleeding diatheses and hyperleukocytosis.¹⁸ APL is now considered the most curable acute leukemia.²⁵

Another important molecular abnormality occurs in the FMS-like tyrosine kinase (TK) 3 or *Flt-3*, which is a member of class 3 TK receptors. Other members of this class are c-Kit, platelet-derived growth factor receptor (PDGFR), and c-Fms. *Flt-3* protein is expressed in early hematopoietic progenitors and has a major role in early stem cell survival and myeloid differentiation. One of the most important mutations in the gene *Flt-3* is the internal tandem duplication (ITD), which results in constitutive activation of the TK activity of *Flt-3*, leading to activation of downstream molecules (STAT5, Ras, Raf, MAP kinases, P13/AKT) that stimulate survival and proliferation signaling pathways.²⁶ *FLT3* ITD are thought to confer a growth advantage to AML and APL cells and have been associated with a higher risk of relapse, but are not felt to be sufficient to cause these diseases themselves.^{17,26–28} There are a number of *FLT3* inhibitors under investigation in combination with standard therapies in an attempt to target this molecular abnormality.

Similar molecular and cytogenetic abnormalities have been identified in the pathogenesis of lymphoid leukemias and provide diagnostic and prognostic information as well as opportunities for targeted therapies.¹² Refined characterization of the mutational status of *immunoglobulin variable gene* (*IgV*) status and genomic attributes in CLL has provided critical prognostic and treatment information. Four distinct prognostic attributes have been identified including mutational status of the heavy chain variable gene (*VH*) 17p deletion, 11q deletion—all unfavorable, and 13q—favorable.^{29,30} The unfavorable attributes are thought to be associated with B-cell receptors and specific antigen-binding pockets that promote clonal expansion of the leukemic cells in response to other cells, cytokines, and chemokines.³⁰

Extrinsic factors that play a role in the pathobiology of the leukemias and MDS include medullary angiogenesis, stromal dysregulation, and the balance of apoptosis and proliferation. The primary mediator of medullary angiogenesis is vascular endothelial growth factor (VEGF) that is over-expressed in the bone marrow of patients with myeloid malignancies and plays an important role in the pathogenesis of these diseases. VEGF overexpression is associated

with myeloblast self-renewal and release of inflammatory cytokines, resulting in increased survival of the malignant clone. The bone marrow stroma is comprised of fibroblasts, fat cells, adhesion molecules, endothelial cells, osteoclasts, and osteoblasts. A primary difference between acute myeloid leukemia and MDS is the balance of apoptosis and proliferation. Apoptosis of stromal cells may be increased in MDS resulting in altered distribution of cell types in the bone marrow, such as atypical localization of immature precursors (ALIP), which is associated with a poor prognosis and early leukemic transformation. Bone marrow stroma derived from patients with MDS has been found to be ineffective in supporting bone marrow progenitor cells of healthy donors.³¹ Large numbers of hematopoietic cells are rapidly proliferating in the bone marrow but are also undergoing apoptosis. Accelerated apoptosis of hematopoietic progenitors leads to ineffective hematopoiesis and eventual bone marrow failure due to premature loss of progenitor cells. Cytokines such as TNF, interleukin-1, and IL-6 have been shown to mediate apoptosis in hematopoietic cells. Excessive apoptosis is an attractive explanation for how clonal expansion of marrow progenitor cells could result in ineffective hematopoiesis, peripheral cytopenias, and marrow failure despite a hypercellular bone marrow. As the disease progresses toward leukemic transformation, the rate of proliferation exceeds apoptosis and the patient will demonstrate increasing peripheral blasts. Several new agents target 1 or more of these areas to induce improvement in hematopoiesis and represent an attempt to affect the underlying disease.

CLASSIFICATION AND STAGING

All of the leukemias represent heterogeneous hematological disorders that originate in the myeloid or lymphoid progenitor cells. Two primary classification systems are used to describe AML, ALL, and MDS. These include the French American British Classification System (FAB) and the World Health Organization (WHO) system. Table 57-2^{32–39} (AML/ALL) and Table 57-3^{40–42} (MDS) provide a review of these classification systems. Both systems assign a specific category of disease based on morphological descriptions of both peripheral blood and bone marrow findings. The FAB classification system was the standard classification system for many decades using morphology, cytochemistry, and immunophenotyping to differentiate myeloid vs lymphoid lineage, blast percentage, and specific point of differentiation for the neoplastic lineage to categorize the specific subtype of leukemia. The FAB classification system classifies the histologic sub-types of AML from M0 through M7. The WHO incorporated more recent molecular and clinical attributes to refine the diagnostic and prognostic relevance of the classification systems.⁴² Several limitations exist in the current classification systems, most notably a limited ability

TABLE 57-2

Selected Criteria From the French American British Classification (FAB) and World Health Organization (WHO) Classification for Acute Leukemia

FAB Subtype WHO Classification	Bone Marrow Morphology and Common Immunophenotype	Additional Clinical Findings
Acute Myeloid Leukemia (AML)		
FAB: AML-M0, undifferentiated AML WHO: AML NOS, without maturation	Blasts are nondescript, difficult to detect without immunophenotyping Auer rods, and positive MPO staining CD13, CD33, CD117	5%–10% of AML Molecular findings: Associated with <i>RUNX1-RUNX1T1</i> Poorer prognosis Presentation with high blast count is common Median age is 46 years
FAB: AML-M1, AML with minimal maturation WHO: AML NOS, with minimal maturation	Sparse cytoplasmic granules, only occasional Auer rods, and positive MPO staining Express early hematopoietic antigens: CD34, CD38, HLA-DR TdT expression in 50% of cases CD7 in 40% of cases	< 5% of AML Inv (3) associated with thrombocytosis Cytogenetic findings: 16%–22% are <i>FLT3</i> ⁺ Molecular findings: <i>RUNX1</i> Poor prognosis in adults Most common in infants or older adults Commonly present with cytopenias and leukocytosis with evidence of bone marrow failure
FAB: AML-M2, AML with maturation WHO: AML, with recurrent cytogenetic abnormalities	More clearly myeloid in origin, increased cytoplasmic granules, MPO positivity, frequent presence of Auer rods Considered AML regardless of blast count CD34, CD13, CD15, HLA-DR	5% of AML 10% of FAB M2 Cytogenetic findings: t(8;21)(core-binding translocation) has a favorable prognosis Molecular findings: Associated with <i>RUNX1-RUNX1T1</i> More favorable response and long-term disease free survival to high-dose cytarabine in the consolidation phase More common in younger patients
FAB: AML-M3, promyelocytic leukemia WHO: AML, with recurrent cytogenetic abnormalities	Intense cytoplasmic granulation that often obscures the nucleus, blasts stain intensely with Sudan black or MPO Considered AML regardless of blast count Low expression or absence of HLA-DR, CD34, CD11a, CD11b, and CD18; high expression of CD33	5%–8% of AML Cytogenetic findings: t(15;17)(q22;q23) Molecular findings: <i>PML/RARα</i> Best prognosis of all AML subtypes Responsive to differentiation therapy: all-transretinoic acid (ATRA) High risk of disseminated intravascular coagulation (DIC) More common in younger adults
AML-M3v (variant)	Abnormal promyelocytes lack granules or Auer rods; weaker cytochemical stains Expression of CD56	Molecular findings: <i>ZBTB16/RARα</i> and variants Poor response to ATRA Correlates to expression of CD56
FAB: AML-M4, myelomonocytic leukemia WHO: AML NOS	Dysplastic features, such as hypogranular cytoplasm and nuclear hyposegmentation, blasts stain with both MPO and nonspecific esterase Myeloid antigens (CD13, CD33, CD56, CD15) and variable expression of monocytic antigens in the blasts (CD14, CD4, CD11, CD64, CD36), HLA-DR	5%–10% of AML Cytogenetic findings: +8 Common Evidence of monocytic and granulocytic differentiation Extramedullary involvement can be seen Median age is 50 years More common in men Favorable prognosis
FAB: AML-M4eo, myelomonocytic leukemia with eosinophilia WHO: AML NOS	Abnormal basophilic eosinophils are seen in the marrow, which is similar to that of M4 Immunophenotype as for M4	5%–8% of AML Cytogenetic findings: Inv(16)/t(16;16) Molecular findings: <i>CBFB/MYH11</i> Intermediate prognosis Extramedullary involvement is often seen Increased risk of central nervous system (CNS) disease/ relapse May present with bleeding disorders

(Continued)

TABLE 57-2

Selected Criteria From the French American British Classification (FAB) and World Health Organization (WHO) Classification for Acute Leukemia (Continued)

FAB Subtype WHO Classification	Bone Marrow Morphology and Common Immunophenotype	Additional Clinical Findings
FAB: AML-M5 A, monocytic leukemia WHO: AML NOS	Blasts with folded nuclei and abundant cytoplasm that stains positively with nonspecific esterase but is MPO negative (CD14, CD4, CD11b, CD11c, CD64, CD36 and lysozyme*) HLA-DR*	Cytogenetic findings: t(11q23) Molecular findings: MLL Poorer prognosis Median age 49 years Extramedullary disease is common Increased risk of CNS disease/relapse
FAB: AML-M5 B, monocytic leukemia with differentiation WHO: AML NOS	As for M5 A except that < 80% of monocytic lineage are blasts As for M5 A, CD34(-)	Cytogenetic findings: t(8;16) Associated with erythrophagocytosis Intermediate prognosis
FAB: AML-M6, erythroid leukemia WHO: AML NOS	Acute erythroid leukemia, may be associated with a variable appearance but usually is accompanied by dysplastic erythroid elements Generally lack myeloid markers Similar to M0 and M1	< 5% of AML Cytogenetic findings: Deletions of 5 and 7 are often seen Poorer prognosis; often preceded by a myelodysplastic syndrome; seen in older patients
FAB: AML-M7, megakaryoblastic leukemia WHO: AML NOS	Requires that more than 30% of blasts be of the megakaryocytic lineage; blasts often display clumping, multinucleation, and cytoplasmic blebbing Immunophenotyping is usually required to make the diagnosis; expression of platelet glycoproteins (CD41, CD16, CD42) and CD36	< 5% of AML Cytogenetic findings: Occasional inv(3) Complex karyotypes common in MDS Poor prognosis Antecedent myeloid disorders are common
Acute Lymphoblastic Leukemia (ALL)		
FAB: ALL-L1 WHO: B lymphoblastic leukemia with recurrent genetic abnormalities	Small cells with minimal cytoplasm and no granules; rare nucleoli B-ALL: CD10, CD19, CD20, CD22, CD34, HLA-DR, TdT cytoplasmic Ig; CD25 associated with t(9;22)	20% of ALL in adults Cytogenetic findings: t(9;22) Molecular findings: BCR-ABL Less favorable than B-ALL without BCR-ABL More common in adults Treatment with imatinib in addition to chemotherapy is recommended
FAB: ALL-L1 WHO: T lymphoblastic leukemia	Small cells with minimal cytoplasm and no granules; rare nucleoli; immunophenotyping is required to differentiate from B-ALL T-ALL: CD2, CD5, CD7, CD8, CD34, may be CD10*	25% of ALL in Adults Variable cytogenetic and molecular findings Most common subtype in children Often present with cytopenias Extramedullary involvement including CNS is common Mediastinal masses are common
FAB: ALL-L2, mature B-cell WHO: B lymphoblastic leukemia	Larger cells with moderate amounts of cytoplasm and prominent nucleoli; TdT positive As for ALL-L1	50% of ALL in adults Cytogenetic findings: 5% t(8;14)/c-myc Molecular findings: IgH in mature B-cell Most common subtype in adults More favorable prognosis
FAB: ALL-L3, B-cell or Burkitt's type leukemia WHO: Variable categories based on cytogenetic and molecular findings	Large round cells with deeply basophilic cytoplasm and vacuoles CD10, CD19, CD20, CD21, CD22, surface Ig	5% of ALL in adults Cytogenetic findings: t(8;14); t(2;8); t(8;22) Poor prognosis with standard ALL treatment regimens

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BCR-ABL, Abelson-breakpoint cluster region; CD, cluster of differentiation; CNS, central nervous system; c-myc, myelocytomatosis viral oncogene; Flt3, FMS-like tyrosine kinase; HLA, human leukocyte antigen; Ig, immunoglobulin; inv, inversion; MLL, mixed lineage leukemia; MPO, myeloperoxidase; NA, not available; NOS, not otherwise specified; PML/RAR α , promyelocytic leukemia protein/retinoic acid receptor α ; RUN, runt-related transcription factor; t, translocations; TdT, terminal deoxynucleotidyl transferase; ZBT B16/RAR α , zinc finger and BTB domain containing protein/retinoic acid receptor α .

Source: Data from Delauney et al³²; Arber et al³³; Vardiman et al³⁴; Scheinberg et al³⁵; Arber et al³⁶; Arber et al³⁷; Borowitz and Chan³⁸; and Borowitz and Chan.³⁹

TABLE 57-3

Selected Diagnostic and Prognostic Criteria for Classification of Myelodysplastic Syndromes (MDS)		
FAB Subtype	WHO Modification	Morphological and Cytogenetic Findings
RA; < 5% blasts	RA	Unilineage dysplasia; <5% blasts; < 15% RS
	RCMD	Dysplasia in $\geq 10\%$ or ≥ 2 myeloid lineages; no Auer rods; $\pm 15\%$ RS
	MDS-U	Dysplasia in < 10% of 1 or more myeloid lineages; < 5% blasts; evidence of cytogenetic abnormalities common in MDS
	MDS with isolated del(5q)-5q syndrome	Normal or increased megakaryocytes; isolated del(5q) abnormality; no Auer rods; < 5% blasts
RARS	RARS	$\geq 15\%$ RS; erythroid dysplasia only; <5% blasts
(RA with $\geq 15\%$ RS)	RCMD-RS	Dysplasia in $\geq 10\%$ or ≥ 2 myeloid lineages; no Auer rods; > 15% RS
RAEB; 5%–20% blasts	RAEB-I (5%–10% blasts)	Unilineage or multilineage dysplasia; 5%–9% blasts; no Auer rods
	RAEB-II (11%–20% blasts)	Unilineage or multilineage dysplasia; 10%–19% blasts; Auer rods may be present
RAEB-t; 21%–30% blasts	AML	Blasts > 20%; characteristics of AML with antecedent hematological malignancy

Abbreviations: AML, acute myeloid leukemia; del, deletion; FAB, French American British; MDS, myelodysplastic syndromes; MDS-U, unclassified MDS; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, RA with excess blasts in transformation; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenias with multilineage dysplasia; RS, ringed sideroblasts; WHO, World Health Organization.

Source: Data from Brunning et al⁴⁰; Harris et al⁴¹; and Vardiman et al.⁴²

to incorporate the rapidly expanding characterization of disease attributes thought to indicate both favorable and unfavorable disease within a morphological subtype or stage of disease. The FAB classification system for ALL is thought to provide limited clinical benefit with the primary determinants of prognosis characterized by immunophenotype and genomics.⁴³ However, historical clinical trials are based on the FAB and WHO criteria and continue to require classification for comparative analysis with any recent clinical trials. Similarly, the use of the FAB classification system alone for AML is felt to be inadequate.⁴⁴ Consideration of specific genetic abnormalities and differentiation of *de novo* AML (DN-AML) and myelodysplasia-related AML (MDR-AML) are suggested as more accurate predictors of prognosis.

Identification of key molecular attributes has led to the development of risk stratification tools and refinement of staging criteria for each disease. For example, the International Prognostic Scoring System (IPSS) (Table 57-4^{45,46}) was developed to include cytogenetic information and specific disease characteristics associated with either favorable or unfavorable prognosis or risk for leukemic transformation in patients with MDS. The IPSS relies on the number of cytopenias, cytogenetic profile, and the percentage of blasts in the bone marrow to group patients with MDS into 1 of 4 prognostic categories as follows: low risk, intermediate 1 risk, intermediate 2 risk, and high risk.⁴⁰ Cytogenetic abnormalities are present in approximately 40% to 50% of *de novo* MDS patients.⁴⁷ The most common abnormalities include deletions of chromosomes 7 (unfavorable), 5, and 20 (favorable), and trisomy

of chromosome 8 (intermediate). Patients with lower risk disease (low-intermediate 1) have more favorable survival projections and are less likely to transform to acute leukemia. Treatment goals for the lower risk patients are aimed at improving hematopoiesis. Patients with higher risk disease (intermediate 2 or high) may transform very rapidly to acute leukemia and prognosis is generally poor. Treatment is aimed at survival. Consideration of diagnostic findings that may favor selection of specific therapies is critical to initiating the therapy with the greatest potential benefit early in the course of disease. More recent analysis of prognostic factors has revealed limitations in this system including the clinical importance of severe (life-threatening) thrombocytopenia or neutropenia, refined cytogenetic risk criteria, anemia, and transfusion requirements.^{42,48,49} However, the IPSS criteria remain widely used in clinical practice to estimate risk and guide treatment selection. It is likely that the criteria will continue to undergo revision as new data emerges in the diagnosis and treatment of MDS.

The chronic leukemias are classified using disease specific descriptions based either on phase of illness (CML) or disease characteristics (CLL). These systems have been modified since their inception to include key molecular attributes found to have prognostic significance. For instance, several key prognostic factors have been identified for CLL including a rapid lymphocyte doubling time, elevated serum β_2 microglobulin, unmutated immunoglobulin heavy chain (*IgVH*), CD38 expression, ZAP-70 expression, and FISH cytogenetics, including 17p-, 11q-, +12, and 13q.^{50,51} As with many of these diseases, the original staging

TABLE 57-4

Risk-Based Stratification of Myelodysplastic Syndromes—International Prognostic Scoring System (IPSS) and Proposed Modifications

Score	0	0.5	1.0	1.5	2.0	Risk Category	Numeric Score
Bone marrow myeloblasts	< 5%	5%–10%		11%–20%	21%–30% (considered AML)	Low Intermediate-1 Intermediate-2 High	0 0.5–1.0 1.5–2.0 ≥ 2.5
Karyotype	Normal, or del(5q), del(Y), del(20q) as sole abnormalities	Other abnormalities	del(7), 7+ or 3+ abnormalities	Proposed revision: Favorable: del(12p), del(9q), t(15q), del(15q), 21+, X-, t(7q), 21- Intermediate-1: del(11q), (8+) Intermediate-2: t(11q23), any del3q abnormality, 19+, del(7q), exactly 3 abnormalities Unfavorable: > 3 abnormalities and t(5q)			
Number of cytopenias	0.1	2.3	Anemia (hemoglobin <10 g/dL), neutropenia (absolute neutrophil count [ANC] <1800/μL), and/or thrombocytopenia (platelets <100,000/μL)				Proposed revision: Adverse risk: Thrombocytopenia at presentation High transfusion burden

Abbreviations: AML, acute myelogenous leukemia; del, deletion; t, translocation

Source: Data from Larson and Anastasi⁴³; Head and Thompson⁴⁴; Malcovati et al⁴⁶; and Kao et al.⁴⁹

systems were developed prior to the availability of molecular testing and the appreciation of the prognostic value of many of these attributes. For CLL the 2 primary staging systems are the RAI (US) and Binet (Europe). These have similar criteria with the difference in the stages represented as numeric or alphabetical. (Table 57-5^{29,52–54}). Similarly, the staging criteria used for CML have evolved over time. The staging for CML reflects phases of illness (chronic phase, accelerated phase and blast phase) rather than an absolute morphological or molecular criteria (Table 57-6^{55,56}). The universal diagnostic criteria is the presence of the *BCR-ABL* fusion gene (t(9;22)).^{55,56}

CLINICAL MANIFESTATIONS

The clinical presentation differs for each disease based on the cell lineage involved, the disease trajectory (acute vs chronic), and the general characteristics of the individual patient. Many of the patients with these diseases are older and commonly present with vague symptoms of fever, fatigue, malaise, night sweats, leukocytosis, lymphocytosis, or unusual bruising associated with underlying cytopenias. Adenopathy, organomegaly, or skin nodules may also be

present and are more common in the lymphoid disorders and selected subtypes of AML. Central nervous system symptoms of headache, visual disturbances, ataxia, nausea or vomiting are most common in ALL resulting from meningeal infiltration and increased intracranial pressure.¹² Symptoms may progress slowly over weeks or months for patients with CLL, CML, or MDS. In contrast, clinical presentation may be abrupt and dramatic for patients with ALL or AML.

ASSESSMENT

A complete family and personal history, medication review, and physical exam are essential to the diagnostic process. Attention to historical episodes of illness is useful in estimating the onset of illness in CLL, CML, and MDS. Careful attention to specific physical findings indicating tissue infiltration, organomegaly, adenopathy, or CNS disease is necessary to identify patients who may be at a higher risk of treatment-related toxicities. Laboratory evaluation should include analysis of the peripheral smear by a hematopathologist, a complete blood count, differential and platelet count, hepatic and renal profiles, hemolysis parameters,

TABLE 57-5

Selected Diagnostic and Prognostic Criteria for Classification of Chronic Lymphocytic Leukemia (CLL)

Diagnostic Criteria	RAI Staging					Binet Staging			Clinical Significance
Stage	0	I	II	III	IV	A	B	C	All Stages in either RAI or Binet Systems
Lymphocytosis (> 15,000/ μ L)	+	+	+	+	+	+	+	+	Key diagnostic factor to differentiate from other mature B-cell neoplasms
Duration of lymphocytosis > 2 years									Validation of chronic disease
Bone marrow lymphocytes >30%									Differentiation from other indolent B-cell neoplasms
Lymphadenopathy (> 1 cm)	-	+	+/-	+/-	+/-				More extensive lymphadenopathy
Lymphadenopathy (> 3 sites), including hepatosplenomegaly						-	+	+/-	Extramedullary sites of disease (liver, spleen) are common, and in the absence of cytopenias or other high-risk features are considered intermediate risk
Hepatosplenomegaly	-	-	+	+/-	+/-	-	+	+/-	
Anemia (hemoglobin < 11 g/dL)	-	-	-	+	+/-				Cytopenias reflect bone marrow infiltration or failure and are indicative of high risk disease
Anemia (hemoglobin < 10 g/dL)						-	-	+	
Thrombocytopenia (< 100,000/ μ L)					+	-	-	+	
High Risk Features for CLL									
CD38 expression in > 30% of lymphocytes									Presence of large-cell transformation
High risk cytogenetics: 14q, 11q, 17p, 12+									Elevated β 2 microglobulin
Unmutated (germline) <i>IgVH</i> gene									Doubling time of lymphocyte count <12 months
ZAP-70 expression in > 30% of lymphocytes									RAI stage 3 or 4, Binet stage C
Elevated serum thymidine kinase									

Abbreviation: CD, cluster of differentiation; IgVH, immunoglobulin heavy chain variable; ZAP-70, zeta-chain (TCR) associated protein kinase.

Source: Data from Seiler et al²⁹; Smith and Boldt⁵²; Rai et al⁵³; and Binet et al.⁵⁴

tumor lysis screen, and coagulation studies in the instance of APL. Additional laboratory parameters may be ordered for specific disease entities as a baseline analysis for potential treatment-related toxicities (Table 57-7^{57,58}). Imaging studies are of particular importance in the lymphoid disorders

and CML, as adenopathy and organomegaly are more common due to extramedullary clonal expansion. Baseline studies for underlying infections or organ function are also important to exclude concurrent illnesses or antecedent organ dysfunction.

TABLE 57-6

Chronic Myelogenous Leukemia: Phases of Disease

Phase	Characteristics
Chronic phase	Indolent course, often asymptomatic, and found incidentally on routine physical exam Predominance of mature white blood cells Approximately 90% of patients are diagnosed at this stage Median survival is 4–6 years (pre-tyrosine kinase inhibitor [TKI] therapy)
Accelerated phase	Transition generally occurs over a period of 1 year or more; duration is 4–6 months Associated with progressive leukocytosis, thrombocytosis or thrombocytopenia, basophilia, splenomegaly, fever, bone pain, and thrombotic or bleeding complications Clonal evolution is present
Blast phase	Lasts only a few months—survival is poor if untreated Associated with increasing blasts ($> 30\%$), progressive splenomegaly despite treatment, and clonal evolution

Source: Data from Calabretta and Perotti⁵⁵; and Cortes et al.⁵⁶

TABLE 57-7

Diagnostic Evaluation of Patients With Acute Leukemias, Chronic Leukemias, and Myelodysplastic Syndrome

Peripheral Blood Evaluation	Clinical Significance
CBC, differential, and platelet count, reticulocyte count with evaluation of the peripheral smear	Evaluate for the presence of leukocytosis, basophilia, thrombocytosis, monocytosis, peripheral blasts, and morphological abnormalities Establish baseline for monitoring of treatment-induced cytopenias
LDH, uric acid, PO ₄ , Ca ⁺⁺ , K ⁺	Evaluation of high cell turnover or tumor burden and increased risk for tumor lysis syndrome
Baseline hepatic, renal, and electrolyte profiles	Mild and transient transaminitis and hyperbilirubinemia are common with treatment Renal toxicities are more common in the elderly Many active therapies have potential renal and hepatic toxicities or may be affected by renal or hepatic insufficiencies
Human leukocyte antigen typing	For possible bone marrow or stem cell transplant
Serum iron, ferritin, TIBC, folic acid, vitamin B12	Evaluate for other possible causes of anemia
LDH, haptoglobin, reticulocyte count, coombs	Evaluate for possible underlying hemolysis
Vitamin B ₁₂ erythropoietin	Baseline evaluation of levels to determine role for growth factors vs active therapies in patient needing treatment for MDS
Other laboratory studies	Clinical Significance
Thyroid profile	Immunomodulatory agents may be associated with hypothyroidism Hypothyroidism may contribute to anemia
Serum testosterone	Hypogonadism is common in elderly men and may contribute to fatigue
Coagulation profile: Fibrinogen, PT, PTT, D-dimer	Presence of DIC: particularly important in APL with induction therapy
Lumbar puncture	Evaluate presence of CNS involvement (most common in ALL)
History, Physical, Radiology Examination	Clinical Significance
History of present illness	Document onset of suspicious symptoms, acute episodes of illness and prior transfusion history
Co-morbid conditions	Co-morbid conditions and effective management may play a critical role in determining potential therapies, including diabetes, hypertension, coronary artery disease, cardiomyopathy, congestive heart failure or pleural effusions, chronic renal disease, hepatitis or hepatic disease
Concomitant medications—including drug allergies	Review of medication profile to identify any potential medication-induced cytopenias, drug–drug interactions, QTc prolongation, or organ toxicity There are numerous potential drug interactions with tyrosine kinase inhibitors used in the treatment of CML
Physical exam	Organomegaly: splenomegaly or hepatomegaly Lymphadenopathy Cutaneous manifestations and baseline skin evaluation—more common with M4 histological subtype of AML Baseline cardiac and pulmonary evaluation
Radiology	Baseline CXR Abdominal ultrasound if further evaluation of splenomegaly is indicated Baseline MUGA scan or echocardiogram for patients with cardiovascular risk factors or for those patients receiving anthracycline therapy CT scan of the chest, abdomen and pelvis for patients with CLL, CML or with adenopathy or organomegaly

(Continued)

TABLE 57-7

Diagnostic Evaluation of Patients With Acute Leukemias, Chronic Leukemias, and Myelodysplastic Syndrome (Continued)

Bone Marrow or Tissue Biopsy	Clinical Significance
Aspirate Should include spicules and be cellular enough to assess at least 500 cells.	Evaluation of morphological abnormalities of hematopoietic precursors to allow FAB/WHO classification (dysplasia, blast percentage, monocytes, ringed sideroblasts, atypical megakaryocytes) Used for flow cytometry, FISH analysis, and cytogenetics
Biopsy Should be of adequate size for evaluation: 1–2 cm	Evaluate cellularity, topography, presence of atypical localization of immature precursors (ALIP; considered a poor prognostic finding), exclusion of other bone marrow disorders or bone marrow infiltration by solid tumors
Cytogenetics	Evaluate for possible nonrandom chromosomal abnormalities Usually based on evaluation of 20 metaphases; greater than 2 metaphases are considered nonrandom See individual disease overviews for prognostic significance
Tissue biopsy	Lymph nodes, cutaneous lesions, pleural effusions, or other focal areas of disease should be sent for cytology, immunophenotyping, and flow cytometry to describe the extent of disease and rule out infectious etiology

Abbreviations: ALIP, atypical localization of immature precursors; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; Ca⁺⁺, calcium; CBC, complete blood count; CNS, central nervous system; COC, complete blood count; CML, chronic myeloid leukemia; CT, computed tomography; CXR, chest x-ray; DIC, disseminated intravascular coagulation; FAB, French American British; FISH, fluorescent in situ hybridization; K⁺, potassium; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MUGA, multigated acquisition scan; PO₄, phosphate; PT, prothrombin time; PTT, partial thromboplastin time; TIBC, total iron-binding capacity; WHO, World Health Organization.

Source: Data from Kurtin⁵⁷; and Kurtin.⁵⁸

The diagnostic process differs for each disease, with a focus on the characteristics of the malignant clone, associated symptoms, and any secondary organ affects. A tissue diagnosis is essential to a precise diagnosis and generally includes peripheral blood, bone marrow aspirate and biopsy, and tissue diagnosis in the presence of lymphadenopathy, organomegaly, or other extramedullary sites of disease. Sampling of the cerebrospinal fluid (CSF) is routine in ALL due to the increased potential for meningeal disease. A variety of diagnostic processes are used to determine the specific subtype of the disease including morphology, cytochemistry, immunophenotyping, cytogenetics analysis, and selected molecular testing using either fluorescent in situ hybridization (FISH) or polymer chain reaction (PCR) technologies. An adequate tissue sample is critical at the time of initial diagnosis as treatment is often initiated immediately and exposure to cytotoxic or targeted therapies may obscure key elements of the pathological diagnosis in subsequent samples. The presence of dysplasia, a hallmark of MDS, is often subtle and requires adequate bone marrow sampling to accurately characterize the disease. A recent analysis of 1317 patients with a diagnosis of AML suggests a delay in induction therapy is associated with inferior complete response and overall survival in patients less than 60 years ($P < 0.001$) but did not seem to correlate with these variables in patients greater than 60 years. This may be critical in allowing additional time to completely analyze the risk profile for the older

patients with AML who have a poorer response to standard induction and a higher incidence of AHD.⁵⁹

THERAPEUTIC APPROACHES AND NURSING MANAGEMENT

The primary treatment modality for these hematological diseases requires a systemic treatment approach using chemotherapy, immunotherapy, and more recently targeted therapies. The role of surgery or radiotherapy is limited. Treatment strategies are based on the need to suppress the malignant clone. The goals of therapy include normalization of hematopoiesis with resolution of cytopenias or leukocytosis/lymphocytosis, effective treatment of potential sanctuary sites or extramedullary disease, elimination of minimal residual disease, and suppression of emerging resistant clones. Minimizing treatment related toxicities while maintaining or improving quality of life is critical to effective treatment. Thus, instituting the most effective therapy based on diagnostic and prognostic profiles will provide the best opportunity for a favorable clinical outcome.

The basic principles of induction therapy (initial aggressive treatment to reduce bulky disease and suppress the malignant clone) followed by consolidation (similar agents often given with decreased intensity) and in some cases long-term maintenance therapy are applied for the

treatment of AML and ALL. More recently, selected targeted therapies have been added for improved response. The specific agents used, drug sequencing, and duration of therapy are different for AML and ALL. Treatment of CML, CLL, and MDS is dependent on the presenting symptoms and specific molecular and cytogenetic attributes. Active therapies may not be initiated at the time of diagnosis for patients with MDS or CLL in the absence of clinical indications for treatment. Active therapy is started immediately in the case of ALL, AML, and CML. Stem cell transplantation remains the only curative therapy for most of these diseases due to the limited effect of standard therapies on the leukemic stem cell. In many cases, an allogeneic transplant is necessary to effect a cure.⁵⁸ The most common treatment toxicities are attributed to the specific agent(s), the underlying disease, and characteristics of the individual patient.

SPECIAL CONSIDERATIONS FOR THE ELDERLY POPULATION

Managing the hematological diseases is complicated by the generally advanced age of the patients (median age ranges from 65 to 70), presence of nonhematological comorbid conditions, and the potential inability of the older patient to tolerate certain intensive forms of therapy. Elderly patients commonly have multiple medical problems, use medications to manage them, and are more likely to have more than 1 healthcare provider involved in their care thereby increasing the risk for drug interactions and treatment toxicities. Manifestations of common toxicities or illnesses may be more subtle in the elderly due to age associated functional deficits in multiple organ systems.⁶⁰ Particularly important to the elderly patient with hematological malignancies is the age related decline in normal bone marrow function, including diminished capacity for response to stressors such as infection or myelosuppressive treatments.^{61,62}

Acute myeloid leukemia in the elderly patient is more often associated with unfavorable disease related factors such as AHD, unfavorable cytogenetics, and the common occurrence of the multidrug resistance gene (*MDR*). Elderly patients with AML, generally defined as age > 60 years in the literature, have been found to have inferior rates of complete response and overall survival when compared to patients younger than age 60.⁶³ Due to the poor outcomes in older patients with AML receiving standard therapies, clinical trials specifically designed to evaluate AML in the elderly have become more common. Several targeted agents have been evaluated in the treatment of the older adult including Anti-CD33 antibodies, *MDR* inhibitors, farnesyltransferase inhibitors (FTI), novel nucleoside analogues, and FLT-3 inhibitors.^{63–67} Chronological age alone, however, should never exclude treatment.

Integrating geriatric and oncology nursing strategies allow an individualized approach to this unique population. As with many diseases in the elderly, reliance on family members or friends to maintain the prescribed treatments, including travel to appointments, may place additional stressors on the patient and their support network. Careful evaluation of functional status, ability to tolerate treatments, effect of disease progression, and general overall health can provide the best opportunity for nursing support of these patients. Assessment of activities of daily living may detect deficiencies or deficits that require early intervention before they become problematic.

TREATMENT STRATEGIES FOR ACUTE MYELOGENOUS LEUKEMIA

General considerations

The clinical presentation of AML, including APL, is generally abrupt and initiation of therapy needs to be immediate. Complete blood count, bone marrow, and radiological testing are essential prior to initiating therapy. Cytogenetic or molecular test results are generally unavailable prior to the administration of induction therapy. Therefore, initial therapy for AML is based on the age of the patient, presenting symptoms, performance status, total white blood cell count, blast count and comorbidities. AML in the older patient has been previously reviewed. The presence of leukocytosis (WBC > 30 × 10⁹ cells) is associated with increased treatment-related death (~50% of cases), often as a result of tumor lysis and aggressive disease.⁶³ Poor performance status, the presence of infection at the time of presentation, and complex or poorly controlled comorbidities are also considered unfavorable findings. Treatment related mortality is associated with increasing age, abnormal organ function, and a poor performance status.¹² Treatment failure is associated with specific karyotypes, AHD, FLT-3 ITD, *MDR1*, other molecular attributes that are less common, and treatment-induced AML. Table 57-8 provides an overview of AML and APL and their treatment.^{25,28,63,68,69}

Induction therapy

The standard regimen for induction-remission therapy in AML continues to be a regimen known as “7+3”, using 7 days of continuous infusion cytarabine with 3 consecutive days of idarubicin or daunorubicin. Alternative anthracyclines and modified doses and schedules of cytarabine may be used in selected patients. Randomized clinical trials to date show no clear superiority with any 1 anthracycline or alternative use of mitoxantrone when used at equivalent doses.¹² Standard induction therapy is indicated for patients with favorable risk profiles and younger patients with intermediate risk disease. Patients with higher risk disease, such

TABLE 57-8

Disease Overview: Acute Myelocytic Leukemia (AML)/Acute Promyelocytic Leukemia (APL)

Feature	Key Findings																				
Epidemiology	New Cases in 2008: 12,810 Average Age at Diagnosis: 67 years																				
Etiology	Genetic instability Chemical exposure Mutagens Tobacco																				
Stem Cell Defect	Myeloid progenitor cell																				
Prognostic factors: genetics	<table><tr><th>Favorable</th><th>Intermediate</th><th>Poor risk</th></tr><tr><td>Translocation (t)(15;17) (APL), t(8;21), and inversion(16)</td><td>+8, +6, +21, -Y, 12p-,</td><td>Complex (> 3 abnormalities)</td></tr><tr><td>Nucleophosmin NPM1 mutation, FMS-related tyrosine kinase 3 (FLT3)</td><td>NPM mutation (Flt3+), C/EBPα mutation</td><td>Abnormalities of chromosome 5 or 7 17p abnormality, t(6;9), t(3;21) 11q23 deletion (del) (common in MDR-AML)</td></tr></table>	Favorable	Intermediate	Poor risk	Translocation (t)(15;17) (APL), t(8;21), and inversion(16)	+8, +6, +21, -Y, 12p-,	Complex (> 3 abnormalities)	Nucleophosmin NPM1 mutation, FMS-related tyrosine kinase 3 (FLT3)	NPM mutation (Flt3+), C/EBPα mutation	Abnormalities of chromosome 5 or 7 17p abnormality, t(6;9), t(3;21) 11q23 deletion (del) (common in MDR-AML)											
Favorable	Intermediate	Poor risk																			
Translocation (t)(15;17) (APL), t(8;21), and inversion(16)	+8, +6, +21, -Y, 12p-,	Complex (> 3 abnormalities)																			
Nucleophosmin NPM1 mutation, FMS-related tyrosine kinase 3 (FLT3)	NPM mutation (Flt3+), C/EBPα mutation	Abnormalities of chromosome 5 or 7 17p abnormality, t(6;9), t(3;21) 11q23 deletion (del) (common in MDR-AML)																			
Additional prognostic factors	Age: Older age is associated with a reduced incidence of complete response Antecedent hematological disorder or secondary AML—These subgroups have a lower incidence of complete response and a reduced overall survival																				
Staging	FAB/WHO (morphology)																				
Clinical Presentation	Leukocytosis, leukemia cutis (leukemic skin infiltrates), cytopenias, infection, bleeding, bleeding diathesis (APL)																				
Indication to Treat	Confirmed diagnosis, presentation with leukocytosis, bleeding diathesis, tumor lysis																				
Key Concepts for Effective Treatment	Induction therapy is aimed at suppression of the malignant clone with induced hypoplasia and resolution of extramedullary sites of disease Consolidation and maintenance therapy are aimed at achieving a durable molecular remission with eradication of minimal residual disease. Allogeneic bone marrow transplantation is the only potentially curative therapy for AML Differentiation agents (eg, all-transretinoic acid) together with anthracyclines can induce cure in up to 95% of APL cases Aggressive management of cytopenias, leukocyte differentiation syndrome and bleeding diathesis is necessary to avoid treatment-related death during induction therapy for APL																				
FDA Approved Therapies	<table><tr><th>AML:</th><th>APL: Induction:</th></tr><tr><td>Induction and Consolidation:</td><td>Daunorubicin or Idarubicin</td></tr><tr><td>Anthracyclines: Idarubicin, Daunorubicin</td><td>All-transretinoic Acid (ATRA)</td></tr><tr><td>Mitoxantrone</td><td>Maintenance:</td></tr><tr><td>Cytarabine</td><td>6-Mercaptopurine</td></tr><tr><td>Relapse:</td><td>Methotrexate</td></tr><tr><td>Gemtuzumab Ozogamicin</td><td>ATRA</td></tr><tr><td></td><td>Relapse:</td></tr><tr><td></td><td>Arsenic Trioxide</td></tr><tr><td></td><td>Gemtuzumab Ozogamicin</td></tr></table>	AML:	APL: Induction:	Induction and Consolidation:	Daunorubicin or Idarubicin	Anthracyclines: Idarubicin, Daunorubicin	All-transretinoic Acid (ATRA)	Mitoxantrone	Maintenance:	Cytarabine	6-Mercaptopurine	Relapse:	Methotrexate	Gemtuzumab Ozogamicin	ATRA		Relapse:		Arsenic Trioxide		Gemtuzumab Ozogamicin
AML:	APL: Induction:																				
Induction and Consolidation:	Daunorubicin or Idarubicin																				
Anthracyclines: Idarubicin, Daunorubicin	All-transretinoic Acid (ATRA)																				
Mitoxantrone	Maintenance:																				
Cytarabine	6-Mercaptopurine																				
Relapse:	Methotrexate																				
Gemtuzumab Ozogamicin	ATRA																				
	Relapse:																				
	Arsenic Trioxide																				
	Gemtuzumab Ozogamicin																				
In Clinical Trials or Used Based on Other Approved Indications	Gemtuzumab Ozogamicin (Anti CD33 Monoclonal Antibodies) PSC833, Zosuquidar (MDR inhibitors) Tipifarnib (FTI) PKC412, CEP701, Sunitinib (FLT3-inhibitors) Clofarabine, Troxacitabine (nucleoside analogs) Valproic Acid, SAHA, MS-275 (HDAC inhibitors) Bcl-2 antisense (anti-apoptotic) Azacitidine, Decitabine (Hypomethylating agents) Cloretazine (Alkylating agent)																				
Key Supportive Care Concerns	Myelosuppression: infection, differentiation syndrome, mucositis, disseminated intravascular coagulation, neurotoxicity, cardiomyopathy																				

Abbreviations: DIC, disseminated intravascular coagulation; HDAC, histone deacetylases; MRD, minimal residual disease; WHO, World Health Organization.

Source: Data from Lo-Coco et al²⁵; Burnett and Knapper²⁶; Estey⁴³; NCCN⁴⁸; and Tallman.⁴⁹

as those over the age of 60, should have modified dosing of cytarabine based on the increased risk of cerebellar toxicity and treatment related toxicity. Improved cure rates have been noted in younger patients and those with favorable cytogenetics $t(8;12)$ and inversion 16 when using high dose cytarabine.⁷⁰ The goal of induction therapy is to clear the bone marrow of leukemic cells and to induce hypoplasia. A repeat bone marrow biopsy is performed 2 weeks after the initial induction to assess treatment response. The absence of disease ($<5\%$ blasts in an aspirate with spicules, no blasts with Auer rods, no persistent extramedullary disease) is considered a favorable finding. As the peripheral blood counts recover, the bone marrow biopsy is repeated. If there continues to be no evidence of disease, the patient is considered to be in a complete remission (CR). Obtaining a CR with the initial induction regimen is the sole outcome measure associated with improved survival in phase III clinical trials.⁷¹ Patients who do not achieve a CR with first induction will be rechallenged with a second cycle of induction therapy often using alternative agents or doses.

The most common treatment-related toxicities during induction therapy include cytopenias requiring transfusion support, treatment of infections, renal, hepatic, and cardiac toxicities related to the specific agents used or preexisting conditions, and gastrointestinal toxicities (nausea, vomiting, diarrhea, mucositis). Drug specific toxicities such as neurotoxicity and acral erythema associated with nucleoside analogs are seen less frequently. Patients are at particular risk for infection as a result of immune compromise due to the disease itself and the presence of neutropenia and concurrent mucositis. Atallah et al.⁷² reviewed records for 1534 patients with AML and found that Grade 3 or 4 neutropenia occurred in 91% of the patients, and febrile episodes were common (94%). Documented infections were noted in 64% of patients, 28% of the patients required admission to the intensive care unit, and respiratory support or dialysis were necessary in 16% of patients demonstrating the potential serious adverse events attributed to induction therapy for AML and the importance of supportive care strategies during this phase of treatment.

Postremission therapy (consolidation therapy)

The second phase of treatment for AML is consolidation therapy with the goal of maintaining a CR by suppressing any microscopic disease. Treatment consists of a modified induction regimen in most cases. The role of stem cell transplant (SCT) in first CR remains controversial. There are variable outcomes related to SCT based on the age of the patient and the underlying characteristics of the disease.⁷³ Careful selection criteria with treatment on a clinical trial is recommended to facilitate refinement of the guidelines for transplantation in the older adult with AML. The advantage of an allogeneic transplant is thought to be related to the graft vs leukemia effect. This is thought to be a result

of immune modulation and suppression of the malignant clone by immunocompetent donor T-cells. A recent meta-analysis of 3100 subjects with AML demonstrated a survival advantage for allogeneic transplantation for patients with high-risk AML (hazard ratio [HR] 1.39) but did not show a survival advantage in patients with favorable risk cytogenetics (HR 0.9).⁷⁴ Patients with secondary AML (treatment-induced or AHD) tend to have resistant disease and should be evaluated for an allogeneic SCT at the time of diagnosis. Patients who fail induction therapy should also be evaluated for an allogeneic SCT. Difficulties in locating a suitable donor prior to disease progression or treatment-related morbidity or mortality make this a particularly high-risk group of patients. Studies have also identified that infusion of donor lymphocytes after the transplant conditioning regimen and an allogeneic hematopoietic stem cell transplant (HSCT), can successfully treat leukemia relapse.⁷⁵

The recent development of molecular testing for minimal residual disease (MRD) has elucidated the molecular pathogenesis of the disease, specifically the presence of a leukemic stem cell.⁷⁶ Minimal residual disease is defined by levels of expression for selected molecular attributes of disease that are not detectable by routine morphological or immunohistochemical techniques.^{66,77} This is thought to contribute to the common occurrence of relapse despite significant tumor reduction with standard chemotherapy. Relapsed AML is frequently resistant to standard chemotherapy. More recent clinical trials have included agents that target some of the unfavorable cytogenetic and molecular attributes including antibody-based therapy targeting CD33, FLT-3 inhibitors, FTI, c-Kit inhibitors, demethylating agents, and histone deacetylase inhibitors, MDR1 antagonists, and BCL-2 antagonists.⁷⁸ Clinical trials participation is critical to fully understanding the role of these newer agents in the suppression of leukemogenesis and improving remission rates in patients who are not candidates for an allogeneic transplant and have poor-risk AML.

TREATMENT STRATEGIES FOR ACUTE PROMYELOCYTIC LEUKEMIA

Induction therapy

Acute promyelocytic leukemia (see Table 57-8) is a distinct histological subtype (M3) of AML and is now thought to be a curable disease in the majority of patients who receive molecularly directed therapy. APL is a subtype of AML defined by the presence of $t(15;17)$ and expression of the PML and retinoic acid receptor α (RAR) resulting in the fusion gene *PML-RAR α* present in more than 95% of cases, which is detectable by FISH or polymerase chain reaction (PCR).¹² APL represents 10% to 15% of all cases of AML and patients tend to be younger than those with other types of AML. APL typically has a rapid onset with

a high risk of treatment-related death during induction therapy due to bleeding diatheses and leukocyte differentiation syndrome (described below). Therefore, identification of this specific subtype of AML is critical at presentation as the treatment is specific to APL and standard therapy for AML is not beneficial. Signs and symptoms that are common in the presentation of APL specifically include mucocutaneous infiltrates with or without hemorrhage, increased coagulation time and elevated fibrinogen levels. Standard therapy for APL consists of a combination of an anthracycline (daunorubicin or idarubicin) and all-transretinoic acid (ATRA) an oral differentiating agent. In patients with APL, ATRA therapy accelerates the terminal differentiation of malignant promyelocytes to mature neutrophils, leading to apoptosis and CR without myelosuppression and bone marrow hypoplasia.⁷⁹

Postremission therapy

Following induction therapy, 2 additional cycles of anthracycline based therapy are administered with continuation of ATRA. This approach to treatment in patients with molecularly confirmed APL has resulted in molecular remissions and CR rates of 90% to 95%. The role of arsenic trioxide (ATO) in the initial treatment of APL has gained attention due to the selective partial differentiation of APL blast cells.²⁵ ATO is currently indicated for relapsed or refractory disease. Additional agents, including FLT-3 inhibitors, are in clinical trials. The role of stem cell transplant is limited in APL due to the high rate of complete molecular remissions with current frontline therapy. Following induction and consolidation, maintenance therapy with ATRA for up to 1 year using intermittent dosing is recommended.

The initiation of treatment for APL requires specific monitoring and institution of preventative supportive care measures. Patients who present with elevated WBC counts ($>10 \times 10^9/L$) are at increased risk for coagulopathies and leukocyte differentiation syndrome.¹² The mechanism for the bleeding diathesis is poorly understood but is known to be associated with fibrinolysis.⁸⁰ The bleeding diathesis is most common in the first week of treatment. Initiating treatment with a differentiation agent (ATRA) together with treatment of the coagulopathy with fibrinogen, fresh frozen plasma, and platelet transfusions to keep the fibrinogen level >150 mg/dL and platelets above 30,000 to 50,000/mm³ have reduced treatment related deaths significantly. The leukocyte differentiation syndrome is associated with administration of ATRA. Fever, a rapid increase in WBCs, pulmonary infiltrates and secondary symptoms of shortness of breath and hypoxia are most common and may occur at variable times during the induction therapy. This syndrome is associated with rapid deterioration in pulmonary function, pleural and pericardial effusions. The immediate institution of dexamethasone at the onset of symptoms can effectively reverse these symptoms.

Arsenic trioxide also requires specific monitoring due to the potential for electrolyte abnormalities and QT

prolongation. Baseline and weekly evaluation of serum electrolytes (calcium, potassium, and magnesium) with replacement as needed to maintain concentrations of potassium above 4.0 mEq/L and magnesium above 1.8mg/dL together with interval electrocardiograms to evaluate QTc intervals (<500 milliseconds) will effectively reduce the potential for serious cardiac events such as torsades de pointe.

TREATMENT STRATEGIES FOR ACUTE LYMPHOCYTIC LEUKEMIA

General considerations

The treatment of ALL is very different than the treatment for AML in a number of ways. (Table 57-9^{45,81-87}) The goals of therapy include restoring normal hematopoiesis, preventing the emergence of resistant clones, effectively treating sanctuary sites including the CNS, and eliminating MRD. To achieve these goals, treatment includes induction, consolidation, CNS prophylaxis, and long-term maintenance therapy using a variety of drugs in complex sequencing. Specific drug combinations given at defined intervals over an extended treatment course (up to 3 years) provides the most favorable outcome in ALL. Short-term dose intensification, common in AML, is not felt to be beneficial in ALL with the exception of mature B-cell ALL. The absence of MRD ($<0.01\%$) during or following completion of initial induction therapy is associated with high levels of CR (up to 85% in adults).⁸¹ Advanced age, high leukocyte count at presentation, delayed time to achieve a CR ($>4-5$ weeks), specific immunophenotype and cytogenetic abnormalities are associated with decreased CR rates, shorter remission duration, decreased overall survival (OS), and increased CNS relapse. Age in particular is felt to be critical in adult ALL patients; patients of age less than 30 years have an OS of 34% to 57% and age greater than 30 years have an OS of 15% to 17%.⁸⁸ Approximately 20% to 30% of adult ALL patients (as many as 50% of elderly patients) have Philadelphia chromosome positive (Ph⁺) disease that is associated with unfavorable outcome.⁸⁹ The addition of tyrosine kinase inhibitors targeting the Ph chromosome given concurrently with standard chemotherapy offers improved response rates. These patients are primary candidates for allogeneic transplantation.

Induction therapy

The most common agents used in the induction phase of treatment for ALL include a corticosteroid (prednisone, dexamethasone), vincristine, and an anthracycline (most often daunorubicin). There are a number of regimens that include a variety of other agents with variable dosing and sequencing including asparaginase, cyclophosphamide, teniposide, and cytarabine. The induction phase of treatment is most often administered in an inpatient setting as the patient is

TABLE 57-9

Disease Overview: Acute Lymphocytic Leukemia (ALL)		
Feature	Key Findings	
Epidemiology	Incidence (per year): 5,430 Median Age at Diagnosis: 13 years	
Etiology	Genetic	Autoimmune disease
Stem Cell Defect	Clonal B cells (most common) or T cells (rare) arrested in the various phases of differentiation	
Chromosomal Findings	Intermediate risk	High risk
	Normal karyotype abn 11q, del(6q), del(17p), del(12p), -13/del(13), t(14q32), t(10;14) Others markers are under investigation	-7(Ph neg), del(7p), +8, t(1;19), t(17;19) t(9;22)—Ph+ t(4;11) with the <i>MLL-AF4</i> gene Complex abnormalities (≥ 5) Other molecular markers are under investigation
Additional Prognostic Factors Indicating High-Risk Disease	BCR-ABL positive disease Undifferentiated leukemia Null ALL CD10 ⁺ (CALLA); mature B-cell ALL WBC $> 30 \times 10^9/L$ at diagnosis Greater than 4–5 wks to achieve a CR ($\geq 0.1\%$ residual disease by PCR) Age > 35 years	
Staging	Based primarily on immunophenotype and WBC at presentation	
Response Criteria	CR = $< 0.1\%$ residual disease by PCR	
Disease Characteristics	B cell ALL	T cell ALL
	Mature B cell less favorable; treated with intense induction followed by Allogeneic SCT	More favorable in adults with initial diagnosis; relapse, however, is difficult to treat More commonly involves extra-medullary sites
Clinical Presentation	Leukocytosis	Infections
	Splenomegaly	Tumor lysis
	Hepatomegaly	CNS Symptoms: Headache, ataxia
Indication to Treat	Confirmation of diagnosis, leukocytosis, tumor lysis, CNS symptoms	
Key Concepts for Effective Treatment	Chemotherapy has been effective alone and in combination with other agents	
	New targeted therapies have increased response rates Chromosomal abnormalities have prognostic value Aggressive concurrent management of infection risk is essential to effective therapy CNS prophylaxis is critical to long-term response	
FDA Approved Therapies	Induction: Most common: Daunorubicin, Vincristine, Prednisone, Asparaginase Ph+ add Imatinib CNS treatment if positive at presentation	
	Consolidation: Cytarabine Etoposide Asparaginase Daunorubicin/Vincristine/Prednisone CNS-Prophylaxis	Maintenance: 6-Mercaptopurine Methotrexate Vincristine Prednisone Imatinib or Dasatinib if Ph+
In Clinical Trials or Used Based on Other Approved Indications	Nelarabine	Rituximab
	Clofarabine	Gemtuzumab Ozogamicin
	Forodesine	SAHA
	MLN518	Valproic Acid
	CEP701	MS275
	Tipifarnib	MK0752
Key Supportive Care Concerns	Tumor lysis syndrome, cytopenias, CNS symptoms: acute and chronic, immunosuppression, neurotoxicity, coagulation abnormalities (asparaginase)	

Abbreviations: ALL, acute lymphocytic leukemia; BCR-ABL, abelson break point cluster region; CNS, central nervous system; CR, creatinine; PCR, polymerase chain reaction; Ph+, Philadelphia chromosome positive; SCT, stem cell transplant; t, translocation; WBC, white blood cell.

Source: Data from Greenberg et al⁴⁵; Pui and Evans⁸¹; Moorman et al⁸²; Pullarkart et al⁸³; Huget et al⁸⁴; Larson⁸⁵; Linker et al⁸⁶; and Kantarjan et al.⁸⁷

newly diagnosed and frequent monitoring for treatment toxicities is necessary. Cytopenias and mucositis are common. Treatment of infections with antibiotic support is similar to that used in AML. Monitoring of coagulation parameters, risk for hypersensitivity, hyperglycemia, and hyperbilirubinemia is necessary with the use of asparaginase.

CNS prophylaxis

Involvement of the central nervous system, a sanctuary site not easily treated with standard systemic therapy, is common over the course of disease with ALL. Although it may be present in fewer than 10% of patients at initial diagnosis, the incidence over the course of disease is as high as 75% at 1 year without specific therapy aimed at treating the CNS.⁸⁶ The primary strategy for CNS prophylaxis is the administration of intrathecal methotrexate with serial testing of the cerebral spinal fluid (CSF) for disease. Cranial irradiation, historically a primary modality, is now reserved for selected high-risk patients (positive CSF, high presenting WBC, T-cell phenotype) due to the treatment related long-term effects including neurocognitive deficits and endocrinopathies.⁸⁹

Postremission therapy (consolidation therapy)

Post-remission consolidation is instituted following hematologic recovery and may include modified repetition of the induction schedule. Use of higher doses of cyclophosphamide and subcutaneous cytarabine are common. Patients with good performance status and support networks can often receive consolidation treatment in an outpatient setting where laboratory testing, transfusion and infusion capabilities are readily available. Late-intensification using a second course of induction therapy administered during the first few months of remission provides improved outcomes for patients of intermediate risk.⁸⁶

Maintenance therapy includes the use of monthly vincristine, pulse doses of prednisone, and daily dosing of 6-Mercaptopurine and methotrexate. All of the drugs except for vincristine are administered orally. This phase of treatment is generally well-tolerated with minimal incidence of cytopenias or mucositis. Transient elevation of transaminase levels is common. Treatment is continued for at least 2 years. Attempts to shorten the maintenance therapy have resulted in inferior outcomes.⁸¹ Patients with Ph+ disease will continue concurrent administration of imatinib throughout the maintenance phase or until they receive an allogeneic HSCT.⁹⁰

TREATMENT STRATEGIES FOR CHRONIC MYELOGENOUS LEUKEMIA

Scientific discovery and clinical advances in the diagnosis and treatment of CML, including identification of

distinct cytogenetic and molecular characteristics, have resulted in the development of targeted therapies that have significantly improved overall prognosis for this disease. (Table 57-10⁹¹⁻⁹⁵) A new class of drugs targeted at the *BCR-ABL* tyrosine kinase, present in all patients with the disease, has improved clinical responses in the chronic phases of the disease to 83% at 5 years.⁹⁶ The first TKI was imatinib that earned FDA approval as first-line therapy for CML in 2001. A second TKI agent, dasatinib, earned FDA approval in 2006 for the treatment of CML in patients with resistance or intolerance to imatinib. Nilotinib, the third TKI, was approved in 2007 for the treatment of CML (Table 57-11⁹⁷⁻¹⁰⁰). However, drug resistance to these new agents may develop over time or be present at the time of diagnosis due to molecular mutations. Complete and thorough diagnostic evaluation of the patient at the time of diagnosis and throughout the course of treatment is essential to optimal therapeutic outcomes.

Chronic phase

Treatment goals have changed with the development of TKI therapies, with a shift from hematological responses and cytogenetic remission to molecular responses (MR). The primary goal is to induce a complete molecular remission (CMR) early in the clinical course of the disease with a tolerable level of toxicity. Reduction of mortality through vigilant monitoring of molecular status to identify suboptimal response, disease progression, or existing or evolving drug resistance is critical to allow selection of the best potential therapy or the need for a change in therapy.

Refinement of the molecular analysis of CML has shifted the definition of treatment response and is critical to identification of patients who will require a change in therapy. Real-time quantitative polymerase chain reaction (RT-PCR) for *BCR-ABL* has become the gold standard for analysis of treatment response and the presence of residual disease. It is performed with peripheral blood and should be monitored consistently at a single institution if possible to minimize any variance. The achievement of a major molecular response (MMR) following 12 months of imatinib therapy was associated with 100% probability of transformation-free survival at 60 months.⁹⁸ Increasing *BCR-ABL* levels that are detected by RT-PCR may indicate mutation or progression of disease.

The National Comprehensive Cancer Network (NCCN) recommends hematological, cytogenetic, and molecular measures at baseline and repeated at regular intervals with initiation of therapy.⁹⁷ Hematological parameters are monitored regularly to evaluate for response and treatment toxicity. Dose escalation should be considered if there is no evidence of hematological response at 3 months. Cytogenetics are evaluated at 6 and 12 months, if a complete cytogenetic response is noted, the patient should continue the same dose. If a partial cytogenetic response is noted, the dose is increased and

TABLE 57-10

Disease Overview: Chronic Myelogenous Leukemia (CML)		
Feature	Key Findings	
Epidemiology	Incidence (per year): 5050 Median Age at Diagnosis: 66 years	
Etiology	Unknown	
Stem Cell Defect	Myeloid progenitor cell	
Prognostic Findings	Favorable: Low WBC count, BCR-ABL positive	
	Unfavorable: High WBC count, organomegaly, BCR-ABL negative disease	
Staging and Classification Disease Characteristics	FAB/WHO Classification of limited prognostic value	
	Chronic Phase	
	Indolent course, often asymptomatic and found incidentally on routine physical exam	
	Predominance of mature white blood cells	
	Approximately 90% of patients are diagnosed at this stage	
	Median survival is 4–6 years (pre-TKI therapy)	
	Accelerated Phase	
	Transition generally occurs over a period of 1 year or more; duration is 4–6 months	
	Associated with progressive leukocytosis, thrombocytosis or thrombocytopenia, basophilia, splenomegaly, fever, bone pain, thrombotic or bleeding complications	
	Clonal evolution is present	
	Blast Phase	
	Lasts only a few months—survival is poor if untreated	
	Associated with increasing blasts (> 30%), progressive splenomegaly despite treatment, and clonal evolution	
Response Criteria	Complete hematological response	Normal CBC and differential, no extramedullary disease
*Cytogenetic response is based on analysis of at least 20 metaphases	Minimal cytogenetic response	65%–95% Ph-positive metaphases (analysis of at least 20 metaphases)
	Minor cytogenetic response	36%–65% Ph-positive metaphases
	Partial cytogenetic response	1%–35% Ph-positive metaphases
	Complete cytogenetic response	0% Ph-positive metaphases
	Major molecular response (MMR)	≥ 3-log reduction of BCR-ABL mRNA
	Complete molecular remission (CMR)	Negativity by RT-PCR
	Negativity by RT-PCR	
Clinical Presentation	Cytopenias or leukocytosis, splenomegaly, fatigue, cutaneous manifestation—less common	
Indication to Treat	Confirmed diagnosis with BCR-ABL by FISH or PCR	
Key Concepts for Effective Treatment	Therapy is likely to continue indefinitely	
	Evaluation of response using hematologic, cytogenetic and molecular benchmarks is critical to effective therapy and early identification of resistance	
FDA approved therapies	Imatinib	Dasatinib
	Nilotinib	Hydrea
		Interferon
In clinical trials	Bosutinib	Decitabine
Key supportive care concerns	Myelosuppression, hepatic function abnormalities, congestive heart failure, gastrointestinal toxicities, QT prolongation, drug-drug interactions	

Abbreviations: BCR-ABL, abelson break point cluster region; CBC, complete blood count; FAB, French American British; FISH, fluorescent in situ hybridization; Ph, Philadelphia chromosome; RT-PCR, real-time polymerase chain reaction; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

Source: Data from Deininger⁹¹; NCCN⁹²; Shah⁹³; Giles et al⁹⁴; and Talpaz et al.⁹⁵

testing is repeated at 18 months. If there is a minor or minimal cytogenetic response at 12 months, recommendations are to change therapy to dasatinib or nilotinib, consider an HSCT, or a clinical trial. Real time quantitative polymerase

chain reaction should be performed every 3 months—indefinitely. If levels are rising the PCR frequency should increase to monthly and testing for *ABL* kinase domain (KD) mutations should be considered. These parameters are being

TABLE 57-11

FDA Approved Therapies for Chronic Myelogenous Leukemia (CML)

Agent	Mechanism of Action	Dosing and route of administration	Common Toxicities
Imatinib	BCR-ABL selective tyrosine kinase inhibitor	400 mg po daily Dose escalation to 600–800 mg/day is indicated in accelerated or blast phase or sub-optimal response Available: 100 mg or 400 mg tablets	Myelosuppression Superficial edema Gastrointestinal toxicities: nausea, vomiting, diarrhea Muscle cramping Rash Pulmonary edema, pleural effusions, ascites: rare QT prolongation
Dasatinib	Second generation BCR-ABL tyrosine kinase inhibitor Indicated for imatinib-resistant disease No benefit with T315I mutation	70 mg po bid (accelerated or blast phase) or 100 mg po q day (chronic phase) Available: 20 mg, 50 mg, 70 mg, and 100 mg tablets	Myelosuppression Superficial edema Gastrointestinal toxicities: diarrhea, nausea, vomiting Headaches Dyspnea or pulmonary edema: most common in blast phase Rash Asthenia Transaminase elevation QT prolongation
Nilotinib	Second generation BCR-ABL tyrosine kinase inhibitor Indicated for imatinib resistant disease	400 mg po twice daily Available: 200 mg capsules	Myelosuppression Gastrointestinal: diarrhea, nausea Hyperbilirubinemia Hyperglycemia Headache Hypophosphatemia Elevated serum lipase Rash Pruritus Arthralgias/myalgias QT prolongation

Abbreviation: BCR-ABL, abelson breakpoint cluster region.

Source: Data from NCCN⁹⁷; Novartis Pharmaceuticals⁹⁸; Bristol-Myers Squibb⁹⁹; and Novartis Pharmaceuticals.¹⁰⁰

refined as new agents are developed and more patients are evaluated in long-term follow up.

Terminal phase

In patients with more advanced disease, control of the accelerated phase of the disease with induction of chronic phase and continued therapies to induce MRD should be the goal.

TREATMENT STRATEGIES FOR CHRONIC LYMPHOCYTIC LEUKEMIA

The overall 5-year survival for patients with newly diagnosed CLL is approximately 60%, depending on disease stage.

(Table 57-12^{7,29,30,101}) For patients with progressive CLL, treatment with conventional chemotherapy is not curative, although allogeneic HSCT can help prolong disease-free survival. Patients with aggressive CLL typically have bulky disease, B symptoms (fever, night sweats, and unexplained weight loss in the previous 6 months), and RAI stage III or IV disease with a compromised marrow indicating a poor prognosis and decreased survival. Given the rapid development of new treatment options and refinement of risk-based treatment selection, the treatment strategies for CLL have been in flux. Watchful waiting is still considered appropriate for patients with low tumor burden and no adverse risk factors. Patients with high-risk or aggressive disease should initiate therapy to avoid further complications associated with the treatment of bulky disease. The most common agents

TABLE 57-12

Disease Overview: Chronic Lymphocytic Leukemia (CLL)

Feature	Key Findings		
Epidemiology	Incidence (per/year): 15,000 Average Age at Diagnosis: 72 years		
Etiology	Genetic Autoimmune disease		
Stem Cell Defect	Clonal B cells arrested in the B-cell differentiation pathway (95%)		
Chromosomal findings	Favorable del(13q) as sole abnormality	Neutral +12	Poor 17p-, t(11q:v), 11q-
Additional prognostic factors indicating high-risk disease	ZAP-70 > 20% (correlates with unmutated Immunoglobulin heavy chain variable gene (IgVh) status; suggests poor outcome) CD38+ (aggressive disease) p53+ (poor response to conventional chemotherapy) Elevated LDH CD69 expression (worse survival outcomes exclusive of ZAP-70 status)		
Staging	Binet and Rai Systems		
Response Criteria	International Working Group (IWG) Response Criteria		
Disease Characteristics	Indolent: Low tumor burden, normal marrow function	Progressive: High tumor burden, impaired marrow function, hypogammaglobulinemia Auto-immune hemolytic anemia	
Clinical Presentation	Lymphocytosis Splenomegaly Hepatomegaly Asymptomatic-20%	Infections (agranulocytosis and hypogammaglobulinemia) Adenopathy Hemolytic anemia	
Indication to Treat	Bulky disease (spleen, liver, nodes) Repeated infections Progressive marrow failure	Autoimmune cytopenias Rapid doubling time (< 6 months) Histological transformation	
Key Concepts for Effective Treatment	Chemotherapy has been effective alone and in combination with other agents New targeted therapies have increased response rates Chromosomal abnormalities have prognostic value Aggressive concurrent management of infection risk is essential to effective therapy		
FDA Approved Therapies	Bendamustine Alemtuzumab Melphalan	Ofatumumab	
In Clinical Trials or Used Based on Other Approved Indications	Flavopiridol Oblimersen Regimens used for indolent lymphomas	Rituximab Lenalidomide	
Key Supportive Care Concerns	Tumor lysis syndrome Infections Infusion reactions	Hemolytic anemias	

Abbreviations: CD, cluster of differentiation; del, deletion; IgVH, unmutated immunoglobulin heavy chain; LDH, lactate dehydrogenase; t, translocation; ZAP, zeta chain (TCR) associated protein kinase 70.

Source: Data from Seiler et al²⁹; Chiorazzi et al³⁰; and NCCN.¹⁰¹

used in the initial treatment of CLL include chlorambucil, the combination of cytoxan, vincristine, and prednisone (CVP) with adriamycin added for more aggressive disease (CHOP), and fludarabine that may be used in combination with cytoxan (FC) and rituximab (FCR).

The most recent NCCN guidelines for CLL have been updated to include several agents recently approved for treatment including bendamustine, alemtuzumab, and various chemoimmunotherapy combinations with pentostatin or fludarabine (Table 57-13^{51,102–106}). Alemtuzumab

is considered the preferred agent for treatment of elderly patients with del(17p) mutation based on clinical response rates.¹⁰¹ Bendamustine, the most recently approved drug for the treatment of CLL has dual mechanisms of action, both as a DNA-alkylating agent and as an antimetabolite purine analog—2 of the primary class of drugs used to treat CLL. It is bound to plasma proteins and blocks cells from progressing from Gap 1 to the Gap 2 phase in the cell cycle. These dual mechanisms of action appear to promote apoptosis in lymphoma cell lines.¹⁰⁷

In addition, several new agents have shown promising results in clinical trials for the treatment of CLL. Lenalidomide, an immunomodulatory agent already approved for the treatment of MDS and multiple myeloma, which is discussed elsewhere, has been shown to have activity in CLL, including in patients with relapsing disease and in patients with del(11q) and del(17p), all indicating high-risk disease.¹⁰⁸ Oblimersen, a Bcl-2 antisense agent has been shown to generate long-lasting CRs and nodular partial remissions when combined with chemotherapy.¹⁰⁹ Ofatumumab is a fully humanized anti-CD20 antibody that appears effective in the presence of few antigen sites, a common characteristic in CLL.

Additional trials have studied treatment specifically in the elderly population, adding to the refinement of selecting individualized therapy to maximize therapeutic outcome and minimize toxicity. Individual risk analysis is necessary,

as the most common complications of treatment include immunosuppression and recurrent or atypical infections, cytopenias, and tumor lysis syndrome. As previously noted, many of the patients with CLL are older and will be at increased risk for these complications.

Hairy cell leukemia

Hairy cell leukemia (HCL) is a rare indolent B-cell malignancy that represents less than 2% of the lymphoid leukemias.¹¹⁰ It is more common in men (male:female ratio—5:1) and the median age at presentation is 50 years.¹¹⁰ Because it is so rare, with less than 1000 new cases each year, the majority of clinical trials have fewer than 50 patients.¹¹¹ The hallmark diagnostic features are hair-like projections noted on the B-cells and a “fried egg” appearance on bone marrow samples. HCL commonly infiltrates the bone marrow, spleen, and liver. Thus hepatomegaly, splenomegaly, and bone marrow fibrosis are common. Patients often present with anemia, fatigue and vague left upper quadrant pain as a result. No distinct chromosomal aberrations are known, although immunophenotyping will reveal high expression of CD45, and antigens common to the B-cell lineage (CD19, CD20, CD22, and CD79). The standard approach to treatment is use of a purine analog such as cladribine and pentostatin.¹¹¹ The overall survival of HCL patients treated with purine analogues is >80%-85% at

TABLE 57-13

FDA Approved Therapies for Chronic Lymphocytic Leukemia (CLL)

Agent	Mechanism of Action	Dosing and Route of Administration	Common Toxicities
Alemtuzumab	Anti-CD52 monoclonal antibody	30 mg IV 3 times per week for 4–12 weeks	Infusion reactions Myelosuppression Lymphopenia Hemolytic anemia: rare
Bendamustine	Combined alkylating agent and purine analog	100 mg/m ² IV on days 1 and 2 repeated every 28 days	Myelosuppression Mild gastrointestinal upset
Chlorambucil	Alkylating agent	Variable dosing Administered orally	Myelosuppression Late effects: secondary malignancies
Fludarabine	Purine analog	25 mg/m ² days 1–5 every 28 days as a single agent Variable dosing in combination regimens	Myelosuppression Infections Hemolytic uremic syndrome: rare
Pentostatin	Purine analog	Used in combination regimens 4 mg/m ² IV on day 1, repeated every 28 days	Myelosuppression Infections Lymphopenia
Rituximab	Anti-CD20 monoclonal antibody	Split dosing recommended with initial dose: 50 mg/m ² day 1, and 325 mg/m ² day 2 Standard dosing in subsequent cycles of 375 mg/m ² Repeated every 28 days	Infusion reactions Reactivation of hepatitis B Rare mucocutaneous reactions

Source: Data from Abbott and Estey⁵¹; Genzyme Corp¹⁰²; Cephalon Inc¹⁰³; Ben Venue Laboratories¹⁰⁴; Pentostatin¹⁰⁵; and Genentech Inc.¹⁰⁶

>8–10 years of follow up. Resistant cases can be treated with rituximab.

TREATMENT STRATEGIES FOR MYELODYSPLASTIC SYNDROMES

General considerations

Supportive care has been the mainstay of treatment for myelodysplastic syndromes (MDS) over the last 20 years. Until recently, no active therapies were available. Supportive care continues to be important in treatment of symptoms associated with the disease or toxicities of newly developed active therapies. Supportive care includes observation, quality of life assessment, growth factors, antibiotics, iron chelation therapies, and transfusion support. However, it is important to recognize that supportive care measures do not change the underlying disease. (Table 57-14^{58,59,110})

The goals of therapy for MDS are based on individualized disease characteristics, patient characteristics, and risk category. Current treatment guidelines are no longer based on age and performance status. Transfusion dependence or progressive or symptomatic cytopenias generally indicate the need for active therapy. For low-risk disease the goals are to improve hematopoiesis, improve quality of life, and minimize toxicity. In high-risk disease, the goal is survival. These patients are at high risk for early transformation to acute leukemia and generally require immediate and aggressive therapy. De-novo MDS is associated with a more favorable outcome when compared to treatment-induced MDS, which is associated with poor response to standard therapies. Three agents have been approved by the FDA since May, 2004, for the active treatment of MDS: azacitidine (approved May, 2004) and decitabine (approved May, 2006), both DNA methylation inhibitors, and lenalidomide (approved December, 2005), an oral agent that has several mechanisms of action and is considered an immunomodulatory agent. Complete disease evaluation is necessary to select the best available therapy for the individual patient. Patients with low serum erythropoietin levels and low transfusion requirements may benefit from erythropoietin stimulating proteins. Lenalidomide is the treatment of choice for patient with del 5q.¹¹⁰ A small subset of patients who are positive for HLA-DR15 may benefit from administration of anti-thymocyte globulin (ATG). Hypomethylating agents are the treatment of choice for patients with intermediate-2 or high-risk disease or in patients with intermediate 1-risk disease not meeting the previous characteristics. Other agents have been used clinically in the treatment of MDS, including thalidomide and ATO. Each agent has been shown to have some activity in the reduction of transfusions and changes in cytogenetic findings. Several other agents are being studied in ongoing clinical trials or in combination with existing agents.

Each agent has specific potential toxicities and nursing implications. (Table 57-15¹¹²⁻¹¹⁴) The most common treatment-related toxicity for active therapies for MDS is myelosuppression. Most therapies require a minimum of 3 to 4 months of treatment to fully evaluate efficacy. Therefore, aggressive management of cytopenias is a critical component of effective treatment.

Transfusion independence, cytogenetic remission, and improvement in quality of life have become the desired end points for clinical trials for MDS. Transfusion independence not only improves the quality of life for MDS patients, but decreases secondary organ effects and decreases the economic and clinical burden. Cytogenetic responses have been shown to correlate with improved survival in patients with chromosome 5q deletion.¹¹⁵ Maturing data have shown improvement in the overall survival of patients receiving azacitidine for high-risk MDS, compared with supportive care alone.¹¹⁶ Survival was not dependent of a complete response.¹¹⁷ Transfusion dependence is common in patients with MDS and secondary iron overload is associated with several negative effects. Administration of iron-chelation therapy is a key supportive care strategy and requires specific monitoring for safe administration. Allogeneic HSCT remains the only potentially curative treatment for MDS and may be considered in younger patients who have a suitable donor.¹¹⁸

SYMPTOM MANAGEMENT AND SUPPORTIVE CARE

Supportive care is an integral component of an effective individualized cancer treatment plan that minimizes potential toxicities, maximizes therapeutic outcomes, and maintains optimal quality of life for the patient. Anemia, neutropenia, thrombocytopenia, and mucositis are some of the most common toxicities associated with treatment of the hematologic malignancies. They may result in dose reductions, dose delays, premature discontinuation of therapy, and increases in morbidity and mortality. Other common treatment related toxicities are summarized in Table 57-16.⁵⁸⁻⁵⁹

Myelosuppression is the most common adverse event as most therapies require marrow hypoplasia to effectively suppress the malignant clone. The duration and severity of cytopenias vary based on the status of the underlying disease including tumor burden and subtype, history of prior therapies, and agents used for treatment. Recent advances in transfusion medicine, the availability of cytokine therapies for anemia and neutropenia, and improved awareness of risk factors and early signs and symptoms of toxicity have improved clinical outcomes. In many cases, effective management of these toxicities has allowed patients to be treated in an outpatient setting. Thrombocytopenia is another common complication of cancer and cancer treatment and

TABLE 57-14

Disease Overview: Myelodysplastic Syndromes (MDS)

Feature	Key Findings		
Epidemiology	Incidence: 15,000–20,000 new cases/year, with 35,000–50,000 existing cases Average Age at Diagnosis: 70 years		
Etiology	Genetic instability Chemical exposure Tobacco	Mutagens Autoimmune disease Unknown in the majority of cases (~80%)	
Stem Cell Defect: Myeloid progenitor cell	Intrinsic Factors: Malignant clone Cytogenetic abnormalities Epigenetic DNA modification	Extrinsic Factors: Bone marrow microenvironment Stromal dysregulation Cytokine abnormalities Imbalance of apoptosis and proliferation	
Chromosomal Findings: Cytogenetic abnormality present in ~50%	Favorable -Y, del 5q, -20q	Intermediate Risk +8 and other	Poor Risk Complex (> 3 abnormalities) Chromosome 7 abnormalities: 7q, -7, del 7p; inv16, t(8:12) implies diagnosis of AML
Additional Prognostic Factors Indicating High-Risk Disease	Increased blast cells (> 20% implies leukemic transformation) Increased transfusion burden (> 2 units in 4 weeks) CD7 or CD56 expression by flow cytometry Atypical localization of immature precursors (ALIP) Ongoing analysis of more sensitive testing for chromosomal and molecular attributes Severe thrombocytopenia or neutropenia		
Staging	FAB/WHO (morphology) and IPSS/WPSS (risk stratification)		
Response Criteria	International Working Group (IWG) Criteria 2006		
Disease Characteristics (All are incurable)	Low-Intermediate 1 Risk Indolent course Low probability of leukemic transformation	Intermediate-High 2 Risk Progressive course with early transformation to acute leukemia	
Clinical Presentation	Cytopenias: anemia most common, infection, fatigue, bleeding		
Indication to Treat	Transfusion dependence, progressive cytopenias, increased blasts		
Key Concepts for Effective Treatment	Supportive care alone does not prevent disease progression (no effect on the underlying disease) Active therapies for MDS generally require a minimum of 3–4 months to achieve a response; premature discontinuation may limit the potential for an optimal response Aggressive concurrent management of cytopenias is essential to effective therapy Treatment goals: reduce transfusion requirements, delay time to leukemic transformation and improve quality of life Chromosomal abnormalities have prognostic value		
FDA Approved Therapies	Azacitidine Decitabine Lenalidomide		
In Clinical Trials or Used Based on Other Approved Indications	TLK199 Src family kinase inhibitors Clofarabine	Arsenic trioxide Valproic acid Thalidomide	
Key Supportive Care Concerns	Iron overload, injection site reactions, cytopenias and infections, gastrointestinal toxicities		

Abbreviations: CD, cluster of differentiation; del, deletion; inv, inversion; IPSS, International Prognostic Scoring System; WHO, World Health Organization; WPSS, WHO-classification based Prognostic Scoring System.

Source: Data from Kurtin⁵⁷; Kurtin,⁵⁸; and Revlimid (lenalidomide) prescribing information.¹¹²

TABLE 57-15

FDA Approved Therapies for Myelodysplastic Syndromes (MDS)

Agent	Mechanism of Action	Dosing and Route of Administration	Common Toxicities
Lenalidomide	Immunomodulatory and antiangiogenic	10 mg/day continuous or days 1–21 every 28 days	Myelosuppression Pruritus (mild) Safety program for potential teratogenicity: RevAssist Diarrhea (mild)
Azacitidine	Demethylating agent	75 mg/m ² /day SC or IV days 1–7 every 28 days for a minimum of 4 cycles or until disease progression Alternative dosing regimens in recent trials	Myelosuppression Injection site erythema Nausea and vomiting Transient elevation of transaminases Low-grade fevers Contraindicated in patients with sensitivity to mannitol or with extensive hepatic disease
Decitabine	Demethylating agent	15 mg/m ² /day IV over 3 hours q 8 hours days 1–3 every 6 weeks 20mg/m ² IV over one hour days 1–5 every 28 days. Alternative dosing regimens in recent trials	Myelosuppression: neutropenia, thrombocytopenia, leukopenia Nausea and vomiting Transient elevation of transaminases Infections Contraindicated in patients with extensive hepatic disease

Abbreviations: IV, intravenous; SC, subcutaneous.

Source: Data from Revlimid (lenalidomide) prescribing information¹¹²; and Pharmion.¹¹³

increases the risk of bleeding for the patient. Standards for treatment rely primarily on platelet transfusions or changes in therapy to reduce the incidence. Oncology nurses can assist the patient by providing instruction for bleeding precautions, avoidance of medications such as aspirin or alcohol that may precipitate bleeding, and immediate reporting of uncontrolled bleeding or bruising.

Mucositis and gastrointestinal toxicities are also common during therapy for AML and ALL, in large part due to the specific agents and doses used for treatment. Mucositis in the presence of sustained neutropenia is a significant risk factor for systemic bacteremia. Close monitoring for fever or other subtle signs of infection with prompt initiation of antibiotic therapies and other supportive measures will reduce the mortality associated with febrile neutropenia. Most interventions for treatment of mucositis have been focused on pain management, improved nutritional support (enteral and parenteral feedings), and prevention of secondary infections (oral rinses, antibiotics, and antifungals). The recent development of cytoprotective agents provides hope for prevention of severe oral mucositis. However, these agents are not likely to eliminate the need for effective oral hygiene regimens. Patients should be instructed in the use of a mucolytic rinse such as bicarbonate solution, followed by a normal saline rinse throughout the day. Antibacterial, antifungal, antihistamine, and

topical anesthetic agents may be used if indicated; however, chronic use of these agents may be associated with adverse secondary effects such as drying of the mucosa.

Tumor lysis syndrome (TLS) is a potentially life-threatening metabolic disorder that develops as a result of cell lysis most commonly seen with bulky disease or aggressive tumors with the initiation of therapy. Intracellular molecules (potassium, nucleic acids, phosphorus) are released into the extracellular fluids with resulting electrolyte imbalances (hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia), and secondary systemic effects. If untreated, patients can develop acute renal failure and cardiac arrhythmia, with the potential for cardiac arrest. Patients with rapidly dividing or bulky lymphoproliferative disorders, such as CLL, are at particular risk. Baseline laboratory analysis and frequent monitoring during therapy is necessary in the first 48 to 72 hours after treatment to allow effective management. Patients at high risk should be treated in an inpatient setting, where renal dialysis and cardiac support services are readily available. Prophylactic treatment with allopurinol instituted 24 to 48 hours prior to therapy is effective in the majority of patients. Rasburicase, a potent IV uric acid-lowering formulation is indicated for patients with TLS prior to initiating treatment or in those who have rapidly dividing tumors. Intensive management in the

TABLE 57-16

Nursing Management of Common Disease or Treatment Related Toxicities

Clinical Findings	Signs and Symptoms	Nursing Considerations
Anemia	Fatigue, dyspnea, dizziness, tachycardia, palpitations	<p>Transfusion management:</p> <p>Patients with underlying cardiac disease are at increased risk for CHF exacerbation and may require diuresis with transfusions</p> <p>Benefits are temporary and rarely restore hematocrit (Hct) to normal</p> <p>Transfusions should be based on symptoms not general hemoglobin (Hgb) or Hct parameters</p> <p>Monitoring for iron overload in transfusion dependent patients and need for iron chelation therapy (initiate at ferritin >1000 ng/mL)</p> <p>Administration of erythropoietin agents for MDS patients with serum erythropoietin (epo) level < 500 or who require > 4 units of PRBCs every 8 weeks</p> <p>Careful monitoring for safety in administration of erythropoietin agents in patients at risk for thrombotic events</p> <p>Initiate active therapies for transfusion dependent MDS patients with serum epo level > 500 or PRBCs > 2 units/4 weeks</p> <p>Assist the patient in maintaining a flow sheet for lab results and transfusion dates, blood type, and any antibodies.</p>
Neutropenia	Fever, cough, dysuria, abdominal pain or diarrhea	<p>Early recognition of infections</p> <p>Patient education for infection precautions and reportable signs and symptoms</p> <p>Patients receiving active therapies may require drug holiday and dose adjustment</p> <p>Monitoring of CBC, differential and platelet count daily for initial treatment of acute leukemia, weekly for the first 8 weeks for active therapies in CML and MDS, and at varied intervals for the treatment of CLL based on the disease and specific treatment</p> <p>Administration of recombinant granulocyte growth factors</p> <p>Should not be administered on the same day of cytotoxic agents</p> <p>Antimicrobial therapy for active infections; prophylactic antibiotics are not generally recommended to avoid resistance</p>
Thrombocytopenia	Petechiae, ecchymosis, epistaxis, hemoptysis, hematuria	<p>Platelet transfusions based on risk of bleeding (platelets < 10,000 mm³ or active bleeding)</p> <p>Careful monitoring of concomitant medications with antiplatelet effect</p> <p>Patient education for bleeding precautions, emergency management and reportable signs and symptoms</p> <p>Aminocaproic acid may be used in transfusion refractory patients</p> <p>Thrombopoiesis stimulating proteins currently in clinical trials</p> <p>Patients receiving active therapies may require drug holiday and dose adjustment</p>
Iron chelation for hemosiderosis (iron overload)	Elevated hepatic enzymes, fatigue, confusion, CHF, vague abdominal bloating and pain, MRI findings of iron overload of the liver	<p>Institute iron chelation therapy for serum ferritin > 1000 ng/mL</p> <p>Selected patients responding to active therapies may benefit from phlebotomy</p> <p>Safety monitoring for iron chelation therapy; renal toxicity; increase in serum creatinine, rare cases of acute renal failure reported, and intermittent proteinuria</p> <p>Baseline and regular monitoring of renal function</p> <p>Hepatotoxicity: elevated transaminase levels</p> <p>Baseline and regular monitoring of hepatic function</p> <p>Pancytopenia: neutropenia, agranulocytosis, thrombocytopenia reported in MDS patients</p> <p>Baseline and regular monitoring of CBC, differential, and platelet count</p> <p>Auditory: high-frequency hearing loss, decreased hearing</p> <p>Baseline and yearly audiology evaluation</p> <p>Ocular: cataracts, lens opacities, increased pressure, retinal disorders</p> <p>Baseline and yearly slit-eye and fundoscopic exam</p>

(Continued)

TABLE 57-16

Nursing Management of Common Disease or Treatment Related Toxicities (Continued)

Clinical Findings	Signs and Symptoms	Nursing Considerations
Tumor lysis syndrome	Hyperkalemia Hyperphosphatemia Hypocalcemia Hyperuricemia Cardiac arrhythmias Acute renal failure	Monitor: comprehensive metabolic profile, LDH, uric acid, phosphorus Clinical observation: vital signs, weight, edema, intake and output Hydration: begin 24–48 hours pre-therapy, continue 48–72 hours post-therapy if high risk ECG: if hyperkalemia Allopurinol: 300–900 mg/day (renal function) Rasburicase: 50–100 U/kg/day (contraindicated if glucose-6-phosphate dehydrogenase [G-6-PD] deficient) Oral phosphate binders: amphogel Hemodialysis
Bleeding diatheses or coagulopathy	Bleeding Mucocutaneous hemorrhage Thrombosis Disseminated intravascular coagulation	Common with initial therapy for APL when using differentiating agents (ATRA, ATO) Baseline coagulation studies including PT, PTT, fibrinogen Administration of coagulation factors and fibrinogen: cryoprecipitate, platelets, and fresh frozen plasma Maintain fibrinogen above 150 mg/dL Maintain platelets above 30,000 mm ³
Mucositis Typhlitis	Oral ulceration and pain Rectal pain and ulceration or abscess	Most often associated with higher doses of cytarabine and anthracyclines Cytoprotective agents may be used in the bone marrow transplant setting Oral hygiene regimens using a mucolytic agent (bicarbonate solution) followed by a normal saline rinse can reduce discomfort and secondary infection Medicated rinses may be used for active infection or for pain management Evaluation of rectal pain is necessary to exclude the presence of a rectal abscess in patients treated with high-dose cytarabine
Central nervous system toxicities	Ataxia Confusion Impaired hand–eye coordination Sensory deficits	Cerebellar toxicity is a dose-limiting toxicity with high-dose cytarabine and dose reductions are recommended in older patients Daily neurological evaluations should be conducted and treatment should be held in the presence of changes Peripheral neuropathies are uncommon with the exception of long-term treatment with vincristine in ALL
Cutaneous toxicities	Painful plantar and palmar erythema Blistering or desquamation if severe	Acral erythema is a possible complication of high-dose cytarabine. Drug-related rashes are common with antibiotics, allopurinol, and selected active therapies; baseline assessment and ongoing monitoring are essential Leukemia cutis may be present at the time of diagnosis Fungal infections may be associated with skin infiltrates; infiltrates should be biopsied to determine the underlying abnormality (disease vs infectious)
Cardiotoxicity	Congestive heart failure Cardiomyopathy QT prolongation and torsades de pointe	Baseline cardiac evaluation including an echocardiogram or MUGA scan Baseline ECG and repeated testing at regular intervals is necessary for ATO and TKI therapy to evaluate QTc interval; treatment should be held for QTc > 500 milliseconds Careful medication review is necessary to identify agents that are associated with QT prolongation Evaluate patients at high risk: cumulative anthracycline dose, history of prior radiotherapy to the chest, and underlying cardiovascular disease
Ocular toxicities	Keratoconjunctivitis	Prophylactic administration of steroid eye drops when using doses of Cytarabine of > 2 gm/m ² Should begin eye drops 24 hours prior to and continue 48 hours beyond the last dose of cytarabine

Abbreviations: ALL, acute lymphocytic leukemia; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-transretinoic acid; CHF, congestive heart failure; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; ECG, electrocardiogram; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PRBCs, packed red blood cells; PT, prothrombin time; PTT, partial thromboplastin time; TKI, tyrosine kinase inhibitor.

Source: Data from Kurtin⁵⁷; and Kurtin.⁵⁸

first few days following therapy may be necessary. Most patients can be effectively treated with no sustained renal or cardiac abnormalities and will be at a lower risk with subsequent treatments due to decreased tumor burden.

CONCLUSION

Strategies for the diagnosis, risk stratification and treatment of hematological malignancies, leukemia and MDS, have expanded at an unparalleled rate offering improved response rates, overall survival, and disease control for patients. Numerous clinical trials are ongoing that offer promising therapies for future use either as single agents or in combinations. Refinement of the diagnostic evaluation and application of prognostic criteria for these disorders has shifted the treatment paradigm from general intensive therapy to selective treatment based on the individual disease and the unique attributes of the patient. Several challenges remain as the rate of scientific discovery has outpaced generalized clinical application. Patient enrolment in clinical trials will be critical to refine the application of molecular and genetic factors in risk analysis and treatment selection. The concept of minimal residual disease, which has been verified for CML and APL does not appear to apply to MDS. Therefore the goal of treatment in each disease may be different based on the current understanding of response vs survival and emphasizes the heterogeneity of these disorders. The consistency and quality of tissue and blood specimens, standardized testing for analysis, and development of clinical guidelines for their use will continue to present a challenge for clinical trials, analysis, and treatment application. Treatment guidelines are likely to be modified frequently as new data emerge. Oncology nurses play a critical role in the daily assessment, treatment, and management of patients with hematological diseases. Understanding novel mechanisms of antitumor activity, associated toxicities, and clinical management strategies for these new therapies is critical to safe and effective management of patients receiving them. Concurrent supportive care is critical to allow continuation of effective therapies. Consideration of the unique characteristics of the individual patient using a life span approach will facilitate individualized treatment strategies.

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