It is clear that the management of adult patients with ALL is an area in which little progress has been made in the last 30 years. Given the disappointing outcomes, the field is one that lends itself to the study of the incorporation of novel agents, including monoclonal antibodies and tyrosine kinase and proteasome inhibitors, as well as to further study of allogeneic transplant.

The management of adult acute lymphoblastic leukemia (ALL) is challenging for a number of reasons, and the successes seen in the treatment of children with this disease remain elusive to oncologists who treat adults. In their review of the management of adult ALL patients, Mathisen, Jabbour, and Kantarjian discuss the current National Comprehensive Cancer Network (NCCN) recommendations for the treatment of adult patients. In addition, they discuss novel areas of study, including the use of pediatric protocols in young adults, monoclonal antibodies, and transplantation as therapies for patients who are newly diagnosed as well as for those with relapsed or refractory disease.

The newest recommendations for upfront therapy from the NCCN include the treatment of patients under the age of 40 using pediatric-based protocols. As is discussed in the review, retrospective analyses of several large studies have provided evidence that young adults have improved survival when treated with pediatric regimens. Based on this, the authors are enrolling patients in a single-institution study using the augmented Berlin-Frankfurt-Mnster (BFM) regimen modeled after Children’s Cancer Group (CCG) 1961.

Nationally, Cancer and Leukemia Group B (CALGB) is leading an intergroup trial with the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group (SWOG) (CALGB 10403) that also aims to address this question. It is enrolling patients into a single arm of a four-arm Children’s Oncology Group (COG) trial that includes a corticosteroid induction and a Capizzi methotrexate interim maintenance regimen in addition to the BFM base regimen. The trial is nearing its accrual goal of 300 young adults and may provide important information regarding the treatment of this subgroup of patients.

The authors of this review indicate that regimen-related toxicity in young adults is considerably higher than in the pediatric population, and the concern is that interruptions in therapy because of toxicity, such as severe pancreatitis, which is seen more frequently in young adults, may prevent use of this treatment program in young adult patients with ALL. It will be important to assess whether there is truly a benefit to the increased intensity of therapy in this population, since outcomes may not be improved if therapy cannot be given in a timely manner.

The review also discusses monoclonal antibodies in the treatment of ALL. This includes the use of the anti-CD20 antibodies rituximab (Rituxan) and ofatumumab (Arzerra). Although CD20 is currently the best-studied target, the degree of activity associated with anti-CD20 therapy is quite limited, so most groups are focusing on other targets. CD19 (blinatumomab, discussed later in the review), CD22 (epratuzumab), CD22-calicheamicin (inotuzumab ozogamicin), CD33 (gemtuzumab ozogamicin), and CD52 (alemtuzumab [Campath]) are among those currently being explored in both the upfront and relapsed/refractory settings.

The targeted therapy with the greatest impact to date is the inhibitor of the tyrosine kinase BCR-ABL seen in Philadelphia chromosome (Ph)-positive ALL. Tyrosine kinase inhibitors (TKIs), such as imatinib (Gleevec), nilotinib (Tasigna), and dasatinib (Sprycel), when added to standard chemotherapy, appear to improve the survival of adults in what was previously a very high-risk subpopulation. The most salient question, which we believe should be the focus of ongoing study, is whether patients with Ph-positive ALL should proceed to allogeneic transplant in first complete remission (CR1) or whether the addition of TKIs to standard therapy makes this traditionally well-accepted approach unnecessary for at least a subgroup of these patients. There are several ongoing trials addressing this question, although a single large randomized trial would be ideal. At the current time, allogeneic stem-cell transplantation (alloSCT) remains the accepted curative option for Ph-positive ALL and for many adult ALL patients. There is some controversy regarding
which patients will most benefit from matched-sibling and matched-unrelated donor transplants. Given that ALL is not as responsive to the graft-vs-leukemia effect as are other leukemias, including chronic myelogenous leukemia and acute myelogenous leukemia (AML), considering an alternate donor strategy may provide improved outcomes for these patients. Specifically, haploidentical transplantation holds promise in this area. Studies at our institution and others have demonstrated that these transplants are associated with no increase in toxicity compared to other types of transplants.[3] In addition, recent studies in ALL have shown promising results, including one study of T-ALL patients that had a 55% leukemia-free survival for patients transplanted in CR1[4], and a second study of high-risk hematologic malignancy patients, including patients with ALL, which demonstrated a 60% 1-year overall survival.[5]

In order for ALL patients who are not transplanted in CR1 to have a successful outcome after relapse, novel salvage therapies are needed, as those currently used are woefully inadequate. The discussion of salvage therapy for ALL in this review is limited, in part reflecting the lack of effective salvage therapies. There are, of course, a large number of ongoing trials, including studies of TKIs, signal transduction inhibitors, and many other novel targets. One study from the pediatric arena involves the addition of the proteasome inhibitor bortezomib (Velcade) to standard chemotherapy.[6] The study showed an impressive 80% response rate in relapsed/refractory B-lineage ALL patients. This regimen should be considered for further study in the adult population.

It is clear that the management of adult patients with ALL is an area in which little progress has been made in the last 30 years. Given the disappointing outcomes, the field is one that lends itself to the study of the incorporation of novel agents, including monoclonal antibodies and tyrosine kinase and proteasome inhibitors, as well as to further study of allogeneic transplant. Unfortunately, at this time, we are left with more questions than answers. The continuing commitment of the oncology community—including the authors of this review and this commentary—to finding novel ways to address these questions gives us hope of an improved future for our adult patients with ALL.

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