ADVANCES IN LLM

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

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B-Cell Receptor Inhibitors in Chronic Lymphocytic Leukemia

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H&O What is the current standard of care for chronic lymphocytic leukemia (CLL)?

IF The current standard of care varies for patients with CLL, based on their age and other comorbidities. For younger patients, a fludarabine-based regimen is typical for first-line therapy, such as fludarabine plus cyclophosphamide and rituximab (Rituxan, Genentech/Biogen Idec) or fludarabine and rituximab. Although it is not entirely clear, some data suggest that these more aggressive regimens are not helpful in treating the older patient population. Single-agent fludarabine, single-agent chlorambucil, and even rituximab have been used and are well-tolerated in older patients. As far as the relapse setting is concerned, there is a wide array of different treatment options. Some of these same regimens that are used in the frontline setting may be utilized if a patient experienced a durable remission. Other combinations, including newer investigational agents, are very attractive options as well.

H&O Can you discuss B-cell antigen receptor (BCR) signaling and what role Bruton's tyrosine kinase (Btk) plays in the BCR signaling pathway/tumor growth?

IF The BCR receptor is required for tumor expansion and proliferation in patients with CLL, as well as a variety of lymphomas. Btk is very important for expansion and growth of B-cell malignancies, and mutations that affect Btk can prevent B-cell maturation. Such is the case for patients with X-linked agammaglobulinemia; there is a defect in Btk, and these patients do not develop B-cells. Laboratory studies have shown that by blocking Btk, BCR signaling can also be blocked. There are many downstream pathways of BCR receptor signaling that are important in proliferation and growth.

H&O Can you provide some background on the novel small molecule inhibitor of Btk, PCI-32765?

IF This is a new investigational agent that has gone through phase I and phase I/II clinical trials. It is a very potent small molecule inhibitor of Btk. PCI-32765 inhibits BCR signaling and is active in animal models of B-cell lymphoma. In CLL cells, it promotes apoptosis and inhibits proliferation, cell migration, and adhesion. It appears to be a very attractive agent to administer in patients with CLL, as well as other lymphoid malignancies, and this is the background that has led to a few current studies involving patients with CLL and lymphoma.

H&O Can you discuss the PCYC 1102 study? What were the findings?

IF This is a single-agent study that examined several different cohorts of PCI-32765 in patients with symptomatic CLL in small lymphocytic lymphoma. There were treatment-naïve patients who were older than 65, as well as a group of patients who were relapsed and refractory to prior therapy. In the latter group, 2 different dose levels—420 mg per day versus 840 mg per day—were studied. The objectives of this trial were to look at response rates, duration of response, and progression-free survival (PFS). Pharmacokinetics and pharmacodynamic aspects were examined as well, and toxicity information was gathered.

In both dosing groups, there was a really high response rate observed in patients who were treatment-naïve, as well as in patients who were relapsed and refractory. The mean number of prior therapies was 3 in the lower dosing regimen group versus 5 in the higher dosing regimen group; thus, patients were heavily pretreated. Nearly 40% of the patients who were previously treated had 17p abnormalities; another 30–40% of patients had 11q abnormalities. These are all high-risk features. Unfor-

tunately, the therapies that are currently available do not produce a high response rate in that patient population. In this study, significant overall response rates (ORR) were observed. However, it was also noted that treatment with PCI-32765 appeared to initially cause a lymphocytosis, which is usually considered a sign of CLL progression. However, when patients stayed on treatment, that lymphocyte count came down, and the ORR at the 420 mg dose was 40% for those patients achieving mostly partial remissions, and 67% for the treatment-naïve patients. Patients had shrinking lymph nodes, even though they had an initial increase in their white blood cell count. This occurrence has been seen with other drugs, such as Syk inhibitors. There is a redistribution of these malignant cells from the nodal environment into the blood, and then ultimately, if patients remain on treatment, the white blood counts begin decreasing as well. It is quite fascinating. However, there are challenges in trying to determine how to judge responses in these patients. For example, if patients stop therapy too quickly because a rise in white blood cell count is seen and interpreted as evidence of disease progression, they will not experience the same benefits that could be seen by remaining on the treatment. For instance, in this trial, patients who had refractory disease and were treated at the 420 mg dose level had a 48% overall response using the traditional criteria. An additional 41% of patients had a nodal response. Their lymph nodes shrank, and I suspect, as we follow these patients longer, a higher proportion will go on to meet the traditional response criteria.

H&O What are the toxicities seen with PCI-32765?

IF PCI-32765 in particular, and most of these targeted drugs, have a very good side effect profile. They have very little in the way of hematopoietic toxicity. The most notable side effect of PCI-32765 is grade I diarrhea. This occurs with a lot of tyrosine kinase inhibitors and is a very manageable side effect, unlike those seen in traditional fludarabine-based regimens or with other cytotoxic chemotherapy, which can cause significant damage to the normal marrow elements.

H&O What do data suggest about the B-cell receptor inhibitor CAL-101?

IF CAL-101 is an oral, p110Î´(delta)-selective phosphatidylinositol 3 kinase (PI3K) inhibitor that has been shown to produce an initial increase in the white blood cell count, sometimes quite dramatically, with rapid shrinking of the lymph nodes. In a phase I study of CAL-101, 54 previously treated CLL patients received the drug once or twice daily continuously in 28-day cycles, until their disease progressed or toxicity became unacceptable. The main objective of this trial was to determine the best dosing regimen for CAL-101. Doses between 50 mg and 300 mg in single or divided doses were explored. This was a difficult population to treat, because 72% of patients had refractory disease, 81% had bulky lymph nodes (which makes it harder for many drugs to work), and 36% of patients had the high-risk 17p deletion. In addition, patients had already received a median of 5 prior therapies. There was an ORR of 26%. However, over 80% of patients experienced a reduction in bulky nodes of at least 50%, which is quite notable. Both pneumonia and neutropenia occurred in 24% of patients, but liver toxicity was only 6%, which is encouraging. It is too early to determine remission length, but 46% of patients remain on treatment, and in the future we will see 150 mg twice daily as the standard dosing regimen for CAL-101.

Investigators from both the PCYC 1102 trial and numerous CAL-101 studies are trying to come together and figure out how to best work on these drugs so that we can demonstrate their amazing activity and dramatic improvement for patients and their disease. However, the current response criteria may indicate that patients are initially progressing in their disease, when in fact they have high response rates when time on treatment is increased.

H&O What role do you think inhibitors will play in the future direction of therapy for patients with CLL?

IF I think they are going to play major roles. I am hoping that we can get away from classic cytotoxic chemotherapy and focus more on these targeted agents. This is very much a paradigm shift. We have had challenges in developing these agents due to issues with lymphocytosis, initially, but I suspect that in coming years, they are going to play a major role in treatment for patients with CLL, low-grade lymphoma, and maybe other lymphoid malignancies as well.

Suggested Readings

Clinicaltrials.gov. Safety and tolerability study of PCI-32765 in chronic lymphocytic leukemia. Identifier: NCT01105247. http://www.clinicaltrials.gov/ct2/show/NCT01105247.

Coutre SE, Byrd JC, Furman RR, et al. Phase I study of CAL-101, an isoform-selective inhibitor of phosphatidylinositol 3-kinase P110d, in patients with previously treated chronic lymphocytic leukemia. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 6631.