Optimizing Treatment of Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Presented by Anthony Mato, MD, MSCE

ABSTRACT

Tremendous progress has been made in the treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) over the past few decades, starting with the development of glucocorticoids and alkylating agents, moving to combination chemotherapy, and then to chemoimmunotherapy. More recently, the advent of targeted agents has led to significant improvements in overall survival, progression-free survival, and quality of life. Most patients with R/R CLL and SLL are now treated with 1 of 5 approved targeted therapies rather than chemoimmunotherapy as standard of care. There are 2 main chemotherapy-free approaches in the R/R setting: Bruton's tyrosine kinase inhibition and venetoclax-based therapy. Treatment after disease progression on first-line therapy depends on the initial choice of therapy, reason for discontinuation of prior lines of therapy, and available options.

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The advent of targeted agents for relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) has led to significant improvements in overall survival (OS), progression-free survival (PFS), and quality of life for this patient population. According to Anthony Mato, MD, MSCE, Director, CLL Program, Memorial Sloan Kettering Cancer Center, most patients with CLL or SLL are now treated with 1 of 5 approved targeted therapies in the R/R setting rather than chemoimmunotherapy as standard of care. At the NCCN 2022 Annual Conference, Dr. Mato discussed chemotherapy-free treatment approaches involving Bruton's tyrosine kinase (BTK) inhibitors, PI3K inhibitors, and the BCL2 inhibitor venetoclax, as well as emerging data on next-generation targeted therapies.

Chemotherapy-Free Approaches

Treatment in the R/R setting of CLL/SLL depends on the treatment selection in earlier lines of therapy. There are 2 main options for chemotherapy-free pathways in the first-line setting: a BTK inhibitor (ibrutinib or acalabrutinib) or venetoclax-based therapy. In the R/R setting, there are even more approved options. In addition to the BTK inhibitors, there are 2 PI3K inhibitors (idelalisib and duvelisib) and venetoclax, which is approved for use with or without rituximab (Figure 1).

"A patient [with CLL or SLL] will be starting on a road that begins with either venetoclax or a BTK inhibitor," said Dr. Mato. "Unfortunately, we have no prospective comparative data for BTK inhibitors versus venetoclax in any line of therapy. In all circumstances, however, the data support a BTK inhibitor or venetoclax before an approved PI3K inhibitor."[1]

Upon relapse or disease progression, the major considerations in selecting the next therapy in the chemotherapy-free pathway are the reasons for prior discontinuation of therapy, available treatment options, and level of evidence.

BTK Inhibitor Versus Venetoclax

Although there are no prospective head-to-head data comparing BTK inhibition and venetoclax as first novel agents in the relapsed setting, Dr. Mato listed several factors to consider. BTK inhibitors offer greater convenience (no infusions or monitoring for tumor lysis syndrome), long-term efficacy, prospective data for efficacy of venetoclax after BTK inhibitors, and several randomized controlled trials demonstrating an OS benefit in the first-line and R/R settings. Conversely, venetoclax is a time-limited therapy with no known cardiac or bleeding risks. There is also less concern for long-term adherence and potential cost-savings if venetoclax leads to a durable response.

Second-Generation BTK Inhibitors

With 2 BTK inhibitors (ibrutinib and acalabrutinib) already approved in the R/R setting and another (zanubrutinib) potentially on the way, comparative data are necessary to select the right agent.

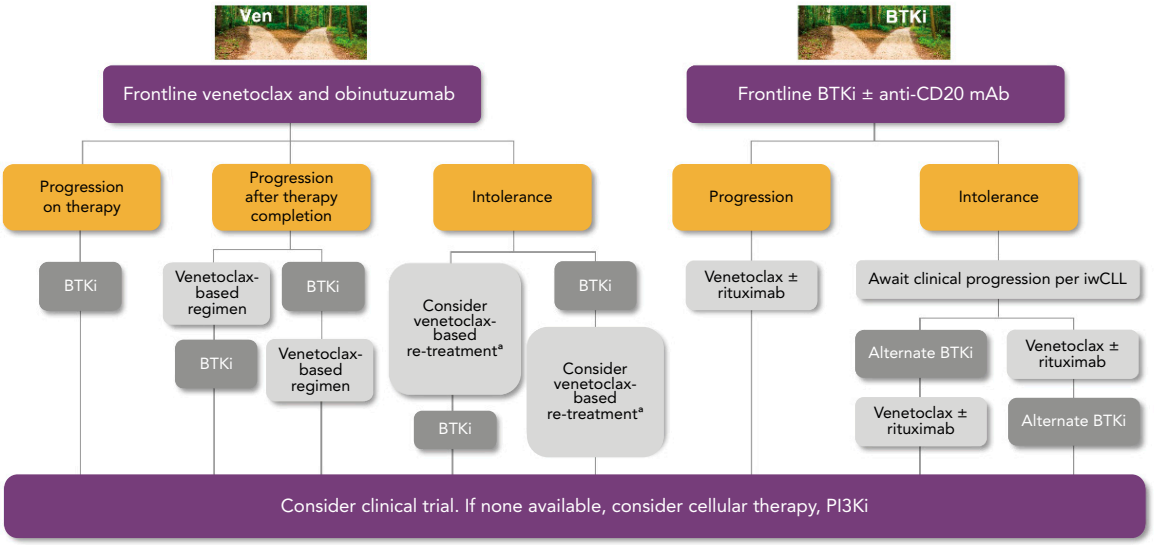

Figure 1. Chemotherapy-free management in CLL (treatment algorithm)
Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mAb, monoclonal antibody; PI3Ki, PI3K inhibitor; Ven, venetoclax.
[a]With adequate supportive care and/or dose reduction.

Long-term follow-up of the first-line RESONATE-2 trial comparing ibrutinib and chlorambucil, which led to the approval of ibrutinib, showed a treatment discontinuation rate of 53% at 7 years, with roughly half of discontinuations caused by adverse effects (AEs).[2] Among the spectrum of AEs associated with ibrutinib, Dr. Mato mentioned atrial fibrillation, arthralgia, infection, diarrhea, hypertension, and bleeding. "Atrial fibrillation is frequent and can cause cardiac morbidity and treatment interruption," said Dr. Mato. "Thankfully, ventricular arrhythmia is infrequent, but it may lead to sudden death or cardiac mortality. Furthermore, hypertension can potentiate other cardiovascular AEs, and the increased risk of bleeding can hinder management of events such as atrial fibrillation," he added.

The ALPINE trial, which compared zanubrutinib and ibrutinib in the R/R setting, showed an improvement in overall response rate from 62.5% with ibrutinib to 78.3% with zanubrutinib, and PFS at 12 months was improved from 84.0% to 94.9%, respectively.[3] Of note, toxicity data also showed significant differences in atrial fibrillation favoring zanubrutinib over ibrutinib (10.1% vs 2.5%), although neutropenia occurred more frequently in patients receiving zanubrutinib. Hypertension was the same with either agent.

The ELEVATE-RR trial, which compared acalabrutinib and ibrutinib, had even more favorable toxicity data for acalabrutinib, said Dr. Mato. He noted significantly less atrial fibrillation, hypertension, bleeding events, diarrhea, and arthralgia among patients receiving the second-generation BTK inhibitor.[4]

Disease Progression After BTK Inhibition

For patients who begin with a BTK inhibitor and experience disease progression or require another therapy in the R/R setting, there is a growing list of options. One strategy is an alternative BTK inhibitor (eg, going from ibrutinib to acalabrutinib or acalabrutinib to ibrutinib), which works best in the setting of intolerance, explained Dr. Mato. Another strategy is treatment with venetoclax (either venetoclax monotherapy or venetoclax + rituximab). A PI3K inhibitor can also be considered. "If the patient discontinues initial therapy with the BTK inhibitor in the setting of intolerance, all options are available. However, if a patient comes off a BTK inhibitor in the setting of resistance, the options are only venetoclax or a PI3K inhibitor," said Dr. Mato, who noted that venetoclax is the standard of care.

Prospective data from patients intolerant to ibrutinib and sequenced to acalabrutinib showed that median PFS has not been reached, with 24- and 36-month PFS rates of 71.9% and 58.3%, respectively.[5] The treatment discontinuation rate due to an AE was 17%.

In a separate study in the setting of BTK or PI3K inhibitor intolerance, patients who switched from ibrutinib, acalabrutinib, or idelalisib to umbralisib (not FDA-approved for CLL) had a median PFS of 23.5 months.[6] Of note, the treatment discontinuation rate due to AEs was 12%. "PI3K inhibitor–associated AEs were quite rare, with very few grade 3 or 4 events, such as colitis, pneumonitis, or transaminitis," said Dr. Mato.

Finally, an updated analysis from the MURANO trial, which compared venetoclax/rituximab given for a fixed 24-month period versus bendamustine/rituximab given for 6 months, showed superior PFS and OS with

venetoclax.[7] Median PFS has now been reached for 53.6 months (vs 17.0), and OS at 5 years for venetoclax-based therapy is 82.1% (vs 62.2%).

Disease Progression After Venetoclax

For patients who begin with venetoclax/obinutuzumab in the first-line setting and experience disease progression, there are several options to consider, including re-treatment with venetoclax or treatment with a covalent BTK inhibitor or a PI3K inhibitor.

With respect to venetoclax re-treatment, a multicenter retrospective study of 25 patients showed an overall response rate of 72.2%.[8]

Treatment with a covalent BTK inhibitor after disease progression on venetoclax is another effective strategy. A study of 44 BTK inhibitor–nave patients demonstrated an overall response rate of 84% and a median PFS of 32 months.[9]

Regarding treatment with a PI3K inhibitor after venetoclax and BTK inhibition, however, real-world studies have demonstrated short remission durations. A study of 17 patients with double-refractory disease who received PI3K inhibition showed an overall response rate of 46.9% and a median PFS of 4 months.

Emerging Data

There are also several noncovalent BTK inhibitors in development. The LOXO-305 molecule (pirtobrutinib) is one that has been shown to overcome resistance to covalent BTK inhibitors. A study of 252 patients treated with pirtobrutinib who had received a prior covalent BTK inhibitor demonstrated an overall response rate of 68%.[10] "This was a very high-risk patient population, with a median number of 3 prior therapies, and median PFS has not yet been reached," said Dr. Mato.

Among patients with double-refractory disease with a median number of 5 prior therapies, median PFS was 18 months with pirtobrutinib. The molecule was also well tolerated, according to Dr. Mato, with a 1% rate of treatment discontinuation due to an AE. Common AEs included fatigue, diarrhea, neutropenia, and contusion. Grade 3 or 4 AEs were reported to be rare, and BTK inhibitor–associated events such as atrial fibrillation or flutter occurred in 2% of patients.

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