ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Idelalisib for Chronic Lymphocytic Leukemia

Jennifer R. Brown, MD, PhD
Director, Chronic Lymphocytic Leukemia Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

H&O Could you provide some brief background on the treatment of chronic lymphocytic leukemia (CLL)?

JB Historically, CLL has not been curable with any of our standard approaches, and therapy generally has been palliative in nature. Oral alkylating agents were the early standard of care, with significant advances later made with the introduction of fludarabine and purine analogues. The monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec) was the first drug that improved overall survival among patients with CLL in randomized clinical trials.

Chemotherapy combined with antibody therapy can be used repeatedly but not indefinitely; patients with CLL eventually develop resistance. In addition, these medications often are not well tolerated by older and sicker patients. The median age of onset for CLL is 72 years, so older, sicker patients represent a significant fraction of the patient population. The development of resistance and the low tolerability led to a relatively quick exhaustion of the standard therapies for people with high-risk disease in the past.

Therefore, there has been a need for novel therapies. We have seen an explosion of targeted therapies in the past 5 years; these predominantly have been focused on signaling systems that are known to be consistently overexpressed in CLL.

H&O What is idelalisib?

JB Idelalisib (Zydelig, Gilead Sciences) is an inhibitor of the δ isoform of phosphatidylinositol 3-kinase (PI3K). These enzymes are constitutively activated in many malignancies and have long been recognized as important in cancer.

It turns out that there are 4 catalytic isoforms of PI3K: α, β, γ, and δ. The α and β isoforms have ubiquitous expression across all cell types. Therefore, targeting these isoforms is associated with certain toxicities that are unrelated to targeting B cells. For example, inhibiting these enzymes can affect glucose homeostasis based on insulin signaling.

By contrast, the γ and δ isoforms have more limited expression in hematopoietic cells. In particular, the δ isoform has a knockout mouse phenotype that primarily affects the B-cell compartment. This limited expression made δ PI3K a very good potential target for B-cell malignancies. Idelalisib is a specific inhibitor of this isoform.

H&O Would the γ isoform also make a good potential target?

JB γ PI3K also has limited expression, but it is expressed in neutrophils and T cells along with CLL cells. There is a γ/δ PI3K inhibitor for CLL currently in development, but we do not yet know how adding γ inhibition will affect efficacy and toxicity.

H&O Is the expression of δ PI3K the same for all CLL patients or are there subtypes of the disease?

JB This target is present universally in CLL. As mentioned above, it is constitutively activated, mainly by stimuli that impinge on CLL cells from the external environment. Interestingly, we do not find mutations that activate this target, which is different from the phenomena we often see in solid tumors, where proteins exist in mutated forms that render them constantly active. In CLL cells, the relevant pathways are kept activated by

the external environment stimulation, which makes the therapies more universal for CLL patients than many targeted agents are for solid tumors.

H&O What led to the combination of idelalisib and rituximab, the regimen used in the clinical trial that led to the approval of idelalisib?

JB There were a couple of reasons for combining these agents. As a single agent, idelalisib elicits an interesting pattern of response in CLL. Like some of the other inhibitors of targets involved in the B-cell receptor pathway, idelalisib leads to lymph node shrinkage, but also an increase in the white blood cell (WBC) count, which may be due to redistribution of CLL cells from lymph nodes and bone marrow into the peripheral blood.

In the phase 1 study of idelalisib, published earlier this year in *Blood* with myself as the first author, we saw a persistent increase in lymphocyte count in heavily pretreated patients. This outcome was concerning because the classic response criteria for CLL require a decrease in WBC count. The criteria have since changed; now, patients with persistently elevated lymphocytes who otherwise meet all criteria for a partial response can be categorized as having a partial response with lymphocytosis. But during this phase 1 trial, there was a concern that the increase in lymphocyte count would pose difficulties in defining response in a potential registration trial.

The addition of rituximab was based on the hypothesis that another agent would help kill the CLL cells in the blood for subsequent elimination from the body, enabling patients to achieve a classic response. The approach makes sense: as cells leave the environment of the lymph node and bone marrow that supports them and keeps them alive, they are easier to kill in the blood. Rituximab, an agent with little toxicity and a proven track record in CLL, was a logical choice to combine with idelalisib.

We do not know what rituximab contributes in terms of the durability of response, only that it converts patients with lymphocytosis into classic responders. We may never know the contribution of rituximab to the outcomes of patients treated with idelalisib because there are no randomized trials of single-agent idelalisib ongoing. Some patients are unable to be treated with rituximab, so it would be useful to know how much it contributes to survival, if at all, but we are unlikely to be able to study this question in a clinical trial setting.

H&O What was the patient population for the phase 3 randomized trial of idelalisib for CLL?

JB The patients enrolled in the phase 3 study were relatively high-risk; that is, they had more or less exhausted the efficacy of standard therapies and/or could not receive these therapies because of toxicity. Patients were required to have relapsed within 2 years of a prior regimen and have some form of comorbid disease, such as other medical problems, reduced renal function, or blood counts that were low because of prior chemotherapy.

Almost half of the enrolled patients exhibited 17p deletion or *TP53* mutation, both indicators of aggressive disease. Patients also had significant comorbidities, based on a formalized rating scale. These patients would not be expected to benefit from standard therapy, a trait that was reflected in the rituximab/placebo control arm, which showed a fairly short median progression-free survival time of 5½ months. We anticipated that the eligibility criteria for this trial would provide a fairly rapid reading of the potential benefit of idelalisib.

H&O What was the structure of the treatment in the trial?

JB Randomization was one-to-one between rituximab plus idelalisib vs rituximab plus placebo. The duration of idelalisib is indefinite, so that patients responding to treatment can continue with it. Rituximab was given for 6 months at 375 mg/m^2 for the first dose, followed by 500 mg/m^2 every 2 weeks for 4 doses, and then monthly for 3 doses.

H&O Could you describe the results?

JB The primary endpoint of the study was progression-free survival. The follow-up at the time of the report, which was published in *New England Journal of Medicine* by Furman and colleagues earlier this year, was only 5 months.

For patients in the placebo-controlled arm, the median progression-free survival was 5½ months. In other words, patients began progression before rituximab therapy had even been completed. For patients receiving idelalisib plus rituximab, the progression-free survival time is not yet known. Longer follow-up of this arm will be of great interest.

Another interesting result is that there was no difference in progression-free survival based on high-risk markers in the idelalisib arm. Patients with 17p deletions or *TP53* mutations did just as well as those without these high-risk markers. Again, longer follow-up is needed, but these data were encouraging.

There was a difference in overall survival time between the 2 arms, although again longer follow-up is needed before this result will be truly meaningful. In terms of toxicity, there were very few adverse events seen with the combination treatment. Three patients enrolled in this arm died during the trial, vs 9 patients in the control arm.

The data are very immature, but these findings do make us sit up and pay attention, because evidence of an improvement in overall survival in CLL is rare.

H&O What side effects were seen among patients receiving idelalisib? Could these side effects be ascribed specifically to idelalisib?

JB The most common side effect was liver function abnormalities, which usually occurred at weeks 4 to 8 of treatment with idelalisib. These abnormalities generally were asymptomatic, and resolved when the drug was halted. Most patients were able to resume treatment after the issue resolved and could continue taking the drug with careful monitoring. This side effect was more common in the experimental arm, and was known from earlier clinical trials.

There are other toxicities known to occur with idelalisib that were not observed in the phase 3 study, most likely because of the short follow-up time thus far. Some patients experience inflammatory colitis that can cause severe diarrhea, although this toxicity usually does not occur until 6 months into treatment. There also have been some cases of drug-related pneumonitis, which occurs in approximately 2% of patients, but in CLL, this adverse effect can be hard to distinguish from pneumonia caused by infection.

H&O As far as you know, is idelalisib being integrated into treatment for CLL in routine clinical practice?

JB We have begun treating patients with idelalisib in our clinic. There is a competitive landscape now between this agent and ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech). For a subset of patients—those who require anticoagulation or have bleeding issues—idelalisib is a better choice because ibrutinib can cause bleeding problems. For patients with known hepatitis or inflammatory bowel disease, ibrutinib may be a better choice. Other than for these patients, in my opinion it is not clear whether one of these agents has an advantage.

H&O Does the use of ibrutinib preclude later use of idelalisib or vice versa?

JB Not that we know of. If a patient progresses on one agent, then the other could be employed. However, as yet we do not have good information about the response rates with the subsequent agent in patients who have progressed on the other.

H&O Could these 2 agents be combined?

JB Yes, absolutely. There is a great deal of interest in combining ibrutinib with idelalisib and in combining idelalisib with Bcl-2 inhibitors currently in clinical development. However, these approaches are experimental and cannot be recommended yet for standard practice.

H&O Will idelalisib be studied as a first-line treatment?

JB There are some data on the use of idelalisib as a first-line treatment for elderly patients, who often have comorbidities and may not tolerate more aggressive chemotherapy. However, randomized controlled trials of this agent in the up-front setting are only now getting underway. We are now moving forward with testing targeted agents in combination with each other and then potentially in the first-line setting, where patients can potentially receive a defined duration of therapy followed by a break for some extended period.

H&O What else do you see as a pressing need to improve the lives of patients with CLL?

JB Combinations of novel agents is a pressing issue, as is assessing the duration of therapy needed. Right now, targeted agents are used as sequential single agents, essentially. But this approach is really a recipe for resistance, and most likely is not in the best interest of all patients. Combining novel agents may better suppress resistance.

A defined duration of therapy may have advantages and disadvantages compared with indefinite therapy. If patients receive a treatment for some defined duration and then have a break, they may not develop resistance and potentially could be re-treated with the same agents.

Suggested Reading

Awan FT, Byrd JC. New strategies in chronic lymphocytic leukemia: shifting treatment paradigms [published online October 7, 2014]. *Clin Cancer Res*. pii:clincanres.1889.2014.

Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390-3397.

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007.

Herman SE, Gordon AL, Wagner AJ, et al. Phosphatidylinositol 3-kinase-delta inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. *Blood*. 2010;116(12):2078-2088.

Hoellenriegel J, Meadows SA, Sivina M, et al. The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. *Blood*. 2011;118(13):3603-3612.

ten Hacken E, Burger JA. Molecular pathways: targeting the microenvironment in chronic lymphocytic leukemia—focus on the B-cell receptor. *Clin Cancer Res*. 2014;20(3):548-556.