Leukemia, Acute Lymphoblastic, in Children

Description/Etiology
Acute lymphoblastic leukemia (ALL), also known as acute lymphocytic leukemia, is a cancer of the bone marrow in which lymphoblasts (lymphoid progenitor cells) proliferate and replace normal hematopoietic bone marrow cells. The leukemia cells interfere with the production of normal blood cells in the bone marrow and can rapidly spread to other parts of the body, such as the liver, spleen, CNS, and testes. ALL is more common in children than in adults, but the prognosis is better in children than in adults.

The exact cause of ALL is unknown, but chromosomal anomalies are found in more than 90% of cases. ALL is classified by immunologic phenotype (B cell or T cell). Patients with ALL typically develop signs and symptoms that reflect bone marrow infiltration and decreased production of normal bone marrow components. The differential diagnosis includes acute myelogenous leukemia (AML), primary bone failure, mononucleosis, pertussis, and cytomegalovirus (CMV) infection. Bone marrow aspiration and biopsy provide definitive diagnosis; immunophenotyping is performed to identify the ALL subtype.

Intensive, long-term chemotherapy consisting of three phases—induction, consolidation, and maintenance—as well as CNS prophylaxis (intrathecal chemotherapy) is used to treat ALL. Induction therapy is aimed at achieving remission and can be given for 4–6 weeks. Consolidation chemotherapy is intensive chemotherapy given for 4–8 months to sustain remission. Maintenance therapy can last for up to 2 years. Total duration of treatment for ALL is usually 2–3 years. Bone marrow transplantation can be used in patients considered to be at high risk for relapse or in those who have experienced relapse.

Facts and Figures
Leukemia, the most common pediatric cancer, has an incidence rate of 4/100,000 children per year—accounting for 1/3 of all cases. (Karrman, 2017) ALL accounts for > 25% cancers and 80-85%of acute leukemias—of which 10-15% if compromised of T-cell ALL—in children under 15 years of age. The estimated annual incidence of ALL in children 0–14 years of age is 3.7–4.9 cases per 100,000; each year in the United States, approximately 3,000 new cases are diagnosed in children. Peak incidence is at 2–5 years of age and 60% of patients diagnosed with ALL are younger than 20 years. ALL occurs more often in Whites than non-Whites and in males more often than females. The 5-year overall survival rate is 86–89% in children, compared to 42–63%in adolescents and young adults, 24% in adults 40–59 years of age, and 18% in adults 60–69 years of age. Infants diagnosed with ALL generally have a poor outcome.

Risk Factors
Rare cases of ALL (< 5%) are associated with inherited genetic syndromes (e.g., Down syndrome, Bloom syndrome, Fanconi anemia, neurofibromatosis type 1, Wiskott-Aldrich syndrome). Risk factors include exposure to electromagnetic fields, ionizing radiation, chemotherapeutic agents, pesticides, or solvents; high birth weight; prenatal exposure to certain viruses (e.g., influenza, varicella); and maternal alcohol use during pregnancy. The established risk factors for ALL account for a small proportion of all cases of ALL and the young age at onset suggests that inherited genetic traits—likely low penetrance susceptibility alleles—play a role in the development of the disease.
Signs and Symptoms/Clinical Presentation

Clinical manifestations include fatigue, pallor, fever, petechiae and bleeding, infection, weight loss, bone pain, and dyspnea. In cases with CNS involvement, the presentation can include headache, nausea, vomiting, lethargy, nuchal rigidity, irritability, and papilledema; patients with an intracranial or spinal mass might develop neurologic symptoms due to nerve compression.

Assessment

› Physical Findings of Particular Interest
  • Lymph nodes can be swollen and the liver, spleen, and/or testes can be enlarged

› Laboratory Tests
  • CBC will likely reveal increased WBC count, decreased RBC and platelet counts, and a low neutrophil count
  • Peripheral blood smears can reveal excessive amounts of lymphoblasts
  • Immunophenotyping (e.g., flow cytometry) can identify and classify cell phenotype
  • Enzyme-linked immunosorbent assays of Fas and its ligand (sFas and sFasL) correlate with disease progression in various malignancies
  • Cytochemistry stain testing can be used to differentiate types of leukemia
  • Molecular and cytogenetic techniques such as fluorescent in situ hybridization (FISH) can identify chromosomal abnormalities
  • Urine and liver tests to evaluate renal and liver function, respectively

› Other Diagnostic Tests/Studies
  • Bone marrow aspiration and histologic examination of biopsy sample to diagnose ALL; diagnosis of ALL typically requires demonstration of ≥ 20% bone marrow lymphoblasts
  • Imaging studies (e.g., chest X-ray, cranial MRI, bone scan) can be used to assess for signs of ALL infiltration and infection

Treatment Goals

› Promote Optimal Physiologic Function, Alleviate Symptoms, and Manage Complications
  • Monitor vital signs, assess all physiologic systems, and review laboratory test results; report abnormalities provide prescribed treatment
  • Assess type, location, and level of pain using a facility-approved pain assessment tool; administer prescribed analgesics
  • Administer prescribed systemic chemotherapeutic agents (e.g., vinCRISTine, L-asparaginase, DAUNORubicin [in high-risk cases]) and intrathecal chemotherapeutic agents (e.g., methotrexate, cytarabine); other chemotherapeutic agents and cancer treatment medications that can be prescribed include 6-mercaptopurine, etoposide, cyclophosphamide, dexamethasone, and predniSONe
    – Monitor for side effects, including hair loss, mouth sores, diarrhea, nausea, fatigue, infection, bruising, bleeding, and thrombosis. If applicable, administer prescribed antiemetics for nausea/vomiting; provide mouth care to prevent stomatitis
  • Administer prescribed colony-stimulating factors (CSFs; e.g., filgrastim, pegfilgrastim) as prescribed to prevent or treat neutropenia
  • Administer blood cell replacement therapy (e.g., packed RBCs, platelets, fresh frozen plasma), as prescribed
  • Administer prescribed prophylactic antimicrobials (e.g., antibiotics such as trimethoprim/sulfamethoxazole and antifungals such as nystatin and clotrimazole) to prevent infection
  • Follow facility pre- and post-procedure protocols if patient becomes a candidate for bone marrow transplantation
    – Reinforce pre- and post-procedure education and verify parental completion of facility informed consent documents
    – Closely monitor for pain, bleeding, and signs of infection; provide prescribed treatment
  • Promote adequate nutrition; monitor nutritional status, fluid intake, and weight loss; administer dietary supplements, as prescribed, and provide choice of favorite foods and snacks between meals

› Provide Emotional/Psychosocial Support
  • Assess child/parent anxiety level and coping ability; educate and encourage discussion about ALL pathophysiology, treatment risks and benefits, and individualized prognosis
  • Encourage child, as age appropriate, and parent to ask questions; provide time for family members to express feelings or concerns regarding diagnosis or treatment
  • Encourage parent/child to participate in decisions regarding treatment and promote parental participation in child’s care
  • Provide anticipatory guidance and support and request referral to social worker if appropriate, to help the patient’s family to cope with the many stressful life changes (e.g., loss of employment, decreased work hours, relocated homes) that are common in the first year of treatment for ALL
Food for Thought

- Increasing survival rates in children with ALL have led to a growing population of long-term survivors of ALL who might experience late effects of treatment; long-term survivors of ALL are at increased risk for all-cause mortality, cardiovascular-related mortality, stroke, neurological problems (e.g., seizures), neuromuscular impairments, weight gain, metabolic syndrome, and other chronic health conditions.

  - Investigators who studied 56 15–24-year-old survivors of childhood ALL found a correlation between cranial radiotherapy and increased body fat and abdominal fat tissue (Siviero-Miachon et al., 2013).
  - In a study of 162 long-term survivors of ALL who were at a median age of 15.7 years at study enrollment, 83% had mild neurological symptoms (e.g., dizziness, neuropathy, tension headache); risk factors for neurological symptoms included female sex, ≥ 10 doses of intrathecal chemotherapy, and history of ALL relapse (Khan et al., 2014).
  - An estimated 25–50% of children with ALL who achieve complete remission after the induction phase of treatment have minimal residual disease (MRD), which carries an increased risk of relapse. Therefore, all children with ALL should be tested during and after the induction phase (National Comprehensive Cancer Network, 2016).
  - In a study on 1848 children diagnosed ALL in Poland, researchers reported a relapse-free survival rate of 73% in children simultaneously diagnosed with Down syndrome versus 81% in children who were not found to have Down syndrome, supporting previous research that children with Down syndrome have a higher risk of developing leukemia, compared with the general population (Zawitkowska et al., 2017).

Red Flags

- Tumor lysis syndrome is a metabolic complication associated with treatment of ALL that can result in hyperuricemia or acute renal failure; to prevent tumor lysis syndrome, sodium bicarbonate and allopurinol or rasburicase should be administered prior to chemotherapy.

- Predictors of poor prognosis include WBC count > 100,000/μL (B cell), WBC count > 100,000/μL (T cell), failure to achieve complete remission within 4 weeks, and hypoploidy (fewer than 44–45 chromosomes); in addition, minimal residual disease (i.e., minute amounts of malignant cells) despite therapy is an important risk factor for ALL recurrence.

- Chemotherapy may not be an effective treatment for some children with a specific type of ALL (e.g., Philadelphia chromosome); (National Cancer Society, 2017).

What Do I Need to Tell the Patient/Patient’s Family?

- When possible, provide written information on ALL to parent/child.
- Discuss treatment options and short- and long-term effects of treatment. Inform child, as age appropriate, and parents that treatment might occur several times a week and last for at least 2 years, and that ongoing follow-up care is needed. Discuss prognosis and the risk of recurrence.
- Instruct child/parents on ways to reduce the risk of infection (e.g., avoid contact with persons with infection, maintain careful personal hygiene, avoid eating fresh fruits and vegetables and undercooked meat) and bleeding.
- Advise parents to seek immediate medical attention for fever or signs of bleeding.
- More information can be obtained from the American Cancer Society at http://www.cancer.org and the Leukemia and Lymphoma Society at http://www.lls.org/

References

