Leukemia in Children

Joel A. Kaplan, DO, MPH

Department of Pediatrics, Atrium Health Levine Children's Hospital, Charlotte, NC

Practice Gaps

Persistent bone pain, limp, back pain, fever, headache, and symptoms of anemia and thrombocytopenia are common ways that pediatric leukemia presents. Many of these symptoms can be seen in common childhood illnesses, so a high index of suspicion in patients with persistent symptoms is required to make the diagnosis. The prognosis for these children is excellent, especially in acute lymphoblastic leukemia, but survivors of childhood leukemia need to be followed closely for long-term toxicities.

Objectives

After completing this article, readers should be able to:

1. Understand the incidence and general epidemiology of childhood leukemia, including syndromes that increase the risk of leukemia in children.
2. Recognize the clinical presentation of childhood leukemia and how this relates to proper interpretation of a complete blood cell count.
3. Understand the potential oncologic emergencies in childhood leukemia.
4. Describe the prognostic factors associated with precursor B-lymphoblastic leukemia, including an understanding of the importance of minimal residual disease.
5. Understand the importance of supportive care in the treatment of childhood acute myelogenous leukemia.
6. Describe the long-term complications of childhood leukemia treatment in the modern era.

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ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia
BMT	bone marrow transplant
CBC	complete blood cell
CML	chronic myelogenous leukemia
CNS	central nervous system
DIC	disseminated intravascular coagulation
EFS	event-free survival
HLA	human leukocyte antigen
MRD	minimal residual disease
Ph	Philadelphia chromosome
TKI	tyrosine kinase inhibitor
WBC	white blood cell

INTRODUCTION

Leukemia is the most common malignancy of childhood, accounting for 30% of cases of childhood cancer. Although there are some associations between environmental or host factors, most leukemia diagnoses in children are sporadic. There are 3 main subtypes of leukemia: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML). ALL is the most common subtype, accounting for approximately 80% of cases.

CML is the least common, and this review touches on this subtype only briefly. There are many subgroups within ALL and AML. These subgroups have variable biological features, prognoses, and treatment regimens. Children generally present with symptoms related to cytopenias or leukemic infiltration of the bone marrow. Other organs, such as the spleen, liver, testes, and central nervous system (CNS), can also be involved. With modern, risk-adapted therapy, most children are cured of their disease. Despite these successes, relapse continues to be a problem. However, we have entered an exciting time of targeted and immunologic therapy that is revolutionizing the treatment of these challenging patients. There are late effects of treatment, and these need to be recognized by the general pediatrician, with an understanding that these late effects are different among the many subtypes of leukemia.

EPIDEMIOLOGY

Childhood cancer is very rare, with approximately 14,000 cases diagnosed in children younger than 18 years in the United States annually. For perspective, there are 80,000 cases of prostate cancer diagnosed each year, which is only the fifth most common cancer in adults. In children, hematologic malignancies predominate, accounting for approximately one-third of all cases of childhood cancer. Cancer remains the most common cause of disease-related death in children. The incidence of ALL is approximately 30 cases per 1 million persons. This incidence varies among different ethnic groups. ALL is more common in white individuals compared with black individuals, with Hispanic people having the highest risk. (1)

Precursor B-cell ALL is much more common than T-cell disease, accounting for approximately 80% of cases of ALL. AML accounts for 18% of cases of childhood leukemia, and CML is very rare and tends to occur in adolescents. Outside of exposure to ionizing radiation, there are very few environmental factors that have shown a strong link with childhood leukemia. Monozygotic twins have a 10% to 15% concordance rate for ALL. The cause of ALL is most likely multifactorial, involving genetic, immunologic, and infectious factors that need further study. (2)

Patients with Down syndrome are at 15 times increased risk of developing leukemia compared with the general population. This risk is increased for both ALL and AML. (3) This is especially true in children with trisomy 21, who had transient myeloproliferative disorder as infants. In this population the risk of developing AML is 16% at a median age of 441 days. (4) Transient myeloproliferative disorder is characterized by peripheral blasts and hepatosplenomegaly in the newborn with trisomy 21. Most cases resolve spontaneously, but some require treatment with low-dose chemotherapy. Interestingly, patients with Down syndrome who develop AML have a favorable outcome compared with those without Down syndrome. Other syndromes, such as Fanconi anemia, Bloom syndrome, Klinefelter syndrome, and neurofibromatosis, are also associated with leukemia.

CLINICAL PRESENTATION

The most common presenting symptoms of leukemia result from the clonal proliferation of leukemic blasts in the bone marrow, preventing normal production of red blood cells, platelets, and neutrophils. The degree of anemia, thrombocytopenia, and neutropenia is highly variable. A significant anemia can cause pallor, fatigue, dyspnea on exertion, headache, dizziness, and near syncope. Although the thrombocytopenia can be severe, most patients with leukemia do not present with bleeding. Many patients can have bruising and petechiae, but serious bleeding is rare. Fevers are very common in patients with leukemia and should be part of the differential diagnosis of fever of unknown origin. Despite sometimes severe neutropenia, infection or sepsis at diagnosis is uncommon.

Children with leukemia have bone marrow that has been replaced with leukemic blasts. This expansion of the bone marrow cavity very commonly causes bone pain, limp, or refusal to walk. Back pain is also found, and a complete blood cell (CBC) count with a differential count should be considered as part of the evaluation of this complaint, along with close interval follow-up until the cause of the back pain is discovered. Patients with bone pain are frequently referred to orthopedics, where a diagnosis of leukemia is sometimes made when magnetic resonance imaging shows diffuse increased signal intensity in the bone marrow.

Leukemia can infiltrate other organs outside of the bone marrow, leading to lymphadenopathy, hepatomegaly, splenomegaly, and kidney lesions. The most impressive splenomegaly is seen with CML. The acute leukemias have variable spleen and liver size. Despite the hepatomegaly, liver dysfunction is uncommon. Testicular disease occurs in approximately 2% of children with ALL. (5) This presents with a painless testicular mass or uniformly enlarged testes. CNS leukemia can be seen in both ALL and AML but is more common in the former. T-cell ALL has the highest risk of CNS disease. This can manifest itself as headache, seizure, visual changes, cranial nerve abnormalities, and change in mental status. CNS disease can also be asymptomatic.

The different types of leukemia tend to exhibit certain features in their clinical presentation. Infantile ALL, defined

as leukemia presenting before 1 year of age, tends to present with very high white blood cell (WBC) counts. When an adolescent male presents with a high WBC count and an anterior mediastinal mass, T-cell ALL should be considered. These patients frequently can have difficulty breathing, especially in the supine position. This can be a medical emergency, and airway management can be difficult. CML can have extremely high WBC or platelet counts, with massive splenomegaly. Acute promyelocytic leukemia, a rare subtype of AML, is strongly associated with bleeding, CNS hemorrhage, and disseminated intravascular coagulation (DIC) at diagnosis. Chloromas are extramedullary collections of leukemic blasts that can occur anywhere in the body, more often in soft tissues and the CNS. They tend to occur more often in AML with monocytic differentiation. Children with trisomy 21 and AML tend to present with isolated thrombocytopenia, many times after a history of transient myeloproliferative disorder.

DIAGNOSIS

It is very important for a pediatrician to understand the proper interpretation of a CBC count with differential count. It is easy to think of a CBC count as a measure of bone marrow function. The marrow produces red blood cells, neutrophils, and platelets. A cytopenia reflects poor marrow function or peripheral destruction of the involved cell. Most patients with leukemia have more than 1 cell line affected at diagnosis. If patients have isolated neutropenia, anemia, or thrombocytopenia, then an appropriate differential diagnosis should be formulated for the individual cytopenia. When more than 1 cell line is affected, the diagnosis of leukemia should be more strongly considered. Diagnoses that can be commonly confused with leukemia include viral suppression, drug-induced cytopenia, immune thrombocytopenic purpura, autoimmune hemolytic anemia or neutropenia, Evan syndrome, transient erythroblastopenia of childhood, aplastic anemia, splenic sequestration, and juvenile idiopathic rheumatoid arthritis.

A bone marrow aspirate is necessary to definitively diagnose leukemia. The diagnosis can also be made from peripheral blood if a sufficient number of blasts are present. This can be helpful in cases where the WBC count is high and making a diagnosis quickly is advantageous. Both morphologic analysis and flow cytometry are used to evaluate the bone marrow. Morphologic analysis evaluates the marrow and leukemic blasts under the microscope (Fig 1). Flow cytometry uses immunophenotypic characteristics to differentiate between the different types of leukemia. ALL and AML can sometimes be differentiated using morphologic features alone, where T- and B-cell ALL look identical under the microscope. The different leukemias have distinctive immunophenotypic markers that can be found using flow cytometry. This modality is required for accurate

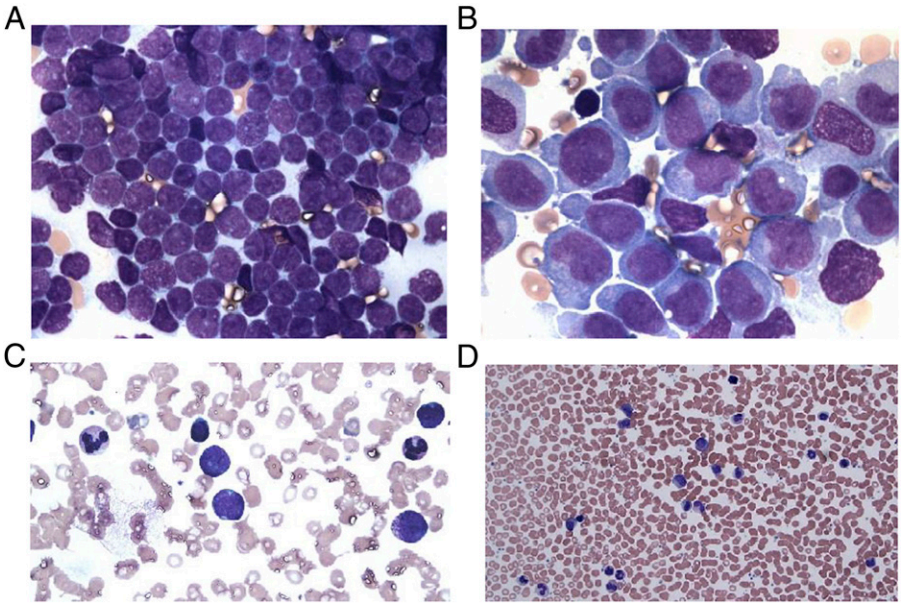

Figure 1. Photomicrographs of different types of leukemia. A. Acute lymphoblastic leukemia. Notice the high nucleus to cytoplasm ratio and uniform-appearing blasts. This morphologic profile is commonly seen in both T- and B-cell leukemia. B. Acute myelogenous leukemia, monocytic subtype. Notice the relatively increased cytoplasm and nuclear indentation. C. Acute promyelocytic leukemia. In the blast on the lower right of the field notice the increased cytoplasm with prominent granules. D. Chronic myelogenous leukemia. Notice the increased number of myeloid progenitors at various stages of differentiation.

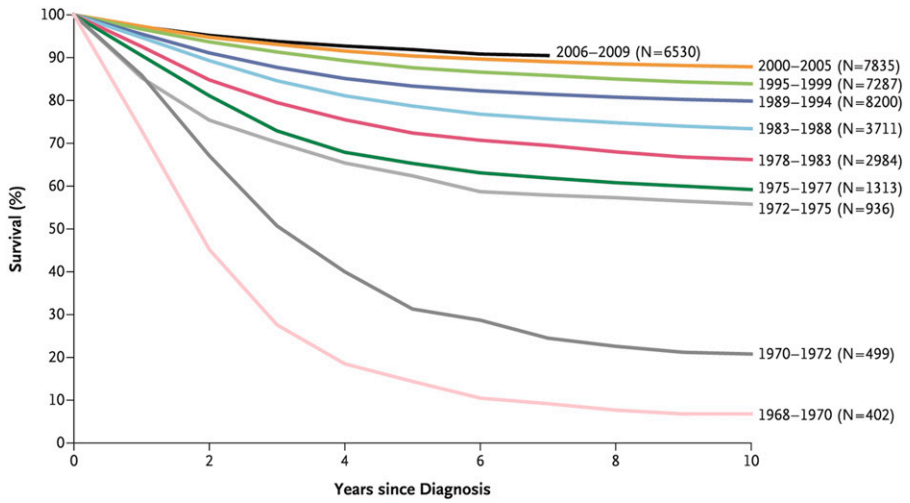

Figure 2. Overall survival among children with acute lymphoblastic leukemia who were enrolled in Children's Cancer Group and Children's Oncology Group clinical trials, 1968–2009. Reprinted with permission from Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* 2015;373(16):1541–1552.

diagnosis. (6) CML has very distinctive characteristics and can be diagnosed using morphologic analysis alone. It is characterized by a proliferation of normal hematopoietic progenitor cells seen in the peripheral blood. All patients with acute leukemia require a lumbar puncture with cerebrospinal fluid sampling to rule out CNS disease. If neurologic symptoms, severe headache, or cranial nerve palsies are present at diagnosis, magnetic resonance imaging may also be necessary. A thorough testicular physical examination should be performed in all male patients.

ONCOLOGIC EMERGENCIES IN NEWLY DIAGNOSED LEUKEMIA

Hyperleukocytosis can be seen in any patient with leukemia and is generally defined as a WBC count of greater than 100,000/μL (>100×10^9/L). This is more common in those with AML, T-cell ALL, and infantile leukemia. The large number of blasts can cause leukostasis, which precipitates decreased tissue perfusion. This is a medical emergency causing neurologic and pulmonary sequelae. Patients with AML have more problems with leukostasis, at lower WBC counts, because AML blasts are larger and stickier. Those with ALL generally only develop signs of leukostasis with extremely high WBC counts.

Signs and symptoms of leukostasis include the following: neurologic—headache, confusion, lethargy, dizziness, blurry vision, ataxia, papilledema, retinal hemorrhage, and CNS hemorrhage; respiratory—tachypnea, hypoxia, infiltrates on chest radiography, respiratory failure, and acute respiratory distress syndrome; vascular—peripheral vascular occlusion and thrombosis; and coagulation—DIC, abnormal tests of coagulation with elevated prothrombin and partial thromboplastin times with a decreased fibrinogen level.

These patients are also at risk for tumor lysis syndrome, defined as hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Tumor lysis syndrome usually develops after therapy is started but can occur at initial presentation. It is caused by the intracellular contents of malignant cells being spilled into the circulation. This can overwhelm the kidney's ability to process the released nucleic acids, potassium, and phosphorus. Without prompt intervention this can lead to cardiac arrhythmias and renal failure. The management of hyperleukocytosis includes the following:

- Place 2 large-bore peripheral intravenous lines if the patient does not yet have a central line.
- Hydrate with dextrose 5% half-normal saline at 125 mL/m^2 per hour. No potassium should be put in intravenous fluids.
- Begin allopurinol therapy.
- Consider rasburicase if the uric acid level is greater than 8.0 mg/dL (>476 μmol/L)
- Every-6-hour renal function panel and uric acid level.
- Transfuse platelets if less than 30×10^3/μL (<30×10^9/L)
- Transfuse fresh frozen plasma and cryoprecipitate for abnormal coagulation studies or DIC.
- Avoid packed red blood cell transfusion if possible. If indicated, start with low volumes.
- Treat tumor lysis syndrome if present.
- Begin induction chemotherapy as soon as possible.
- Early consultation with pediatric nephrology.

The use of leukapheresis has fallen out of favor in patients with hyperleukocytosis. This therapy requires central line access, significant planning with the blood bank, and resources, all delaying definitive therapy. Leukapheresis is also of questionable benefit in these patients and carries its own risks. (7) Therefore, induction chemotherapy should be started as soon as possible. If delayed, cytoreduction can be achieved with hydroxyurea or corticosteroids, the latter being used only with a known diagnosis of ALL. Leukapheresis is reserved for patients who have persistent or worsening symptoms of leukostasis despite appropriate attempts at cytoreduction.

T-cell ALL is commonly associated with an anterior mediastinal mass. This mass can be very large and cause significant symptoms, including dyspnea on exertion, shortness of breath, tachypnea, orthopnea, and stridor. Patients with significant respiratory compromise require admission to the ICU and prompt initiation of leukemia-directed therapy. Reduction in size of the mass can be achieved with the use of corticosteroids alone, and responses are usually prompt, avoiding the need for intubation. Induction therapy should be started after definitive diagnosis is made.

Acute promyelocytic leukemia is a very rare subtype of AML that is associated with severe coagulopathy. Patients can present with DIC, bleeding, and thrombosis. Prompt diagnosis is necessary and can be done preliminarily using morphologic analysis alone (Fig 1). Left untreated, patients can develop pulmonary or cerebrovascular catastrophic bleeding. Platelet counts should be maintained at greater than $50\times10^3/\mu L$ ($>50\times10^9/L$) and coagulation abnormalities treated with fresh frozen plasma and cryoprecipitate, the latter being used for hypofibrinogenemia. Leukapheresis is contraindicated in these patients.

THERAPY

Acute Lymphoblastic Leukemia

ALL is a rapidly progressive disease that causes excess, very immature WBCs called *blasts* to proliferate in the bone marrow at the expense of normal hematopoietic cells. The bone marrow can then no longer produce adequate red blood cells, platelets, and neutrophils. The cell of origin of these blasts is in the lymphocyte developmental line and can infiltrate the CNS, peripheral blood, lymph nodes, spleen, liver, and kidneys. Childhood ALL was an almost universally fatal disease in the 1960s. It is now one of the most curable diseases seen in pediatric oncology, with an event-free survival (EFS) of approximately 90%. In fact, there are subsets of ALL in children younger than 10 years that have an EFS of close to 100%. These advances can be attributed to the success of cooperative group trials. These trials allowed for study of a rare disease that otherwise would not have been possible (Fig 2). Multiagent chemotherapy has been improved by identifying risk groups with variable prognosis and tailoring therapy to individual patients. (8) This is based on patient characteristics, biological factors, and degree of response to initial treatment. At diagnosis, patients are classified as either standard risk or high risk based on criteria from the National Cancer Institute. Standard-risk patients are aged 1 to 10 years, have WBC counts less than $50{,}000/\mu L$ ($<50\times10^9/L$), are of B-cell origin, and do not have CNS or testicular disease (Table 1). To be high risk requires only 1 discordant criteria. Treatment of childhood leukemia is truly a team effort. It requires all the resources of a children's hospital along with specialized physicians across multiple disciplines, advanced care practitioners, nurses, nurse navigators, social workers, psychologists, pharmacists, and research support.

The following types of ALL are treated on different treatment regimens: precursor B cell, T cell, Philadelphia chromosome (Ph) positive, and infantile.

Minimal residual disease (MRD) testing allows for the accurate detection of very small amounts of leukemic blasts in the bone marrow. MRD has been shown to be a strong prognostic indicator across all leukemia subtypes. Historically, remission was defined as having less than 5% blasts in the bone marrow by morphologic analysis alone after initial induction chemotherapy. This has been largely replaced with the use of MRD testing of the bone marrow at the end of induction using flow cytometry. Clinical trials in precursor B-cell ALL showed that MRD was highly prognostic. More than 2,000 children were studied, with a significant EFS advantage even in patients with negative MRD compared with those with low-level MRD of 0.01% to 0.1% (EFS: 88% versus 59%). This advantage was seen in all risk groups. (9) The use of MRD is also prognostic in T-cell, Ph-positive, infantile, and relapsed ALL.

Precursor B-cell ALL is treated with multiagent chemotherapy in 5 phases: induction, consolidation, interim maintenance, delayed intensification, and maintenance (Table 2). The total time of therapy is approximately 2 to 3 years for boys and 2 years for girls. The intensity of therapy is individualized based on the final risk group designation. High-risk patients receive a more intensive therapy compared with standard-risk patients. Much of the treatment time is spent in maintenance, which is the least intensive phase of therapy. During maintenance, patients receive oral mercaptopurine and methotrexate. A 5-day corticosteroid pulse and vincristine are used variably depending on the regimen. During maintenance it is impossible to tell that a

TABLE 1. **Prognostic Factors in Precursor B-cell Acute Lymphoblastic Leukemia**

PROGNOSTIC FACTOR	LOW RISK (EFS ~98%)	STANDARD RISK (EFS ~95%)	HIGH RISK[a] (EFS ~60%–95%)
Age, y	1–9.99	1–9.99 y	≥10
White blood cell count at diagnosis, /μL ($\times 10^9$/L)	<50,000 (<50)	<50,000 (<50)	≥50,000 (≥50)
Central nervous system status	Negative	Negative	Positive
Testicular disease	No	No	Yes
Cytogenetics (detects genetic alterations in leukemic cells)	ETV6-RUNX1 or trisomy 4 and 10	No genetic alteration or a genetic alteration present with no prognostic significance	IAMP21, MLL, hypodiploid, t(9;22) translocation
Minimal residual disease at day 29 of induction, %	<0.01	<0.01	≥0.01

EFS=event-free survival.
[a]*Only 1 factor required.*

patient is being treated for leukemia. Children return to school, adolescents return to sports, and young adults return to work. Compliance with mercaptopurine and methotrexate therapy is extremely important and has prognostic significance. (10) In difficult social situations and in the adolescent and young adult population this can be challenging and requires a team approach to ensure compliance. CNS disease is rare at diagnosis, but CNS prophylaxis is required to prevent subsequent CNS relapse. This is done through the instillation of methotrexate into the cerebrospinal fluid at multiple time points throughout treatment. Without this prophylaxis, the CNS relapse rate is approximately 50%. Cranial radiation is reserved for only the very few patients who present with CNS disease at diagnosis.

T-cell ALL historically was considered to have a poor prognosis compared with precursor B-cell leukemia, and a higher percentage of patients were treated with cranial radiation for CNS prophylaxis. With modern treatment regimens this difference has been largely eliminated. (11) The treatment of T-cell disease is very similar to that of high-risk precursor B-cell ALL. CNS prophylaxis is especially important for this population because CNS disease is more common. With the current protocols, only a very small number of patients require cranial radiation.

Ph-positive ALL (*BCR-ABL1* positive) and infantile ALL make up a very small percentage of childhood leukemias and are treated with separate protocols. Until recently, Ph-positive ALL was treated with bone marrow transplant (BMT) in first remission. In the era of tyrosine kinase inhibitors (TKIs), many patients can be cured with chemotherapy alone. (12) Infants with ALL are an especially challenging group of patients to treat. They have unique molecular characteristics as most patients have the mixed lineage leukemia rearrangement gene and are very young. Infants who are older than 6 months tend not to have this molecular abnormality and have a significantly better prognosis. Disease control can be challenging because infants tend to relapse early on in therapy and are difficult to get back into remission. New agents are required to improve survival in this patient population.

Ph-like ALL is characterized by gene expression similar to that of the Ph (*BCR-ABL1*–positive ALL). It was recently discovered that approximately 15% of patients with high-risk ALL harbor these mutations. These patients were also found to have an inferior prognosis compared with those without Ph-like rearrangements (EFS: 63% versus 86%). (13) Current research is aimed at targeting these mutations to improve EFS.

All patients with ALL require prophylaxis for *Pneumocystis carinii* pneumonia. First-line therapy is trimethoprim-sulfamethoxazole. If the patient has an allergy or does not tolerate this medication secondary to myelosuppression, alternatives include dapsone, inhaled pentamidine, and atovaquone. Dapsone has the relatively common adverse effect of methemoglobinemia, and inhaled pentamidine can sometimes cause bronchospasm, which can be prevented with albuterol nebulization. Atovaquone is rarely used. Vaccinations should be avoided during treatment except for the influenza vaccine. Vaccinations of siblings of patients with leukemia can be completed on a normal schedule. Any

TABLE 2. **Drugs Used in the Treatment of Acute Lymphoblastic Leukemia as per Children's Oncology Group Regimens**

TREATMENT PHASE	DRUGS	ADVERSE EFFECTS
Induction	Vincristine Dexamethasone/prednisone Pegylated asparaginase Daunorubicin (not in standard risk) Intrathecal cytarabine/methotrexate	Constipation, peripheral neuropathy, hypertension, hyperglycemia, infection (including invasive fungal), poor wound healing, anaphylaxis, thrombosis, pancreatitis, myelosuppression, cardiomyopathy, methotrexate neurotoxicity
Consolidation (combination varies by risk group)	Standard risk: 6-Mercaptopurine Vincristine Intrathecal methotrexate High risk: 6-Mercaptopurine Vincristine Cyclophosphamide Cytarabine Pegylated asparaginase Intrathecal methotrexate	Significant myelosuppression with transfusion requirements in high risk, infection (including invasive fungal in high risk), peripheral neuropathy, constipation, fever, myalgias, rash, anaphylaxis, thrombosis, pancreatitis, methotrexate neurotoxicity
Interim maintenance	Standard risk: Intravenous methotrexate (escalating dose) Vincristine Intrathecal methotrexate High risk: Intravenous methotrexate (high dose) Vincristine Intrathecal methotrexate	Mucositis, renal insufficiency, myelosuppression, constipation, peripheral neuropathy, neurotoxicity
Delayed intensification	Vincristine Decadron Pegylated asparaginase Daunorubicin 6-Thioguanine Vincristine Cyclophosphamide Cytarabine Pegylated asparaginase Intrathecal methotrexate	Significant myelosuppression with transfusion requirements in all patients, sinusoidal obstructive syndrome of the liver, infection (including invasive fungal), peripheral neuropathy, constipation, fever, myalgias, rash, anaphylaxis, thrombosis, pancreatitis, methotrexate neurotoxicity
Maintenance	6-Mercaptopurine Oral methotrexate Vincristine Dexamethasone/prednisone pulses Intrathecal methotrexate	Neutropenia, avascular necrosis (osteonecrosis), knees and hips most often, peripheral neuropathy, constipation, methotrexate neurotoxicity

exposure to varicella zoster, measles, or other significant virus can be serious, and patients should be referred to the treating institution immediately for infectious disease consultation. Fever should always be taken seriously, with blood cultures collected from the central line and early institution of broad spectrum antibiotics.

Relapsed ALL continues to be a therapeutic challenge, and many patients die of their disease. Depending on timing and site of relapse, some patients can be cured with very intensive chemotherapeutic regimens. Patients who relapse late with isolated disease in the CNS or testes have the best prognosis. Those who relapse early in the bone marrow or have T-cell disease have the worst outcomes. Many relapsed patients require BMT for a chance at definitive cure.

Targeted immunotherapy is revolutionizing the treatment of relapsed patients with precursor B-cell ALL (Table 3).(14)(15)(16)(17)(18) Leukemic blasts express CD19, CD20, and CD22 on their surface, and these antigens are not expressed on many other cells, making them attractive targets for therapy. These drugs include the bispecific T-cell–engaging antibody blinatumamab, the anti-CD22 antibody drug conjugate inotuzumab, and chimeric antigen receptor T-cell therapy. These treatments have shown excellent results in very heavily pretreated patients with acceptable toxicity profiles. In the next generation of

TABLE 3. **Targeted Therapies in ALL**

AGENT	MECHANISM OF ACTION	CLNICAL EFFICACY	FUTURE RESEARCH
Blinatumomab	Bispecific T-cell engager antibody targeting CD19	Study of heavily pretreated adults with persistent minimal residual disease: 16 of 21 patients became minimal residual disease negative (14) 39% complete response rate in relapsed/refractory children (15)	Ongoing randomized trial in relapsed ALL Possible use in future trials in newly diagnosed patients
Inotuzumab ozogamycin	Monoclonal antibody-drug conjugate targeting CD22	INOVATE trial in relapsed adult patients had a complete response rate of 81% (16) Retrospective data only in children	Ongoing single-agent trial in relapsed ALL Possible use in future trials in newly diagnosed patients
Chimeric antigen receptor T-cell therapy	Reprogramming of T cells to identify malignant cells with tumor-specific antigen recognition (17) Can target CD19, CD22, or both	Excellent activity with complete response rates of 70%–90% in heavily pretreated patients (18)	Multiple ongoing trials for relapse Possible use in refractory or newly diagnosed patients at very high risk for relapse
Imatinib/dasatinib	Tyrosine kinase inhibitors	Excellent efficacy in newly diagnosed patients with Ph-positive ALL Case reports of use in newly diagnosed patients with Ph-like ALL	Ongoing nonrandomized trial in newly diagnosed patients with Ph-like ALL
Ruxolitinib	Janus kinase 1 and 2 inhibitors	Phase 1 study as a single agent in relapsed solid tumors and leukemia in children (18)	Ongoing nonrandomized trial in newly diagnosed patients with Ph-like ALL (*CRLF2* and *JAK1/2* mutations)

ALL=acute lymphoblastic leukemia, Ph=Philadelphia chromosome.

precursor B-cell ALL trials, these agents will be evaluated in the upfront setting.

Acute Myelogenous Leukemia

AML is also a rapidly progressive disease. Excess blasts proliferate in the bone marrow as well as in the blood and can affect multiple organ systems. The cell of origin is in the myeloid line. Granulocytes, monocytes, erythrocytes, and megakaryocytes can all be the immature cell of origin, creating the varied morphologic appearance of this disease. AML has seen a significant improvement in survival, albeit not to the same degree as with ALL. Relapse-free survival of patients with AML is approximately 60%. This has been accomplished by intensifying chemotherapeutic regimens, delineating the appropriate use of BMT, and improving supportive care. Patients with favorable cytogenetic and molecular features and those who are MRD negative after induction can be treated with chemotherapy alone. Patients with unfavorable cytogenetics and molecular features or poor response to induction therapy require BMT. The group with the best prognosis has relapse-free survival of approximately 80%. Other groups can have relapse-free survival as low as 20%.

Patients who do not require a BMT are treated with 4 to 5 cycles of chemotherapy. In many patients, the first 2 cycles use a combination of cytarabine, etoposide, and daunorubicin. MRD is measured at the end of cycle 1. The remaining chemotherapy is based on high-dose cytarabine, which has long been recognized as an excellent drug for the treatment of AML. CNS prophylaxis is required with intrathecal cytarabine.

Patients with poor risk features require a BMT. This is usually performed after the third cycle of chemotherapy but can vary between institutions and therapeutic trials. BMT works best if the patient is MRD negative, but this is not always possible to achieve in children whose disease is very difficult to treat. Some patients can undergo BMT with MRD-positive disease and be cured.

The possible donor sources for BMT include human leukocyte antigen (HLA)–identical sibling, HLA-matched unrelated donor, HLA-mismatched unrelated donor, haploidentical (half-match) from a parent or sibling, and cord blood.

Most clinical trials call for the use of the best available donor when a BMT is required. An HLA-identical sibling is usually the most preferred source, but many patients will not have this option as each sibling has only a 25% chance of being an HLA match. When an HLA-identical sibling is not available, the decision of what donor source to use varies among transplant centers. Each source has its own advantages and disadvantages, and further clinical trials are needed in this area.

Supportive care is extremely important in the treatment of children with AML because the therapy can be very toxic and myelosuppressive, causing long periods of transfusion dependence and severe neutropenia. Most patients are kept in the hospital during their initial induction therapy until recovery of the absolute neutrophil count. Risk of infection is the most problematic toxicity in AML treatment, and watching patients closely in the hospital allows for prevention and prompt intervention in the event of fever or signs of sepsis. A patient with AML who presents with fever and neutropenia should be considered a medical emergency. Appropriate blood cultures should be drawn and broad spectrum intravenous antibiotics immediately started. These antibiotics should include a third- or fourth-generation cephalosporin (ceftazidime or cefepime) with vancomycin. Vancomycin is active against the organism streptococcal viridans. This organism can cause severe sepsis and death in patients who have received AML-directed chemotherapy, especially those receiving high-dose cytarabine. Invasive fungal infections are also a problem in AML and should be considered in patients who are persistently febrile despite broad spectrum antibiotic drug use. Appropriately diagnosing fungal disease can be a challenge, and early consultation with pediatric infectious disease is very important. Many patients will require computed tomography, bronchoscopy, or biopsy of suspicious lesions for definitive diagnosis and treatment planning. The use of antifungal prophylaxis can benefit patients with AML, (19) and antibacterial prophylaxis can also be used. (20) Antibacterial and antifungal prophylaxis regimens used by individual institutions vary.

Down syndrome–associated AML has its own unique biological and prognostic characteristics. Overall, patients with Down syndrome have an 80% EFS because the leukemia tends to be more sensitive to cytarabine and daunorubicin. (21) This survival advantage can be accomplished with less intensive chemotherapy. This is very important because children with Down syndrome are at increased risk for therapy-related toxicity. Recent clinical trials have successfully reduced therapy burden with reduction in anthracycline use, high-dose cytarabine, and CNS-directed therapy. (22) As in other patients with AML, supportive care is extremely important in this patient population.

Relapsed AML continues to be a therapeutic challenge with a very poor prognosis. Many patients with relapsed disease can be difficult to induce remission or make MRD negative. This makes BMT impossible or less effective. The chemotherapy used in these patients is very toxic, with significant short- and long-term risks. Patients who relapse after BMT have an extremely poor prognosis and have limited therapeutic options. Future clinical trials are needed for this group of patients using more targeted therapies. Unfortunately, this field has not grown nearly to the same degree seen in ALL.

Chronic Myelogenous Leukemia

CML was the first malignancy linked to a specific genetic translocation causing uncontrolled proliferation of myeloid cells, including varied stages of granulocytes, red blood cells, and platelets. The disease can develop slowly with a very long prodrome before diagnosis. This very distinctive disease can cause extremely high WBC counts along with thrombocytosis. Although CML makes up a very small percentage of childhood leukemia, its unique presentation, molecular characteristics, and therapeutic advances are fascinating. CML presents more commonly in adolescence but can occur at any age. Its morphologic characteristics are unique, with an elevated WBC count, neutrophilia, increased metamyelocytes and myelocytes, eosinophilia, basophilia, and thrombocytosis. The t(9;22) translocation, or Ph, and the resulting fusion gene *BCR-ABL* are pathognomonic of the disease and are required to make the diagnosis. This can be accomplished using peripheral blood, making the diagnosis relatively uncomplicated. Children and adolescents present similarly to adults with signs and symptoms related to extremely high WBC counts and sometimes massive hepatosplenomegaly. Patients can be asymptomatic or have fatigue, fever, night sweats, weight loss, abdominal distention, or mood disturbance.

Treatment of CML has been revolutionized with the development of TKIs. This class of medication targets enzymes that are responsible for cell growth and division. In CML the Bcr-Abl tyrosine kinase is responsible for abnormal cell growth because it has abnormally increased activity. The TKIs imatinib and dasatinib are potent inhibitors of this tyrosine kinase. Historically, the outlook for these patients was poor, with BMT being the only curative treatment. TKIs allow for excellent disease control with

relatively minimal toxicity. In children, the current standard of care is to begin imatinib or dasatinib at diagnosis. Even in patients who have an HLA-matched sibling, BMT is reserved only for the rare cases where the disease becomes resistant to TKI therapy. The challenge going forward is to decide how long patients need to remain on TKI therapy. The long-term toxicity associated with using these medications also needs to be explored. There are current ongoing trials in adults evaluating groups of patients who can be taken off TKIs after many years of therapy. This needs further research in children.

LATE EFFECTS OF THERAPY

The long-term complications of leukemia treatment vary widely by diagnosis and regimen. The late effects seen in a patient with standard-risk ALL are very different than those experienced by a patient with AML who required a BMT. Many pediatric oncology centers now have programs dedicated to survivorship. These multidisciplinary clinics include physicians, advanced care practitioners, dietitians, psychologists, social workers, school counselors, and easy access to other pediatric specialties. Survivors of childhood leukemia should be followed in these clinics yearly. These clinics are a conduit to primary care pediatricians and provide tailored outlines of potential long-term complications with required follow-up and screening.

Standard-risk patients with ALL have relatively few long-term complications. Most of these are related to the neuropsychological consequences of intrathecal methotrexate. Past studies evaluating the neurocognitive effect of treatment included those that received cranial radiation, thereby making extrapolating possible outcomes for today's survivors difficult. Survivors of childhood ALL have problems with processing speed, attention, and impaired executive functioning. These changes can be subtle in many cases and require formal neuropsychological testing to be found. This testing should be performed if the patient has problems in school or before a change in academic rigor. In general, patients should have testing before entering kindergarten, middle school, high school, and college. This will allow for interventions before problems start, and educational strategies can be tailored to the individual student's strengths and weaknesses.

Osteonecrosis is a very common adverse effect of contemporary ALL therapy. This complication can have significant effects on quality of life by causing arthritis, difficulties with activities of daily living, pain, and reduced range of motion. Adolescents are much more likely to be affected by osteonecrosis, and it can be seen in up to 20% of this age group. (23) Corticosteroids, particularly dexamethasone, are the major cause of this problem. Corticosteroids cause marrow fat cell hypertrophy and elevated intraosseous pressure. This leads to decreased blood flow and eventual marrow and bone necrosis. Host factors also may play a role. (24) The knees, hips, shoulders, and ankles can all be affected. Treatment is generally supportive, with some patients requiring arthroplasty when the disease is severe.

Long-term cardiac toxicity is a concern in patients with leukemia secondary to the use of anthracyclines. The risk of cardiotoxicity is directly related to the total dose used. The cumulative dose of anthracyclines used in ALL is very low, as is the risk of long-term cardiac toxicity. (25) However, there may not be a truly safe dose of anthracycline because small structural changes in the heart can be found, albeit with questionable clinical significance, even in those receiving lower doses. (26) AML therapy incorporates the use of both daunorubicin and mitoxantrone, both members of the anthracycline class. Patients with AML require much larger doses of anthracyclines compared with those with ALL. These patients require yearly echocardiograms to screen for cardiomyopathy and heart strain. If an abnormality is found, prompt referral to a pediatric cardiologist is warranted. Dexrazoxane is a cardioprotective agent that can be used in patients with AML to reduce the risk of future cardiomyopathy, but its use is not universal. There is evidence that this agent decreases the long-term risk of cardiomyopathy in those receiving higher doses of anthracyclines. (27)

Other late effects, including obesity, the associated metabolic syndrome, endocrine abnormalities, secondary malignancies, and growth disturbances, have been found in patients with leukemia. These are much more common in patients who received a BMT or cranial radiation. Infertility is uncommon in most patients with AML or ALL who did not receive a BMT. However, all patients at diagnosis should be counseled and offered sperm banking and egg harvesting or ovarian cryopreservation if appropriate.

Summary

- Based on strong research evidence (level A) in the form of numerous phase 3 clinical trials and clinical observation, childhood leukemia presents with signs and symptoms of cytopenias, fever, bone pain, limp, and refusal to walk. Patients may also have hepatosplenomegaly and symptoms related to central nervous system disease.
- Based on strong research evidence (level A) in the form of clinical observations and clinical studies, hyperleukocytosis should be treated immediately with appropriate supportive care. In most patients the use of leukapheresis can be avoided. (6)
- Based on strong research evidence (level A) in the form of multiple phase 3 clinical trials, acute lymphoblastic leukemia (ALL) in children has an excellent prognosis. T-cell disease now has a similar prognosis to B-cell disease. The event-free survival varies among different ALL subgroups, and therapy should be tailored accordingly. (7)(10)
- Based on strong research evidence (level A) in the form of phase 3 clinical trials, patients with trisomy 21 and acute myelogenous leukemia (AML) have a favorable prognosis. (15)
- Based on strong research evidence (level A) in the form of multiple phase 3 clinical trials, minimal residual disease testing has prognostic significance across ALL and its subgroups and AML. (7)(8) Phase 3 clinical trials compare the existing standard of care treatment with a new treatment called the experimental arm of the study. The experimental arm can be used to test the effectiveness of a new drug, dose, or schedule. Many phase 3 pediatric oncology trials are accomplished with a large number of patients using the cooperative group model.
- Based on strong research evidence (level A) in the form of clinical trials, Philadelphia chromosome–positive ALL has much improved outcomes with the use of tyrosine kinase inhibitors. (11)
- Based on strong research evidence (level A) in the form of clinical research and clinical guidelines, supportive care is extremely important in patients with AML. Special attention should be given to fever and the development of streptococcal viridans sepsis.
- Based on strong research evidence (level A), the targeted immunotherapies blinatumamab, chimeric antigen receptor T-cell therapy, and inotuzumab show excellent results for relapsed patients with ALL. (13)(14)(15)(16)(17)

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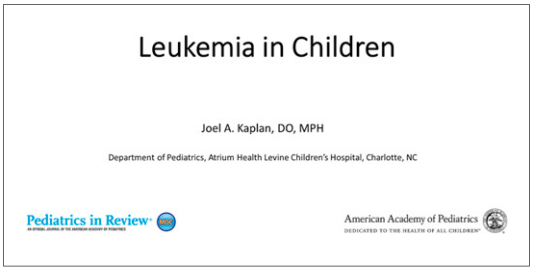

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1. A 3-year-old boy is brought to the office with complaints of fever and pain in the legs. The fever has been intermittent and as high as 101.5°F (38.6°C) for the past 5 days, and the pain in the legs is waking him up at night. He has a negative medical history, and his immunizations are up-to-date. The mother noted that he has had some bruising on the arms and legs, but she accounts for that by his active play. He had a viral infection approximately 3 weeks ago that resolved without treatment. Vital signs include a temperature of 100.8°F (38.2°C), a heart rate of 120 beats/min, a respiratory rate of 24 breaths/min, blood pressure of 100/60 mm Hg, and oxygen saturation of 100% on room air. There is mild cervical lymphadenopathy, and results of the heart and lung examinations are normal. The abdomen is soft, without hepatosplenomegaly. The extremities show mild discomfort, with scattered ecchymoses. Neurologic examination findings are normal. Laboratory studies show a white blood cell (WBC) count of 1,500/μL (1.5×10^9/L), a hemoglobin level of 8.5 g/dL (85 g/L), a hematocrit value of 24%, a platelet count of $75\times10^3/\mu$L (75×10^9/L), a reticulocyte count of 0.4%, and a differential count of 5% neutrophils, 85% lymphocytes, 5% eosinophils, and 5% monocytes. Which of the following is the most likely diagnosis in this patient?
   A. Acute lymphocytic leukemia.
   B. Aplastic anemia.
   C. Chronic lymphocytic leukemia.
   D. Infectious mononucleosis.
   E. Viral suppression.
2. A 14-year-old girl is brought to the emergency department with a history of fatigue, pallor, and bruising. On physical examination the vital signs show a temperature of 100.0°F (37.8°C), a heart rate of 100 beats/min, a respiratory rate of 20 breaths/min, and BP of 110/65 mm Hg. Physical examination shows a pale adolescent in no acute distress. There is mild cervical adenopathy, and the lungs are clear. A grade 2/6 systolic murmur is heard. The abdomen is soft, with the spleen palpable 3 cm below the left costal margin. The liver is 1 cm below the right costal margin. Neurologic examination findings are normal. Extremities show scattered bruising. Laboratory data show a WBC count of 150,000/μL (150×10^9/L); a hemoglobin level of 6 g/dL (60 g/L); a hematocrit value of 18%; a platelet count of $10\times10^3/\mu$L (10×10^9/L); a differential count of 95% atypical lymphocytes, 2% monocytes, and 3% neutrophils; a blood urea nitrogen level of 10 mg/dL (3.6 mmol/L); a creatinine level of 0.5 mg/dL (44.2 μmol/L); and a potassium level of 3.0 mEq/L (3.0 mmol/L). The patient is admitted to the hospital, and flow cytometry on a bone marrow aspirate shows pre–B-cell acute lymphocytic leukemia. The girl begins chemotherapy with vincristine, doxorubicin, and prednisone, with planned L-asparaginase on day 4 of therapy. Twenty-four hours after beginning therapy the nurse calls and says that the patient has not urinated in 8 hours. The blood pressure is now 140/90 mm Hg. Laboratory data show a blood urea nitrogen level of 30 mg/dL (10.7 mmol/L), a creatinine level of 2.5 mg/dL (221.0 μmol/L), a phosphorus level of 6 mg/dL (1.9 mmol/L), a calcium level of 7.5 mg/dL (1.9 mmol/L), a lipase level of 100 U/L (1.7 μkat/L), and a potassium level of 5.0 mEq/L (5.0 mmol/L). Which of the following is the most likely explanation for the change in the patient's status and laboratory data?
   A. Cardiac failure.
   B. Dehydration.
   C. Gastrointestinal bleeding.
   D. Pancreatitis.
   E. Tumor lysis syndrome.

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3. As treatment is continued, the treating physician discusses the diagnosis with the parents, who ask about the prognosis and treatment for their child. Which of the following is the most appropriate response to the family?

   A. High risk and will require a bone marrow transplant.
   B. High risk and will require chemotherapy.
   C. High risk and will require treatment with tyrosine kinase inhibitors.
   D. Low risk and will require a bone marrow transplant.
   E. Standard risk and will require chemotherapy.

4. A 16-year-old boy is brought to the emergency department for complaints of fatigue and abdominal fullness. He has had intermittent fever to 101.0°F (38.3°C) for the past week but has been continuing to go to school. His physical examination shows a pale adolescent in no acute distress. His temperature is 99.5°F (37.5°C), heart rate is 90 beats/min, respiratory rate is 18 breaths/min, and blood pressure is 110/70 mm Hg. Heart and lung examination findings are normal, and the abdomen shows the spleen to be palpable 4 cm below the left costal margin. Neurologic examination findings are normal. The skin shows facial acne. Laboratory data show a WBC count of 150,000/μL (150×10^9/L), a hemoglobin level of 10 g/dL (100 g/L), a hematocrit value of 28%, a platelet count of $400\times10^3/\mu$L (400×10^9/L), and a differential count of 3% blasts, 8% myelocytes, 10% metamyelocytes, 20% bands, 40% neutrophils, 5% basophils, and 14% lymphocytes. Which of the following is the most likely chromosomal abnormality to be seen in this patient?

   A. t(8;21).
   B. t(9;22).
   C. 11q23.
   D. t(15;17).
   E. Trisomy 21.

5. A 15-year-old boy is brought to the office for routine health care maintenance. He has been generally doing well, but his medical history is significant for acute myelogenous leukemia treated with cytarabine, daunorubicin, etoposide, and mitoxantrone. He has been off therapy and in continuous remission for 7 years and is doing well in school. His physical examination shows no abnormalities. He is Tanner stage 4. Which of the following is the most appropriate test to perform in this patient?

   A. Echocardiography.
   B. Hearing evaluation.
   C. Hemoglobin A1c.
   D. Serum follicle-stimulating hormone, luteinizing hormone, and testosterone.
   E. Radiographs of the hips.

Leukemia in Children

Joel A. Kaplan

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