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ADVANCES IN PEDIATRICS

Recent Advances in the Understanding and Treatment of Pediatric Leukemias

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Keywords
• Pediatric leukemia • Treatment • Hematopoietic • Stem cell transplant

Key Points
- Acute Lymphoblastic Leukemia: significant progress made in all groups, genomic technologies increasing understanding and identifying new potential therapeutic targets.
- Acute Myeloid Leukemia: Risk group classification now applies to pediatric AML to help guide therapy and choice of hematopoietic stem cell transplantation (HSCT).
- Chronic Myelogenous Leukemia: therapy now with tyrosine kinase inhibitors, unclear role now for HSCT.
- HSCT: 1. improving morbidity risks, increasing use of unrelated adult and cord blood stem cell donors, current transplant approaches and current indications for transplant in pediatric leukemia.

INTRODUCTION AND OVERVIEW

Leukemia is the most common pediatric cancer accounting for 31% of cancers that occur before 15 years of age and 25% that occur before 20 years of age [1]. The proportion of the 3 major types of leukemia changes considerably during childhood. The annual incidence of acute lymphoblastic leukemia (ALL) reaches a maximum of 80 to 90 cases per million at 2 to 3 years of age, starts to decrease significantly at 5 to 6 years of age, drops to about 20 cases per million at 8 to 11 years of age, and decreases gradually to about 10 cases per million at 20 years of age. In contract, the incidence of acute myeloid leukemia (AML) is about 5 to 10

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cases per million throughout the first 20 years of life, and the incidence of chronic myeloid leukemia (CML) is only about 2 cases per million until 15 years of age and then doubles to about 4 cases per million by 20 years of age. Thus, for children younger than 5 years, ALL accounts for about 80% of leukemias, AML 15%, and CML 2% to 3%. In contrast, the distribution is approximately 50% ALL, 35% AML, and 10% CML for adolescents aged 15 to 19 years. In the early 20s, the incidence of AML passes that of ALL and remains higher throughout adulthood. Even though cure rates have increased considerably over the past few decades for all subtypes of disease, leukemia accounts for 30% of pediatric cancer deaths and remains the most common cause of death from cancer during childhood. This predominance extends until about 35 years of age [2].

The most recent National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program estimates show 5-year survival rates in the 2000-2004 era for children less than 15 years of age being 87.5% for ALL and 59.9% for AML, with projected increases to 90.6% for ALL and 64.8% for AML in the 2005-2009 era [3]. The SEER survival estimates in the 2000-2004 era were much lower for adolescents aged 15.0 to 19.99 years: 61.1% for ALL and 47.2% AML [4,5]. Because of the rarity of CML, it is difficult to obtain good population-based estimates of survival rates among younger children. The SEER data showed an estimated 82.3% 5-year survival rate for persons with CML 15 to 24 years of age during 2000-2004 [4]. As discussed later, the survival for CML has increased significantly since the development of BCR-ABL1 tyrosine kinase inhibitors (TKI).

During recent years, there have been significant advances in understanding the molecular pathogenesis of different subtypes of leukemia and improvements in therapy. In particular, advances in genomic medicine are leading to rapid changes in knowledge of the genomic landscape for leukemias; it is hoped that this will translate to further improvements in cure rates during the next 5 to 10 years.

ALL

Overview of chemotherapy used to treat ALL

Several different individual institutions and cooperative groups have shown steady improvements in event-free (EFS) and overall survival (OS) for children with ALL over the past 10 to 15 years, leading to predictions that 85% to 90% of children and adolescents diagnosed with ALL in the current era will be long-term survivors [6]. Almost all of these improvements have occurred through optimizing the use of about 10 different chemotherapy drugs that have been used to treat childhood ALL since the 1970s [7–12]. Imatinib and related TKIs are the only new drugs introduced successfully into treatment regimens for children newly diagnosed with ALL over the past 4 decades and these agents are only relevant for the 3% to 5% of children with Philadelphia chromosome positive (Ph^+) ALL. The basic outline of ALL treatment regimens has been stable since the early 1980s and includes 4 phases: induction, central nervous system (CNS) preventative therapy, consolidation or intensification, and maintenance or continuation. The first 3 more intensive phases of