Adult Acute Lymphoblastic Leukemia

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CME Activity

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Abstract

Conventional cytotoxic chemotherapy used to treat acute lymphoblastic leukemia (ALL) results in high cure rates in pediatric patients but is suboptimal in the treatment of adult patients. The 5-year overall survival is approximately 90% in children and 30% to 40% in adults and elderly patients. Adults with ALL tend to have higher risk factors at diagnosis, more comorbidities, and increasing age that often requires dose reductions. Major advancements have been made in redefining the pathologic classification of ALL, identifying new cytogenetic-molecular abnormalities, and developing novel targeted agents in order to improve survival. The addition of new monoclonal antibodies and tyrosine kinase inhibitors to conventional chemotherapy in the frontline setting has resulted in increased rates of complete remission and overall survival. These new developments are changing the treatment of adult ALL from a "one therapy fits all" approach to individualized treatment based on patient's cytogenetic and molecular profile.

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Acute lymphoblastic leukemia (ALL) is a hematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites. Although ALL occurs predominantly in children, it is adult ALL that is more challenging to treat. Treatment of adult ALL is largely modeled after the multiagent chemotherapy regimen utilized in pediatric ALL designed 5 decades ago. This regimen consists of induction, consolidation, and maintenance therapy and central nervous system (CNS) prophylaxis that has produced a

cure rate of 90% and 60% in children and adolescents, respectively.[1,2] Unfortunately, the treatment success of pediatric ALL has not been mimicked in adult ALL. Despite high rates of complete remission (CR) (80%-90%) in adult ALL, the cure rates are only 40% to 50% because of relapses.[3-5] The 5-year overall survival (OS) is approximately 90% in children and 30% to 40% in adults and elderly patients.[4] This problem may be attributed to adults harboring higher-risk features at diagnosis, increased comorbidities, and the development of chemotherapy resistance after relapse. The need for improvement in adult ALL outcomes has led to major advancements in drug development, reassessment of risk stratification, and better knowledge of disease pathogenesis. The incorporation of targeted therapies in the frontline and salvage settings has improved survival compared with that of conventional chemotherapy in adult ALL. However, the goal is to further optimize treatment regimens so it can one day be revered as a success story similar to pediatric ALL.

EPIDEMIOLOGY AND ETIOLOGY

ALL has a bimodal distribution with the first peak occurring in individuals around 5 years of age and the second peak at around 50 years of age. It is mainly considered a pediatric leukemia with 80% of cases occurring in children and 20% occurring in adults.[4-7] The median age at diagnosis is 14 years, and approximately 60% of patients are diagnosed at younger than 20 years of age, 25% at around 45 years of age, and 11% at around 65 years of age.[8] ALL is relatively uncommon during late childhood, adolescence, and young adulthood. According to the Surveillance, Epidemiology, and End Results program database, the estimated annual incidence in the United States was approximately 6590 new cases and 1430 deaths in 2016.[9] The age-adjusted incidence rate in the United States is 1.7 per 100,000 men and women per year.

The etiology of ALL is largely unknown. Less than 5% of cases can be attributed to genetic syndromes such as Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, and Nijmegen breakdown syndrome.[10-16] Other risk factors include increasing age (>70 years) and exposure to radiation. There has also been an association between Epstein-Barr virus in mature B-cell ALL, human T-lymphotropic virus type 1 in adult T-cell leukemia/lymphoma, and human immunodeficiency virus in lymphoproliferative disorders.[17,18] The fetal environment is thought to play a vital role in the development of pediatric ALL.[19] The hypothesis is that as cells proliferate during fetal development, random alterations occur creating a preleukemic clone. As exposure to the pathogen increases during early childhood, there is an increase in lymphoid proliferation leading to ALL.

CLINICAL PRESENTATION AND LABORATORY ABNORMALITIES

The clinical presentation of ALL is nonspecific, and thus, patients can present with an array of ailments such as "B symptoms" (ie, fever, unexpected weight loss, night sweats), infection, easy bruising/bleeding, dyspnea, and fatigue due to low blood cell counts.[8] Patients may exhibit petechiae, pallor, and ecchymosis on physical examination, but children may present with only joint pain.[19]

Approximately 20% of patients will have leukemic infiltration in the spleen and/or liver leading to splenomegaly and/or hepatomegaly.[8] Other extramedullary presentations can occur in the testis, skin, or mediastinum (specifically in T-cell ALL).[19,20] Patients with mature B-cell ALL (Burkitt leukemia) may present with an abdominal mass and spontaneous tumor lysis syndrome due to high disease burden. The CNS is one of the sanctuary sites of ALL, and approximately 5% to 8% of patients initially present with CNS involvement such as cranial neuropathies and meningeal infiltration.[2,4,19] Patients with Burkitt-like ALL may experience chin numbness as a result of cranial nerve involvement.[19,20]

DIAGNOSTIC EVALUATION

The diagnosis of ALL requires the presence of 20% or more lymphoblasts in the bone marrow.[8] Further assessment by flow cytometry, morphological studies, immunophenotyping, and cytogenetic testing is important. Historically, the diagnosis of ALL was based on the French-American-British morphological criteria that described 3 subtypes of

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