Pediatric Acute Myeloid Leukemia

Biology and Therapeutic Implications of Genomic Variants

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KEYWORDS

• Acute myeloid leukemia • Pediatrics • Epigenetic • Genomic • Therapy

KEY POINTS

- Pediatric acute myeloid leukemia (AML) has a genomic and epigenetic profile distinct from that of adult AML.
- Somatic mutations and epigenetic alterations contribute to myeloid leukemogenesis, and can evolve from diagnosis to relapse.
- Next-generation sequencing technologies are providing novel insights into the biology of AML and are highlighting potential targets for therapeutic intervention.
- Cytogenetic alterations, somatic mutations, and response to induction therapy contribute to current risk stratification and appropriate therapy allocation.

INTRODUCTION

Acute myeloid leukemia (AML) is a hematopoietic malignancy that is the culmination of genetic and epigenetic alterations in the hematopoietic stem/progenitor cells, leading to dysregulation of critical signal transduction pathways and resulting in the expansion of undifferentiated myeloid cells. AML can be broadly divided into 2 categories, de novo AML and secondary AML. Secondary AML refers to evolution of AML subsequent to prior exposure to cytotoxic therapy or antecedent hematopoietic insufficiency (eg, myelodysplastic syndrome [MDS], marrow failure), leading to evolution of distinct karyotypic and molecular alterations including *MLL* translocations following exposure to topoisomerase inhibitors. In contrast to secondary AML, AML that evolves without a prior cytotoxic exposure is referred to as de novo AML.

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Numerous somatic, karyotypic and molecular alterations have been identified in de novo AML; however, despite association of many of these alterations with clinical phenotype, most have no prognostic value, nor do they identify a specific target or a distinct pathway that can be readily exploited for therapeutic intervention. The observed age-associated evolution of molecular alterations reveals a profile for younger children with AML distinct from that of older children and adolescents with AML. Furthermore, the landscape of genetic alterations differs markedly from AML in adults and the paucity of potential therapeutic targets is more notable in childhood AML.

EPIDEMIOLOGY OF ACUTE MYELOID LEUKEMIA

AML is diagnosed in very young children and comprises nearly 25% of pediatric leukemias; however, it is far more prevalent in adults, and is generally considered a disease of older adults whereby the median age at diagnosis is nearly 70 years. Incidence of AML can be better appreciated by close evaluation of the most recent SEER (Surveillance, Epidemiology, and End Results) data. Initial evaluation demonstrates low incidence of AML in children and young adults, with a significant increase in older adults (**Fig. 1**A).[1] However, closer examination of the data demonstrates highest incidence of AML in younger patients (<40 years) to be in infancy with an incidence of 1.6 cases per 100,000, similar to that in the fourth decade of life. After infancy, there is a declining incidence of approximately 0.12 cases per 100,000 per year in the first decade of life (see **Fig. 1**B) to an incidence of 0.4 per 100,000 by age 10. In the following 3 decades, there is a steady increase in AML incidence of approximately 0.02 cases per 100,000 per year to 1.3 cases per 100,000 per year by age 45 years, nearly equivalent to that seen in infants. A substantial increase in the rate of AML diagnosis occurs in the fifth decade to nearly 10 times the observed rate in the previous 3 decades, to an incidence of 6.2 per 100,000 by age 65. After age 65, AML diagnosis increases again substantially, more than 30-fold higher than that seen in younger patients (age 10–40), likely attributable in part to its evolution from an underlying MDS. This epidemiologic observation parallels the underlying known and emerging karyotypic and genomic makeup of AML, and provides insight into the contribution of genomic alterations to the evolution of AML.

Inherited Susceptibility of Acute Myeloid Leukemia

Although AML is a rare event in childhood, there are a wide range of inherited chromosomal and gene defects and marrow failure syndromes that predispose to the development of AML. Some of the more common AML predisposition syndromes include trisomy 21 (Down syndrome [DS]), Fanconi anemia, dyskeratosis congenita (DC), Shwachman-Diamond syndrome (SDS), and Kostmann syndrome (severe congenital neutropenia or SCN). Down syndrome is associated with 10- to 20-fold increased risk of leukemia, as well as high incidence of development of transient myeloproliferative disorder (TMD) in the first 3 months of life that resembles AML, but in most cases the disease undergoes spontaneous resolution.[2] Fanconi anemia is an autosomal recessive disorder caused by mutations in DNA repair genes, and has been estimated to show a cumulative incidence of AML/MDS of approximately 50% by age 40 years.[3] DC is an X-linked disorder caused by mutations in the dyskerin gene, *DKC1*, which is a key subunit of ribosomal RNA processing and the telomerase complex. Autosomal recessive forms of DC exist and are due to mutations in *TERC*, the RNA component of telomerase, or *TERT*, the enzymatic component of telomerase.[4] SDS is an autosomal recessive disorder caused by mutations in the *SBDS*