

Leukemia in Children

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Introduction

- Leukemia is the most common malignancy of childhood
- There are 3 main subtypes of leukemia in children:
 - Acute lymphoblastic leukemia (ALL)
 - Most common subtype, accounting for 80% of cases
 - Acute myelogenous leukemia (AML)
 - Chronic myelogenous leukemia (CML)
- Children present with symptoms related to cytopenias or leukemic infiltration of the bone marrow
- The spleen, liver, testes, and central nervous system (CNS), can also be involved

Introduction

- Most children are cured with modern, risk-adapted therapy
- Relapse continues to be a problem
- We have entered an exciting time of targeted and immunologic therapy that is revolutionizing the treatment of these challenging patients
- Late effects of treatment need to be recognized by the general pediatrician
 - As cure rates increase, the number of adult, childhood cancer survivors increases
 - There is no one size fits all. Each disease and treatment regimen have varied late effects

Epidemiology

- Childhood cancer is very rare with, 14,000 cases diagnosed annually
- In children, hematologic malignancies predominate
 - 1/3 of all oncology cases
- The incidence of ALL is approximately 30 cases per 1 million persons
- Environmental factors do not have a strong link with childhood leukemia
- The cause of ALL is most likely multifactorial, involving genetic, immunologic, and infectious factors
- Trisomy 21 patients have an increased risk of leukemia, especially if they have had transient myeloproliferative syndrome

Clinical Presentation

- The degree of anemia, thrombocytopenia, and neutropenia is highly variable
- Anemia
 - Pallor, fatigue, dyspnea on exertion, headache, dizziness, and near syncope
- Thrombocytopenia
 - Bruising and petechiae
 - Serious bleeding is rare
- Neutropenia
 - Infection or sepsis at diagnosis is uncommon

Clinical Presentation

- Fever
- Expansion of the bone marrow cavity
 - Bone pain
 - Limp
 - Refusal to walk
- Back pain
 - Always requires close interval follow-up as can be a sign of childhood cancer
 - Do not treat this like an adult

Clinical Presentation

- Lymphadenopathy
- Hepatomegaly
- Splenomegaly
- Kidney lesions or infiltration
- Testicular disease occurs in approximately 2% of children with ALL
 - Nodule or enlargement
 - Testicular exam required with any new diagnosis

Clinical Presentation

- CNS leukemia can be seen in both ALL and AML
 - More common in ALL, especially T-cell disease
 - Headache
 - Seizure
 - Visual changes
 - Cranial nerve abnormalities
 - Mental status change
 - Asymptomatic
- Anterior Mediastinal Mass (T-cell ALL)
 - Chest pain, shortness of breath, dyspnea on exertion

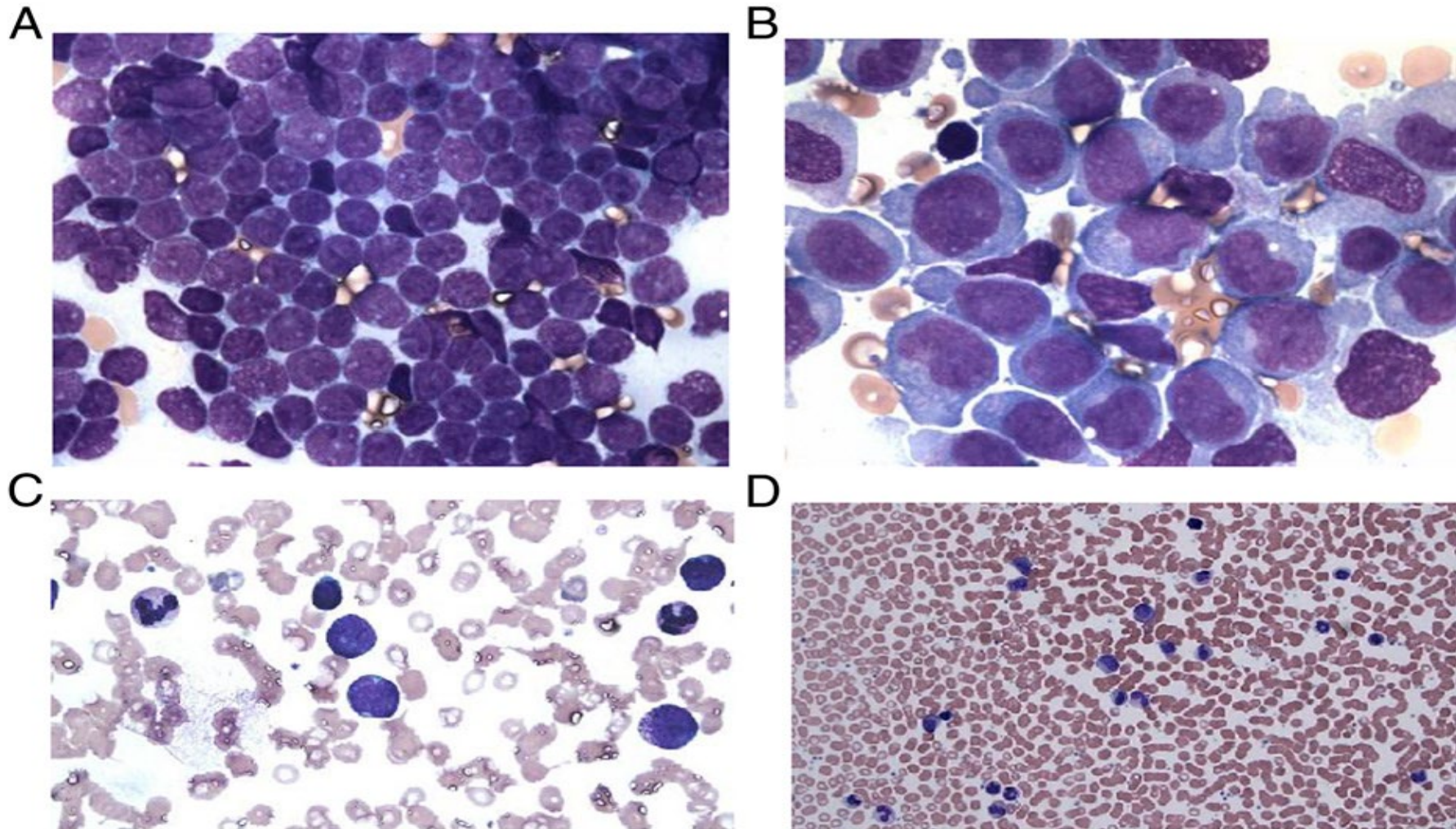


Figure 1. Photomicrographs of different types of leukemia. A. Acute lymphoblastic leukemia. Notice the high nucleus to cytoplasm ratio and uniform appearing blasts. This morphologic profile is commonly seen in both T- and B-cell leukemia. B. Acute myelogenous leukemia, monocytic subtype. Notice the relatively 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.

Oncologic Emergencies in Newly Diagnosed Leukemia

- Hyperleukocytosis: WBC count of greater than 100,000/mL
 - More common in AML, T-cell ALL, and infantile leukemia
 - Leukostasis precipitates decreased tissue perfusion
 - Neurologic and pulmonary sequelae
- Signs and symptoms of leukostasis
 - 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
 - Coagulation
 - DIC, abnormal tests of coagulation with elevated PT and PTT with decreased fibrinogen

Oncologic Emergencies in Newly Diagnosed Leukemia

- Tumor lysis syndrome
 - Hyperkalemia
 - Hyperphosphatemia
 - Hyperuricemia
 - Hypocalcemia
 - Usually develops after therapy is started but can occur at initial presentation
 - Can lead to cardiac arrhythmias and renal failure

Treatment of Hyperleukocytosis

- The use of leukapheresis has fallen out of favor
- 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 125mL/m² per hour; no potassium should be put in intravenous fluids
- Begin allopurinol
- Consider rasburicase if the uric acid level is greater than 8.0 mg/dL (>476 mmol/L)
- Every-6-hour renal function panel and uric acid level
- Transfuse platelets if less than 30,000
- 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

Prognostic Factors in Precursor B-cell ALL

PROGNOSTIC FACTOR	LOW RISK (EFS approximately 98%)	STANDARD RISK (EFS approximately 95%)	HIGH RISK *Only 1 factor required (EFS approximately 60%-95%)
Age	1-9.99 years	1-9.99 years	> or = 10 years
White blood cell Count at diagnosis	<50,000/uL ($50 \times 10^9/L$)	<50,000/uL ($50 \times 10^9/L$)	> or = 50,000/uL ($50 \times 10^9/L$)
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%	> or = 0.01%

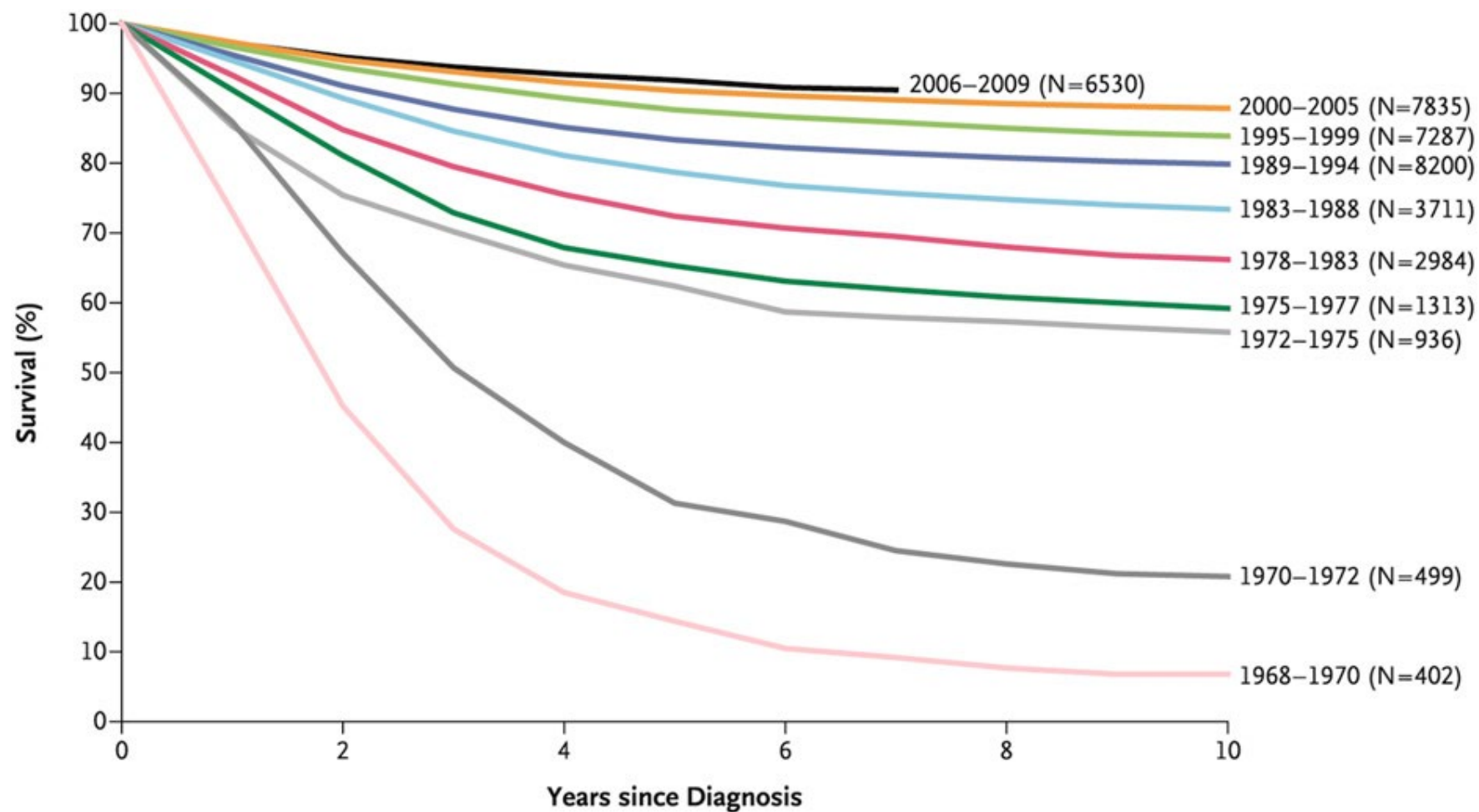


FIGURE 2. Overall survival among children with acute lymphoblastic leukemia who were enrolled in Children's Cancer Group and Children's Oncology Group clinical trials, 1968–2009. From Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015;373(16):1541–1552.

ALL: Treatment

- Cooperative group trials vital
 - Allow for study of rare diseases
- Multiagent chemotherapy
 - Has been improved by identifying risk groups with variable prognosis and tailoring therapy to individual patients
 - Patient characteristics
 - Biological factors
 - Degree of response to initial treatment
- B cell, T cell, Philadelphia chromosome (Ph) positive, and infantile ALL are treated on different regimens

TREATMENT PHASE for ALL	DRUG	SIDE EFFECTS
Induction	Vincristine Decadron/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: IV Methotrexate (Escalating dose) Vincristine Intrathecal methotrexate HIGH RISK: IV 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 Decadron/Prednisone pulses Intrathecal methotrexate	Neutropenia, avascular necrosis (osteonecrosis): knees and hips most often, peripheral neuropathy, constipation, methotrexate neurotoxicity

ALL: Treatment

- Minimal residual disease (MRD) testing allows for the accurate detection of very small amounts of leukemic blasts in the bone marrow
 - Highly prognostic in all ALL subtypes
- The intensity of therapy is individualized based on the final risk group designation
- CNS disease is rare at diagnosis, but CNS prophylaxis is required to prevent subsequent CNS relapse
 - Intrathecal Methotrexate
 - Cranial radiation used very rarely

ALL: Treatment

- Relapsed ALL continues to be a therapeutic challenge
 - 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
 - Bone marrow transplant is required in a majority of these patients
 - Targeted and immunotherapy is revolutionizing the care of these patient

ALL: Supportive Care

- 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
 - Atovaquone (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

ALL: Supportive Care

- Fever
 - Should always be taken seriously
 - Fever and neutropenia is a medical emergency
 - Blood cultures from central line
 - Early institution of broad spectrum antibiotics
- 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

ALL: Targeted Therapy

AGENT	MECHANISM OF ACTION	CLINICAL EFFICACY	FUTURE RESEARCH
Blinatumomab	Bispecific T-cell engager antibody targeting CD-19	<ul style="list-style-type: none"> ➤ Study of heavily pre-treated adults with persistent minimal residual disease: 16/21 patients became minimal residual disease negative¹ ➤ 39% complete response rate in relapsed/refractory children² 	<ul style="list-style-type: none"> ➤ Ongoing randomized trial in relapsed acute lymphoblastic leukemia ➤ Possible use in future trials in newly diagnosed patients
Inotuzumab ozogamycin	Monoclonal antibody-drug conjugate targeting CD-22	<ul style="list-style-type: none"> ➤ INOVATE Trial in relapsed adult patients had a complete response rate of 81%.³ ➤ Retrospective data only in children. 	<ul style="list-style-type: none"> ➤ Ongoing single agent trial in relapsed acute lymphoblastic leukemia ➤ Possible use in future trials in newly diagnosed patients
Chimeric Antigen Receptor T-cell therapy	<ul style="list-style-type: none"> ➤ Reprogramming of T-cells to identify malignant cells with tumor specific antigen recognition⁴ ➤ Can target CD-19, CD-22, or both 	<ul style="list-style-type: none"> ➤ Excellent activity with complete response rates of 70-90% in heavily pretreated patients⁵ 	<ul style="list-style-type: none"> ➤ Multiple ongoing trials for relapse ➤ Possible use in refractory or newly diagnosed patients at very high risk for relapse
Imatinib/Dasatinib	Tyrosine Kinase Inhibitors	<ul style="list-style-type: none"> ➤ Excellent efficacy in newly diagnosed patients with Philadelphia chromosome positive acute lymphoblastic leukemia ➤ Case reports of use in newly diagnosed patients with Ph-like acute lymphoblastic leukemia 	<ul style="list-style-type: none"> ➤ Ongoing non-randomized trial in newly diagnosed patients with Ph-like ALL
Ruxolitinib	Janus Kinase 1 and 2 inhibitor	<ul style="list-style-type: none"> ➤ Phase 1 study as a single agent in relapsed solid tumors and leukemia in children⁵ 	<ul style="list-style-type: none"> ➤ Ongoing non-randomized trial in newly diagnosed patients with Ph-like ALL (CRLF-2 and JAK 1/2 mutations)

AML

- AML has seen a significant improvement in survival, albeit not to the same degree as with ALL
- Relapse-free survival of patients with AML has improved to 60%
 - Intensifying chemotherapeutic regimens
 - Delineating the appropriate use of BMT
 - 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

AML

- Treatment
 - Patients who do not require a BMT are treated with 4 to 5 cycles of chemotherapy
 - The first 2 cycles use a combination of cytarabine, etoposide, and daunorubicin
 - Etoposide may not be necessary
 - High-dose cytarabine is important in subsequent cycles
 - CNS prophylaxis is required but not to the same degree as in ALL

AML

- BMT is required in patients with poor risk features
 - Donor sources for BMT
 - Human leukocyte antigen (HLA)-identical sibling
 - HLA-matched unrelated donor
 - HLA-mismatched unrelated donor
 - Haploidentical donor from a parent
 - Cord blood
- An HLA-identical sibling is usually the preferred source, but many patients will not have this option as each sibling has only a 25% chance of being an HLA match.
- The decision of what donor source to use varies among transplant centers; each source has its own advantages and disadvantages
 - Further clinical trials are needed in this area

AML: Trisomy 21

- Down syndrome–associated AML has its own unique biological and prognostic characteristics
- 80% event-free survival
- Leukemia tends to be more sensitive to cytarabine and daunorubicin
- This survival advantage can be accomplished with less intensive chemotherapy, which 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

AML: Relapse

- Very poor prognosis
- Can be difficult to get to MRD-negative
 - This makes BMT impossible or less effective
- Patients who relapse after BMT have an extremely poor prognosis
 - 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

AML: Supportive Care

- Therapy very 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
 - Fever and neutropenia
 - Medical emergency
 - Third- or fourth-generation cephalosporin (ceftazidime or cefepime) with vancomycin
 - Meropenem can also be used
 - Vancomycin is active against the organism streptococcal viridans, which can cause severe sepsis and death in patients who have received AML-directed chemotherapy, especially those receiving high-dose cytarabine

AML: Supportive Care

- Invasive fungal infections are a problem in AML
 - Should be considered in patients who are persistently febrile despite broad spectrum antibiotics
 - Diagnosing fungal disease can be a challenge and early consultation with pediatric infectious disease is very important
 - Diagnostic modalities for definitive diagnosis and treatment planning
 - Computed tomography
 - Bronchoscopy
 - biopsy of suspicious lesions
- Antifungal and antibacterial prophylaxis can be beneficial
 - Regimens vary by institution

CML

- CML was the first malignancy linked to a specific genetic translocation
- Uncontrolled proliferation of myeloid cells, including varied stages of granulocytes, red blood cells, and platelets
- Can develop slowly with a very long prodrome before diagnosis
- CML presents more commonly in adolescence but can occur at any age
- The t(9;22) translocation, or Ph, and the resulting fusion gene BCRABL are pathognomonic of the disease and are required to make the diagnosis

CML: Presentation

- Elevated WBC count, neutrophilia, increased metamyelocytes and myelocytes, eosinophilia, basophilia, and thrombocytosis
- Massive hepatosplenomegaly
- Can be asymptomatic
- Fatigue
- Fever, night sweats, weight loss
- Abdominal distention
- Mood disturbance

CML: Treatment

- Tyrosine kinase inhibitors have replaced the need for BMT in this disease
- Bcr-Abl tyrosine kinase is responsible for abnormal cell growth
- Imatinib and dasatinib are potent inhibitors of this tyrosine kinase
- TKIs allow for excellent disease control with relatively minimal toxicity
- The challenge going forward is to decide how long patients need to remain on TKI therapy
 - Ongoing studies in adults

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