CLINICAL UPDATE

Novel Approaches to Disease Management

Novel Treatments in Acute Lymphocytic Leukemia

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H&O What is acute lymphocytic leukemia (ALL)?

AS ALL is a malignancy that originates in hematopoietic cells in the bone marrow. An estimated 6020 new cases will be diagnosed in the United States this year: 3140 in male patients and 2880 in female patients. ALL is the most common cancer in children. Studies have suggested that risk factors for childhood ALL include exposure to chemicals, such as those found in pesticides and household paint. There is an increased incidence of ALL among Hispanics, although the reason is unknown.

H&O How does the prognosis differ according to age?

AS The prognosis in children is very good; 80% to 90% of ALL patients ages 12 years and younger will survive. Prognosis worsens in adolescence and young adulthood (<30 years). Among the 1440 ALL patients who die from the disease each year, most are adults. Approximately 60% to 80% of adults with ALL will achieve full remission with standard treatments, and 35% to 40% will survive beyond 2 years with aggressive treatment. Survival rates are higher in younger adults than in older adults. Older patients have a worse prognosis for 2 main reasons: the high-risk variant Philadelphia chromosome–positive ALL is more common in older patients, and older patients are often unable to tolerate intensive chemotherapy.

H&O What are the traditional treatment approaches?

AS Treatment usually begins with multidrug induction chemotherapy that lasts for 4 weeks. The goal is to achieve remission. After those first 4 weeks, treatment will differ according to the patient's age. Most childhood ALL patients will receive an intensive regimen consisting of consolidation/intensification therapy and maintenance therapy. Patients older than 18 years who achieve remission will be treated with further consolidation and maintenance therapy, or they will receive a transplant (from a sibling, if they have one). Stem cell transplant is often used in adults in first remission because the relapse rate is 45% to 65% vs less than 25% in pediatric patients. Patients with the Philadelphia chromosome will receive a tyrosine kinase inhibitor in addition to chemotherapy. The addition of a tyrosine kinase inhibitor to standard chemotherapy improves the complete response rate and reduces levels of minimal residual disease, allowing more patients to proceed to transplant and thereby improving overall outcome.

In the recently completed Intergroup Trial C10403, treatment used in children was administered to patients ages 16 to 39 years to evaluate whether pediatric protocols would improve outcomes in adolescents and young adults. Toxicity results presented at the 2013 American Society of Hematology (ASH) meeting showed that the pediatric management protocol was feasible in older patients. Outcome data require further maturation.

H&O Are there any recent drug approvals in ALL?

AS A vincristine sulfate liposome injection (Marqibo, Spectrum Pharmaceuticals) was approved for ALL in 2012. In standard regimens of vincristine, the dosage does not exceed 2 mg to minimize the risk of neuropathy. With the liposomal formulation, the dosage of vincristine can be increased to 2.25 mg/m^2 so that more

Table. Responses in a Phase 2 Trial of Vincristine Sulfate Liposome Injection in ALL

	Number of Patients (%)	95% CI
Overall CR	13 (20)	11.1-31.8
CR	7 (11)	4.4-20.9
CRi	6 (9)	3.5-19.0
Partial remission	6 (9)	3.5-19.0
Bone marrow blast response	4 (6)	1.7-15.0
Overall response	23 (35)	23.8-48.3

ALL, acute lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematologic recovery.

Data from O'Brien S et al. *J Clin Oncol.* 2013;31(6):676-683.

of the drug can access the bone marrow and eradicate the leukemia. The US Food and Drug Administration indication of vincristine sulfate liposome injection is for the treatment of adults with Philadelphia chromosome–negative ALL in second or greater relapse or whose disease has progressed following at least 2 antileukemia therapies.

In a phase 2 study by O'Brien and colleagues of 65 patients with ALL, the overall response rate was 35% (see the table). The study's primary endpoint, complete response or complete response with incomplete hematologic recovery, was reported in 20%. Among these patients, the median duration of documented remission was 23 weeks. A neuropathy-associated adverse event occurred in 86% of patients. Grade 3 treatment-related adverse events were reported in 39% of patients, and grade 4 events were reported in 19%. Grade 3 events related to peripheral neuropathy (eg, hypoesthesia, hyporeflexia, peripheral neuropathy, limb pain, and motor weakness) occurred in 23% of patients. There was 1 report of a grade 4 event related to peripheral neuropathy (sensory peripheral neuropathy). There were no reports of grade 3/4 nausea or vomiting.

Vincristine sulfate liposome injection is given once a week, so it can be administered in the outpatient setting. In patients with relapsed leukemia who have failed other treatments, vincristine sulfate liposome injection can be used as a bridge therapy to allow patients to get to transplant.

H&O Is vincristine sulfate liposome injection being evaluated in earlier ALL settings or other malignancies?

AS There are no clinical trials currently evaluating the use of vincristine sulfate liposome injection in earlier ALL settings.

Vincristine sulfate liposome injection was evaluated in 60 patients with untreated diffuse large B-cell lymphoma (DLBCL). Results were presented at the 2013 ASH meeting by Fredrick Hagemeister. This phase 2 trial substituted vincristine sulfate liposome injection for nonliposomal vincristine in the regimen of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Among all patients, the overall response rate was 95%, including a complete response rate of 90% and an unconfirmed complete response rate of 2%. The median progression-free survival and overall survival were not reached after a median follow-up of 8 years and 10.2 years, respectively. At 10 years, progression-free survival was 64%, and overall survival was 87%. In patients older than 60 years, the substitution of vincristine sulfate liposome injection was associated with an overall response rate of 91%, a 10-year overall survival of 65%, and a 10-year progression-free survival of 48%. Among patients older than 60 years who had an age-adjusted International Prognostic Index score of 2 or 3, the overall response rate was 92%, which consisted entirely of complete responses. The median progression-free survival was 118 months. At 10 years, progression-free survival was 27%, and overall survival was 50%. Grade 3 peripheral neuropathy occurred in 3% of patients, and there were no reports of grade 4.

Vincristine sulfate liposome injection was also studied in 22 patients with heavily pretreated, relapsed/refractory CD20-positive DLBCL or mantle cell lymphoma. Results of the study were presented at the 2013 ASH meeting by Lawrence Kaplan. The overall response rate was 59%, including a complete response in 27% and a partial response in 32%.

H&O Are there any areas of research in ALL?

AS There are 3 main areas of research. One is using targeted monoclonal antibodies directed at CD19 or CD22 (antigens found on most ALL cells) with either chemotherapy or immunotoxin conjugates. An anti-CD22 antibody-drug conjugate (inotuzumab) has shown high complete remission rates (57%) in a phase 2 study in patients with relapsed/refractory ALL (N=49).

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In another approach, gene-modified T cells obtained from the patient are being evaluated in the relapsed setting, and the results are very promising. An alternative to modified gene cells is the use of blinatumomab, which is a bispecific T cell–engaging (BiTE) antibody. Blinatumomab consists of an antibody specific to CD19—so it attaches to the ALL cells—linked to an antibody specific for CD3 for T-cell recruitment and activation. Once the antibody attaches to the leukemic cell, it then activates the patient's own T cells and redirects them to attack the ALL cells. Blinatumomab has shown high complete remission rates (67%) in patients with relapsed/refractory ALL (N=18).

Editor's Note

This article differs from the print version in that the data on vincristine sulfate liposome injection were updated on April 28, 2014.

Suggested Readings

Advani AS, Sanford B, Luger S, et al. Frontline-treatment of acute lymphoblastic leukemia (ALL) in older adolescents and young adults (AYA) using a pediatric regimen is feasible: toxicity results of the prospective US Intergroup Trial C10403 (Alliance) [ASH abstract 3903]. *Blood*. 2013;122(21)(suppl).

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O'Brien S, Schiller G, Lister J, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome–negative acute lymphoblastic leukemia. *J Clin Oncol*. 2013;31(6):676-683.

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