ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

A New Formulation of Vincristine for Acute Lymphoblastic Leukemia

Leonard Heffner, Jr, MD
Associate Professor of Hematology and Oncology
The Emory Clinic
Atlanta, Georgia

H&O How has conventional vincristine been used in the treatment of acute lymphoblastic leukemia (ALL)?

LH Vincristine sulfate is a chemotherapy agent that was developed from the periwinkle plant in 1959 and was originally called *leurocristine*. The drug is cell-cycle specific and binds to tubulin, causing depolymerization of microtubules with resultant metaphase arrest. Vincristine and prednisone together have been the backbone of ALL treatment for many years. Vincristine was first reported to be an active agent in 1962, when it was studied as a single-agent therapy in 13 patients with acute leukemia (12 of whom had ALL). In this study from the National Cancer Institute reported by Karon and colleagues, 54% of patients achieved complete remission. In the mid-1960s, the group at St. Jude Children's Research Hospital took that information and incorporated vincristine into their sequential childhood ALL protocols. This use resulted in the marked improvements that have occurred within the treatment group, and certainly within pediatric patients with ALL.

H&O What are the advantages and disadvantages to vincristine treatment?

LH The obvious major advantage to vincristine is that it is a highly active cytotoxic agent against lymphoid malignant cells. It induces apoptosis through its effect on the microtubules, resulting in metaphase arrest. This unusual mechanism of action makes vincristine non–cross-resistant when it is used with most of the other active agents in ALL. Resistance seems to be fairly low, and it has a short infusion time. The disadvantages are two-fold and relate primarily to the metabolism of the drug. With its limited bioavailability—evidenced by a rapid elimination from the circulation (it has a half-life of about 1.5 hours)—vincristine has a low area under the concentration time curve and a low volume of distribution. These characteristics likely account for some of the toxicity, which is the other major disadvantage of the drug.

The primary toxicity is neurologic. Vincristine disrupts the neuronal axonal microtubules, just like it affects the microtubules of the malignant cell. This effect results in peripheral neuropathy, which can manifest as both a sensory neuropathy as well as a motor neuropathy, and also intestinal toxicity, which may cause severe constipation or obstipation in some patients. Alopecia may occur in approximately 20% of cases. There have been rare cases of syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH).

Another important concern is the potential for injury to the subcutaneous tissues if there is extravasation of the drug outside the vein. For that reason, we like to have central venous access when giving the drug on a frequent basis and also typically give the drug as a brief infusion rather than as an intravenous push. This approach has resulted in a current dosing recommendation for aqueous vincristine of 1.4 mg/m^2, which is almost always capped at 2 mg primarily to minimize neurotoxicity. Early literature describing development of the drug states that it was given in doses up to 0.075 mg/kg, which in a 70-kg person would translate to 5.25 mg.

H&O Could you describe the newer formulation of this agent, vincristine sulfate liposomes injection (VSLI)?

LH VSLI (Marqibo, Talon Therapeutics) is a liposomal encapsulation of vincristine. There is more than one way to design the liposomal encapsulation. This particular method uses the sphingomyelin-cholesterol liposomal formulation because it renders the encapsulated drug less susceptible to acid hydrolysis and less likely to leak out inappropriately. This formulation increases the half-life of the drug from 1.5 hours to between 6.5 and 7 hours. This results in an increased area under the concentration time curve; it also limits the volume of distribution and decreases the systemic exposure to the free drug as compared to the aqueous formulation of vincristine. The pharmacokinetic characteristics alone do not really explain the antitumor activity. It is thought that the liposomal encapsulation of the drug allows it to penetrate into the fenestrated tumor vasculature where the free drug can then be released more slowly and be exposed to the tumor for a longer time.

The preparation of the drug is different with this encapsulated formulation as well, because it requires a reconstitution process. VSLI starts as a 3-vial combination of the liposome, vincristine, and a buffer. These are combined in a warm water bath that then creates a pH gradient that allows the vincristine to migrate across the lipid bilayer of the membrane, which is made more permeable by the heat. The process takes between 60 and 90 minutes. The drug is then infused over the course of 60 minutes. This administration results in an increase in dose intensity. In one of the pharmacokinetic studies conducted by Silverman and colleagues, it was confirmed that there is a median dose intensification of 116% compared to standard vincristine capped to 2 mg.

H&O Could you discuss the new data on VSLI in ALL presented at the 2010 American Society of Hematology (ASH) conference?

LH There have been 2 moderately sized studies of the use of VSLI in ALL. The first was the VSLI-06 study, which was a phase I/II, 3-institution trial with a dose escalation of VSLI in relapsed/refractory ALL. It consisted of 36 patients, 35 of whom were Philadelphia (Ph) chromosome–negative. They received weekly VSLI at one of 5 different dose levels, beginning at 1.5 mg/m^2 and increasing up to 2.4 mg/m^2. They also received dexamethasone 40 mg on days 1–4 and 11–14 of each 4-week cycle. The study goal was to determine the maximum tolerated dose, which was 2.25 mg/m^2. The dose-limiting toxicity at the 2.4 mg/m^2 dose (the highest dose tested in this study) consisted of 1 case of grade 3 motor neuropathy, 1 case of grade 4 seizure, and 1 case of grade 4 hepatotoxicity.

The other study, known as the RALLY (Safety and Efficacy of Marqibo® in Relapsed Acute Lymphoblastic Leukemia) trial, or VSLI-07, was a phase II, multinational trial of single-agent VSLI at the 2.25 mg/m^2 dose for 65 patients with Ph chromosome-negative ALL who had experienced at least 2 relapses or had progressed after at least 2 prior lines of therapy. The drug was given weekly until the occurrence of either disease progression—in which case stem cell transplant was an option—or toxicity.

The data from both of these studies were presented in combination at the 2010 ASH meeting in December. The study characteristics were very similar, aside from some increases in the percentage of patients with extramedullary disease and those who had prior stem cell transplant in the RALLY trial compared to the VSLI-06 trial. Prior vincristine therapy had been administered in 100% of patients. The responses and toxicities were identical for both trials, which is really interesting. There was a 20% overall complete remission rate in this heavily pretreated population, with 19% in the VSLI-06 and 20% in the RALLY trial. The overall response rate (ORR), when combining the 101 patients in the 2 trials, was 31%; it was slightly higher in the RALLY trial at 35% versus 22% in the VSLI-06 study. Hematologic improvement was seen in 13% of patients overall, and another 26% of patients were considered to have stable disease. The combination of the patients who achieved ORR, hematologic improvement, or stable disease (ie, all patients who had some kind of benefit within the study), was 70% of the total population.

With regard to toxicity, 2 major events were expected, which are also seen with the free drug: neurologic toxicity and constipation. There was a 68% incidence of peripheral neuropathy with the combined studies, and these were grade 3 or less. There was no grade 4 or 5 peripheral neuropathy. Constipation was similar in both studies and occurred in 57% of patients overall. Gastrointestinal problems were the other major component of the toxicity and included anorexia (32%), diarrhea (37%), and nausea (48%). Fever occurred in 41%, and febrile neutropenia occurred in 39% of patients. I think these are not unexpected problems that occur in this particular patient population, and it is difficult to say whether the drug alone had something to do with causing them.

Another important part of the analysis is the 5.3-month median duration of complete remission, defined as full complete remission, incomplete hematologic recovery complete remission, or a lack of platelet recovery. This finding is significant because such duration allows very adequate time to attempt a stem cell trans-

plant, which would still be a potential curative therapy for that group of patients. In these studies, 15% of the patients went on to receive stem cell transplantation.

H&O What are some future directions of ALL research?

LH Vincristine is a drug that has been around for 50 years, and we have not moved very far beyond it with regard to treatment. Although the new formulation of the drug (VSLI) is certainly a significant advance, we have yet to make the necessary advances in disease research. The use of tyrosine kinase inhibitors (TKIs) such as imatinib (Gleevec, Novartis) and subsequent generations of these agents have made a major impact in Ph chromosome-positive ALL. What remains to be seen is exactly how much of an impact there will be as we learn about the long-term survival of these patients.

We clearly need to better understand the biology of the disease. In doing so, new targets like TKIs can be developed. Gene mutations, such as IKZF1, EBF1, and PAX5, are being identified in an increasing percentage of patients, particularly among the pediatric population. Once we can identify gene mutations, it is hoped that we will be able to develop drugs that will target those abnormalities, ultimately resulting in some disease improvement.

We have always distinguished pediatric ALL and adult ALL, and in the past decade we have discovered that the disease behaves somewhat differently in 4 age groups: pediatrics (younger than 16 years), adolescents and young adults (16–30 years), adults (30–60 years), and the elderly (older than 60 years). By employing the pediatric regimens in the adolescent and young adult population, great strides have been made, resulting in better responses and outcomes. However, such regimens cannot be used in older populations, since those patients cannot tolerate the increased doses and schedules of the drugs that younger patients can. Other drugs that are well tolerated and effective in the older population still need to be discovered, which is where identifying the targets really comes into play. The concept of minimal residual disease, long established in the pediatric population, is being recognized more and more in the adult population. In general, a patient should be checked for minimal residual disease once remission is achieved hematologically or at 4 weeks of therapy. Patients who still have evidence of disease based on either chromosome abnormalities or molecular changes will not do well, even though they may ultimately achieve a remission. Those patients should probably undergo transplant, which is becoming an increasingly available option in older populations when reduced intensity conditioning is used.

Ultimately, there is a lot to look forward to with regard to the future direction of ALL therapy, but many challenges remain. The development of more agents, as we identify more targets, will help us tremendously.

Suggested Readings

O'Brien S, Thomas DA, Heffner LT, et al. Marqibo® (vincristine sulfate liposomes injection; VSLI) in the treatment of adult patients with advanced, relapsed/refractory acute lymphoblastic leukemia (ALL): a combined analysis of the VSLI-06 and RALLY studies. *Blood* (ASH Annual Meeting Abstracts). 2010;116. Abstract 2143.

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