Updates in the Management of CLL/SLL: Management of Relapsed/Refractory Disease and the Role of Minimal Residual Disease

Presented by Jennifer R. Brown, MD, PhD

ABSTRACT

In relapsed chronic lymphocytic leukemia (CLL), the choice of therapy depends on the risk profile, prior therapy, and patient comorbidities. The first novel agent for patients who had previously received chemoimmunotherapy is typically a BTK inhibitor or combination venetoclax + rituximab. For patients with problematic comorbidities, however, a PI3K inhibitor can be used, but generally this is reserved for later lines of therapy. For those who stop ibrutinib due to adverse events, there are broad options but data are still limited. For those whose disease progresses on a BTK inhibitor, the only prospective data are for use of venetoclax. For patients who have been treated with venetoclax + rituximab and experience relapse, retreatment is a possibility if they have had a durable remission. Finally, undetectable minimal residual disease is strongly predictive of durability of response for time-limited regimens but not for continuous BTK inhibition, and is generally not indicated for monitoring patients.

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The landscape of relapsed chronic lymphocytic leukemia (CLL) has changed dramatically over the past few years primarily due to changes in the frontline setting. During the NCCN 2021 Virtual Annual Conference, Jennifer R. Brown, MD, PhD, Director, CLL Center, Division of Hematologic Malignancies, and Institute Physician, Dana-Farber Cancer Institute, and Professor of Medicine, Harvard Medical School, discussed appropriate therapy for patients after relapse from various first-line treatments, including ibrutinib and venetoclax.

Ibrutinib

Ibrutinib, a BTK inhibitor, was the first targeted therapy studied in the relapsed/refractory setting. Data from a phase I study of ibrutinib demonstrated a progression-free survival (PFS) of 32% after 7-year follow-up, with approximately 1 in 5 patients still on the drug.¹ Results of this study also showed that patients with del(17p) and del(11q) have a shorter PFS compared with those with other cytogenetic abnormalities. Furthermore, complex karyotype combined with del(17p) is significantly more adverse than del(17p) or complex karyotype alone. No difference in outcome based on IGHV mutational status has been observed.

Final results of the RESONATE trial,² which compared ibrutinib with ofatumumab in previously treated patients with CLL who had undergone 2 to 3 prior regimens, showed a median PFS of 44 months for the ibrutinib arm in this high-risk population. Analysis by dual

abnormality [TP53 and del(17p)] showed decreased PFS compared with patients without those abnormalities.

Acalabrutinib

Acalabrutinib, a highly selective next-generation BTK inhibitor, has also been studied in the relapsed/refractory setting. In the first trial to compare targeted agents head-to-head, patients with relapsed/refractory CLL were randomized to acalabrutinib or investigator's choice of idelalisib + rituximab or bendamustine + rituximab.³ After a median follow-up of 22 months, acalabrutinib prolonged 18-month PFS versus investigator's choice therapy (82% vs 48%, respectively). Interestingly, said Dr. Brown, there was no difference in PFS based on del(17p) or TP53 mutation status in the acalabrutinib arm, and no difference based on IGHV status.

There are still no head-to-head data comparing acalabrutinib and ibrutinib, but the ELEVATE-RR study has been reported to have met its primary endpoint of non-inferiority for PFS.⁴

Zanubrutinib is also in development and is being actively studied in a largely accrued phase III trial in the relapsed setting. Data from the phase I trial with 24-month follow-up showed PFS rates of 91% in patients with relapsed/refractory disease.⁵

Venetoclax

Venetoclax, an inhibitor of BCL-2, depletes tumor cells much more rapidly by triggering apoptosis. In the

MURANO study,⁶ patients with CLL who received a median of one prior regimen were randomized to venetoclax/rituximab or bendamustine/rituximab. The venetoclax/rituximab arm included 6 months of rituximab and 2 years of venetoclax. With 5-year follow-up, median PFS was 54 months with venetoclax/rituximab versus 17 months with bendamustine/rituximab. Five-year overall survival also favored the venetoclax arm at 82%.

According to Dr. Brown, undetectable minimal residual disease (MRD) on venetoclax has also been shown to be associated with improved PFS in several contexts.

When choosing between a BTK inhibitor and venetoclax/rituximab for a first novel agent, Dr. Brown noted that ibrutinib has longer follow-up data, and the use of a next-generation BTK inhibitor has improved the toxicity profile. In addition, a high overall response rate with venetoclax after treatment with a BTK inhibitor has been well established, but there are less data on BTK inhibition after venetoclax. Furthermore, the intense early monitoring with venetoclax favors BTK inhibition.

Conversely, high complete response rates and undetectable MRD favors the use of venetoclax/rituximab. There are also fewer long-term adverse effects with the latter combination. There is also the potential to use venetoclax/rituximab again in patients who stop as planned and have a durable remission. Many patients prefer venetoclax/rituximab because it's a time-limited therapy, which also has the benefit of significantly less cost, said Dr. Brown.

Ibrutinib + Venetoclax

The phase II CLARITY study, which combined ibrutinib and venetoclax for patients with relapsed/refractory CLL, had a primary endpoint of MRD eradication after 12 months.⁷ Study results showed that rates of undetectable MRD increased progressively during the first 2 years on therapy, and provided interesting data on the relationship between the rate of disease depletion and PFS, said Dr. Brown. Most patients with rapid depletion were able to stop therapy and sustain undetectable MRD, with only 1 of 25 patients becoming positive after discontinuation. Among patients with <2 log depletion, however, only 20% were able to stop therapy with sustained undetectable MRD.

"Lower level of residual disease was generally associated with longer time to progression, while relapse tends to occur earlier with less depletion of disease," she observed. "Another notable element about this study is that the 3-year PFS rate was 96%," she added. "That's very encouraging for a population of patients with relapsed/refractory CLL."

MRD in General Practice

Currently, MRD is used only for prognostic purposes with time-limited therapy. Undetectable MRD at end of treatment on the venetoclax regimen is strongly

associated with the durability of remission, said Dr. Brown, but this does not apply to evaluating single-agent BTK inhibitors. "For time-limited therapies, we are very interested in performing studies to learn whether MRD can guide treatment decisions so that patients can stop treatment after achieving MRD negativity instead of having a fixed duration of therapy," said Dr. Brown. "For patients who achieve undetectable MRD but then have recurrent positivity, we'd also like to see whether they might benefit from earlier re-treatment."

PI3K Inhibitors

PI3K inhibitors are another class of drug used to treat CLL. Idelalisib + rituximab received the first approval in the relapsed/refractory setting, with a median PFS of 19.4 months in heavily pretreated patients with comorbidities.⁸ "This looked encouraging," said Dr. Brown. "Unfortunately, 40% of patients discontinued after 2 years due to adverse events, including diarrhea, colitis, transaminitis, infection, and pneumonitis."

Nevertheless, patients not developing an autoimmune toxicity or an infection experience few adverse effects. Importantly, she said, combination idelalisib + rituximab is not contraindicated in cardiac or renal disease and is appropriate for use in older, pretreated patients with significant comorbidities that impact BTK inhibition (cardiac) or venetoclax tolerability (renal).

Treatment After Ibrutinib

A retrospective analysis of toxicities and outcomes for patients treated with ibrutinib showed a median PFS of 36 months, and overall survival has not been reached.⁹ With a median follow-up of 17 months, however, the estimated discontinuation rate on ibrutinib was 42% and median time to discontinuation was 6 months.

A real-world retrospective analysis of 683 patients with CLL demonstrated that use of venetoclax or an alternate kinase inhibitor after discontinuation on ibrutinib or idelalisib was associated with superior PFS versus chemotherapy or monoclonal antibodies.¹⁰ Median PFS on either venetoclax or alternate kinase inhibitor has not yet been reached but follow up is still relatively short.

For patients who experience progression on ibrutinib, however, Dr. Brown called the data "more worrisome." Prospective data evaluating venetoclax in CLL patients demonstrated an overall response rate of 65%, but only 9% of patients experienced a complete response,¹¹ which is "lower than that seen in patients who have not been previously treated with ibrutinib," said Dr. Brown. Median PFS was approximately 2 years.

Treatment After Venetoclax

For patients whose disease relapses after venetoclax/rituximab, the data are encouraging, said Dr. Brown, who

noted that 48% of patients re-treated thus far from the MURANO study received venetoclax, whereas 27% received a BTK inhibitor.¹² Response rates to subsequent venetoclax-based therapy were high (72%), and to subsequent BTK inhibitor-based therapy were even higher (100%).

Patients who experience disease relapse after both BTK inhibition and venetoclax should be encouraged by recent data on LOXO-305, a potent and selective noncovalent inhibitor of wild-type and C481-mutant *BTK*. In patients with CLL treated with LOXO-305, results of a phase I/II study showed an overall response rate of 63%, which improved to 86% for patients on treatment for >10 months.¹³

“Responses occurred regardless of whether patients received prior BTK inhibition or prior venetoclax, and

regardless of whether they discontinued their BTK inhibitor for progression or for toxicity,” said Dr. Brown. “Additionally, the rate of grade 3 and 4 adverse events was extremely low, so this drug looks quite encouraging, although follow-up is still short.”

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