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Reaping the Benefits of Recent Advances for Adults With Acute Lymphoblastic Leukemia

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In adults, acute lymphoblastic leukemia (ALL) is a rare cancer, even among hematologic malignancies, and is generally associated with long-term survival rates of approximately 40%. Conversely, ALL is the most common cancer in children and, with steady advances fueled by systematic randomized clinical trials over the decades, is now curable in more than 80% of cases.

One of the most important reasons for the worse outcomes among adult patients with ALL is intrinsic disease biology. Poor-risk genetic features occur with higher frequency, and favorable-risk genetic features occur with lower frequency in adults compared with children. A striking example of this is Philadelphia chromosome–positive (Ph+) ALL, which occurs in 25% of adult patients with ALL but in fewer than 5% of childhood patients. Importantly, the addition of BCR-ABL tyrosine kinase inhibitors (TKIs) to chemotherapy for Ph+ ALL appears to markedly improve responses. Notwithstanding these clear differences in disease biology in adults compared with children, evidence is emerging that adopting a pediatric-inspired treatment approach for adolescents and younger adults (AYAs) with ALL results in improved survival.

The impetus for developing the first NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for ALL (in this issue) arose from our desire for every adult diagnosed with ALL in 2012 and beyond to reap the benefits of 2 major recent advances that have redefined “standard of care” for adult ALL: 1) recognition that pediatric-inspired treatment regimens are both feasible and associated with improved survival in younger adult patients compared with traditional “older adult” regimens, and 2) recognition that including TKIs in the treatment of Ph+ ALL is associated with improved response and survival.

Pediatric-Inspired Regimens for Younger Adults

Over the past several years, major adult and pediatric cooperative groups in Europe and North America compared outcomes for contemporaneously treated patients with ALL aged 15 to 21 years enrolled in adult versus pediatric protocols. General conclusions are that survival is superior in those treated on pediatric protocols and that the major difference between the pediatric and adult approaches is greater intensity of nonmyelosuppressive drugs (e.g., steroids, vincristine, asparaginase) and central nervous system–directed treatment in the pediatric protocols. The adult cooperative groups subsequently undertook

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prospective studies to determine the feasibility and efficacy of treating a variably defined group of “young adults” with pediatric-inspired treatment regimens in adult hematology-oncology practices.

The initial results from these studies are quite encouraging showing that this approach is feasible and is associated with improved outcomes compared with historical controls. However, these studies also highlighted some of the unique challenges associated with delivering a complex, toxic, and extended treatment protocol to AYA patients. These challenges include psychosocial and socioeconomic issues (e.g., access to care and adherence to therapy), as well as medical issues (e.g., enhanced asparaginase-related toxicity). The NCCN Guidelines for ALL address these issues by 1) providing separate treatment algorithms for the AYA population, which we define as ages 15 through 39 years, with the important caveat that “chronologic age alone is a poor surrogate for determining patient fitness for therapy; patients should therefore be evaluated on an individual basis”; 2) providing detailed information regarding monitoring for and managing asparaginase-related toxicities; and 3) linking to the recently published NCCN Guidelines for AYA Oncology (to view the most recent version of these guidelines, visit NCCN.org).

Use of TKIs for Ph+ ALL

The use of TKIs in patients with Ph+ ALL represents an extraordinary advance in the treatment of patients with a particularly adverse-risk form of ALL. TKIs first showed clinical effectiveness in Ph+ chronic myelogenous leukemia (CML). They are now the accepted standard of care for the management of CML, and continued therapy can produce extended hematologic and molecular responses.

TKIs have also been used for salvage therapy in patients with lymphoid blast crisis CML and refractory/relapsed Ph+ ALL. In an early clinical trial, imatinib produced a response rate of 70%, with complete responses seen in 4 of 20 patients. Several investigators have subsequently extended the use of TKIs to upfront therapy for patients with Ph+ ALL. In this setting, the combination of a TKI with standard induction therapy resulted in initial complete response rates of up to 95%. Combination treatment with either imatinib or dasatinib also appears to result in improved overall survival rates, even among elderly patients for whom intensive chemotherapeutic options are inappropriate. TKI resistance has been reported in Ph+ ALL; however, second-generation agents may provide an effective alternative for some patients with imatinib resistance.

Before TKI-based therapies were available, patients with Ph+ ALL had a very poor prognosis, with 10% of patients or fewer experiencing disease-free survival with conventional-dose chemotherapy. Historically, hematopoietic cell transplantation has been viewed as the most effective, with long-term remission rates of up to 65% in patients who undergo transplantation during first complete remission. The advent of chemotherapy/TKI combinations may provide an effective therapeutic alternative for adult patients who do not have an appropriate HLA-compatible donor, and it may allow transplantation to be deferred in select pediatric patients.

“Take Home Messages” From the NCCN Guidelines

In addition to the 2 major themes discussed previously, the NCCN Guidelines for ALL address several important diagnostic and therapeutic aspects for managing adult patients with ALL. The following “take home messages” should also be highlighted:

- Adults with newly diagnosed ALL should be referred to specialized treatment centers, preferably for enrollment on clinical trials.
- Minimal residual disease testing should be considered for risk stratification in adults with ALL.
- Hematopoietic stem cell transplantation has an evolving role in the treatment of adults with ALL.
- Central nervous system–directed treatment is required for optimal management of adult ALL.
- Treatment of adults with ALL presents unique supportive care challenges.

We hope that the new NCCN Guidelines for ALL will help ensure that adults with this disease receive the treatment that provides the best chance for favorable outcomes, and we pledge to incorporate future advances as the march towards higher and higher cancer cure rates continues.

Biographies

Patrick A. Brown, MD, is an Associate Professor of Oncology and Pediatrics in the Johns Hopkins University School of Medicine and Director of the Pediatric Leukemia Program at the Sidney Kimmel Comprehensive Cancer Center. His independent translational laboratory is focused on the molecular biology of leukemia, preclinical evaluation of targeted therapies, and correlative laboratory science in the context of clinical trials of molecularly targeted agents. He is a principal investigator of several active cooperative group and consortium clinical trials. He serves on the acute lymphoblastic leukemia and myeloid leukemia steering committees in the Children’s Oncology Group, and co-chairs the NCCN Guidelines Panel for Acute Lymphoblastic Leukemia.

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