

PEDIATRIC LEUKEMIAS

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Learning Objectives

1. Analyze the prognostic factors for acute lymphoblastic leukemia and determine the outcome based on the patient's individual risk factors and pharmacogenetics.
2. Design a treatment plan based on the diagnosis and individual risk factors for acute pediatric leukemias.
3. Construct individualized therapy for patients with acute leukemias.
4. Demonstrate an understanding of some of the pharmacogenetic tests that can be performed in patients with leukemia.
5. Demonstrate an understanding of the incidence, pathophysiology, classification, and risk factors for acute myeloid leukemia (AML).
6. Develop an understanding of the therapeutic management of AML.
7. Devise a plan for the use of antimicrobial drugs in patients receiving AML therapy.
8. Demonstrate an understanding of the incidence and etiology of the late complications of chemotherapy in leukemia survivors.

Introduction

Childhood acute leukemias represent a heterogeneous group of disorders. Although recent advancements have been made in improving the survival rate of children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), the survival rates of AML remain substantially lower than ALL. Because more pediatric patients are surviving their malignancies and living into adulthood, there is an increased focus on managing late effects of survivors.

Acute Lymphoblastic Leukemia

Epidemiology

Acute lymphoblastic leukemia is the most common childhood malignancy. It accounts for one-fourth of all pediatric malignancies and 75% to 80% of childhood leukemias. The annual incidence of ALL in the United States is 29.2 per million, with a peak incidence occurring between the ages of 2 years and 5 years. In the United States, ALL affects white children more often than African American children, and its incidence is higher in boys than girls.

Genetics

Acute leukemia is a clonal disorder of the hematopoietic system, arising from a single cell mutation that is then passed on. In most cases, acquired genetic abnormalities are associated with leukemia. However, inherited genetic abnormalities have been implicated in 5% of acute leukemias. Down syndrome is the most common genetic syndrome associated with acute leukemias, with studies suggesting a 10- to 20-fold increased risk of leukemia. Other genetic disorders associated with acute leukemias include Bloom syndrome, neurofibromatosis type I, Shwachman syndrome, and ataxia-telangiectasia.

Pathophysiology

Leukemia arises from a single mutant hematopoietic progenitor cell that is capable of indefinite self-renewal and gives rise to malignant, poorly differentiated hematopoietic precursors. It is unknown where in normal differentiation the leukemia arises, and it may be highly variable. This event most likely occurs in committed lymphoid precursors many years before clinical presentation.

Abbreviations in This Chapter

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CNS	Central nervous system
CR	Complete remission
HSCT	Hematopoietic stem cell transplantation
MRD	Minimal residual disease
MTX	Methotrexate
WBC	White blood cell

Clinical Presentation

The presentation of pediatric ALL is quite variable and depends on the extent of bone marrow involvement and extramedullary spread of the disease. The clinical findings and symptoms are a result of the neutropenia, thrombocytopenia, and anemia associated with ALL. The most common presenting features are fever, pallor, fatigue, bone pain, petechiae, and bleeding. Signs of extramedullary disease spread include lymphadenopathy, hepatomegaly, and splenomegaly. The duration of these symptoms may vary from days to months before diagnosis.

T-cell ALL, which accounts for about 15% of ALL cases, has distinct clinical features. This type of ALL usually occurs in adolescent boys, presents with an elevated white blood cell (WBC) count, and is commonly associated with a mediastinal mass. About half of the children with T-cell ALL have mediastinal masses, and one-third to one-half have initial WBC counts greater than 100×10^3 cells/mm³. Patients with T-cell leukemia are also more likely to have central nervous system (CNS) disease at diagnosis.

Extramedullary disease spread is manifested by the site of organ involvement. Ocular leukemia may present as retinal hemorrhage; it may also be associated with leukemic infiltration of the orbit, optic nerve, retina, iris, cornea, or conjunctiva, which may produce blurred vision, photophobia, or pain. A painless, enlarged scrotum may be a sign of testicular involvement or hydrocele. Overt testicular leukemia is rare at diagnosis, occurring in about 2% of male patients. Typically, testicular leukemia is diagnosed in infants or adolescents with T-cell ALL who present with a mediastinal mass and elevated WBC count.

Abnormal WBC counts are reflective of the degree of bone marrow involvement and the extent that the bone marrow has been replaced by leukemic lymphoblasts. The median WBC count at diagnosis is 12×10^3 cells/mm³. Hyperleukocytosis (WBC greater than 100×10^3 cells/mm³) occurs in 15% of patients. Thrombocytopenia (platelets less than 50×10^3 cells/mm³) is typically present at diagnosis. Even with a low platelet count, severe hemorrhage is uncommon. More than 75% of the patients present with anemia that is typically normochromic, normocytic, and associated with normal to low reticulocyte counts. Patients who present with increased WBC count or heavy tumor burden are at a higher risk of developing tumor lysis syndrome on initiation of therapy.

Diagnosis

A bone marrow aspirate is generally necessary to confirm the diagnosis of ALL. A biopsy may be performed in select instances. Examining the bone marrow is diagnostic because it is usually replaced with leukemic lymphoblasts. Cerebrospinal fluid should also be obtained. Central nervous system leukemia is defined as the presence of at least five WBC per microliter of cerebrospinal fluid, with leukemic blast cells or cranial nerve palsies.

Classification

Because ALL is a heterogeneous disease, its classification involves the use of morphology, immunophenotype, and genetics. There have been many attempts to classify ALL based on morphology. These systems have classified cells based on criteria such as size, nuclear-to-cytoplasmic ratio, nuclear shape, nucleoli, and other similar features. The French-American-British Cooperative Working Group system is the only one that has been routinely accepted. This group defines three categories of lymphoblasts (L1, L2, and L3); about 85% of children have L1 morphology, 14% have L2, and 1% have L3. Currently, the World Health Organization recognizes two immunophenotypic subtypes of ALL: precursor B-cell and precursor T-cell lymphoblastic leukemia/lymphoma.

The cytogenetics of pediatric ALL can be analyzed by conventional or molecular cytogenetics. Conventional cytogenetics uses standard chromosomal analysis and is the initial screening method used to detect abnormalities in leukemic cells. These conventional studies detect only chromosomal abnormalities in mitotically active cells. Molecular cytogenetic studies are able to detect chromosomal abnormalities in nonmitotically active leukemic cells. These types of screenings include DNA probes, fluorescence in situ hybridization, and reverse transcriptase polymerase chain reaction. Cytogenetic abnormalities associated with pediatric ALL include chromosomal number (ploidy) and structural rearrangements (translocations). Ploidy is determined by directly counting the number of chromosomes in a metaphase or by an indirect method of measuring DNA by flow cytometry. When measured by flow cytometry, the DNA content is expressed as the DNA index. The DNA index, or ploidy, is a ratio of the amount of fluorescence in a normal diploid cell to the fluorescence in the bone marrow blast. Among the different ploidy groups, only hyperdiploidy (more than 50 chromosomes per cell) and hypodiploidy (less than 44 chromosomes per cell) have clinical relevance. Hyperdiploidy mostly occurs between the ages of 1 year and 10 years and is associated with a lower WBC count and a favorable prognosis. Hypodiploidy is associated with a poor prognosis.

Structural rearrangements or translocations are common in ALL. These chromosomal translocations are found only in the leukemic cells. Only the most common translocations are discussed in this chapter. *TEL-AML1* fusion, or t(12;21), is the most common translocation associated with pediatric ALL. This fusion occurs in up to 25% of pediatric patients and is associated with a good prognosis. Another common translocation associated with pediatric ALL is *E2A-PBX1* fusion or t(1;19). This rearrangement occurs in 3% of white patients and 11% of African American patients. This translocation is commonly seen with precursor B-cell

phenotype, pseudodiploidy, increased WBC count, and CNS disease, and it is associated with an improved outcome if intensive therapy is administered. *MLL* rearrangements, including t(4;11), are typically associated with a poor outcome. The t(4;11) is common in infant ALL and is associated with an increased WBC count and CNS leukemia. *BCR-ABL* fusion or t(9;22) occurs in less than 5% of ALL cases and has a dismal prognosis. It is positively associated with age and elevated WBC count.

Prognostic Factors

Patients are assigned to various treatment groups based on prognostic factors that can be predicted at diagnosis. Various clinical and laboratory features have prognostic significance.

For patients with precursor B-cell ALL, initial WBC count is predictive of outcome. Patients who present with a higher WBC count have a worse outcome. Although there is no definitive WBC count, a presenting WBC count greater than 50×10^3 cells/mm³ correlates with a poorer outcome. Infants and patients with T-cell leukemia often present with increased WBC count.

Age, associated with precursor B-cell ALL, is predictive of outcome. Patients younger than 1 year or older than 10 years have a worse prognosis. Adolescents often present with other high-risk features, including increased WBC count, T-cell leukemia, and extramedullary disease. Infants also have a very poor prognosis. In addition to presenting with an increased WBC count and extramedullary disease, including CNS leukemia, up to 60% of infants also have t(4;11) translocation. In most studies, girls typically have a better prognosis than boys. This may be because boys can have a testicular relapse; however, it is most likely associated with the frequency of diagnosis of T-cell leukemia in boys and a lower DNA index. Commonly, patients with T-cell leukemia have fared worse compared with those with precursor B-cell leukemia. However, with the use of more intensive treatment, long-term survival is now 70% or better.

The prognostic value of race is a controversial topic. Older studies have shown poorer outcomes associated with African American race, but studies from the 1980s and early 1990s showed equivalent outcomes when patients were stratified for risk group at diagnosis. Historically, the difference in outcomes based on race has been attributed to socioeconomic factors. In addition, differences in the pharmacogenetic profile of patients from various ethnic backgrounds may play a significant role in outcome.

Although the above factors are important in determining a patient's risk group, the most important prognostic indicator is initial response to therapy. Patients who do not achieve remission within 4–6 weeks of induction therapy have a higher rate of relapse and shortened survival. The response to therapy is based on both leukemic cell genetics and host pharmacogenetics. Minimal residual disease (MRD) measurement can assess a level of sensitivity and specificity not obtained by morphologic examination. Patients who achieve a remission with less than 10^{-4} cells (0.01%) at the completion of 6 weeks' remission induction therapy have a higher rate of survival than those who have measurable disease at this time.

Risk stratification varies among institutions. The National Cancer Institute has developed a risk classification system that is used by most institutions that treat pediatric leukemias. According to the National Cancer Institute, patients with precursor B-cell ALL are initially assigned to a standard-risk or high-risk group based on age and initial WBC count (age 1–9.99 years and WBC count less than 50×10^3 cells/mm³ are considered standard risk). All children with T-cell phenotype are considered high risk. Early treatment response (assessed by day 7 or day 14 marrow morphology and end induction MRD assessment) and cytogenetics are subsequently used to modify initial classification.

Patients with standard-risk ALL and rapid morphologic response (day 14 marrow with less than 5% blasts, MRD less than 0.1%, and day 29 marrow with less than 5% blasts) are assigned to one of two groups based on cytogenetics. Patients with t(12;21) or trisomies of chromosomes 4, 10, and 17 are considered standard risk low; patients presenting without these cytogenetic abnormalities are considered standard risk average. Patients with standard-risk ALL and either slow morphologic response (day 7 or day 14 marrow with less than 5% blasts or MRD greater than 0.1% on day 29) are assigned to a standard-risk high group and receive more intensive consolidation treatment. Patients with high-risk precursor B-cell ALL are divided into rapid responder and slow responder groups. Patients are classified as very high risk if they have any of the following features (regardless of initial risk group): t(9;22); hypodiploidy; *MLL* translocation with a slow early morphologic response; day 29 marrow with greater than 5% blasts or day 29 and day 43 MRD greater than 1%.

Treatment

Therapy has been influenced by the realization that ALL is a heterogeneous group of disorders and the identification that patients should be classified based on risk group. Combination chemotherapy is the primary treatment modality used. The goal of therapy for pediatric ALL is cure. Table 1-1 contains a list of chemotherapy agents used in the treatment of ALL and AML.

Remission Induction

The goal of initial therapy is to induce remission by the eradication of 99% of the initial leukemic cell burden. This phase of treatment usually uses three or four agents: (1) vincristine, (2) glucocorticoid (prednisone or dexamethasone), plus either (3) asparaginase or (4) an anthracycline, or both. Prednisone has typically been the glucocorticoid of choice. However, studies have shown that dexamethasone may be a more potent cytotoxic agent and have better CNS penetration. For this reason, some cooperative groups have switched to this glucocorticoid. Dexamethasone may be associated with more acute infections and long-term neurologic sequelae. Patients treated with glucocorticoids are also at risk of osteonecrosis or avascular necrosis (10% to 20% incidence in children with ALL older than 10 years). Several anthracyclines have been used during remission induction treatment. No one anthracycline has superior efficacy.

There are various formulations of asparaginase: asparaginase (derived from *Escherichia coli*); pegaspargase (*E. coli* asparaginase bound to polyethylene glycol, also

Table 1-1. Antineoplastic Agents Used in Pediatric ALL and AML

Name	Therapeutic Category	Major Adverse Effects
Asparaginase	Enzyme antineoplastic	Pancreatitis, thrombosis, hyperglycemia, hypersensitivity reactions
Cyclophosphamide	Alkylating agent	Hemorrhagic cystitis, SIADH, hepatotoxicity, sterility
Cytarabine	Pyrimidine antimetabolite	Chemical conjunctivitis, mucositis, neurotoxicity
Daunorubicin, doxorubicin	Anthracycline	Congestive heart failure; cardiotoxicity; mucositis; neutropenia; radiation recall; discoloration of saliva, sweat, urine, and tears; vesicant
Dexamethasone, prednisone	Corticosteroid	Hyperglycemia, avascular necrosis, osteopenia, osteoporosis
Etoposide	Epipodophyllotoxin	Hypotension, secondary leukemia
Gemtuzumab ozogamicin	CD33 antimetabolite	Sinusoidal obstructive syndrome, neutropenia, hepatotoxicity, mucositis, thromboembolic events
Mercaptopurine	Purine antimetabolite	Neutropenia, hepatotoxicity
Methotrexate	Antifolate antimetabolite	Mucositis, encephalopathy, hepatotoxicity, nausea, vomiting
Mitoxantrone	Anthracedione	Cardiotoxicity, discoloration of skin and urine, interstitial pneumonitis, vesicant
Vincristine	Vinca alkaloid	Peripheral neuropathy, constipation, paralytic ileus, jaw pain, SIADH, vesicant

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; SIADH = syndrome of inappropriate antidiuretic hormone.

called PEG-L asparaginase); and crisantaspase (asparaginase derived from *Erwinia chrysanthemi*, available in the United States on a compassionate use basis only). All three preparations differ pharmacokinetically, and dosages are different. Studies that have shown differences in efficacy and toxicity used nonequivalent doses.

Patients who have the *BCR-ABL* translocation should be treated with a tyrosine kinase inhibitor (e.g., imatinib, dasatinib) throughout therapy.

Intensification (Consolidation) Therapy

Although oncologists now agree that this phase of therapy is essential to the treatment of ALL, there is no consensus regarding the best treatment. For example, St. Jude Children's Research Hospital uses high-dose methotrexate (MTX) given every 2 weeks with continuous mercaptopurine. The dose of MTX is 5 g/m² given intravenously over 24 hours for standard-risk and high-risk patients and 2.5 g/m² given intravenously over 24 hours for low-risk patients. Patients with T-cell leukemia accumulate fewer MTX polyglutamates (active metabolites) than patients with B-lineage leukemia; patients with T-cell leukemia therefore require higher serum concentrations. The Children's Oncology Group uses different regimens based on the risk classification. The regimens include combinations of vincristine, mercaptopurine, pegaspargase or cyclophosphamide, and cytarabine.

Continuation (Maintenance) and Reinduction Therapy

Children with ALL require long-term treatment to maintain remission. In general, treatment should continue for at least 2.5 years. Many oncologists prefer to treat boys for 3 years based on their higher risk of relapse. The backbone of maintenance therapy is weekly MTX and daily mercaptopurine. In addition, pulses of a glucocorticoid and vincristine have improved survival. Dexamethasone is typically the glucocorticoid of choice during maintenance.

Delayed intensification or reinduction involves a repetition of the chemotherapy used during remission induction at 3 months after remission. Investigators found that one course of delayed intensification was most beneficial for standard-risk leukemias. It was then shown that two courses of delayed intensification improved outcomes in high-risk patients.

Reintensification Therapy

Patients with high-risk ALL may receive reintensification therapy to maximize killing of leukemic cells before hematopoietic stem cell transplantation (HSCT). At St. Jude Children's Research Hospital, the chemotherapy agents used include dexamethasone, cytarabine, etoposide, asparaginase, and triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine.

CNS Therapy

The need for CNS prophylaxis is based on the idea that the CNS can act as a sanctuary site for leukemic cells. Prophylaxis of the CNS can be achieved by various modalities, including radiation, intrathecal therapy, high-dose systemic chemotherapy, or a combination of these. Cranial radiation is the most effective CNS-directed therapy; however, toxicity (including neurotoxicity, endocrinopathy, and brain tumors) offsets its efficacy. A study performed on survivors 10 years after ALL diagnosis demonstrated that patients who received cranial radiation were at a 21% higher risk of developing a second neoplasm than the general population and had an increased unemployment rate. An earlier study resulted in a similar outcome for children who received triple intrathecal therapy with MTX, hydrocortisone, and cytarabine together with systemic chemotherapy compared with cranial radiation. The St. Jude Children's Research Hospital reported two studies that suggested early intensive triple intrathecal therapy decreased CNS relapse and increased event-free survival.

Pharmacogenetics of Therapy

Mercaptopurine is anabolized by hypoxanthine phosphoribosyl transferase to thioinosine monophosphate and eventually to triphosphates of 6-thioguanosine, called 6-thioguanine nucleotides. These metabolites interfere with normal DNA and RNA synthesis. Mercaptopurine is catabolized by thiopurine S-methyltransferase to methylmercaptopurine. The activity of this enzyme undergoes a common genetic polymorphism. About 1 in 300 individuals is homozygous deficient for the enzyme, 10% are heterozygous, and the remaining are homozygous wild type. Patients heterozygous for thiopurine S-methyltransferase mutations require a dosage reduction to avoid myelosuppression compared with patients who are homozygous wild type. However, patients who are homozygous deficient may require a 10-fold dosage reduction of mercaptopurine.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation has been reserved for individuals with Philadelphia chromosome–positive ALL, patients whose disease fails to achieve a remission at the end of 4–6 weeks of induction therapy, and patients with early hematologic relapse. Other high-risk patients (e.g., infants who have ALL with *MLL* rearrangements) have not shown an improvement in outcomes with HSCT.

Treatment of Specific Risk Groups

Infant ALL

Infant ALL accounts for 2.5% to 5% of children with leukemia. The most common genetic abnormality is the *MLL* gene rearrangement of 11q23 seen in up to 80% of the infants. Very young age (younger than 6 months), high initial WBC count, any 11q23/*MLL* rearrangement, and a poor early response to therapy predict a poor outcome in this population. It is known that infant blasts in vitro have an increased sensitivity to cytarabine.

Down Syndrome

Children with Down syndrome have a 10- to 20-fold increased risk of developing leukemia (either ALL or AML). Until the age of 5 years, the risk of developing AML is 4 times higher than for ALL; after the age of 5 years, ALL is more common. Patients with Down syndrome are more likely to have a precursor B-cell phenotype. These patients are less likely to be hyperdiploid, have a T-cell phenotype, or have CNS leukemia at diagnosis. Patients with Down syndrome and AML and ALL have an outcome similar to other patients, excluding patients with non Down syndrome AML M7; however, they are more likely to have mucositis, myelosuppression, and infection. Patients with Down syndrome are more sensitive to MTX and require a dosage reduction. These patients also have a delayed clearance of MTX; this is most likely caused by the reduced folate carrier gene on chromosome 21, which may lead to increased accumulation of MTX polyglutamates and therefore to increased toxicity.

Relapsed ALL

Clofarabine is a deoxyadenosine nucleoside analog approved for the treatment of patients with relapsed ALL or ALL refractory to at least two previous treatment regimens.

Compared with other agents in this class (cladribine or fludarabine), clofarabine has the theoretical advantage of working through two antiproliferative mechanisms as well as having proapoptotic effects. Clofarabine may be more resistant to bacterial purine nucleoside phosphorylase, which may reduce the toxicity of the drug, especially the neurotoxic effects. Clofarabine achieved an overall response rate of 32% (five complete remissions [CRs], two partial remissions) in a Phase I study of 25 pediatric patients (median age 12 years) with relapsed or refractory ALL. In this study, six dosage levels were used (11.25–70 mg/m²/day); the maximal tolerated dose was 52 mg/m²/day given intravenously for 5 days. In an open-label study of 49 pediatric patients with relapsed or refractory ALL, clofarabine induced a CR in 12.2% of patients. All of the patients in the study group had received at least two previous treatment regimens.

Nelarabine, a prodrug of the deoxyguanosine analog 9-beta-D-arabinofuranosyl guanine (ara-G), is demethylated by adenosine deaminase to ara-G, monophosphorylated by deoxyguanosine kinase and deoxycytidine kinase, and then converted to active 5'-triphosphate. Accumulation of the triphosphate form in leukemic blast cells permits its incorporation into DNA, leading to inhibition of DNA synthesis and cell death. Nelarabine is indicated for the treatment of patients with T-cell ALL whose disease has not responded to or has relapsed after treatment with at least two chemotherapeutic regimens. In a study conducted by the Children's Oncology Group (COG P9673), 84 patients age 21 years or younger with relapsed or refractory T-cell ALL or T-cell lymphoblastic lymphoma received nelarabine 650 mg/m² intravenously over 1 hour/day for 5 days. Complete remission was achieved in 13% of the patients. The number of patients who achieved CR combined with the number of patients with partial hematologic recovery was 23%. The median time to CR was 3.4 weeks, and the duration of response ranged from 3.3 weeks to 9.3 weeks. The median overall survival was 13.1 weeks.

Acute Myeloid Leukemia

Epidemiology and Risk Factors

Acute myeloid leukemia is the second most common acute pediatric leukemia. The annual incidence of AML in the United States is 1.6 per million. Its rate of occurrence differs by race: Hispanics are more likely to have AML than African American children, followed by white children. This disease is more common in patients 2 years or younger. Although AML accounts for only 15% to 20% of all acute leukemia cases, it is responsible for more than 30% of pediatric leukemia deaths. Recent advances in both therapy for AML and supportive care measures have increased the overall survival from this disease to 60%.

Genetic and nongenetic risk factors have been identified in the development of AML. Patients with genetic disorders such as Fanconi anemia, Li-Fraumeni syndrome, Down syndrome, neurofibromatosis type I, and severe congenital neutropenia have a greater risk of developing AML. Nongenetic risk factors include exposure to ionizing radiation, organic solvents (e.g., benzene), herbicides, and pesticides. Although the number of de novo AML cases has reached a plateau, the incidence of secondary AML has

Table 1-2. French-American-British Classification of Acute Myeloid Leukemia

Subtype	Common Name (pediatric incidence %)	Characteristic Findings	Associated Translocations and Rearrangements	Prognosis
M0	Acute myeloblastic leukemia with no maturation (< 3%)	CD13, CD33, CD117	inv(3q26) and t(3;3)	
M1	Acute myeloblastic leukemia with minimal maturation (20%)	CD13, CD15, CD33, CD34		
M2	Acute myeloblastic leukemia with maturation (30%)		t(8;21) and t(6;9)	Good
M3	Acute promyelocytic leukemia (5% to 10%)	Auer rods	t(15;17), t(11;17), t(5,17)	Good
M4	Acute myelomonocytic leukemia (25% to 30%)	CD13, CD15, CD33	11q23, inv(3q26) and t(3;3), t(6;9)	
M4Eo	Acute myelomonocytic leukemia with abnormal eosinophils		inv(16), t(16;16)	Good
M5	Acute monocytic leukemia (15%)	CD14, CD33	11q23, t(8;16)	Poor
M6	Acute erythroleukemia (5%)			Poor
M7	Acute megakaryoblastic leukemia (5% to 10%)	CD13, CD33, CD41, CD61	t(1;22)	Poor

increased in the past three decades because of exposure to alkylating agents or topoisomerase II inhibitors.

Clinical Presentation

The clinical presentation of AML is identical to that of ALL with a couple of exceptions. Chloromas (solid collections of leukemic cells outside the bone marrow) and leukemic infiltration of the gum are more common in AML, whereas mediastinal masses are less common. In addition, the median WBC count at diagnosis for patients with AML is $20\text{--}50 \times 10^3$ cells/mm³ (70% of the patients present with a WBC in this range). Moreover, the incidence of hyperuricemia and the development of tumor lysis syndrome is lower compared with ALL.

Diagnosis, Classification, and Prognostic Factors

The diagnostic work-up of AML is similar to that of ALL. The bone marrow aspirate and biopsy should contain at least 20% of myeloid blasts for a diagnosis of AML. The classification of AML involves the use of morphologic, histochemical, immunophenotyping, and cytogenetic characteristics. Currently, there is no classification method for AML that is specific to pediatric patients. The French-American-British classification (Table 1-2) has been widely used, but its application to pediatric AML has several shortcomings, leading to an inability to classify some children. Another classification now gaining acceptance and being incorporated in most pediatric AML trials is that of the World Health Organization.

Patient age and cytogenetics are among the most important prognostic factors of newly diagnosed AML. The older the patient, the poorer the prognosis; this is because these patients tend to have more genetic mutations leading to multidrug resistance, which in itself carries a poor prognosis. In general, inversion(16) AML carries a favorable prognosis, whereas monosomy 5 or 7 carries a poor prognosis. Finally, the faster remission is achieved, the better the prognosis.

Treatment

The goal of therapy for pediatric AML is cure. Most AML treatment regimens consist of intensive induction

chemotherapy, followed by a consolidation (postremission) phase. The goal of induction is to achieve a complete molecular and morphologic remission, whereas consolidation therapy aims at maintaining this remission and preventing relapse. The role of maintenance therapy remains controversial; it is not discussed here because most cooperative groups no longer incorporate it in AML trials.

Induction Therapy

This phase of treatment usually consists of administering a *backbone* of cytarabine and an anthracycline agent. This backbone, usually called a 7+3 regimen, consists of giving cytarabine for 7 days and daunorubicin for 3 days. Certain groups have incorporated etoposide or thioguanine into their induction therapy. However, it is unclear if the addition of these agents contributes to increased remission rates or if they are attributed to the better use and dosing of the cytarabine and anthracycline. The optimal dosage of cytarabine has yet to be determined and varies significantly among study groups. Dosages from as low as 100 mg/m²/day to as high as 6000 mg/m²/day given intravenously have been used, and no one regimen has shown a significant improvement in the remission rate. Because cytarabine is secreted through the tear ducts, it can irritate the cornea and cause chemical conjunctivitis. To decrease this adverse effect, all patients who receive high dosages of cytarabine should receive corticosteroid or lubricating eye drops from the beginning of cytarabine therapy until 24 hours after the last dose of this agent.

Several anthracyclines are used during the induction phase, including daunorubicin (most commonly used), idarubicin, and mitoxantrone. Idarubicin is thought to be taken up by the leukemic blasts faster and retained in the cells for a longer period; it is speculated to be less cardiotoxic. The active metabolite of idarubicin is also longer acting than all the other anthracyclines and has been reported to have antileukemic activity in the cerebrospinal fluid. Mitoxantrone, however, is thought to be more myelosuppressive, leading to increased risk of infection. Studies comparing daunorubicin with idarubicin

or mitoxantrone have demonstrated that they are equally efficacious in the treatment of AML.

Consolidation (Intensification) Therapy

Consolidation therapy is important to maintain disease remission; however, there is no consensus about the antineoplastic agents that should be combined. The number of courses and the intensity at which chemotherapy is administered vary by institution. This phase of treatment consists of giving patients cytarabine together with a variety of agents that include, but are not limited to, anthracycline, cladribine, asparaginase, etoposide, mitoxantrone, and gemtuzumab ozogamicin. At St. Jude Children's Research Hospital, the consolidation regimen differs based on the disease's response to induction therapy and the patient's cytogenetics. In some institutions, standard-risk and high-risk patients who have a matched related donor usually undergo HSCT if they achieve remission after the first course of consolidation.

CNS Prophylaxis

Cranial radiation to prevent CNS relapses is no longer routinely used in the management of patients with AML, mostly because of the devastating neurologic sequelae associated with radiating the brains of children. Triple intrathecal therapy is used to prevent leukemic spread to the CNS. To date, all but one of the major AML treatment groups have shown CNS relapse rates of less than 5% with the use of intrathecal chemotherapy.

Antimicrobial Prophylaxis

The morbidity and mortality of patients with AML during therapy remains an issue. Chemotherapy for AML is very dose-intensive, and patients remain pancytopenic for most of their therapy. In addition, the administration of high-dose cytarabine has increased the odds of developing oral mucositis and typhlitis, both of which disrupt the integrity of the wall of the gastrointestinal tract, which allows translocation of organisms into the bloodstream. The most common and life-threatening bacterial infection these patients develop is *Viridans streptococcus* sepsis. High rates of fungal infections (mostly aspergillosis and candidiasis) have also been reported. Some institutions place patients on a third- or fourth-generation cephalosporin or quinolones and an antifungal agent to minimize these events and improve survival. The use of prophylactic antibiotics in this fashion is controversial because of the risk of developing resistance.

Relapsed AML

Although 80% to 90% of patients with AML achieve a CR during induction therapy, about 30% to 50% of these patients suffer a relapse of their disease. Overall survival after a first relapse of AML is less than 25%, with the most common site of relapse being the bone marrow. Patients whose disease relapses early have a worse prognosis than those who relapse later because the former group tends to be resistant to chemotherapy. Central nervous system relapse accounts for 10% to 20% of all cases and is often seen in patients who had CNS involvement on presentation. Cytarabine and anthracyclines remain the mainstay drugs used in relapsed disease. Other drugs include the purine

analogues such as fludarabine or cladribine and, more recently, clofarabine. This class of drugs inhibits the activity of ribonucleotide reductase while increasing the activity of deoxycytidine kinase, leading to a higher intracellular concentration of cytarabine triphosphate (the active form of cytarabine). Studies with gemcitabine (another purine analog) are now under way to determine its effectiveness for relapsed pediatric AML.

Most AML blast cells express the CD33 antigen, which makes them a target for the anti-CD33 monoclonal antibody gemtuzumab ozogamicin. This drug is approved for the treatment of adult patients older than 60 years with AML in their first relapse if they are not candidates for HSCT. Gemtuzumab ozogamicin is now being used in pediatric patients with AML who have refractory or relapsed disease; at a dosage of 6 mg/m² intravenously, this drug achieves remission in about 30% of the children, thus allowing them to undergo HSCT. Patients receiving gemtuzumab ozogamicin should be premedicated with methylprednisolone to decrease infusion-related adverse effects such as fever, chills, hypotension, and dyspnea. Sinusoidal obstruction syndrome (previously known as hepatic venoocclusive disease) is a rare but potentially life-threatening adverse effect of this drug. It is manifested by right upper quadrant pain, rapid weight gain, increased abdominal girth, hepatomegaly, and elevation of bilirubin and transaminase concentrations. Patients who receive an HSCT after having received therapy with gemtuzumab ozogamicin have a higher incidence of developing sinusoidal obstruction syndrome (up to 40% in some reports). To avoid this complication, there should be at least 4–8 weeks between the last dose of gemtuzumab ozogamicin and the HSCT.

Tipifarnib, an oral farnesyltransferase inhibitor, has demonstrated promising results in the treatment of relapsed AML. Phase II studies of tipifarnib in elderly patients with relapsed or refractory AML have shown a 54% response rate. Clinical trials are under way to determine its effectiveness in the pediatric population. Another class of drugs that has shown promising results is tyrosine kinase inhibitors (e.g., sorafenib, sunitinib). These agents have mostly been used in adult patients with relapsed or refractory AML who have an FLT₃ mutation. An advantage of these agents is that they are orally bioavailable and can be given at home.

Treatment-Related AML

Although the cure rates of most pediatric cancers have increased during the past decades, so has the occurrence of treatment-related AML (also called secondary AML). Most treatment-related AML cases are caused by the patient's exposure to DNA topoisomerase II inhibitors (including epipodophyllotoxins and anthracyclines) or alkylating agents. The prognosis for these patients is usually dismal, with survival rates varying between 10% and 20%. Treatment options include chemotherapy, HSCT, targeted therapies (e.g., imatinib), and palliative care. The best strategy is prevention. Avoiding excessive use of agents known to cause secondary leukemias can decrease the incidence of secondary AML; however, there is no clear information yet about what is a safe maximal lifetime exposure.

Long-Term Complications After Leukemia Therapy

Almost 80% of children with a diagnosis of a malignancy become long-term survivors, but almost half of them have a moderately to severely decreased health status. Studies comparing cancer survivors with their siblings have shown that survivors suffer from long-term complications of their therapy, most commonly chronic cardiovascular, skeletal, and endocrine conditions. Survivors are also more likely to develop secondary malignancies, whether caused by their inherited genetic condition or the therapy they receive for the treatment of their primary malignancy. For a more comprehensive overview, the reader is referred to the Children's Oncology Group long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers at www.survivorshipguidelines.org.

Cardiac Toxicity

By limiting anthracyclines to a total cumulative lifetime dose of 450 mg/m² of doxorubicin (or its equivalent), the occurrence of cardiac toxicity has been greatly decreased. Cardiac complications occur primarily because of the use of anthracyclines. The long-term cardiac effects of anthracyclines are a major complication of childhood cancer therapy, and their consequences can greatly affect the patient's quality of life.

The cardiotoxicity is thought to be caused by depressed cardiac contractility from loss of cardiac myocytes, resulting in left ventricular dysfunction and, subsequently, congestive heart failure. Patients with cardiovascular complications can be divided in two categories: those with subclinical cardiotoxicity who are usually asymptomatic (thought to occur in as much as 56% of patients having received anthracyclines) and those with clinical cardiotoxicity who are symptomatic (with an incidence of 9.8% at 20 years in patients who have received cumulative doses greater than 300 mg/m²). Risk factors for the development of cardiotoxicity include age younger than 4 years at the time of administration of the anthracycline agent, female sex, and higher cumulative doses. Administration of doxorubicin at dosages greater than 45 mg/m²/week has also been associated with an increased risk of the development of heart failure. Contrary to previous assumptions, continuous infusion of anthracyclines does not have a cardioprotective benefit compared with bolus administration. Patients who develop congestive heart failure are usually treated with digoxin and should be managed by a cardiologist.

Endocrinopathies

Thyroid Dysfunction

Hypothyroidism is a complication that occurs when patients receive head and neck radiation. It is thought that there is a larger number of undiagnosed subclinical thyroid disorders than overt primary thyroidism cases. This number is expected to drop in the future because cranial radiation is no longer routinely performed in patients with leukemia.

Gonadal Dysfunction

Oncologists should present the option of sperm and oocyte preservation to all eligible patients once malignancy is diagnosed. Patients who undergo bone marrow transplantation, as well as patients with solid tumors who receive high doses of alkylating agents, experience varying degrees of gonadal dysfunction. Fertility of patients who undergo treatment for low-risk or standard-risk leukemia therapy is usually preserved.

The ovaries of girls are relatively resistant to chemotherapy-induced damage but are much more sensitive to radiation therapy. Almost all girls who receive total body irradiation during adolescence develop acute ovarian failure, whereas only 50% of those younger than 10 years suffer this complication. For patients who survive through puberty and achieve normal ovarian function, the risk of developing early menopause (before age 40) is elevated. Options for oocyte preservation in girls are limited compared with sperm preservation in boys. Cryopreservation of unfertilized oocytes is an option, but it must be performed before the start of radiation and chemotherapy.

Spermatogenesis is also affected by radiation and exposure to alkylating agents. Testicular radiation in patients with ALL always results in azoospermia. Exposure to moderate or high doses of cyclophosphamide or ifosfamide causes oligospermia and azoospermia, whereas regimens using both agents cause azoospermia in almost all patients. Sperm cryopreservation is very successful in patients who pursue this option; however, because spermatogenesis occurs around age 13, sperm banking is not an option for young children. Although sperm and oocyte banking provides patients the option of conceiving a child in the future, this method of fertility preservation is not considered by everyone because it is expensive.

Obesity

Obesity is more commonly reported in survivors of ALL than AML and has been reported in as many as 57% of ALL survivors. Recent studies suggest there might be an age association with the development of obesity: the younger the age at diagnosis, the more likely the patient will become obese. To date, both sexes seem to be equally affected with this endocrinopathy. Some researchers have suggested that prolonged exposure to high doses of corticosteroids during ALL therapy is responsible for pituitary dysfunction, causing growth hormone deficiency and decreased sensitivity to leptin. One way to manage this complication is to treat patients with growth hormone because it has lipolytic properties.

Skeletal Abnormalities

High doses of corticosteroids (especially dexamethasone), cranial radiation, and the use of MTX and cyclophosphamide have all been associated with the occurrence of osteopenia and osteoporosis in pediatric survivors of leukemias. All patients should be vigilantly screened for any signs of bone demineralization to prevent and reduce the risk of fractures and other complications of osteoporosis. Avascular necrosis is a complication of prolonged exposure to high-dose steroids; it is manifested by severe bone pain and has been reported to have a 3-year cumulative incidence of 9.3%. The incidence of avascular necrosis is higher in patients who

are white, older than 10 years (14.2% vs. 0.9% for younger patients), and of the female sex, and it is directly related to the duration of exposure to dexamethasone. In advanced cases, patients require joint replacement surgery.

Secondary Malignancies

The occurrence of secondary malignancies after leukemia is estimated to be lower than solid tumors. Central nervous system and thyroid cancers are the most commonly observed malignancies in long-term survivors of acute leukemias. The most common types of brain tumors reported are high-grade gliomas, followed by peripheral neuroectodermal tumors, ependymomas, and meningiomas. High-grade gliomas have a dismal prognosis, whereas meningiomas are curable. Secondary AML after ALL therapy is reported mostly in patients who have received etoposide or teniposide (average onset is 33 months). The incidence of this secondary malignancy is likely to decrease because this class of drugs is no longer used in the initial management of patients with ALL. The use of intermittent granulocyte colony-stimulating factors is also implicated in the occurrence of secondary AML. Independent risk factors for the development of secondary malignancies include previous craniospinal radiation, relapsed disease, and female sex.

The Role of the Pharmacist

Clinical pharmacists play an integral role in managing pediatric patients with malignancies. The pharmacist must know all the different protocols that patients receive and how to manage adverse effects of therapy to provide patients with a better quality of life. Supportive care issues in treating patients with malignancies are often left to the pharmacist to manage, so it is important to know the short- and long-term complications of anticancer agents. Monitoring adherence to oral chemotherapy drugs is also important to prevent resistance and relapse. With the advent of pharmacogenetics, the role of the pharmacist in drug dosing will become even more critical.

Annotated Bibliography

1. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006;354:166–78.

The authors of this article review in depth the treatment of ALL, the most common malignancy affecting pediatric patients. Factors predicting clinical outcome are discussed, including clinical features of the patient, genetics of the leukemic cells, and host pharmacodynamics and pharmacogenetic features. Included in the discussion are risk factors that may predispose the patient to therapy-related adverse events. Current treatment strategies are discussed, focusing on the different courses of therapy and the goals of each course. With a cure rate approaching 90%, future directions are discussed that focus on novel agents that may further improve outcomes. Studies are needed with these newer agents to improve the cure rate without increasing toxicity.

2. Roden DM, Altman RB, Benowitz NL, Flockhart DA, Giacomini KM, Johnson JA, et al. Pharmacogenomics: challenges and opportunities. *Ann Intern Med* 2006;145:749–57.

Drug therapy has often been known to have an unpredictable outcome. In addition to having a beneficial effect, the effect of drug therapy can range from lack of efficacy to toxicity, sometimes serious. Some of the variability of effect can be explained with or through pharmacogenetics and pharmacogenomics. The authors of this article describe various mechanisms for the variable responses of drugs based on pharmacokinetics and pharmacodynamics. The authors next discuss the challenges that must be overcome to apply the information obtained with genetic testing. Only if the challenges that pharmacogenetics presents are overcome can improvements be made in drug development and individualized therapy be accomplished.

3. Evans WE. Pharmacogenetics of thiopurine S-methyltransferase and thiopurine therapy. *Ther Drug Monit* 2004;26:186–91.

The efficacy and toxicity of drugs vary widely among patients. Pharmacogenetics is an emerging field of study looking at genetic differences that may predict efficacy as well as toxicity in individuals receiving certain drugs. The genetic polymorphism associated with thiopurine S-methyltransferase is one of the best-described examples of pharmacogenetics. Most people (90%) inherit high activity; 10% have intermediate activity because of heterozygosity; and 0.3% have low or no detectable enzyme activity because they inherit two nonfunctional alleles. Knowing the patient's thiopurine S-methyltransferase activity before initiating mercaptopurine therapy can reduce the incidence of toxicity, because patients who inherit two nonfunctional alleles require significant decreases in mercaptopurine (to 5% to 10% of standard dosages) to prevent toxicity.

4. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood* 2008;111:5477–85.

It was previously determined that MRD is a predictor of relapse in patients with ALL. This prognostic factor had not been studied in relation to other variables that predict outcome. The Children's Oncology Group studied 2143 patients with precursor B-cell ALL and assessed MRD in the peripheral blood at day 8 of induction and in the bone marrow at the end of induction and the end of consolidation. Across all risk groups, patients who were MRD positive had a lower event-free survival. Patients who still had detectable disease noted by the presence of MRD in the marrow at the end of consolidation had a very poor response. The authors concluded that more intensive therapy might be necessary for patients with positive MRD at the end of induction. This more intensive therapy will need to increase survival, without increasing toxicity.

5. Larson RA. Three new drugs for acute lymphoblastic leukemia: nelarabine, clofarabine and forodesine. *Semin Oncol* 2007;34(6 Suppl 5):S13–S20.

Current treatment strategies for pediatric ALL have cure rates approaching 90%. New therapies should be developed to continue to improve outcomes and decrease the toxicity associated with current therapies. Three purine nucleoside analogs (i.e., nelarabine, clofarabine, and forodesine) have

been developed that show activity in patients with relapsed or refractory ALL. Nelarabine has shown activity against T-cell leukemia. Clofarabine is effective for the treatment of relapsed ALL and may be effective for the treatment of AML. Forodesine is the newest agent with activity against B- and T-cell leukemias. More studies are needed to further assess the activity and toxicity of these agents when used with traditional treatment or as single-agent therapy as part of salvage regimens.

6. Rocha JC, Cheng C, Liu W, Kishi S, Das S, Cook EH, et al. Pharmacogenetics of outcome in children with acute lymphoblastic leukemia. *Blood* 2005;105:4752–8.

The outcomes of 246 children with ALL were studied to identify relationships of 16 genetic polymorphisms that affect the pharmacodynamics of antileukemic agents. If high-risk patients had the glutathione S-transferase nonnull genotype, they had a greater risk of hematologic relapse ($p=0.03$). This outcome was increased by the thymidylate synthase 3/3 genotype ($p=0.03$). For low-risk patients, no genotype was predictive of relapse. The vitamin D receptor start site ($p=0.02$) and the intron 8 genotype ($p=0.04$) were predictive of CNS relapse in the high-risk group. For low-risk patients, the thymidylate synthase 3/3 genotype ($p=0.04$) was predictive of CNS relapse. The authors conclude that these genotypes are predictive, based on the specific treatment patients received, and that additional studies of host genetic features should be undertaken. Pharmacogenetic testing should be undertaken to maximize therapy while minimizing toxicity.

7. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572–82.

The Childhood Cancer Survivor Study Group conducted this study to estimate the overall incidence of chronic health conditions faced by long-term survivors of childhood cancer. It retrospectively compared patients with their siblings, which is a very good way of comparing two groups because the cohorts are matched for ethnicity and socioeconomic status (among other factors). Compared with their siblings, survivors have an 8.2-fold (95% confidence interval [CI], 6.9–9.7) greater chance of developing a severe to life-threatening and disabling condition. For example, the relative risk of a childhood cancer survivor requiring major joint replacement surgery was 54 times higher (95% CI, 7.6–386.3). An advantage of this study is that it is one of the largest observational trials to be published about long-term follow-up survivors of childhood malignancies (10,397 survivors and 3034 siblings). This article shows that survivors of childhood malignancies must be monitored by a physician very closely because they are more prone to suffer from chronic health conditions.

8. Illmer T, Ehninger G. FLT3 kinase inhibitors in the management of acute myeloid leukemia. *Clin Lymphoma Myeloma* 2007;8(Suppl 1):S24–S34.

This article provides a good overview of the FLT3 kinase inhibitors currently undergoing evaluation as treatment options for patients with AML. Although this article mainly discusses the successful use of these agents in adult patients with AML, most of these agents are currently being investigated for use in pediatric patients with AML. The advantage of these FLT3 kinase inhibitors (sunitinib, sorafenib, and lestaurtinib [CEP701]) is that they are orally bioavailable and thus have the potential of providing patients

with a better quality of life during treatment. Finally, the use of these agents is limited to patients with AML who have FLT3 mutations, so patients will have to be checked for this mutation.

9. Harousseau JL, Lancet JE, Reiffers J, Lowenberg B, Thomas X, Huguet F, et al. A phase 2 study of the oral farnesyltransferase inhibitor tipifarnib in patients with refractory or relapsed acute myeloid leukemia. *Blood* 2007;109:5151–6.

The authors of this article conducted an open-label Phase II trial to assess the effectiveness of tipifarnib in adult patients with refractory or relapsed AML. Tipifarnib inhibits the ras protein–signaling pathway leading to inhibition of cell proliferation. Some 252 patients received tipifarnib at a dose of 600 mg orally twice daily for 21 days of a 28-day cycle. Complete remission was achieved in 4% of patients, and disease stabilization occurred in 5% of patients. Pharmacokinetic analyses were performed in 17 patients after administration of tipifarnib. An advantage of this study is that it was conducted in North America, Europe, and Asia, which eliminates patient selection bias because many people from different ethnic backgrounds were treated with the same regimen. An advantage of tipifarnib is that it is an oral drug, and because the prognosis of patients with relapsed and refractory AML is not good, it provides them with a better quality of life than if they were receiving intravenous chemotherapy. There are no published trials about the use of tipifarnib in pediatric patients.

10. Arceci RJ, Sande J, Lange B, Shannon K, Franklin J, Hutchinson R, et al. Safety and efficacy of gemtuzumab ozogamicin in pediatric patients with advanced CD33⁺ acute myeloid leukemia. *Blood* 2005;106:1183–8.

This is the first reported study to use gemtuzumab ozogamicin in pediatric patients with AML. The authors report their experience with 29 patients in this Phase I open-label study. Gemtuzumab ozogamicin was given at a starting dose of 6 mg/m² intravenously every 14 days for two doses with a planned dose escalation to 9 mg/m². Eight patients (28%) achieved CR (four of them had CR except for full recovery of their platelets). The authors concluded that the 6-mg/m² dosage was tolerated in most patients and that additional pediatric studies should use this dose as their starting point. This was a pivotal trial because it served as a stepping-stone from which many other groups have used gemtuzumab ozogamicin in combination with standard AML therapies to treat both patients with de novo and relapsed or refractory AML.

11. Hijjiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm F, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *JAMA* 2007;297:1207–15.

This article retrospectively assessed the incidence of secondary neoplasms in 2169 patients with ALL treated at St. Jude Children’s Research Hospital. Some 123 patients developed a second malignancy after they went into remission, with AML being reported in 37 cases (30%) and CNS malignancies (mainly meningiomas) occurring in 38 cases (31%). Compared with the general population, patients who had ALL were at a 13.5% (95% CI, 10.9–16.8) overall increased risk of developing a second malignancy. Those who received craniospinal or cranial radiation had a 45.8% (95% CI, 26–64.2) increase in overall risk of developing a CNS malignancy. The authors of this article reviewed the medical records of a large number of long-term survivors of ALL for

an extended period and give the reader good insight into the different neoplasms that can develop. One limitation of this study is that patients were followed up for 10 years after their diagnosis or until they reached their 18th birthday (whichever came later), so those who developed malignancies after that period were not accounted for.

12. Lange BJ, Smith FO, Feusner J, Barnard DR, Dinndorf P, Feig S, et al. Outcomes in CCG-2961, a Children's Oncology Group phase 3 trial for untreated pediatric acute myeloid leukemia (AML): a report from the Children's Oncology Group. *Blood* 2008;111:1044–53.

This article relates the results of the latest AML trial performed by the Children's Oncology Group. The anthracycline agent used in this trial for both induction and consolidation was mostly idarubicin. Patients were also randomized to receive fludarabine during consolidation therapy, and some of them received aldesleukin. The goal of this study was to assess the survival and response rates of patients with AML treated with fludarabine and idarubicin. Some 901 patients with de novo AML were enrolled in the study; overall survival was $52\% \pm 4\%$, whereas event-free survival was $42\% \pm 3\%$, which is similar to results of other studies performed in patients with AML by other cooperative groups. The authors conclude that aldesleukin is not an effective agent against AML and that additional studies of this agent in this disease are not warranted. The authors also compared the idarubicin-treated group with a historical cohort of patients treated with daunorubicin; both cohorts achieved similar remission rates.

13. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Available at www.survivorshipguidelines.org. Accessed February 24, 2009.

This Web site, set up by the Children's Oncology Group, is an excellent resource for anyone interested in setting up a program to monitor long-term survivors of pediatric malignancies. It provides information on how often patients should be followed up depending on the treatment modality they received. It also provides a detailed summary of the specific health conditions that survivors are at risk of developing based on the drugs they received. This Web site is useful for all health care professionals wanting to learn about the types and severity of chronic health conditions cancer survivors face.

SELF-ASSESSMENT QUESTIONS

Questions 1–3 refer to the following case.

Z.P. is a 2-year-old white girl given a diagnosis of precursor B-cell acute lymphocytic leukemia (ALL). Her original complete blood cell count revealed a white blood cell (WBC) count of 28×10^3 cells/mm³; hemoglobin 6.5 mg/dL; and platelet count 55,000 cells/mm³. All her blood chemistry test results were within normal limits. Z.P.'s initial lumbar puncture was negative; her DNA index was 1.22.

1. In addition to prednisone and intrathecal therapy, which one of the following is the best therapy to initiate for Z.P.?
 - A. Cyclophosphamide, doxorubicin, and mercaptopurine.
 - B. Vincristine, daunorubicin, and asparaginase.
 - C. Cytarabine, daunorubicin, and asparaginase.
 - D. Cytarabine, cyclophosphamide, and mercaptopurine.
2. Based on the toxicity profile of chemotherapeutic agents commonly used in induction, which baseline studies are best performed before the initiation of therapy in Z.P.?
 - A. Chest radiograph and computed tomography of the chest.
 - B. 24-hour urine collection and liver enzymes.
 - C. Echocardiogram, direct bilirubin, and liver enzymes.
 - D. Thyroid studies and echocardiography.
3. At the end of induction, Z.P. has less than 0.01% minimal residual disease (MRD) in her bone marrow. Which one of the following best describes how this will affect her risk classification?
 - A. Does not change her risk classification.
 - B. Changes her to standard risk.
 - C. Changes her to high risk.
 - D. Changes her to very high risk.

Questions 4 and 5 refer to the following case.

T.V., a 6-year-old white boy receiving maintenance therapy for ALL, presents to the clinic with persistently low platelet, WBC, and red blood cell counts. The patient is neutropenic without lymphoblasts on his blood smear.

4. Which one of the following genetic tests is best to perform on T.V.?
 - A. Thymidylate synthase.
 - B. Thiopurine S-methyltransferase.
 - C. Glutathione S-transferase.
 - D. Dihydrofolate reductase.
5. T.V.'s family is administering mercaptopurine correctly. The genetic test used to determine mercaptopurine metabolism confirms that T.V. is heterozygous for that polymorphism. Which one of the following is the best recommendation for T.V.?

- A. Continue the same mercaptopurine dose.
- B. Increase the mercaptopurine.
- C. Decrease the mercaptopurine.
- D. Discontinue the mercaptopurine.

6. M.P. presents to the clinic with redness and pain at his injection site the morning after receiving his third dose of asparaginase. His thigh on the side of the injection is swollen. Which one of the following is the best adjustment to M.P.'s therapy?
 - A. Continue asparaginase but decrease the dose.
 - B. Change to pegaspargase.
 - C. Continue asparaginase but premedicate M.P. next time.
 - D. Give no additional asparaginase.
7. C.D. is a 1-year-old white girl with Down syndrome and a diagnosis of ALL. The patient is due for high-dose methotrexate (MTX). Which one of the following changes in drug dosage is best for C.D.?
 - A. No dosage modification is necessary.
 - B. The dose should not be higher than 500 mg/m².
 - C. No dosage modification is needed as long as aggressive leucovorin rescue is administered.
 - D. C.D. should not receive high-dose MTX.
8. Z.C. is a 7-year-old boy with relapsed ALL. He originally relapsed 18 months after therapy was discontinued. After receiving front-line therapy for relapsed ALL, Z.C. still has persistent disease. The decision is made to treat Z.C. with a combination of clofarabine, cyclophosphamide, and etoposide. Which one of the following adverse events should be lessened by clofarabine?
 - A. Nephrotoxicity.
 - B. Hepatotoxicity.
 - C. Pulmonary toxicity.
 - D. Neurotoxicity.

Questions 9 and 10 refer to the following case.

A.Y. is a 20-month-old girl with acute myeloid leukemia (AML). She has received two courses of induction therapy with cytarabine, etoposide, and daunorubicin. She is now undergoing disease evaluation, and her MRD is 6%. She has tolerated her previous therapy except for some mild liver dysfunction.

9. Which one of the following options is the best treatment for A.Y. at this time?
 - A. Gemtuzumab ozogamicin.
 - B. Hematopoietic stem cell transplantation (HSCT).
 - C. Cytarabine, etoposide, and daunorubicin.
 - D. Tipifarnib.

10. Assuming A.Y. does not require HSCT, which of the following long-term complications is A.Y. at greatest risk of developing once she reaches adulthood?
- Congestive heart failure, second malignant neoplasm, and hypothyroidism.
 - Renal failure, hearing loss, and cardiac arrhythmias.
 - Second malignant neoplasm, congestive heart failure, and cardiac arrhythmias.
 - Hearing loss, avascular necrosis, and ovarian failure.

Questions 11 and 12 refer to the following case.

N.F., a 7-year-old patient with newly diagnosed AML, is currently undergoing induction therapy. This patient is expected to be immunosuppressed for the duration of induction therapy.

11. Which one of the following antimicrobial regimens is best for N.F.?
- Meropenem, vancomycin, and caspofungin.
 - Voriconazole, oxacillin, and palivizumab.
 - Voriconazole, vancomycin, and ciprofloxacin.
 - Amphotericin B, metronidazole, and levofloxacin.
12. Which one of the following pathogens would most likely cause infections in N.F.'s case?
- Gram-negative bacilli.
 - A fungal organism.
 - Gram-positive cocci.
 - Parasites.

Questions 13 and 14 refer to the following case.

A.L. is a 2-year-old white girl given a diagnosis of AML (M4). Her original complete blood count was WBC count 20×10^3 cells/mm³, hemoglobin 5 mg/dL, and platelets 7×10^3 cells/mm³. Cytogenetics show that she has the inv(16) translocation.

13. Which one of the following combinations of findings and symptoms did A.L. most likely have on presentation?
- Mediastinal mass, gum bleeding, and pallor.
 - Fever, splenomegaly, and hyperuricemia.
 - Chloroma, gum bleeding, and pallor.
 - Chloroma, fatigue, and bone marrow blasts less than 20%.
14. Which one of the following is the best therapy for A.L. after induction therapy?
- HSCT and maintenance therapy.
 - Consolidation therapy and radiation therapy.
 - Maintenance therapy and radiation therapy.
 - Central nervous system (CNS) prophylaxis and consolidation therapy.
15. A 19-year-old patient who is now 6 years off therapy for ALL presents with low platelet and red blood cell counts and fatigue. On further examination, he is found to have secondary AML. His therapy for ALL included MTX, cyclophosphamide, daunorubicin, mercaptopurine, etoposide, vincristine, and asparaginase. Which of the

following drugs are most likely to have contributed to his secondary AML?

- Daunorubicin and MTX.
 - Cyclophosphamide and etoposide.
 - Vincristine and cyclophosphamide.
 - Asparaginase and MTX.
16. G.H. is a 16-year-old boy receiving induction therapy for AML. His induction regimen consists of cytarabine, daunorubicin, and etoposide. Which one of the following drugs is best while G.H. is receiving his induction therapy?
- Dexamethasone eye drops with cytarabine.
 - Dexrazoxane to be given before daunorubicin.
 - A fluid bolus to be given before etoposide.
 - Digoxin to be given before daunorubicin.
17. A.P., a 3-year-old boy, recently received a diagnosis of AML. His cytogenetics show that he has inv(16) AML. Based on the current classifications of this disease, which one of the following AML subtypes is A.P. most likely to have and what is his prognosis?
- AML M1 with a poor prognosis.
 - AML M5 with a good prognosis.
 - AML M2 with a very poor prognosis.
 - AML M4Eo with a good prognosis.
18. B.T. is a 17-year-old male patient who was treated for ALL at the age of 3 years. His treatment consisted of conventional chemotherapy together with cranial radiation for CNS prophylaxis. Which one of the following long-term complications is B.T. most likely to have because of his cranial radiation?
- Hypothyroidism and secondary brain tumor.
 - Hypothyroidism and congestive heart failure.
 - Azoospermia and obesity.
 - Secondary brain tumors and osteoporosis.
19. S.R. is a 6-year-old boy who now has relapsed refractory AML. He has already completed four different treatment regimens. His parents still want him to receive curative chemotherapy, so the oncologist is going to enroll him in an investigational study. Which one of the following classes of chemotherapy agents is S.R. most likely to benefit from?
- DNA topoisomerase I inhibitor.
 - Nitrogen mustard alkylating agent.
 - Farnesyltransferase inhibitor.
 - Tyrosine kinase inhibitor.
20. E.T. is a 4-year-old white girl who presents with a normal WBC count, decreased hemoglobin, and decreased platelet count. She is given a diagnosis of precursor B-cell ALL. Standard induction therapy is initiated while awaiting cytogenetics. Based on E.T.'s age and diagnosis, which one of the following translocations is she most likely to have?
- TEL-AML1*.
 - MLL* gene rearrangement.
 - E2A-PBX1*.
 - BCR-ABL*.