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Considerations in the Frontline Treatment of Chronic Lymphocytic Leukemia



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H&O When is frontline therapy initiated in chronic lymphocytic leukemia (CLL)?

SO The standard approach to CLL is still watch-and-wait. If patients are asymptomatic and have minimal disease, we do not intervene. This approach is based on the fact that approximately a third of patients with CLL will never need treatment. The idea behind watch-and-wait is to spare those patients who would never require therapy. We begin frontline treatment when patients develop problematic symptoms related to the disease, such as bulky lymph nodes, anemia, or low platelets.

My first choice for the management of patients with CLL is always to enroll them in a clinical trial. We cannot advance the science without enrolling patients on clinical trials.

H&O What are the approved frontline therapies?

SO The chemoimmunotherapy regimen fludarabine/cyclophosphamide/rituximab (Rituxan, Genentech/Biogen; FCR) is approved for these patients. The anti-CD20 monoclonal antibodies ofatumumab (Arzerra, Novartis) and obinutuzumab (Gazyva, Genentech) are each approved in combination with chlorambucil. Bendamustine (Treanda, Teva) was approved as a single agent for frontline CLL, based on a randomized trial that

compared it with chlorambucil. However, bendamustine is most commonly used in combination with rituximab, which is known to improve the outcome of chemotherapy. The most recent approval in the frontline setting was for ibrutinib (Imbruvica, Pharmacyclics/Janssen).

H&O What data led to the approval of ibrutinib in the frontline setting?

SO Ibrutinib is the only targeted therapy available for frontline treatment. Approval of ibrutinib was based on a randomized trial comparing it with chlorambucil in older patients with CLL. Patients were older than 70 years or between the ages of 65 to 70 years and with a comorbidity that precluded them from receiving more substantive chemotherapy. The trial showed that ibrutinib was significantly better than chlorambucil. In fact, the progression-free survival achieved with ibrutinib was far superior to that seen in trials evaluating chlorambucil plus a monoclonal antibody.

Ibrutinib first received a frontline indication in patients with CLL who have the 17p deletion. This indication was followed by approval for all patients, regardless of 17p status. Interestingly, although the randomized trial was restricted to older patients, the approved indication is not. Theoretically, ibrutinib can be used as frontline treatment in any patient with CLL.

H&O How do the data for ibrutinib compare with those for chemoimmunotherapy?

SO The data for ibrutinib are clearly much more favorable than those for chlorambucil. Studies are now comparing ibrutinib vs FCR or bendamustine/rituximab in a younger, fit population. Two large, randomized trials from the Intergroup reached accrual in the past year. A 2-arm trial is comparing FCR vs ibrutinib and rituximab. A 3-arm trial is evaluating bendamustine and rituximab vs single-agent ibrutinib vs ibrutinib in combination with rituximab.

H&O How does the older treatment algorithm in CLL differ from your new treatment algorithm?

SO The older treatment algorithm from the German CLL study group had 3 categories. The “go-go” patients were fit, not elderly, and could tolerate a regimen like FCR. The “slow-go” patients were somewhat older or less fit, but still well enough to receive a treatment such as bendamustine/rituximab. A chlorambucil-based regimen might be used in patients who were less well. The “no-go” patients were elderly and had a poor performance status. These patients would receive palliative care, which most often consists of a single-agent antibody in the United States.

My new treatment algorithm also divides patients into 3 groups, but based on different criteria. The first group is older or less-fit patients, who I prefer to treat with ibrutinib irrespective of their mutation status. In younger, fit patients with the immunoglobulin variable region heavy chain (IgVH) mutation, I lean toward FCR. The final decision, however, would be made after discussion with the patient. In younger patients without the IgVH mutation, absent a clinical trial, I begin treatment with ibrutinib.

Historically, it made sense to base the selection of treatment on age and comorbidities because all of the treatments involved chemotherapy. Now that we have ibrutinib, which is so well-tolerated, that older algorithm has less relevance. For me, older patients are still grouped together. For younger patients, the biggest deciding factor is IgVH mutation status.

H&O Does ibrutinib improve outcome when added to chemotherapy?

SO The HELIOS trial (Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, Bendamustine, and Rituximab for Previously Treated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma) randomly assigned patients with relapsed

CLL to receive bendamustine/rituximab chemotherapy alone vs bendamustine/rituximab plus ibrutinib. The addition of ibrutinib clearly improved outcomes. But what was not answered by this trial is whether bendamustine/rituximab plus ibrutinib is better than ibrutinib alone. The early data appeared comparable. The updated data, however, showed a significant rise in the complete response rate among patients who received bendamustine/rituximab and ibrutinib, much higher than what is seen with ibrutinib alone. The more recent data are starting to suggest that the combination may be better than ibrutinib alone. A benefit to ibrutinib, like many targeted therapies, is that it avoids the adverse events associated with chemotherapy, such as myelosuppression. Combining ibrutinib with chemotherapy may increase efficacy, at least in the minority of patients who are achieving a complete response, but at the expense of potentially increasing toxicity for all patients who receive it. The choice to add chemotherapy to ibrutinib in the relapsed setting is not an easy one.

H&O What adverse events are associated with ibrutinib?

SO In general, ibrutinib is very well-tolerated. The most common side effect is diarrhea, which is usually mild and self-limiting. There are some significant side effects. Atrial fibrillation occurs in 7% to 10% of patients. There is also an increased risk of bleeding caused by interference with the glycoprotein-mediated platelet-aggregation pathway. Most of the bleeding is minor, usually in the form of ecchymosis, but it can also be severe. The risk of bleeding is a particular concern in patients who are receiving an anticoagulant.

Arthralgia is another potential adverse event. It is generally not severe, but it can become problematic in the long-term. Ibrutinib is administered indefinitely, and continual pain, even low-grade, can be difficult for patients to bear. On the rare occasions when I have discontinued treatment with ibrutinib, the most common reason was arthralgia rather than diarrhea or any of the serious side effects.

H&O Do patients with lymphocytosis or baseline cytopenias require a reduced dose of ibrutinib?

SO Patients with lymphocytosis do not require a reduced dose of ibrutinib. Most patients with CLL can have lymphocyte counts in the hundreds of thousands and still be completely asymptomatic. Therefore, lymphocytosis is generally not a concern.

For patients with baseline cytopenias, I generally

start with the full dose. Although there is some sporadic myelosuppression associated with ibrutinib, for the most part, ibrutinib is very good at reversing cytopenias. In contrast, we often reduce the starting dose of chemotherapy in patients with baseline cytopenias.

H&O What factors impact your choice of frontline treatment?

SO In older or less-fit patients, I use ibrutinib regardless of the 17p deletion status because it is clearly better than chlorambucil and much less toxic. The real question concerns younger, fit patients. Most physicians would not treat a younger, more-fit patient with chlorambucil; they would select a better, somewhat more aggressive regimen. For example, FCR or bendamustine and rituximab are more myelosuppressive, but they also produce significantly longer progression-free survival than a chlorambucil-based regimen. I divide younger, fit patients into 2 groups based on their IgVH mutation status. Those with the IgVH mutation are candidates for FCR. This approach is supported by 3 articles published in the last year in Germany, Italy, and the United States. The American study, by Thompson and colleagues at MD Anderson, clearly showed very consistent results in terms of a significant plateau in the progression-free survival curve associated with FCR in patients with a mutated IgVH gene. The study from MD Anderson has the longest follow-up, because this regimen was developed there. At 12 to 16 years of follow-up, remission persisted in approximately 60% of patients with a mutated IgVH gene. The big question is whether to consider some of these patients cured. I would say yes. After this long-term follow-up, some of the patients remained negative for minimal residual disease. Even if they do ultimately relapse, it can still be considered a great outcome if patients remain in remission for 15 years after receiving 6 months of chemotherapy.

For my younger patients with the IgVH mutation, I discuss in detail the pros and cons of using chemotherapy. Chemotherapy is associated with more toxicity in the short-term, but it is administered for a limited duration. It can potentially lead to a very long remission, but it carries a small, but real, risk of late acute myeloid leukemia. Ibrutinib is easier to take than chemotherapy, but it is continuous therapy. Long-term data are starting to be reported. At the 2016 American Society of Hematology (ASH) meeting, I presented an analysis of 5-year data from a phase 2 trial of ibrutinib in patients with untreated or relapsed/refractory CLL or small lymphocytic leukemia. At 5 years, progression-free survival was 92% in the treatment-naïve patients and 43% in the relapsed/

refractory patients. Median progression-free survival was not reached in the treatment-naïve cohort and 52 months in the relapsed/refractory cohort. Median overall survival was not reached for both cohorts. At 5 years, overall survival was 92% for the treatment-naïve patients and 57% for the relapsed/refractory patients. Over time, the rates of complete response increased to 29% in the treatment-naïve patients and to 10% in the relapsed/refractory patients.

We know that in relapsed patients who have received ibrutinib, absent a 17p deletion (which is uncommon in frontline patients), the median progression-free survival is 53 months. I would certainly think it would be longer in the frontline setting, but whether that will be 5 years or 10 years, or whether there will even be a plateau, are unknowns.

H&O Which agents would you consider for patients who are intolerant to ibrutinib?

SO Chemoimmunotherapy is always a possibility, and as far as small molecules, one approved combination is idelalisib (Zydelig, Gilead) and rituximab. The other option is venetoclax (Venclexta, AbbVie/Genentech), although the current indication is only for patients with the 17p deletion. There are, thus far, limited clinical trial data for patients who require treatment after ibrutinib. Mato and colleagues recently published an analysis of pooled data from several institutions evaluating patients who had failed or were intolerant to one kinase inhibitor, whether idelalisib or ibrutinib, and then went on to receive the other one. The response rate to the second inhibitor was approximately 50%. Among patients who were truly resistant to the first kinase inhibitor (as opposed to intolerant), the median progression-free survival was only 7 months. To me, shifting from one kinase inhibitor to another is not an attractive option. It might buy some time and serve as a bridge to transplant in a younger, fit patient. However, it is not a long-term solution.

Jones and colleagues are evaluating venetoclax in patients who have failed ibrutinib or idelalisib. Preliminary results show that the response rates are a bit higher than those achieved by crossing over to another tyrosine kinase inhibitor. Dr Jones presented updated data at the 2016 ASH meeting. Objective response was 70% among patients refractory to ibrutinib and 62% in patients refractory to idelalisib. After 11.8 months of follow-up, median duration of response, progression-free survival, and overall survival have not been reached. The estimated 12-month progression-free survival was 80%. As mentioned, however, venetoclax is approved only for patients with the 17p deletion.

Disclosure

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Suggested Readings

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