

The Acute Leukemias

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Although acute leukemias are generally evaluated and treated by hematologists, it is important for general internists to have an understanding of these diseases. Patients often present to their internist with vague symptoms such as fever, malaise, or lethargy. The physical examination and laboratory evaluation provide clues to the diagnosis of acute leukemia. It is critical to distinguish these malignant diseases, which require rapid therapeutic intervention, from benign hematologic disorders. This article provides a general overview of the acute leukemias and highlights the underlying pathophysiology, clinical presentation, prognosis, and outcome.

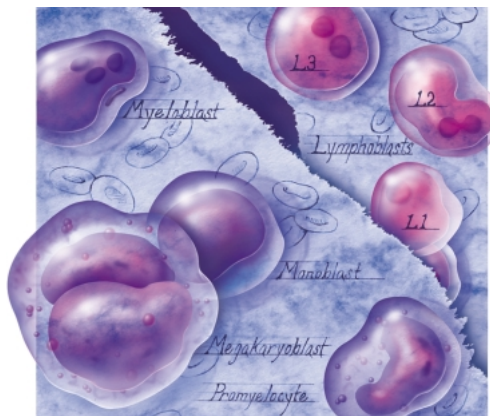
EPIDEMIOLOGY

The acute leukemias are divided into 2 categories, depending upon their cell of origin. Leukemia evolving from the myeloid/granulocyte cell line is called acute myelogenous leukemia (AML). Lymphocytic precursors give rise to acute lymphocytic leukemia (ALL). Each year in the United States, approximately 10,000 persons develop AML and 3000 develop ALL.¹

AML is the most common type of acute leukemia in adults, accounting for 80% of new cases. AML is uncommon in children. The incidence increases steadily with age, with a sharp increase after 45 years. ALL is the most common malignant disease affecting children, accounting for approximately 30% of all childhood cancers.² ALL has a bimodal age distribution, peaking in children between 3 and 5 years of age and again in persons older than 65 years.

RISK FACTORS

The development of acute leukemia, whether AML or ALL, has been associated with potential etiologic factors (Table 1). The mechanisms whereby certain factors



predispose patients to develop leukemia are unclear. Some predisposing factors (eg, genetic syndromes, hematologic dyscrasias) may be associated with chromosomal mutations and thus activate certain oncogenes or damage the DNA repair mechanisms in the body. A genetic predisposition is also demonstrated by the high concordance rate for the development of acute leukemia between identical twins.² Exposure to

chemicals and chemotherapeutic agents also increases the risk for the development of leukemia later in life. Potential agents include benzene, petroleum products, pesticides, hair dyes, tobacco smoking, and ionizing radiation. Treatment with certain chemotherapeutic agents, including alkylating agents and topoisomerase inhibitors, increases the risk of developing secondary leukemias. Certain viruses have also been shown to increase the risk of acute leukemia. The human T-cell leukemia virus 1 (HTLV-1) is associated with T-cell leukemia/lymphoma, and Epstein-Barr virus is associated with acute B-cell ALL.²

CLASSIFICATION OF ACUTE LEUKEMIAS

The original classification scheme proposed by the French-American-British (FAB) Cooperative Group divides AML into 8 subtypes (M0 to M7) and ALL into 3 subtypes (L1 to L3). Although AML blasts evolve from common myeloid precursors, the 8 subtypes differ in degree of maturation (Table 2). The blasts characteristic of the subtype M0 are undifferentiated, whereas those characteristic of M1 to M4 possess granulocytic

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Table 1. Predisposing Factors for the Development of Acute Leukemia

Genetic syndromes
Down syndrome
Bloom syndrome
Neurofibromatosis
Ataxia telangiectasis
Fanconi's anemia
Medications
Alkylating agents
Topoisomerase inhibitors
Environmental exposures
Hydrocarbons
Benzene
Radiation
Hematologic conditions
Myelodysplastic syndromes
Viruses
Epstein-Barr virus
HTLV- I

HTLV- I = human T-cell leukemia virus I.

differentiation with varying degrees of maturation. M5 blasts are predominantly monocytic in origin, and those associated with M6 and M7 are erythroid and megakaryocytic, respectively. The FAB classification of ALL includes 3 subtypes (L1 to L3), which are differentiated based on morphology, including cell size, prominence of nucleoli, and the amount and appearance of cytoplasm (**Table 3**). Approximately 75% of adult ALL cases have blasts with the B-cell phenotype, and 25% have blasts with the T-cell phenotype.

The FAB classification of ALL and AML is based on morphology and cytochemical staining of blasts.^{3,4} However, the recent classification schemes proposed by the World Health Organization (WHO) require the additional evaluation of the leukemic blasts by molecular analysis and flow cytometry.⁵ The results of these 4 methods of evaluation (ie, morphology, staining, molecular analysis, flow cytometry) not only differentiate ALL from AML, but also categorize the subtypes of acute leukemia. Table 3 gives the classification of ALL based on immunophenotypic analysis by flow cytometry. This analysis divides B-cell ALL into 4 subtypes and T-cell ALL into 2 subtypes based on surface markers as determined by the degree of maturation. **Table 4** summarizes the new classification of AML as proposed by

Table 2. French-American-British (FAB) Classification of Acute Myelogenous Leukemia

FAB Type	Descriptive Term
M0	Acute myeloblastic leukemia, undifferentiated
M1	Acute myeloblastic leukemia, without maturation
M2	Acute myeloblastic leukemia, with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5	Acute monocytic leukemia
M6	Erythroleukemia
M7	Acute megakaryoblastic leukemia

WHO. Knowing the subtype of a patient's leukemia helps in predicting the clinical behavior of the disease and the prognosis, and in making treatment recommendations. This classification also improves the reproducibility of diagnoses and stresses the heterogeneity of the subtypes of AML and ALL. Recent advances in molecular biology have shown that various subtypes of AML and ALL behave differently and should not be treated similarly. For example, the identification of M3 AML (acute promyelocytic leukemia) is crucial because it is associated with disseminated intravascular coagulation (DIC), and retinoic acid, in addition to chemotherapy, is the treatment of choice.

CLINICAL PRESENTATION

Signs and symptoms of acute leukemia result from infiltration of bone marrow or extramedullary sites by blasts. As a result, initial symptoms may be due to the presence of anemia, neutropenia, or thrombocytopenia. Patients generally present with nonspecific complaints including weakness, lethargy, fatigue, dyspnea, fever, weight loss, or bleeding. Blasts may also infiltrate organs or lymph nodes, resulting in hepatosplenomegaly or adenopathy. Bone marrow infiltration with blasts can result in bone pain.

Physical findings may include pallor, lymphadenopathy, hepatomegaly, splenomegaly, or bone tenderness. Mucosal bleeding, petechiae, ecchymosis, and fundal hemorrhages may occur as a result of thrombocytopenia. Patients with acute promyelocytic leukemia (APL) characteristically present with coagulopathy and signs of DIC. It should be noted, however, that rapid cell turnover can result in DIC in any form of acute

Table 3. Morphologic and Immunophenotypic Classification of Acute Lymphocytic Leukemia

Morphologic Classification		Immunophenotypic Classification*
FAB Type	Salient Features of Blasts	
L1	Small cells with scant cytoplasm; nucleoli indistinct and not visible	B-cell lineage Early precursor B-cell ALL Common ALL
L2	Large, heterogeneous cells with moderately abundant cytoplasm; clefting and indentation of nucleus; large and prominent nucleoli	Precursor B-cell ALL B-cell ALL
L3	Large cells with moderately abundant cytoplasm; regular, oval-to-round nucleus; prominent nucleoli; prominent cytoplasmic basophilia and cytoplasmic vacuoles	T-cell lineage Precursor T-cell ALL T-cell ALL

ALL = acute lymphocytic leukemia; FAB = French-American-British Cooperative Group.

*Based on surface markers.

leukemia. DIC may also arise during induction chemotherapy for APL.

Extramedullary involvement is more commonly observed in patients with ALL, as compared to patients with AML. Common sites of extramedullary involvement in ALL include the central nervous system (CNS), lymph nodes, spleen, liver, and testes. The testes are frequent sites of relapse but may also be involved at the time of diagnosis, presenting with painless enlargement or firmness. CNS involvement affects fewer than 10% of adults with ALL at the time of diagnosis. Patients with CNS involvement may be asymptomatic or may have symptoms related to increased intracranial pressure (eg, headache, nausea, vomiting, irritability). All patients newly diagnosed with ALL should have a lumbar puncture for cytologic analysis of the cerebrospinal fluid; for AML, however, this is performed only in patients with symptoms indicative of CNS involvement.

Skin involvement (leukemia cutis) or gingival infiltration is seen in approximately 10% of AML patients and is usually associated with monocytic AML (M4 or M5). Chloromas, also called granulocytic sarcomas, are nodules of leukemic blasts. These extramedullary tumors occur in less than 15% of patients with AML and can be located anywhere within the body, but they often occur in the skin. Mediastinal masses are commonly seen in patients with T-cell ALL.

Patients with very high blast counts (greater than $50 \times 10^3/\text{mm}^3$) may present with signs or symptoms of leukostasis. Leukostasis occurs more commonly in patients with AML than in those with ALL. This syndrome, caused by clumping of leukocytes in the vasculature of the lungs and brain, often results in hypoxia, dyspnea, confusion, and coma, and may be fatal. The

patient requires emergent leukapheresis to rapidly reduce the leukocyte count.

Adult T-cell leukemia/lymphoma is a distinct form of ALL that presents with progressive lymphadenopathy, hepatosplenomegaly, and hypercalcemia. It involves the skin, lungs, bone marrow, intestinal tract, and CNS. This disease is associated with HTLV-1 and is endemic in the Caribbean, southeastern United States, Africa, and Japan. Circulating tumor cells have a characteristic "cloverleaf"-shaped nucleus.⁶ A large mediastinal mass is often observed on chest radiograph.

LABORATORY FEATURES

At the time of presentation, the leukocyte count in a patient with acute leukemia is generally elevated, but it may be normal or reduced. Fewer than 20% of patients have a leukocyte count greater than $100 \times 10^3/\text{mm}^3$. Peripheral blood smears show blasts in most cases. Other notable findings include anemia and thrombocytopenia; these result from the increased percentage of blasts in the bone marrow, which leaves little room for erythroid and megakaryocytic precursors. Severe thrombocytopenia (fewer than 50×10^3 platelets/ mm^3) is present in more than half of patients presenting with acute leukemia. Abnormal results of coagulation tests (ie, hypofibrinogenemia, elevated fibrin split products, deficiency of coagulation factors) are seen in patients presenting with signs and symptoms of DIC.

Serum electrolyte levels are typically normal in patients with acute leukemia. Lactate dehydrogenase and uric acid levels may be elevated due to rapid cell turnover; this can lead to urate nephropathy and acute renal failure. Rapid lysis of tumor cells, especially when chemotherapy is instituted, can result in tumor lysis

Table 4. Proposed World Health Organization Classification of Acute Myelogenous Leukemia

AML with recurrent cytogenetic translocations
 AML with t(8;21)
 Acute promyelocytic leukemia [AML with t(15;17)]
 AML with abnormal bone marrow eosinophils [inv(16) or t(16;16)]
 AML with 11q23 (*MLL* gene) abnormalities

AML with multilineage dysplasia
 With prior myelodysplastic syndrome
 Without prior myelodysplastic syndrome

AML and myelodysplastic syndromes, therapy-related
 Alkylating agent-related
 Etoposide-related
 Other therapy-related types

AML not otherwise categorized
 AML minimally differentiated
 AML without maturation
 AML with maturation
 Acute myelomonocytic leukemia
 Acute monocytic leukemia
 Acute erythroid leukemia
 Acute megakaryocytic leukemia
 Acute basophilic leukemia
 Acute panmyelosis with myelofibrosis

AML = acute myelogenous leukemia.

syndrome, manifested by hypocalcemia, hyperkalemia, hyperphosphatemia, and hyperuricemia.

DIAGNOSIS OF LEUKEMIA

The diagnosis of acute leukemia requires that blasts comprise 30% or more of bone marrow cells or circulating white cells.³ (For AML, the new WHO classification proposes to change this to 20% blasts.) For differentiating ALL and AML, a bone marrow aspirate and biopsy are necessary. Components of a comprehensive evaluation of a patient with acute leukemia are shown in **Table 5**.

A peripheral blood smear may provide clues to the type of acute leukemia. Myeloblasts exhibit great variability in size, abundant pale blue cytoplasm with azurophilic (bluish) granules, and distinct nucleoli. The presence of Auer rods, appearing as pink strands within the cytoplasm of the myeloblast, is characteristic of AML (**Figure 1**). Lymphoblasts tend to be small,

Table 5. Components of the Evaluation for Acute Leukemia

Complete history and physical examination
 Complete blood count with differential
 Examination of peripheral blood smear
 Coagulation studies (PT/PTT, fibrinogen level)
 Serum chemistries (renal function tests; calcium, uric acid, phosphorus, and lactate dehydrogenase levels)
 Bone marrow aspirate and biopsy: specimen to be sent for smears, flow cytometry, cytogenetics, and immunohistochemistry
 Lumbar puncture: in all patients with ALL, in symptomatic patients with AML
 HLA typing: required for future blood transfusions and potential bone marrow transplant

ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; PT = prothrombin time; PTT = partial thromboplastin time.

with scant cytoplasm and indistinct nucleoli (**Figure 2**).

Because it is extremely difficult to characterize leukemia as lymphoblastic or myeloid based on morphologic appearance of blasts, additional analyses of the blasts are necessary, including cytochemical staining, phenotypic analyses via flow cytometry, and molecular evaluation for chromosomal abnormalities (ie, cytogenetic studies).

The most important cytochemical stains for determining lineage are myeloperoxidase, Sudan black B, and the esterases. Positive myeloperoxidase reaction or staining with Sudan black B in 3% or more of blast cells indicates myeloid origin. Acid phosphatase is present in early T cells, and demonstration of its activity can differentiate T-cell ALL from non-T-cell ALL. Generally, lymphoblasts stain with terminal deoxynucleotidyltransferase (Tdt), although a small percentage of myeloblasts may be positive as well.

Immunophenotyping by flow cytometry will confirm the diagnosis of leukemia or establish the diagnosis in cases in which morphology and cytochemical stains are equivocal. Cytogenetic studies are important because two thirds of patients diagnosed with AML or ALL and 90% of patients with secondary leukemia will have leukemic blasts showing clonal chromosomal abnormalities.⁷ The chromosomal abnormalities differ between AML and ALL and among the various subtypes. Immunophenotyping and cytogenetic analyses assist in risk stratification and provide information that has important clinical, prognostic, and treatment implications (**Table 6**).⁷⁻⁹

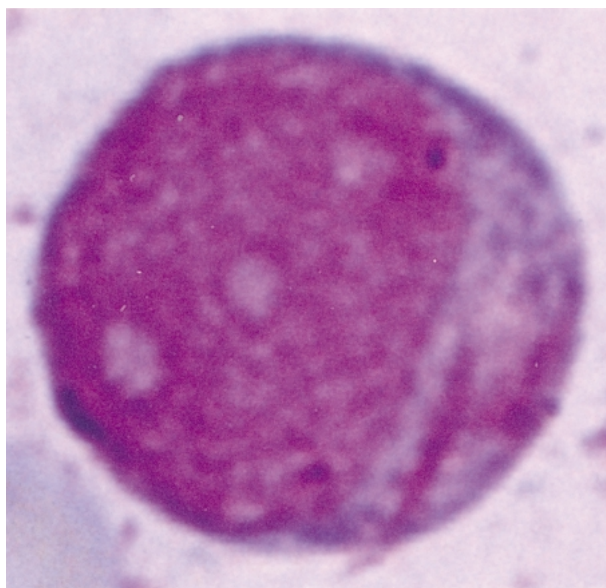


Figure 1. Photomicrograph of a myeloblast showing 3 nucleoli and an Auer rod within the cytoplasm.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute leukemia includes other conditions in which patients present with an elevated leukocyte count, anemia, and thrombocytopenia. These include leukemoid reactions and deep-seated infections, which may be associated with an elevated leukocyte count and a left shift. Infection with Epstein-Barr virus may cause severe lymphocytosis with atypical lymphocytes present on peripheral smear. The diagnosis can be made easily by the absence of blasts in these conditions.

Patients with acute leukemia may also present with low leukocyte counts together with anemia and thrombocytopenia. The differential diagnosis of this presentation includes the primary bone marrow diseases of myelodysplastic syndrome and aplastic anemia. Infiltration of the bone marrow by other neoplasms, including solid tumors and hematologic malignancies, may also present with anemia and/or thrombocytopenia. Immature forms of leukocytes resembling blasts may be seen in severe megaloblastic anemia due to folate and vitamin B₁₂ deficiency. The work-up shown in Table 5 will assist in differentiating these diseases from an acute leukemia.

TREATMENT OF ACUTE LEUKEMIAS

Acute leukemia is a fatal disease if untreated, with a median survival of 3 months or less. The therapy for acute leukemias, both AML and ALL, is separated into

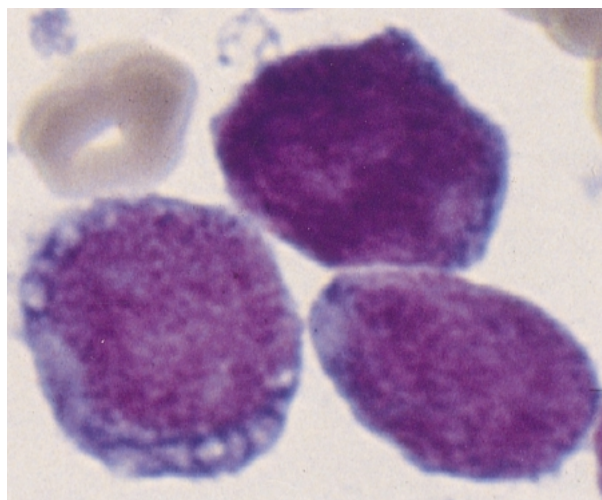


Figure 2. Photomicrograph of lymphoblasts with multiple nucleoli and prominent vacuoles within the cytoplasm.

2 phases: the induction phase and the postremission phase. Induction therapy consists of multiple drugs administered over a period of days to weeks, with the intent of eradicating all blasts from the bone marrow and peripheral blood. Postremission therapy is initiated approximately 4 to 8 weeks after induction chemotherapy has ended, once the patient has recovered from the side effects of therapy and their blood counts have begun to normalize.

Although the majority of patients with AML or ALL will achieve remission following induction therapy, a high relapse rate exists. As a result, postremission therapy is administered with the intention of preventing relapse. The medications and durations of the postremission phase of therapy differ greatly between AML and ALL, as outlined below. The major causes of morbidity and mortality during induction and postremission therapy are infection and hemorrhage. Cooperative group clinical trials are continuously trying to optimize the induction and postremission treatments of both AML and ALL with the hope of improving survival rates.

Induction Therapy for AML

Induction chemotherapy for AML consists of a combination of a cytosine analog (cytarabine, ara-C) and an anthracycline (idarubicin or daunorubicin). The standard regimen includes 7 days of continuous infusion of cytarabine plus 3 daily infusions of idarubicin or daunorubicin, often called the "7 & 3" regimen. The complete response (CR) rate is 50% to 70%.^{10,11} Patients with aggressive types of AML, such as secondary AML or

Table 6. Prognostic Factors in Acute Leukemias

Type of Leukemia	Good Prognosis	Poor Prognosis
Acute myelogenous leukemia	Young age (< 45 y) Presence of Auer rods t(8;21)* (FAB subtype M2) t(15;17)* (FAB subtype M3) inv(16)* (FAB subtype M4)	Secondary leukemia Elevated LDH Hyperleukocytosis FAB subtypes M0, M6, M7 Abnormalities of chromosomes 5 or 7 Trisomy 8
Acute lymphocytic leukemia	Age 2–6 y L1 blast morphology Hyperdiploidy	Age < 2 y or > 10 y Male sex High leukocyte count L3 blast morphology Central nervous system involvement Delay in achieving complete remission t(9;22) (Philadelphia chromosome)* t(4;11)*

FAB = French-American-British subclassification; LDH = lactic dehydrogenase.

*Chromosomal abnormalities.

AML with unfavorable cytogenetic characteristics, may be treated with more aggressive therapy, including very high doses of cytarabine (HIDAC) alone or in combination with amsacrine, mitoxantrone, or etoposide.^{12–14}

Postremission Therapy for AML

Postremission therapy generally consists of a chemotherapy regimen administered monthly for 3 to 4 cycles. Although the number of cycles required is currently unknown, postremission therapy lowers the relapse rate and improves survival.¹¹ Recently, the emphasis has shifted toward using HIDAC regimens, especially in patients younger than 60 years with favorable cytogenetics.¹⁵ Postremission therapy yields a median leukemia-free duration of 12 to 18 months, with approximately 20% to 25% of these patients being cured of their disease.^{11,15}

Acute leukemias that develop in patients 60 years or older often have unfavorable prognostic factors (ie, unfavorable cytogenetics). As a result, the CR rates in elderly patients following induction chemotherapy are usually in the 40% to 60% range, and the median remission duration is less than 1 year. These patients should be considered for participation in clinical trials of experimental therapies.¹⁶

Therapy for APL

Treatment of APL differs significantly from the standard therapy for other types of AML. APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, resulting in the union of portions of the promyelocytic leukemia gene with the retinoic acid receptor- α gene. All-*trans*-retinoic acid (ATRA) differentiates APL blasts into mature cells. Unfortunately, this effect is transient, lasting weeks to months. As a result, induction therapy for APL includes ATRA combined with the standard 7 & 3 chemotherapy.¹⁷ Another drug with activity against APL is arsenic trioxide.¹⁸

Induction Therapy for ALL

In contrast to the induction therapy for AML, which uses 2 medications administered over 1 week, induction therapy for ALL consists of a complex schedule of multiple drugs administered over 2 to 4 weeks. Medications that may be used include vincristine, corticosteroids, anthracyclines, cyclophosphamide, cytarabine, methotrexate, and asparaginase. Current treatment regimens yield a CR of 80% to 90%.^{19–23} Specific disease characteristics, such as the chromosomal abnormality t(9;22) (Philadelphia chromosome), L3 subclass, or older age of the patient will reduce the likelihood of disease-free survival (Table 6).

Postremission Therapy for ALL

Unlike AML, postremission therapy for adults with ALL involves weeks to months of chemotherapy in combination with prophylactic treatment of the CNS. Although there are many approaches to postremission therapy, in general, it comprises 2 phases. These phases differ in their aggressiveness and, therefore, in their toxicities. The first phase, termed *consolidation* or *intensification* therapy, utilizes multiple chemotherapeutic agents administered over a 1- to 2-week period each month for 3 to 4 months.

Following consolidation, maintenance therapy is initiated. This phase of therapy includes daily oral chemotherapy (6-mercaptopurine) with weekly infusions of methotrexate. The optimal duration of maintenance treatment is unknown, but it usually lasts for approximately 2 years. It is unlikely that any of the multiple proposed regimens is clearly superior. The long-term survival rate following maintenance therapy is about 30% to 40%.¹⁹⁻²³

CNS Prophylaxis in ALL

Although fewer than 10% of adults with ALL have CNS involvement at the time of diagnosis, this area is frequently involved at the time of relapse. Without CNS prophylaxis, 20% to 50% of ALL patients who relapse have CNS involvement. Current prophylactic therapies include intrathecal administration of methotrexate or cytarabine, irradiation, or systemic administration of chemotherapeutic agents that cross the blood-brain barrier (eg, methotrexate, cytarabine).²⁴

ROLE OF BONE MARROW TRANSPLANTATION

Both allogeneic and autologous bone marrow transplantation have been advocated for selected patients with acute leukemia.²⁵ Allogeneic bone marrow transplantation should be considered in patients with acute leukemia who relapse after standard therapy. Patients with AML or ALL with poor prognostic factors should be evaluated for allogeneic transplant during their first complete remission. However, in patients with favorable cytogenetics, transplant can be delayed to first relapse or second complete remission.²⁶

The role of autologous bone marrow transplantation in first remission is controversial. It should be considered as a salvage therapy in patients with relapsed acute leukemia who lack an HLA-matched donor, patients who are older than 60 years, or have comorbid medical conditions that preclude allogeneic transplant.²⁷

FUTURE TRENDS

Recent advances in molecular biology have helped

to characterize the various cellular abnormalities of leukemic blasts at the genetic level. New drugs with different mechanisms of action on blasts are being explored to improve survival and remission rates. Some of these drugs include differentiation agents (retinoids); monoclonal antibodies directed against CD33 and CD45 antigens, which are present on myeloid blasts; tyrosine kinase inhibitors; antiangiogenesis agents; and drugs that modulate multidrug resistance in leukemia cells (MDR blockers).^{28,29} New combinations of chemotherapeutic agents are being studied in an attempt to increase the response rates.³⁰ Our understanding of the pathogenesis of the various acute leukemias has progressed markedly over the past 10 years. These advances, along with active investigations into novel therapies, may improve future outcomes for patients with acute leukemia. **HP**

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