Advances in Pediatric Acute Lymphoblastic Leukemia Treatment

BY RICHARD SIMONEAUX

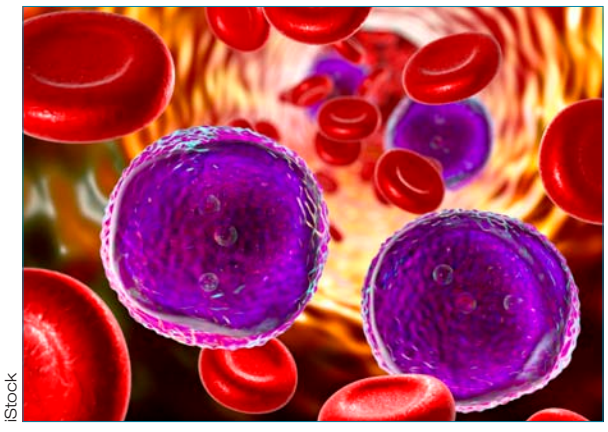
Acute lymphoblastic leukemia (ALL) is the most frequently diagnosed pediatric hematologic malignancy, representing approximately 75-80 percent of all childhood acute leukemias. Statistically, the median age of diagnosis is approximately 15 years, while more than 55 percent of patients with ALL are under 20 years of age. As a result of the significant impact of ALL in the pediatric population, the National Comprehensive Cancer Network (NCCN), a non-profit consortium of 30 of the top cancer centers, issued guidelines for the diagnosis, genetic characterization, classification, and treatment of pediatric patients with ALL (*J Natl Compr Canc Netw* 2020; doi: 10.6004/jnccn.2020.0001).

The lead author on these NCCN guidelines, Patrick Brown, MD, Director of the Pediatric Leukemia Program at Johns Hopkins Hospital, recently granted an interview with *Oncology Times* regarding these guidelines.

"With the ever-increasing pace of discoveries in the fields of molecular biology and nucleic acid sequencing techniques, the need for guidance in the diagnosis and treatment of ALL in pediatric patients has never been greater," Brown noted. "These guidelines are meant to incorporate the latest diagnostic techniques, as well as the most current targeted therapies to treat patient subpopulations according to the genetic changes driving the leukemia. The guidelines for pediatric ALL arose as a result of multidisciplinary meetings of pediatric ALL experts; our goal was to provide recommendations for standard treatment approaches based on current evidence."

ALL Disease Characteristics

ALL is a hematologic malignancy in which immature lymphoid cells undergo excessive proliferation. In the U.S., the age-adjusted frequency is approximately 1.4 cases per 100,000 individuals per year, with an estimated 5,930 new cases and 1,500 deaths in 2019. While roughly 55 percent of newly diagnosed cases of ALL are for patients 20 years or younger, 28 percent of diagnoses are for patients 45 years or older and approximately 12 percent are for those 65 years or older.



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"Over the last few decades, there has been steady improvement in the care for pediatric ALL patients," Brown stated. "Cure rates have drastically improved as better understanding of the molecular underpinnings of the disease, as well as risk stratification and advances in treatments such as optimizing the use of chemotherapy and incorporating targeted therapies."

Pediatric ALL Presentation

"Symptoms that we frequently see in our pediatric patients at their initial visit are fatigue or lethargy, fevers, night sweats, weight loss, pain in the extremities or joints, shortness of breath, dizziness, infections, and easy bruising or bleeding," Brown observed. Patients with the presence of CNS or cranial nerve involvement may also display focal neurologic symptoms.

"For children with ALL, these symptoms are variable and quite non-specific, and this can complicate making a diagnosis. An abnormal complete blood count is often what brings the possibility of leukemia to immediate attention," he stated.

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For a diagnosis of ALL, generally, the presence of 20 percent or greater bone marrow lymphoblasts in hematopathology reviews of bone marrow aspirates or other biopsy samples is required. "Unlike in myeloid leukemia, there is no clear lower limit for the diagnosis of ALL. However, since presentations of ALL with low blast counts are not common, diagnosis of ALL should not be avoided when the marrow blast count is less than 20 percent," Brown explained.

In cases where there is a significant amount of circulating disease, according the NCCN Pediatric ALL panel, peripheral blood may be used as the biopsy sample if there are ≥1,000 circulating lymphoblasts per microliter or ≥20 percent lymphoblasts.

Genetic Typing

When queried about genetic typing utilized for pediatric patients with ALL, Brown replied, "Previously, karyotyping was the primary means for identifying genetic aberrations. However, diagnostic methods have evolved, and current analyses include those of fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS) techniques such as RNA-Seq. With karyotyping, cells are cultured and then, when it is thought that many are in metaphase, cells are arrested and then stained for viewing under a microscope."

Regarding the limitations for karyotyping, he noted, "ALL cells are notoriously difficult to culture, and additionally, this analysis is cell cycle-dependent, being limited to those in metaphase. In addition, a number of relevant genetic anomalies are not detectable using this method."

When asked about FISH, Brown stated, "This method has a number of significant technical advantages over older karyotyping techniques, including greater sensitivity, increased number of aberrations recognized, and lastly, cell cycle independence, as it is not necessary that the cells be cultured until they enter metaphase prior to analysis."

The use of NGS assays has allowed the sequencing and identification of a number of previously unidentified mutations associated with ALL.

"The most significant advance to come from the use of NGS diagnostics has been the ability to detect Ph-like ALL cases," Brown said. "Interestingly, the NGS sequences of many of the fusions we now know to define Ph-like ALL were initially discarded during quality control filtering processes. It was only after subsequent analyses that these were discovered and recognized as defining aberrations for cases of Ph-like ALL."

Genetic Abnormalities

Since there are now known to be several genetically distinct subtypes of ALL with different disease characteristics, the differentiation of these different subtypes becomes especially important when determining the optimal treatment course for each patient, as some ALL subtypes are associated with more or less favorable clinical outcomes.

Among the genetic anomalies that are noted in pediatric B-cell ALL are hyperdiploidy (51-67 chromosomes); hypodiploidy (44 chromosomes); t(9;22)(q34.1;q11.2), BCR-ABL1; t(v;11q23.3), KMT2A rearranged; t(12;21)(p13.2;q22.1), ETV6-RUNX1; t(1;19)(q23;p13.3), TCF3-PBX1; and t(5;14)(q31.1;q32.1), IL3-IGH.

"The BCR-ABL1 fusion gene is of great historical importance," Brown stated, "as this is the so-called Philadelphia chromosome discovered by researchers at the University of Pennsylvania and Fox Chase Cancer Center.

"In 2016, two new subtypes were added to the classification of B-ALL: B-lymphoblastic leukemia/lymphoma with translocations in-

volving tyrosine kinases or cytokine receptors, termed BCR-ABL1–like ALL or Ph-like ALL, and B-lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iAMP21)."

Favorable Patient Outcome Subtypes

A number of frequently encountered genetic aberrations are associated with favorable patient outcomes. The most frequently observed chromosomal anomaly in pediatric ALL is hyperdiploidy (i.e., 50 chromosomes), which is noted in approximately 25 percent of this patient population, as compared to 7 percent of adult ALL cases. Another commonly noted B-cell ALL anomaly is the ETV6-RUNX1 subtype, which arises from the t(12;21) chromosomal translocation; it is more frequently observed in pediatric (25%) relative to adult (2%) ALL cases. Both of these favorable subtypes are more frequently observed in younger children with ALL than the older adolescent-young adult counterparts.

Less-Favorable Patient Outcome Subtypes

There are a significant number of chromosomal aberrations that are well-documented biomarkers associated with higher-risk ALL across all age groups. These include low hypodiploidy (30-39 chromosomes), near haploidy (less than 30 chromosomes), histone lysine methyltransferase 2A (*KMT2A* or *MLL1*) translocations, t(17;19)/TCF3-HLF fusion, and BCR-ABL1.

"Hypodiploidy has a strong association with poor patient outcomes and is noted in 1-2 percent of pediatric ALL patients, and low hypodiploidy is associated with frequently occurring TP53 alterations, which are germline for roughly half of these cases," Brown stated.

"Chromosomal rearrangements of KMT2A, which was previously called the human mixed lineage leukemia (MLL) gene, occur in roughly 5 percent of pediatric ALL cases, being more frequently observed in 70-80 percent of infant cases. These rearrangements, especially those with the t(4;11) translocation, are associated with poor outcomes, particularly in infants," Brown explained.

Ph-Like ALL Subtypes

In 2009, two separate research groups, one at St. Jude Children's Research Hospital and the other one in the Netherlands, independently discovered the Ph-like subtype of ALL (*N Engl J Med* 2009;360:470-480; *Lancet Oncol* 2009;10:125-134). This ALL subtype, like Philadelphia chromosome positive (Ph+) disease, is characterized by a high incidence of concomitant IKZF1 alterations. Ph-like ALL is more frequently observed in males and in those with Down syndrome (*Clin Lymphoma Myeloma Leuk* 2017;17(8):464-470). The prevalence of the disease varies across different age groups: children 12 percent; adolescents (16-20 years) 21 percent; young adults (21-39 years) 27 percent; and adults (over 40) 20-24 percent.

Clinically, a significant portion of pediatric patients with Ph-like ALL display poor event-free survival and have minimal residual disease positivity after remission induction. However, roughly 40 percent of these pediatric patients did show good response to chemotherapy and could be cured with fairly low-intensity treatments.

"It is of interest to note that clinical outcomes tended to be negatively correlated with increased age at diagnosis," Brown observed.

Ph-like ALL is considered to be both biologically and clinically heterogeneous. "This disease can be driven by a diverse set of gene fusions; there can be literally hundreds of different gene combinations that can give rise to this ALL subtype," Brown explained.

These genetic modifications result in dysregulated cytokine receptor and kinase signaling. One particularly common anomaly is the CRLF2 rearrangement, which is present in approximately half of Ph-like ALL cases. In addition, the translocations of non-receptor tyrosine kinases, such as ABL-class and Janus kinases, are frequently observed. Those with fusions of ABL-class tyrosine kinases have displayed a clinical response to ABL1 tyrosine kinase inhibitors. In preclinical studies, Ph-like ALL activated by JAK-STAT alterations has shown sensitivity when treated with JAK inhibitors.

"Further studies are clearly needed to assess the feasibility and effectiveness of adding targeted tyrosine kinase inhibitors to intensive chemotherapy treatment regimens for patients having Ph-like ALL," Brown commented.

Current State of Diagnosis & Treatment

Summarizing the current state of diagnostics for pediatric ALL, Brown noted, "I think that to some degree we may have reached a plateau with regards to the development of new diagnostics; the pace of discoveries has clearly slowed down. The discovery of new diagnostics has clearly outpaced our ability to translate those findings into effective targeted therapies for our pediatric patients with ALL."

When asked about future directions for pediatric ALL, Brown stated, "One area that clearly needs further exploration is the application of new targeted therapies to the appropriate patient subpopulations. We have already found targeted therapies, such as tyrosine kinase inhibitors for patients with Ph-like ALL having ABL-class fusions or JAK inhibitors for those with JAK-activating mutations.

"The majority of Ph-like ALL cases consist of ABL1-class and JAK-STAT modifications; however, there are a number of alterations of kinases not inhibited by ABL-class or JAK inhibitors," he noted. "Future studies are necessary to assess the potential for selectively targeted inhibitors of these kinases." OT

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