Acute lymphoblastic leukemia:

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Introduction

Background

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children, representing nearly one third of all pediatric cancers. The peak incidence occurs in children aged 2-5 years.

Although a few cases are associated with inherited genetic syndromes (ie, Down syndrome, Bloom syndrome, Fanconi anemia), the cause remains largely unknown. Many environmental factors (ie, exposure to ionizing radiation and electromagnetic fields, parental use of alcohol and tobacco) have been investigated as potential risk factors, but none has been definitively shown to cause acute lymphoblastic leukemia. Various viruses may be linked to the development of leukemia, particularly when prenatal viral exposure occurs in mothers recently infected with influenza or varicella.
Acute lymphoblastic leukemia may also occur in children with various congenital immunodeficiencies (ie, Wiskott-Aldrich syndrome, congenital hypogammaglobulinemia, ataxia-telangiectasia) that have an increased predisposition to develop lymphoid malignancies.

Pathophysiology

In acute lymphoblastic leukemia, a lymphoid progenitor cell becomes genetically altered and subsequently undergoes dysregulated proliferation, survival, and clonal expansion. In most cases, the pathophysiology of transformed lymphoid cells reflects the altered expression of genes whose products contribute to the normal development of B cells and T cells. Several studies indicate that leukemic stem cells are present in certain types of acute lymphoblastic leukemia.[1,2]

Mortality/Morbidity

Overall cure rates for children with acute lymphoblastic leukemia now approach 80%. The 4-year event-free survival (EFS) rate for high-risk patients is approximately 65%.

Race

The overall incidence of acute lymphoblastic leukemia varies among different racial groups within the United States. White children are more frequently affected than black children.

Sex

Acute lymphoblastic leukemia occurs slightly more frequently in boys than in girls. This difference is most pronounced for T-cell acute lymphoblastic leukemia.

Age

The incidence of acute lymphoblastic leukemia peaks in children aged 2-5 years.

Clinical

History

Children with acute lymphoblastic leukemia (ALL) generally present with signs and symptoms that reflect bone marrow infiltration and extramedullary disease. Because leukemic blasts replace the bone marrow, patients present with signs of bone marrow failure, including anemia, thrombocytopenia, and neutropenia. Clinical manifestations include fatigue and pallor, petechiae and bleeding, and fever. In addition, leukemic spread may manifest as lymphadenopathy and hepatosplenomegaly. Other signs and symptoms of leukemia include weight loss, bone pain, and dyspnea.

Signs or symptoms of CNS involvement, even when it occurs, are rarely observed at the time of the initial diagnosis. The signs and symptoms include headache, nausea and vomiting, lethargy, irritability, nuchal rigidity, and papilledema. Cranial nerve involvement, which most frequently involves the seventh, third, fourth, and sixth cranial nerves, may occur. Also, leukemia can present as an intracranial or spinal mass, which causes numerous neurologic symptoms, most of which are due to nerve compression.

Testicular involvement at diagnosis is rare. However, if present, it appears as painless testicular enlargement and is most often unilateral.

Physical

Physical findings in children with acute lymphoblastic leukemia reflect bone marrow infiltration and extramedullary disease. Patients present with pallor caused by anemia

and petechiae and bruising secondary to thrombocytopenia. They also have signs of infection because of neutropenia. In addition, leukemic spread may be seen as lymphadenopathy and hepatosplenomegaly.

Careful neurologic examination to look for CNS involvement is important because the treatment for leukemia with CNS involvement is different.

In male patients, testicular examination is necessary to look for testicular involvement of leukemia.

Causes

Although a small percentage of cases are associated with inherited genetic syndromes, the cause of acute lymphoblastic leukemia remains largely unknown.

Differential Diagnoses

Acute Myelocytic Leukemia
Anemia, Acute
Anemia, Fanconi
Juvenile Rheumatoid Arthritis
Leukocytosis
Mononucleosis and Epstein-Barr Virus Infection
Neuroblastoma
Non-Hodgkin Lymphoma
Osteomyelitis
Parvovirus B19 Infection
Rhabdomyosarcoma

Other Problems to Be Considered

Aplastic anemia
Idiopathic thrombocytopenic purpura (ITP)

Workup

Laboratory Studies

The following studies are indicated in acute lymphoblastic leukemia (ALL):

- Basic laboratory tests
    - Upon initial evaluation, obtain a CBC count. A hematologist or hematopathologist must evaluate the peripheral smear for the presence and morphology of lymphoblasts. An elevated leukocyte count of more than 10 X 10^9/L (>10 X 10^3/µL) occurs in one half of patients with acute lymphoblastic leukemia. Neutropenia, anemia, and

thrombocytopenia may be observed secondary to inhibition of normal hematopoiesis by leukemic infiltration. Rare cases of acute lymphoblastic leukemia may initially manifest with pancytopenia.

- Various metabolic abnormalities may include increased serum levels of uric acid, potassium, phosphorus, and calcium, and lactate dehydrogenase (LDH). The degree of abnormality reflects the leukemic cell burden and destruction (lysis). Although not universally performed, coagulation studies can be helpful, including tests of the prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level to assess for disseminated intravascular coagulation; these studies are particularly important in a child who is acutely toxic.

- Immunophenotyping
  - Complete morphologic, immunologic, and genetic examination of the leukemia cells necessary to establish the diagnosis of acute lymphoblastic leukemia.
  - Nevertheless, acute lymphoblastic leukemia can be broadly classified as B-lineage or T-lineage acute lymphoblastic leukemia.
  - The diagnosis of B-cell leukemia, depends on the detection of surface immunoglobulin on leukemic blasts. Lymphoblasts with this phenotype have a distinctive morphology, with deeply basophilic cytoplasm containing prominent vacuoles. This morphologic pattern is designated L3 in the French-American-British (FAB) system . Prominent clinical features include extramedullary lymphomatous masses in the abdomen or head and neck and frequently involve the CNS.
  - Approximately 80% of childhood acute lymphoblastic leukemia involves lymphoblasts with phenotypes that correspond to those of B-cell progenitors. These cases can be identified by their cell-surface expression of 2 or more B-lineage–associated antigens .
  - T-cell acute lymphoblastic leukemia is identified by the expression of T-cell–associated surface antigens. Clinical features most closely associated with T-cell acute lymphoblastic leukemia are high blood leukocyte counts and CNS involvement. About one half of patients have a mediastinal mass at the time of diagnosis. The prognosis of patients with T-cell acute lymphoblastic leukemia has historically been worse than that of patients with B-lineage acute lymphoblastic leukemia.
- Cytogenetic and molecular diagnosis

    - In more than 90% of acute lymphoblastic leukemia cases, specific genetic alterations can be found in the leukemic blasts. These alterations include changes in chromosome number (ploidy) and structure; about half of all childhood acute lymphoblastic leukemia involves recurrent translocations.
- Risk assessment: Current risk assessment includes clinical features (age and WBC at diagnosis), biological characteristics of the leukemic blasts, response to the induction chemotherapy, and MRD burden.

Imaging Studies

- Chest radiography: Evaluate for a mediastinal mass. In general, no other imaging studies are required. However, if the physical examination reveals enlarged testes, perform ultrasonography to evaluate for testicular infiltration.
- Testicular ultrasonography: Perform testicular ultrasonography if the testes are enlarged upon physical examination.
- Renal ultrasonography: Some clinicians prefer to evaluate for leukemic kidney involvement to assess the risk of tumor lysis syndrome.
- Echocardiography and ECG: Obtain an echocardiogram and an ECG before anthracyclines are administered.

Procedures

- Bone marrow aspirate and biopsy: The results confirm the diagnosis of acute lymphoblastic leukemia. In addition, special stains (immunohistochemistry), immunophenotyping, cytogenetic analysis, and molecular analysis help in classifying each case.
- Lumbar puncture with cytospin morphologic analysis: These tests are performed before systemic chemotherapy is administered to assess for CNS involvement and to administer intrathecal chemotherapy.

Histologic Findings

According to the French-American-British (FAB) classification system, acute lymphoblastic leukemia is classified into 3 groups based on morphology.

- L1: Cells are usually small, with scant cytoplasm and inconspicuous nucleoli. L1 accounts for 85% of all cases of childhood acute lymphoblastic leukemia.

- L2: Cells are larger than in L1. The cells demonstrate considerable heterogeneity in size, with prominent nucleoli, and abundant cytoplasm. L2 accounts for 14% of all childhood ALL.
- L3: Cells are large and notable for their deep cytoplasmic basophilia. They frequently have prominent cytoplasmic vacuolation and are morphologically identical to Burkitt lymphoma cells. L3 accounts for 1% of childhood acute lymphoblastic leukemia cases.

Treatment

Medical Care

Because leukemia is a systemic disease, therapy is primarily based on chemotherapy. Different forms of acute lymphoblastic leukemia (ALL) require different approaches for optimal results. Excluding mature B-cell acute lymphoblastic leukemia which is treated with short-term intensive chemotherapy, including high-dose methotrexate (MTX), cytarabine, and cyclophosphamide, acute lymphoblastic leukemia treatment typically consists of a remission-induction phase, intensification (consolidation) phase, and continuation therapy targeted at eliminating residual disease. The addition of cyclophosphamide and intensive treatment with asparaginase is also beneficial in the treatment of T-cell acute lymphoblastic leukemia.

- Tumor lysis syndrome
    - Before and during the initial induction phase of chemotherapy, patients may develop tumor lysis syndrome, which refers to the metabolic derangements caused by the systemic and rapid release of intracellular contents as chemotherapy destroys leukemic blasts. Because some cells can die before therapy, such metabolic changes can occur even before therapy begins.
    - Primary features of tumor lysis syndrome include hyperuricemia (due to metabolism of purines), hyperphosphatemia, hypocalcemia, and hyperkalemia. The hyperuricemia can lead to crystal formation with tubular obstruction and, possibly, acute renal failure requiring dialysis. Therefore, electrolyte and uric acid levels should be closely monitored throughout initial therapy.
    - To prevent complications of tumor lysis syndrome, patients should initially receive intravenous (IV) fluids at twice the maintenance rates, usually without potassium.

        - Sodium bicarbonate is added to the IV fluid to achieve moderate alkalinization of the urine (pH level, 7.5-8) to enhance the excretion of phosphate and uric acid. A urine pH level higher than this should be avoided to prevent crystallization of hypoxanthine or calcium phosphate.
        - The standard treatment for malignancy-associated hyperuricemia also includes allopurinol. By blocking the enzyme xanthine oxidase, allopurinol blocks uric acid formation. Patients at high risk for tumor lysis still need to excrete preexisting uric acid, which is unaffected by the use of allopurinol.
        - Rasburicase, a recombinant urate oxidase, has demonstrated increased efficacy in pediatric patients at high risk for tumor lysis by catalyzing the enzymatic oxidation of uric acid to a much more urine soluble product, allantoin.
- Phases of therapy
    - The treatment of childhood acute lymphoblastic leukemia, with the exception of B-cell acute lymphoblastic leukemia, has 5 components: induction, consolidation, interim maintenance, delayed intensification, and maintenance.
    - The goal of induction is to achieve remission or less than 5% blasts in the bone marrow. Induction therapy generally consists of 3-4 drugs, which may include a glucocorticoid, vincristine, asparaginase, and possibly an anthracycline.
    - Consolidation therapy is given soon after remission is achieved to further reduce the leukemic cell burden before the emergence of drug resistance and relapse in sanctuary sites (ie, testes, CNS). In this phase of therapy, the drugs are given at doses higher than those used during induction or the patient is given different drugs (ie, high-dose MTX and 6-mercaptopurine [6-MP]), epipodophyllotoxins with cytarabine, or multiagent combination therapy.
    - In interim maintenance, oral medications are administered to maintain remission and allow the bone marrow to recover.
    - This occurs for 4 weeks and is followed by delayed intensification, which is aimed at treating any remaining resistant leukemia cells.
    - The last phase of treatment is maintenance. This consists of intrathecal MTX every 3 months, monthly vincristine, daily 6-MP and weekly MTX.

- Duration of therapy
    - Whereas B-cell acute lymphoblastic leukemia is treated with a 2-month to 8-month course of intensive therapy, achieving acceptable cure rates for patients with B-precursor and T-cell acute lymphoblastic leukemia requires approximately 2-2.5 years of continuation therapy.
    - Most contemporary protocols include a continuation phase based on weekly parenterally administered MTX given with daily, orally administered 6-MP interrupted by monthly pulses of vincristine and a glucocorticoid.
- CNS disease
    - If the patient has blasts in the peripheral blood and the lumbar puncture is traumatic (containing $\geq$5/mL WBCs and blasts), CNS disease (CNS 3) is present if CSF WBC count divided by the CSF RBC count is more than 2 times blood WBC count divided by the blood RBC count.
    - Although cranial irradiation effectively prevents overt CNS relapse, concern about subsequent neurotoxicity and brain tumors has led many investigators to replace irradiation with intensive intrathecal and systemic chemotherapy for most patients.
- High-risk patients
    - Some centers recommend allogeneic stem-cell transplantation (SCT) soon after first remission is achieved. For patients without a matched family donor, transplantation of marrow from an unrelated donor is a reasonable treatment option.
- Treatment of relapse: In general, relapsed acute lymphoblastic leukemia cells acquire resistance to exposed chemotherapy drugs. Therefore, treatment of relapse is intensive and often includes SCT. However, the outcome of relapse is poor.
- Molecular targeted therapy
    - A drug targeted at the underlying molecular defect that is unique to certain leukemias can have potent and specific antileukemic activity while producing minimal toxicity to normal cells.
    - The best example of molecular targeted therapy is imatinib mesylate, a selective *BCR-ABL* tyrosine kinase inhibitor.
- Genetic studies and future challenges
    - More than 80% of children with acute lymphoblastic leukemia now can be cured. However, the cause of treatment failure in the remaining 20% of patients is largely unknown.

Diet

Because of the use of MTX, avoid folate supplementation.

Medication

Drugs commonly used during remission induction therapy include dexamethasone or prednisone, vincristine, asparaginase, and daunorubicin. Consolidation therapy often includes methotrexate (MTX) and 6-mercaptopurine (6-MP). Drugs used for intensification or continuation include cytarabine, cyclophosphamide, etoposide, dexamethasone, asparaginase, doxorubicin, MTX, 6-MP, and vincristine. Intrathecal chemotherapy includes MTX, hydrocortisone, and cytarabine.