Progress and Prospects in Pediatric Leukemia

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Pediatric leukemia is the single most common malignancy affecting children, representing up to 30% of all pediatric cancers. Dramatic improvements in survival for acute lymphoblastic leukemia (ALL) have taken place over the past 4 decades with outcomes approaching 90% in the latest studies. However, progress has been slower for myeloid leukemia and certain subgroups like infant ALL, adolescent/young adult ALL, and relapsed ALL. Recent advances include recognition of molecularly defined subgroups, which has ushered in precision medicine approaches. We discuss the current understanding of the biology of the various childhood leukemias, recent advances in research, and future challenges in this field.

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Introduction

Pediatric leukemia is the most common malignancy affecting children, representing up to 30% of all pediatric cancers.[1–3] Approximately 3000 children are diagnosed with leukemia every year in the United States. Pediatric leukemias span diverse clinical and biological subgroups and recent advances in genomics continue to provide ever increasing insight into the underlying pathogenic mechanisms responsible for malignant transformation. The discovery of tumor specific mutations (targets), the development of targeted therapy, and breakthroughs in immunotherapy offer great promise in improving outcome for all patients. In this article, we will describe individual subtypes of pediatric leukemia, address current challenges, and discuss opportunities for integration of novel therapy.

Acute Lymphoblastic Leukemia

Epidemiology

Acute lymphoblastic leukemia (ALL) accounts for about 80% of all pediatric leukemia.[1] It is the most common in children aged 2–5 years, but occurs across all age groups.[1–3] The incidence is highest among Caucasians and Hispanic populations. ALL is also more common in boys than in girls and boys have a slightly poorer prognosis. In all, 85% of pediatric ALL is of B-precursor origin while the remaining 15% is T-cell derived.[4]

Biology

An inherited predisposition and environmental exposures are thought to have minor roles in the genesis of ALL with an underlying predisposing condition being found in less than 5% of cases. The commonest inherited genetic syndrome associated with B-ALL has been Trisomy 21 or Down's syndrome (DS). Children with Down's syndrome are at higher risk for leukemias, both myeloid and lymphoid.[5,6] Leukemias and lymphomas are also seen in patients with Li-Fraumeni syndrome (germline *TP53* mutation), and hypodiploid ALL has been associated with both somatic and germline mutations in *TP53*.[7] ALL is also known to occur in syndromes with defects in DNA repair like Fanconi's anemia, Bloom syndrome, and Nijmegen breakage syndrome. Recent genome-wide association studies have shown certain single nucleotide polymorphisms in genes like *ARID5B*, *IKZF1*, *CEBPE*, *CDKN2A*, *PIP4K2A*, and *GATA3* to be associated with an increased risk for developing ALL.[8] However, these findings do not account for the vast majority of cases.

Pathogenesis

There is a wide spectrum of tumor specific (i.e., somatic) genetic alterations observed in ALL such as

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chromosomal translocations, DNA copy number changes (e.g., deletions and amplifications), and single nucleotide variations. The most common of these alterations is hyperdiploidy (gain of chromosome number, >50 chromosomes), which is seen in up to 25% of cases and has been associated with a good prognosis.[9–11] It is a matter of debate whether the excellent outcomes are related to overall chromosome gain or occurrence of specific trisomies like trisomy 4, 10, and 17. In contrast hypodiploidy (<44 chromosomes) is associated with a very poor prognosis.[12] Characteristic chromosomal translocations resulting in a chimeric protein product also occur, with the *ETV6-RUNX1* t (12; 21) (previously known as *TEL-AML1*) being associated with a good prognosis.[12] But internal amplification of *RUNX1* (iAMP 21) within the same chromosome, which is found in less than 2% of cases, is associated with a poor prognosis.[13] The Philadelphia (Ph) chromosome, *BCR–ABL* fusion t(9; 22) (q34; q11) is found in 2–3% of pediatric B-ALL in contrast to a much higher incidence in adult ALL.[11] Ph-positive ALL historically had a poor prognosis with an event-free survival (EFS; Table 1) of up to 34% at 5 years,[14] but the advent of tyrosine kinase inhibitors has remarkably improved outcomes to an EFS of 70% at 5 years, without hematopoietic stem cell transplantation (HSCT).[15] Mixed myeloid leukemia gene or *MLL* gene rearrangements are seen in about 80% of infant ALL and are associated with a poor prognosis.[16] These rearrangements can also be seen in 3–5% of older children, in whom prognostic implications can vary depending on the exact fusion partner, with t (4; 11) almost universally still being considered a poor prognostic marker.[12]

TABLE 1. Common measures of survival in cancer trials

Disease Free Survival (*DFS*): The length of time after completion of therapy, that the patient remains free from the primary malignancy.

Event-Free Survival (*EFS*): The length of time after completion of therapy, that a patient remains free from significant "events," defined within the study, which include recurrence of primary malignancy and other complications like serious drug toxicity.

Overall Survival (*OS*): Overall survival is a measure of the time from diagnosis or start of therapy until death of the patient from any cause. Also described as the percentage of patients on a study who are alive at a fixed time point (commonly 5 years) after diagnosis or start of therapy.

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Further genetic profiling of ALL has been possible through multiple platforms like gene expression profiling, copy number analysis, and methylation arrays. Copy number alterations are characteristic of B-ALL, particularly deletion of B-cell differentiation genes (e.g., *PAX5* and *IKZF1*)[17] and appear to collaborate in leukemogenesis with the sentinel genetic events described in the preceding paragraph. Gene expression analysis has helped define a unique group of "Ph-like" ALL patients where the leukemic blasts share a similar gene expression profile, but do not express the *BCR-ABL1* fusion protein.[18] Ph-like ALLs either have translocations similar to the *BCR/ABL* (e.g., fusions involving *ABL1* (non-BCR), *ABL2*, *CSF1R*, and *PDGFRB*) or defects in the Janus kinase (JAK) pathway. Thus, they are candidates for treatment with TKIs and JAK inhibitors, respectively.

The most common mutations in T-ALL are those that constitutively activate NOTCH1.[11,17] These are seen in 50% of T-ALL and another 20% carry mutations in the gene encoding Fbox protein *FBXW7*, which are responsible for the degradation of NOTCH1. Unlike B-ALL, cytogenetic changes in T-ALL are not utilized to stratify therapy.

Clinical Presentation

ALL classically presents with symptoms related to bone marrow infiltration with resulting cytopenias, such as fever, fatigue, pallor, bruising, and bone pain. Hepatosplenomegaly or lymphadenopathy is seen in 50–60% of children. Approximately 60–70% of patients with T-ALL have a mediastinal mass and WBC counts are often higher than 100,000/μL.[19] CNS leukemia, which is present in only 2–3% of cases, can present with signs of raised intracranial pressure (headache, vomiting, lethargy, etc.) or with signs of cranial nerve involvement like ptosis and facial paralysis.[20] Testicular disease, also rare, manifests as testicular enlargement, which is usually painless and can be unilateral or bilateral.[21]

Diagnosis and Risk Stratification

A blast count of >25% in the bone marrow is required for a diagnosis of ALL. ALL is divided into