

Chapter 2

Overview of the Leukemias

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Introduction

The previous chapter described malignant cells that originate in lymphoid organs, such as lymph nodes and the spleen. Leukemias are also cancers of the immune system, but these neoplasms originate within hematopoietic stem and progenitor cells in the blood and bone marrow. Leukemias can arise from lymphoid cells (B cells and T cells), like lymphomas, or from cells of the myeloid lineage. Clonal expansion of one cell line results in underproduction of normal red blood cells, platelets, and other leukocytes. Cytopenias lead to requirement for blood product transfusions. Also, cytopenias result in weakening of the immune system and increased risk of infection, which is the most common cause of death in patients with leukemia. Importantly, leukemias not only occupy the bone marrow space, but can also infiltrate organs such as the liver, spleen, skin, and central nervous system (CNS). Major CNS consequences result from leptomeningeal spread of disease, parenchymal infiltration by leukemia cells, paravertebral masses leading to spinal cord or cauda equina compression, hemorrhage in the setting of disseminated intravascular coagulation, and leukostasis. These CNS complications can cause central and peripheral nerve palsies, seizures, and altered sensorium. Treatment of CNS involvement may involve leukapheresis, radiation, intrathecal chemotherapy, and systemic chemotherapy using agents capable of traversing the blood-brain barrier.

Normal and Malignant Hematopoiesis

Bone Marrow Architecture

Production of hematopoietic cells occurs within the bone marrow, located within the proximal regions of long bones of the body, ribs, sternum, vertebrae, ileum,

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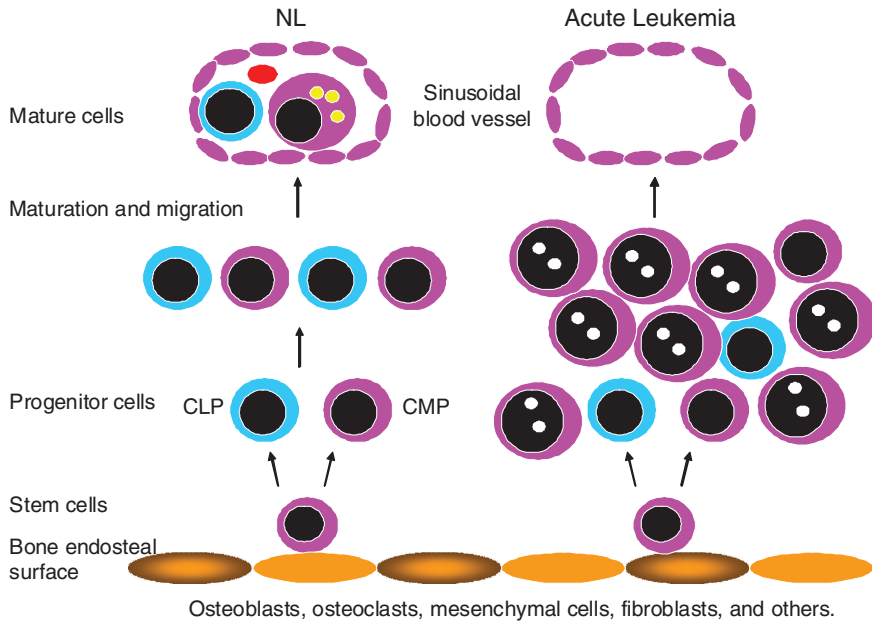


Fig. 2.1 The bone marrow environment is comprised of hematopoietic cells, which include stem, progenitor, and precursor cells, which terminally differentiate to form mature elements of blood. Malignant transformation results in accumulation of lymphoblasts, or myeloblasts, in the bone marrow, which causes a reduction in the normal hematopoietic elements and cytopenias

and calvarium. Bone marrow is comprised of hematopoietic cells that participate in the formation of blood and supportive cells, which provide cytokines and physical support for hematopoietic cells. Osteoblasts and osteoclasts are involved in maintenance of bone structure, but also contribute to hematopoiesis (Fig. 2.1).

Hematopoietic Stem and Progenitor Cells and Differentiation

The adult bone marrow contains approximately 500,000 hematopoietic stem cells (HSCs) and, from these, approximately 10^{10} blood cells are formed hourly. HSCs, like other stem cells, have the property of self-renewal, whereby one of the daughter cells retains stem cell-like function to prevent the depletion of the HSC pool [1]. Hematopoiesis occurs in a unidirectional manner, with cells gradually losing the capacity for self-renewal as they acquire more differentiated characteristics. HSCs divide and differentiate to form hematopoietic progenitor cells (HPCs), comprised of common myeloid and lymphoid progenitors (CMPs, CLPs), respectively. CLPs give rise to lymphoid progenitors. Progenitor cells divide to form precursor cells, which form the bulk of the bone marrow cellularity when viewed by light microscopy. Precursor cells then terminally divide and differentiate to form the

mature elements of blood: leukocytes, red blood cells, and platelets. T cells, B cells, and plasma cells are derived from CLPs while RBCs, platelets, granulocytes (neutrophils, eosinophils and basophils), monocytes, dendritic cells, and macrophages are derived from the CMPs.

The differentiation process is guided by several principles. First, hematopoietic cells lose the capacity for self-renewal, with the accumulation of differentiated characteristics. Second, differentiation is considered unidirectional – differentiated cells are unable to “de-differentiate” to a more primitive, stem-like form.

Upon maturation, cells gradually transmigrate to bone marrow sinusoidal vessels and are released into the circulatory system. Even rare HSCs and HPCs transiently leave the bone marrow, circulate, and return to the bone marrow, often at other sites. A large number of these HSCs and HPCs may enter the circulation in response to agents such as G-CSF, CXCR4 inhibitors like AMD3100, and cytotoxic chemotherapy agents like cyclophosphamide. In fact, these agents are used to mobilize HSCs to the blood to facilitate collection for the purpose of allogeneic stem cell transplantation.

Hematopoietic Support Cells

HSCs receive and are dependent on enumerable cues from their microenvironment, or niche. The role of the niche in HSC function was first emphasized by Schofield who proposed that the fate of HSC progeny was dependent on the surrounding niche [2].

The various cells and extracellular macromolecules present in the hematopoietic tissue are collectively referred to as stroma. The stromal cells consist of adipocytes, fibroblast-like cells, endothelial cells, osteoblasts, and mesenchymal stem cells. These stromal cells are important sources of many paracrine and juxtacrine growth factors, which are necessary for self-renewal, and differentiation of HSCs and progenitors [3, 4]. In addition, the stroma plays a role in the homing and trafficking of HSCs to hematopoietic organs via ligand-receptor interactions [5]. This is of great importance for engraftment of HSCs given peripherally during a stem cell transplant.

The cells of the osteoblastic lineage form an integral component of the HSC niche and support hematopoiesis. Periosteal marrow is enriched for HSCs and selective ablation of osteoblasts in mice reduces bone marrow cellularity and promotes extramedullary hematopoiesis, underscoring the contribution of osteoblasts to normal hematopoiesis [6, 7].

Mesenchymal stem cells (MSCs) are pluripotent stem cells found in the marrow, which have the capacity to replicate as undifferentiated multipotent cells and to differentiate into a variety of lineages of mesenchymal origin [8]. MSCs have been shown to support hematopoiesis and regulate immune responses by suppressing T cell activation [9] and hence, are under investigation for treatment of graft versus host disease [10].

Malignant Transformation

Both lymphoid and myeloid cells may undergo malignant transformation. However, the exact cell of origin of a leukemia is unclear. Further complicating the identification of the malignant cell is the observation that some individuals have biphenotypic leukemias, which display both myeloid and lymphoid cell surface markers, or multilineage leukemias, where two or more populations of malignant cells of lymphoid, myeloid, or hybrid immunophenotypes may be identified.

Whether a hematopoietic stem or progenitor cell can undergo transformation is not fully understood. However, leukemias arise from activation of oncogenes, inactivation of tumor suppressor genes, and alterations in transcription factors that block differentiation. Identifying the specific genetic lesions is important as specific cytogenetic and molecular mutations have implications for diagnosis, risk stratification, and treatment.

The concept of a “leukemia stem cell” (LSC) has arisen and describes the capacity for certain populations of bone marrow cells from individuals with leukemia to give rise to leukemia in murine xenotransplant model systems; these LSCs have the capacity for enhanced self-renewal and are likely responsible for the perpetuation of the leukemia while other cells, which may form the bulk of the leukemia, are incapable of perpetuating the disease. This recapitulates the hierarchy found in the normal hematopoietic system where a rare, self-renewing stem cell maintains the entire population of terminally differentiated, non self-renewing cells [11]. The relationship of the LSC to the normal HSC is unclear and different leukemias likely emerge from different cells along the hematopoietic cascade.

Classification of Leukemias

Leukemias represent malignant, clonal leukocyte proliferations, which may be grossly classified based on the myeloid or lymphoid cell of origin. Lymphoid leukemias, such as B-ALL, T-ALL, and Burkitt’s leukemia/lymphoma, may involve the CNS in up to 25% of patients, while myeloid malignancies, such as MDS, AML, and myeloproliferative disorders, rarely involve the CNS.

A second distinction is made based upon the chronicity of the leukemias. Acute leukemias, such as AML and ALL, have a rapidly evolving clinical course, with changes in the peripheral blood counts and clinical status occurring over days and weeks. Aggressive treatment is required within days or, sometimes, hours of diagnosis. In contrast, chronic leukemias, like CLL and CML, demonstrate indolent clinical courses, with subacute changes in the blood counts and clinical signs and symptoms. Treatment may be delayed to provide time for accurate diagnosis and, in some cases of CLL for example, treatment may be delayed for years from the time of diagnosis.

Diagnosis of Leukemias

Leukemia is suspected in patients with abnormal peripheral blood counts. Some individuals present with cytopenias, while others have elevated leukocyte counts. It is crucial to obtain a complete blood count (CBC) and differential from individuals suspected of having a bone marrow disorder. Patients with acute leukemia may have “blasts,” myelo- or lymphoblasts, evident within the blood differential. However, some individuals simply have cytopenias without abnormal cells evident within the peripheral blood. While myeloblasts differ from lymphoblasts morphologically, the two cell types are very similar and only flow cytometry can reliably distinguish between them. Occasionally, Auer rods can be seen within the cytoplasm of blasts, providing definitive morphologic evidence that a cell is of myeloid origin.

A bone marrow biopsy is required to diagnose leukemia, myelodysplastic syndrome (MDS), and most cases of myeloproliferative disorders. The bone marrow biopsy consists of a liquid aspirate, approximately 5 cc in volume. A portion of the aspirate is spread over a glass slide at the bedside. Some institutions prepare a buffy coat, which is similarly used to prepare slides. The slides are stained with Wright-Giemsa stain and the bone marrow cellular morphology, examined by light microscopy. The percentage of bone marrow blasts is derived from the morphologic analysis of the bone marrow aspirate. The aspirate is also used for flow cytometric analysis, where fluorochrome-labelled antibodies are incubated with the bone marrow cells and the presence or absence of cell surface markers are used to characterize the bone marrow cells. In addition, cytogenetic analysis is performed on the bone marrow and is crucial to the diagnosis and treatment of leukemias. Lastly, molecular analyses may be conducted on the bone marrow aspirate.

The second component of the bone marrow biopsy involves obtaining a 1–2 cm bone core. “Touch preps” are prepared by applying the bone core to a glass slide and depositing a thin layer of cells on the slide. This is particularly useful in patients who have a “dry tap,” where a aspirate cannot be obtained due to elevated bone marrow reticulin fibrosis or the presences of a marrow “packed” with leukemia cells. The slide is then stained with Wright-Giemsa and interpreted similarly to an aspirate. The bone core is then placed in a decalcification and fixation solution. Following a period of decalcification, the bone core is sectioned, stained with hematoxylin and eosin, and analyzed by light microscopy. Immunohistochemistry may also be performed on sections of the core. The core provides information on the ratio of bone marrow cellularity to fat in addition to morphology. Proper bone marrow analysis is highly complex and a specialized hematopathologist should be consulted throughout the process.

For patients with CNS symptoms, or patients at high risk of CNS involvement, a lumbar puncture (LP) should be performed for CSF analysis. AML, MDS, and MPDs rarely involve the CNS and an LP is not performed routinely as part of diagnosis and treatment in the absence of CNS symptoms. In contrast, ALL more frequently involves the CNS. In such patients, an LP is performed at diagnosis and several times during treatment, even in the absence of CNS symptoms. Useful diagnostic samples include analysis of the white blood cell count and differential,

red blood cells, total protein, glucose, cytology, flow cytometry, and microbiologic studies. In patients who are receiving intrathecal therapy for active disease or who are receiving routine prophylactic intrathecal chemotherapy, a cell count is often the only test sent at the time of these LPs because once the presence or absence of CNS disease is established, repeated flow cytometric analysis of the CSF is not required. Patients with acute leukemias are often treated according to research protocols, and the specific guidelines for timing of diagnostic and therapeutic LPs, and instillation of chemotherapy, are established by the protocol.

Treatment of Leukemias

Appropriate leukemia treatment requires the involvement of a leukemia specialist. Once the diagnosis is established using the techniques outlined above, a treatment plan is developed. For acute leukemias, risk stratification is extremely important in developing the treatment plan. Important risk factors include patient age, WBC count at diagnosis, presence of extramedullary or CNS disease, and cytogenetic and molecular analyses of the leukemia.

Most patients undergo a period of intense therapy oriented toward achieving disease remission. This period, termed “induction,” often requires a 4-week inpatient hospitalization. Once a remission is achieved, multiple cycles of consolidation chemotherapy may be employed to lessen the risk of disease recurrence. For patients with lymphoid leukemias, CNS-directed therapy involving intrathecal therapy, radiation, and systemic chemotherapies that traverse the blood-brain-barrier may be incorporated prophylactically or therapeutically.

For patients in remission following induction, stem cell transplantation (SCT) may be recommended. Autologous SCT has a role for some patients with acute leukemias, particularly for patients with relapsed disease. For patients with high-risk disease, allogeneic stem cell transplantation may be recommended once they are in remission. Allogeneic stem cell transplantation provides the potential benefit of a “graft-versus-leukemia” effect, which may reduce the chances of disease recurrence over chemotherapy alone. For individuals who achieve a remission but later relapse, treatment with reinduction, or salvage, chemotherapy is utilized to achieve a second remission. Allogeneic SCT is often recommended for such high-risk patients. The presence of CNS disease at diagnosis, or upon relapse, is considered a highly adverse risk factor and is frequently used to support a recommendation for allogeneic SCT.

The following outline summarizes the subtypes of leukemia that will be reviewed in detail.

- Myelodysplastic Syndromes (MDS)

- Myeloid Leukemias

 - Acute Myelogenous Leukemia (AML)

 - Chronic Myelogenous Leukemia (CML)

Lymphoid Leukemias

Acute Lymphoblastic Leukemia (ALL)

B-cell subtype

Precursor B-cell

Mature B-cell

T-cell subtype

Precursor T-cell

Mature T-cell

Chronic Lymphoblastic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Myelodysplastic Syndromes (MDS)

Epidemiology and Etiology of MDS

Myelodysplastic syndromes (MDS) represent clonal malignant neoplasms of the bone marrow that result in cytopenias and, in some patients, heightened risk of developing AML. The median age of diagnosis is 68 years; there are approximately 15,000 cases of MDS in the United States each year, and the estimated prevalence is 50,000–100,000 cases. The disease is slightly more common in men compared to women with a ratio of 1.2:1, except for a rare variant of MDS known as the 5q-syndrome, which is more common in women at a ratio of 2:1.

Most patients with MDS have *de novo* disease – that is, disease which arises spontaneously. However, approximately 10% of patients have secondary disease, arising after an antecedent hematologic disorder, or after a period of exposure to chemotherapy or radiation. Individuals with secondary, or therapy-related, MDS have higher risk disease and require more aggressive treatment than those with *de novo* disease.

Clinical Presentation, Evaluation, and Staging of MDS

Cytopenias represent the most common manifestation of MDS and, because of the indolent clinical nature of MDS, the disease may be suspected upon routine blood testing. Anemia represents the most common cytopenia, experienced in 85% of patients. Approximately 50% of patients develop leukopenia and 25% thrombocytopenia. Symptoms are caused by the cytopenias. Patients with anemia develop dyspnea, fatigue, and depression, while those with leukopenia have increased risk of sinopulmonary and other infections. Individuals with thrombocytopenia may develop epistaxis, easy bruising, hematuria, hematochezia, and have an increased risk of intracranial hemorrhage after falls.

Diagnosis involves careful examination of the peripheral blood counts and exclusion of alternative causes of cytopenias. Thus, the CBC with differential, and

measurements of serum B12, folate, iron, ferritin, and the transferrin saturation are useful. The erythropoietin level and reticulocyte count are also considered.

A bone marrow biopsy with cytogenetic analysis is required for the diagnosis of MDS. A hallmark of diagnosis is the presence of dysplasia within 10% or more of cells in at least one lineage. Dysplasia represents the morphologic abnormality, resulting from impaired cellular maturation due to the diseased hematopoietic stem cell clone responsible for MDS. Any of the three blood lineages may demonstrate dysplasia, though it is most commonly observed within the erythroid lineage. Red blood cells may demonstrate nuclear irregularities, frequent mitotic figures, and nuclear:cytoplasmic asynchrony. Myeloid cells may display nuclear atypia, hypogranulation, and the pseudo-Pelger-Huet nuclear abnormality. Lastly, dysplastic megakaryocytes may demonstrate nuclear hypolobation and clustering.

The bone marrow in MDS is hypercellular for age and may have increased myeloblasts as demonstrated on the bone marrow aspirate. The blasts may be normal in quantity, < 5% of the bone marrow cellularity, or may be increased in the range of 5–19%. If the blasts reach or exceed 20%, a diagnosis of AML is made.

Cytogenetic studies are important in the diagnosis and treatment of MDS. Cytogenetics are normal in 50% of individuals with MDS. However, when abnormal, the cytogenetics may suggest either low-, intermediate-, or high-risk disease based on the specific aberration(s) found. Cytogenetics are abnormal in > 80% of persons with secondary MDS. Chromosome 5q represents the most common chromosomal alteration in MDS, observed in 20% of individuals.

Individuals with an interstitial deletion within the long arm of chromosome 5q between bands 31 and 33 may have a 5q-syndrome. This syndrome is more commonly observed in women, is associated with anemia, thrombocytosis, excellent prognosis, and excellent clinical response to the class of medications known as immunomodulators, or IMiDs (ex. thalidomide, lenalidomide).

Natural History, Prognosis, and Treatment of MDS

Left untreated, MDS is associated with progressive cytopenias. Eventually, colony-stimulating factors, such as epoetin alfa to stimulate RBC production, and filgrastim to stimulate WBC production, are required. Individuals may develop transfusion dependence. Approximately 30% of patients with *de novo* disease, and most patients with secondary MDS, transform to AML. Thus, the goals of treatment are to improve quality of life, delay progression to AML, decrease transfusion dependence, and prolong overall survival.

The appropriate treatment for MDS is complex and is based on multiple factors, such as *de novo* versus secondary disease, cytogenetic status, patient age and wishes, and the presence of comorbid factors. The international prognostic scoring system (IPSS) takes into account the percentage of bone marrow blasts, cytogenetic status, and number and degree of cytopenias. The IPSS score correlates with median survival and time to development of AML, and may help guide treatment decision-making.

Allogeneic SCT represents the only possible cure for MDS, though it is a possible therapy for fewer than 20% of patients due to advanced age at diagnosis and lack of suitable donors. Supportive care consists of colony stimulating factors, blood product transfusions, and antibiotics. Hypomethylating agents, such as azacitidine and decitabine, have clinical benefit in reducing transfusion requirements and delaying development of AML. The primary cause of death is infection.

Acute Myelogenous Leukemia (AML)

Epidemiology and Etiology of AML

In the United States, there are roughly 10,000 new cases of AML diagnosed annually with a slight male predominance and a median age of onset of approximately 70 years. AML results from the improper maturation of myeloid cells, giving rise to a clonal population of myeloblasts. Excessive myeloblasts dominate the bone marrow and prevent normal hematopoiesis. No cause can be identified in most cases of AML; however, there are certain syndromes and exposures which can increase the risk of developing AML. Secondary AML, like secondary MDS, arises after a history of an antecedent hematologic disease or exposure to genotoxic agents, such as chemotherapy or radiation. A history of MDS is the most common risk factor for developing AML; other hematologic disorders, such as polycythemia vera and myelofibrosis, can also progress to AML. Individuals with trisomy 21, or Down's syndrome, have a 20-fold higher risk of leukemia than the general population. Smoking, exposure to benzene, and radiation exposure have also been associated with a higher risk of developing AML. A personal history of exposure to chemotherapy or radiation presents a risk for developing MDS and AML, and approximately 0.5% of patients receiving chemotherapy for a solid tumor will develop a myeloid malignancy. The agents most commonly associated with secondary AML include topoisomerase II inhibitors, which can predispose to AML within 1–3 years, and are frequently associated with abnormalities at chromosome 11q23, the mixed-lineage leukemia (MLL) gene. Alkylating agents, such as melphalan, chlorambucil, cyclophosphamide, and ifosfamide increase the risk of MDS and AML, with peak incidence 3–7 years after exposure, and is often associated with aberrancies of chromosomes 5 and 7. A history of radiation therapy can also increase the risk of AML.

Clinical Presentation, Diagnosis, and Classification of AML

Presenting symptoms of AML include fatigue, dyspnea, bleeding (e.g. gastrointestinal, pulmonary, gingival), and/or infection, reflecting the patient's underlying anemia, thrombocytopenia, or neutropenia. Other individuals can present with abdominal fullness or pain from splenomegaly, gum swelling, or symptoms of

leukostasis, like dyspnea or confusion, when the white blood cell count approaches > 100,000 cells/microliter. Symptoms and signs can include pallor, dyspnea, petechiae, ecchymoses, splenomegaly, or altered mental status.

Laboratory Findings

Common abnormal laboratory findings are anemia, thrombocytopenia, and leukopenia or leukocytosis. Coagulation studies may also be abnormal, especially in cases of acute promyelocytic leukemia (APML), which often presents with disseminated intravascular coagulopathy (DIC). The original French-American-British (FAB) system classified subtypes of AML based on the morphologic appearance of the myeloblasts. Under the FAB system, AML was defined by the presence of > 30% blast cells in the bone marrow. The more recent World Health Organization (WHO) system defines AML by the presence of at least 20% blasts in the peripheral blood or bone marrow; however, certain cytogenetic rearrangements are diagnostic of AML, regardless of the blast percentage. Classification is based on a combination of microscopy, histo- and cytochemical stains, cytogenetics, flow cytometry, and molecular analysis of peripheral blood and bone marrow.

Microscopy and Histochemistry

Blast cells often have prominent nucleoli and little cytoplasm. Auer rods, azurophilic granules within lysosomes, can sometimes be seen in myeloblasts on routine microscopy and are a characteristic of myeloid blasts, but not lymphoid blasts. AML cells stain positively with Sudan Black and myeloperoxidase, while ALL cells stain with periodic acid Schiff (PAS). Staining for nonspecific esterase, for example, can distinguish acute monocytic leukemia from other subtypes of AML.

Cytogenetics

Karyotyping and fluorescence in situ hybridization (FISH) often reveal characteristic cytogenetic abnormalities in AML and have become an integral part in the diagnosis, treatment, and prognosis of this disease. The t(15;17)(q22;q12) translocation is frequently seen in APML and creates a fusion product between the PML gene on chromosome 17 and the retinoic acid receptor alpha (RAR α) gene on chromosome 15. This specific translocation is the basis for the excellent response and overall survival of APML to treatment with chemotherapy combined with all trans-retinoic acid (ATRA), which induces cellular differentiation. Other recurrent cytogenetic abnormalities in AML are summarized in Table 2.1. About 40% of individuals with AML have normal cytogenetics.

Table 2.1 Cytogenetic findings in AML

Cytogenetics	Prognosis	Distinguishing features
t(8;21)(q22;q22)	Good	AML1-ETO; myeloblastic with differentiation
t(15;17)(q22;q12)	Good	PML-RAR α ; (APML) excellent response to all trans-retinoic acid
Inversion 16(p13;q22)	Good	CBFB-MYH11; myelomonocytic with eosinophilia
Normal	Intermediate	Normal cytogenetics are observed in ~40% of AML
t(9;11)(p22;q23)	Intermediate	MLL3-MLL, monocytic, more common in children
Deletion 5q	Poor	Associated with prior treatment with alkylating agents
Deletion 7q	Poor	Associated with prior treatment with alkylating agents
11q23	Poor	MLL gene
>3 abnormalities	Poor	

Flow Cytometry and Molecular Analysis

Immunophenotyping (flow cytometry) is used to detect cell markers that help identify the lineage of leukemic cells. For example, myeloid cells often display markers such as CD13, CD33, and CD11c, whereas lymphoid cells more commonly demonstrate expression of the CD3, CD4, CD10, CD19 and CD20 markers. Other molecular studies provide additional diagnostic and prognostic information in patients with AML and are especially important in determining prognosis in patients with normal cytogenetics. The *FLT3* gene (Fms-like tyrosine kinase 3) is commonly mutated, duplicated, or overexpressed in patients with AML and is associated with worse outcomes. Mutations in the *NPM1* gene (nucleophosmin) are present in approximately 30% of AML cases; when found in the absence of other genetic abnormalities, *NPM1* mutations confer a better prognosis. Similarly, *CEBPA* mutations, found in about 15% of AML patients, are associated with more favorable outcomes.

Natural History, Prognosis, and Treatment of AML

Approximately one-third of AML patients less than age 60 will survive longer than 5 years after diagnosis; the outcome in older patients is worse, with only about 10% surviving 5 years. As noted above, certain chromosomal rearrangements and genetic abnormalities correlate with patient outcome. Treatment regimens differ based on the subtype of AML, the age of the patient, and the presence of other co-morbidities. With the exception of APML (discussed below), most patients are treated initially with “7+3” induction therapy, which consists of 7 days of arabinosylcytosine (ara-C) and 3 days of an anthracycline (e.g. daunorubicin or idarubicin). Approximately

50–80% of patients achieve a remission with this combination; those with evidence of residual leukemia after a single induction can sometimes undergo reinduction with a second round of chemotherapy. After induction, AML patients with a favorable prognosis, such as those with the t(8;21) translocation, are often treated with consolidation therapy with several cycles of high-dose ara-C.

In patients with high-risk cytogenetic and molecular features, however, this strategy has a low probability of achieving cure. For these individuals, and for those who relapse after consolidation therapy, consideration is given to SCT. While allogeneic SCT offers the best chance of cure for AML, it is also associated with a high rate of treatment-related mortality, especially in older patients. Early life-threatening complications of SCT include infection, major bleeding, and organ failure. If engraftment of donor stem cells successfully occurs, transplant recipients can go on to develop graft-versus-host disease (GVHD), which itself carries a risk of morbidity and mortality.

In addition to induction, consolidation, and SCT, a number of novel therapeutic agents for AML are undergoing evaluation in clinical trials. These include demethylating agents (e.g. decitabine, azacitidine), Flt3 inhibitors (e.g. PKC 412), purine analogues (e.g. clofarabine), and monoclonal antibodies that target the CD33 cell surface marker present on many AML cells (e.g. lintuzumab, gemtuzumab).

Acute promyelocytic leukemia (APML) is a rare condition, but has a relatively high early mortality if it is not recognized and treated early. Induction therapy begins with oral all trans-retinoic acid (ATRA) followed by chemotherapy with an anthracycline and ara-C; this regimen can achieve complete remission in > 90% of APML cases. After remission, patients undergo multiple rounds of consolidation chemotherapy, often including arsenic trioxide (AsO₃) and maintenance therapy with ATRA.

Diligent supportive care during treatment of AML is essential in avoiding adverse outcomes. This includes transfusion of red blood cells and platelets. Patients with APML are especially prone to disseminated intravascular coagulation (DIC) and its consequences, including intracranial hemorrhage, and thus should be supported with transfusions of fresh frozen plasma or cryoprecipitate and platelets. Prophylactic antibacterial, antifungal, and antiviral agents are usually administered once therapy is initiated. In neutropenic patients with fever, early treatment with broad-spectrum intravenous antibiotics is crucial.

Chronic Myelogenous Leukemia (CML)

Epidemiology and Etiology of CML

CML comprises roughly 20% of all adult leukemias, with a median age at diagnosis of approximately 50 years. CML is characterized by the translocation t(9;22), the so-called Philadelphia chromosome, which creates a fusion product between the *BCR* and *ABL* genes, and creates a fusion product with constitutive tyrosine kinase

activity. The cause of this chromosomal rearrangement is unknown, but it may be observed at increased frequency in individuals previously exposed to radiation.

Clinical Presentation and Diagnosis of CML

Most patients with CML present in the stable phase of the disease (<5% of blasts in the bone marrow) and are asymptomatic at diagnosis. In these patients, diagnosis is often suspected when splenomegaly or leukocytosis is discovered on routine evaluations. Patients in the accelerated phase of CML (5–20% blasts) can sometimes present with weight loss, night sweats, and lymphadenopathy. Those in blast crisis (>20% blasts) present similarly to patients with acute leukemia, with symptoms of anemia, thrombocytopenia, or infection.

The CBC, peripheral blood smear, and bone marrow all usually reveal increased numbers of precursor and mature myeloid cells (blasts, myelocytes, metamyelocytes, granulocytes). These cells often have low enzyme activity, as reflected by the low leukocyte alkaline phosphatase (LAP) score. Definitive diagnosis is made by detection of the BCR-ABL translocation by cytogenetics or FISH. The translocation may also be detected by polymerase chain reaction (PCR) analysis of the blood and bone marrow.

Natural History, Prognosis, and Treatment of CML

The natural history and prognosis for patients with CML has improved dramatically in recent years since the development of molecular therapies that target the BCR-ABL fusion product. Prior to the development of tyrosine kinase inhibitors, most patients with CML would progress to blast crisis within 3–5 years, with generally a poor outcome at that point. These patients were formerly managed with medications such as hydroxyurea, busulfan, and interferon and, where possible, allogeneic stem cell transplantation. Imatinib mesylate, an oral tyrosine kinase inhibitor, revolutionized the treatment of CML. Among patients in the stable phase of disease, treatment with imatinib can achieve a 95% hematologic remission (normal WBC count), a 75% cytogenetic response (no detected Philadelphia chromosomes), and a 40% molecular remission (no BCR-ABL transcripts amplified by RT-PCR). Mutations in *BCR-ABL* or amplification of the gene can generate resistance to imatinib, as can activation of BCR-ABL-independent pathways. Second-generation tyrosine kinase inhibitors, such as dasatinib and nilotinib, are being used for treatment of imatinib-resistant CML.

SCT, once the only curative therapy for CML, is currently considered only for very young patients with CML or for those who do not respond to tyrosine kinase inhibitors. While SCT carries attendant risks, cure rates for CML reach 70%. Patients who develop chronic graft-versus-host disease (GVHD) after transplant have improved outcomes, implicating a strong role of graft-versus-leukemia effect in this disease.

Acute Lymphoblastic Leukemia (ALL)

Epidemiology and Etiology of ALL

Acute lymphoblastic leukemia (ALL) is a cancer of white blood cells of the lymphoid lineage (B- and T-cells). Approximately two-thirds of ALL cases occur in children under the age of 15, with a peak incidence in children ages 2–5. The incidence of ALL is higher among Caucasians and male children. Although ALL is the most common leukemia among children, it is relatively uncommon in adults. Specific causative factors have not been clearly linked to ALL, but it can occur in association with various genetic syndromes, such as Down syndrome, Klinefelter syndrome, neurofibromatosis, and ataxia telangiectasia. A higher concordance rate is observed for ALL in monozygotic twins with a monochorionic placenta over dizygotic twins. The presence of leukemic translocations in neonatal blood spots from individuals who later developed ALL suggests that the initial leukemogenic mutations are prenatal in onset, at least in the pediatric form of this leukemia [12].

Clinical Presentation, Diagnosis, and Classification of ALL

Like other leukemias, ALL can present with anemia, neutropenia, and thrombocytopenia, as well as hepatosplenomegaly, lymphadenopathy, and bone pain. The CNS and testes form sanctuary sites for this leukemia and are potential sites for relapse, albeit less so in recent years. CNS involvement is more common in ALL than in myeloid leukemias; individuals with concurrent CNS and systemic ALL may present with headache, nausea, vomiting, and cranial nerve palsies.

Laboratory Findings

The diagnostic evaluation for ALL is similar to that for AML and includes CBC with differential, flow cytometry, cytogenetics, molecular studies, and analysis of the peripheral smear and bone marrow. The blood count and smear may demonstrate an elevated number of WBCs, with a lymphoblast predominance, often with anemia and thrombocytopenia. Other serum tests may reflect the rapid cell turnover that often accompanies ALL, such as high uric acid, phosphate, and lactate dehydrogenase (LDH), as well as low calcium. For diagnosis, bone marrow must demonstrate at least 25% lymphoblasts, although most patients present with an even greater percentage of blasts. Although other cell lines may be reduced in number, the general appearance and function of myeloid cells, erythroid cells, and megakaryocytes are preserved. Less than 5% of ALL patients have clinical manifestations of CNS leukemia; in this subset, LP and analysis of the CSF can reveal high opening pressure, low glucose, high protein, and pleocytosis with lymphoblasts. An LP is performed in all patients with ALL to detect CNS disease and

concomitantly deliver prophylactic intrathecal chemotherapy. Imaging may demonstrate hepatosplenomegaly or lymphadenopathy; 5–15% of patients have an anterior mediastinal mass, which is more typical of T-cell ALL.

Flow Cytometry

Analysis of cell markers with flow cytometry is essential in the classification of ALL. Expression of terminal deoxynucleotidyltransferase (TdT), by IHC or flow cytometry, distinguishes precursor B- and T-cell leukemia/lymphomas from more mature non-Hodgkin lymphomas. Precursor B-cell ALL accounts for about 80% of ALL cases; these cells usually express the markers CD19 and CD10 (also called the common ALL antigen, cALLa), as well as other B-cell markers, such as CD20, CD24, CD22, CD21, or CD79. Mature B-cell ALL accounts for only 2–3% of ALL cases and represents disseminated Burkitt's lymphoma; these cells express CD19 and CD20.

The markers expressed by T-cell leukemias vary depending on their stage of maturation. Precursor T-cells usually express CD7, TdT, cytoplasmic CD3, and CD1a, whereas more differentiated cells express CD2, CD5, and then CD4 or CD8. Mature T-cells express T-cell receptor (TCR) and surface CD3.

Cytogenetics

As in AML, certain cytogenetic abnormalities are common in ALL and correlate with subtype, prognosis, and response to therapy, especially in precursor B-cell subtypes. In children, favorable cytogenetic findings include the t(12;21) translocation (*ETV-6*), hyperdiploidy (i.e. > 50 chromosomes per cell), and trisomies 4, 10, and 17. Unfavorable rearrangements in precursor B-cell ALL include the translocations t(4;11) (*MLL-AF4*), t(9;22) (Philadelphia chromosome, *BCR-ABL*), and t(1;19) (*E2A-PBX1*). Chromosomal and genetic abnormalities in T-cell ALL are not as well correlated with prognosis. About half of T-cell leukemias have activating mutations in the *NOTCH1* gene and translocations involving the TCR are also common.

Natural History, Prognosis, and Treatment of ALL

For children with ALL, the rate of remission exceeds 95%, with four-fifths of patients surviving for 5 or more years after diagnosis. While 85% of adults achieve complete remission, only 25–40% survive 5 years. Unfavorable prognostic factors for children (summarized in Table 2.2) include age less than 1 year or over 10 years, high WBC count at presentation, poor response to initial therapy, mature B-cell or precursor T-cell ALL subtypes, certain cytogenetic rearrangements, and involvement of CNS.

Table 2.2 Prognostic factors for children with ALL

Characteristic	Favorable	Unfavorable
Age	1–9 years	<1 or >10 years
Subtype	Precursor B-cell	Mature B-cell Precursor T-cell
Location/distribution	No extramedullary disease	Involvement of mediastinum, and CNS
WBC count at presentation	<50,000/microliter	>50,000/microliter
Cytogenetics	t(12;21)ETV6-RUNX1 or TEL-AML1 Hyperdiploidy >50 Trisomies 4, 10, 17	t(9;22) BCR-ABL t(4;11) AF4/MLL t(1;19) E2A/PBX Hypodiploidy
Response to therapy	Clearance of peripheral blasts in 1 week; <5% marrow blasts at day 8 or 15; MRD < 0.1% at day 29	>5% marrow blasts on day 15 or > 0.1% MRD at day 29, failure to achieve CR by day 29

High-risk prognostic factors for adults have not been as clearly identified. Age > 30 is associated with a lower likelihood of achieving complete remission, earlier relapse, and worse overall survival. As with children, higher WBC count is unfavorable, as is the presence of a mediastinal mass.

For precursor-ALL subtypes, treatment involves a stepwise series of regimens: remission induction, intensification, maintenance, and CNS prophylaxis. The goal of remission induction is to normalize cell counts in the blood and marrow, reduce the blast burden to less than 5%, and eliminate extramedullary disease, including the CNS. This stage of treatment employs a steroid (e.g. prednisone), vincristine, L-asparaginase, and often, an anthracycline. In children, the presence of residual disease in a bone marrow aspirate 8 or 15 days after the start of induction predicts a higher risk of relapse [13]. For higher-risk patients and adults, additional agents are used. Intensification or consolidation aims to further reduce minimal residual disease (MRD) and prevent both relapse, as well as the selection of drug-resistant leukemic cells. In children, this phase may include courses of cyclophosphamide and cytarabine or high-dose methotrexate and is often followed by a reinduction regimen; for adults, a 5-drug regimen is typically used [14]. Maintenance therapy for children involves 2–3 years of weekly methotrexate and daily mercaptopurine with pulses of vincristine and steroid, along with intermittent intrathecal chemotherapy, in an effort to reduce relapse.

For mature B-cell ALL, Burkitt leukemia, the treatment regimen is similar to that of precursor ALL, with an emphasis on short intervals of time between cycles.

CNS Disease

Although clinically evident CNS leukemia is rarely seen and less than 10% of patients have blasts in the CSF at diagnosis, if the CNS is not treated

prophylactically, leptomeningeal leukemic relapse is highly likely, despite a systemic remission. The initial diagnostic LP should be performed by a skilled clinician to avoid contamination of the CSF, with circulating leukemic lymphoblasts. At the time of the LP concomitant, intrathecal chemotherapy (methotrexate or cytarabine) should be given. Particularly in children, the LP may be performed under sedation to minimize the risk of trauma, especially given evidence that an initially traumatic LP in patients, with evidence of CNS disease at presentation is associated with inferior survival [15]. In adults, the LP is sometimes delayed until the peripheral blasts are cleared to minimize the theoretical risk of introducing blasts during the procedure.

In most children, CNS prophylaxis is accomplished using intrathecal chemotherapy, whereas cranial irradiation is reserved for patients who are at high-risk of CNS relapse (T cell ALL) or who have evidence for CNS disease at diagnosis or relapse [16]. Cranial irradiation is reserved for high-risk situations due to the concerns for long-term neurotoxicity. In adults, prophylactic intrathecal therapy and cranial irradiation are commonly utilized in combination, and are repeated at the time of CNS relapse. Intrathecal therapies commonly utilized include methotrexate and cytarabine, alone or in combination, and hydrocortisone is added when there is evidence for CNS disease. Liposomal cytarabine with systemic corticosteroids represents another therapeutic option. An Ommaya reservoir may be placed for patients who are receiving frequent intrathecal injections to enhance convenience and accuracy of drug administration, or where the LP is technically difficult due to anatomic considerations. However, hydrocortisone is often eliminated if administering chemotherapy through an Ommaya reservoir, as it may induce severe vomiting.

Stem Cell Transplantation

Autologous SCT is rarely utilized for adults with ALL, however, allogeneic SCT is considered for young adults with a matched sibling donor [17]. For individuals with relapsed disease, including within the CNS, allogeneic SCT is considered.

Chronic Lymphocytic Leukemia (CLL)

CLL, the appearance of mature, malignant lymphocytes within the blood may coexist with or occur independently of SLL when these cells involve lymph nodes. This is discussed in Chapter 1.

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