Optimizing Treatment Approaches for Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Presented by Jennifer R. Brown, MD, PhD

ABSTRACT

The choice of therapy for chronic lymphocytic leukemia (newly diagnosed as well as relapsed/refractory disease) depends on the disease (presence or absence of del(17p) or *TP53* mutation) and patient characteristics (age, comorbidities, functional status and patient preference). Many patients can choose between continuous treatment with a Bruton's tyrosine kinase (BTK) inhibitor or time-limited therapy with venetoclax/obinutuzumab. For patients with 17p deletions, the data support the use of continuous treatment with a BTK inhibitor, although these patients should also be referred to clinical trials evaluating novel combination therapy options with minimal residual disease monitoring. The choice of therapy for relapsed disease also depends on prior therapy and duration of response to prior therapy in addition to the disease and patient characteristics (as mentioned earlier). BTK inhibitor- or venetoclax-based regimens are recommended for patients experiencing relapse following chemoimmunotherapy. In the case of disease relapse following BTK inhibitor therapy, prospective data are available only for venetoclax-based regimens, whereas disease relapse (after a period of durable remission) following time-limited therapy with venetoclax-based regimens can be managed through re-treatment with venetoclax or a BTK inhibitor.

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In the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), targeted agents now dominate therapy, according to Jennifer R. Brown, MD, PhD, Director, CLL Center, and Institute Physician, Dana-Farber Cancer Institute, and Professor of Medicine, Harvard Medical School.

“We have continuous therapy with several Bruton's tyrosine kinase (BTK) inhibitors, and we have time-limited therapy with the B-cell lymphoma 2 (BCL2) inhibitor venetoclax plus an anti-CD20 antibody—typically obinutuzumab in the frontline setting and rituximab in the relapsed setting,” Dr. Brown noted at the NCCN 2021 Virtual Congress: Hematologic Malignancies. “But we still, nonetheless, have many unanswered questions.”

According to Dr. Brown, current efforts in the field are focused on determining (1) if continuous or time-limited therapy is preferred, (2) what the preferred regimens are in each category, (3) if there is a preferred sequence, and (4) if anyone should still receive chemoimmunotherapy.

BTK Inhibitors in the Frontline Setting

In the frontline setting, the BTK inhibitors ibrutinib and acalabrutinib are both approved, as is venetoclax/obinutuzumab. Results of a registration trial of zanubrutinib will be reported soon, but data so far are promising, with an 18-month progression-free survival (PFS) of 91% among patients with a 17p deletion.¹

Ibrutinib, a potent covalent inhibitor of BTK, has now been studied in a number of randomized clinical trials. The ALLIANCE trial of patients with untreated CLL who are aged >65 years showed the superiority of ibrutinib-based regimens over bendamustine/rituximab, but there was no benefit of adding rituximab to ibrutinib therapy.² In a parallel study of younger patients (ECOG 1912) in which ibrutinib/rituximab was compared with FCR (fludarabine/cyclophosphamide/rituximab), a significant PFS benefit was seen with ibrutinib in patients with unmutated *IGHV* (89% at 3 years vs 65% with FCR).³

“In the *IGHV*-mutated subgroup, there was not a significant difference [in PFS], and this is important because this group does have the potential for long-term PFS with FCR,” she said. “I think this is the group where chemoimmunotherapy is still most reasonable, because of the potential for very long-term durability of response, or even cure.”

Although older patients with mutated *IGHV* typically lack the same potential for long-term plateau, chemoimmunotherapy may still be a reasonable option because of its short duration and affordability compared with targeted agents.

Among patients in the ECOG 1912 study who discontinued ibrutinib for reasons other than progression or death, the median time from discontinuation to disease progression or death was about 2 years. “That’s a reasonable duration of benefit,” Dr. Brown said. “If I do need to

stop someone who's been on treatment for a reasonable length of time because of adverse events, I don't treat them right away. I let them cool off, let their toxicity resolve, and wait for their disease to start progressing. At that point, usually they feel better, and it's a totally new discussion again."

What About Other BTK Inhibitors?

Acalabrutinib and zanubrutinib are the next-generation covalent inhibitors designed to be more specific for BTK than ibrutinib. Randomized trials comparing each of these BTK inhibitors to ibrutinib have shown similar efficacy and improved tolerability.

In the ELEVATE-TN study, older patients with untreated CLL were randomly assigned to receive acalabrutinib/obinutuzumab, acalabrutinib monotherapy, or obinutuzumab/chlorambucil.⁴ At 4 years of follow-up, the acalabrutinib/obinutuzumab group showed a PFS rate of 87% compared with 78% for acalabrutinib alone. Patients in the obinutuzumab/chlorambucil group had a PFS rate of 25%.

"This study showed quite marked activity of acalabrutinib and an interesting 9% improvement with obinutuzumab," Dr. Brown noted. "Although this was not a planned comparison, the shape of the curves is pretty convincing that this appears to be a real effect."

Patients with del(17p) and/or mutated *TP53* did well, (75% PFS at 4 years) but saw no additional benefit with obinutuzumab. The higher CR rate and undetectable minimal residual disease (MRD) rate were observed in patients who received acalabrutinib/obinutuzumab compared with acalabrutinib alone (not just those with unmutated *IGHV*).

"I think the deeper remissions with obinutuzumab here are translating into a better PFS," Dr. Brown said. "And these data do provide additional evidence, beyond suggestions from earlier trials, that deeper remissions with BTK inhibitors may in fact help patients."

The benefit of time-limited therapy with venetoclax and obinutuzumab was established in the CLL14 trial, in which this combination led to a 4-year PFS rate of 74%.⁵ Undetectable MRD appears to be an important marker of durability of remission with venetoclax + obinutuzumab. In the trial, 75% of patients treated with combination of venetoclax and obinutuzumab had undetectable MRD in peripheral blood versus 57% in bone marrow. At 18 months of follow-up, half of the patients still had undetectable MRD.

The Changing Landscape of Relapsed CLL

According to Dr. Brown, patients with relapsed CLL can be divided into a number of categories. The first comprises patients with disease relapse after minimal therapy (a group she essentially thinks of as frontline patients). A second group includes patients with disease relapse after effective chemoimmunotherapy. Although most of the data with ibrutinib, acalabrutinib, zanubrutinib, and venetoclax/rituximab pertain to this group, clinicians are

seeing fewer and fewer of these patients, she noted. The final group involves patients experiencing disease relapse after prior targeted therapy, including those exposed to BTK inhibitors who had to discontinue due to adverse events, those who experienced disease progression during therapy, those with disease relapse after venetoclax (or PI3K inhibitors), and those experiencing disease relapse after treatment with BTK and BCL2 inhibitors.

"For a patient with disease progression on a BTK inhibitor, the only prospective data are with venetoclax, and I do usually add an antibody," she said. "If patients had time-limited venetoclax plus an anti-CD20 antibody, they can probably be re-treated if they had a durable remission or switch to a BTK inhibitor."

Final analysis of the RESONATE trial of ibrutinib versus ofatumumab in patients with CLL treated with 3 prior regimens showed a median PFS of 44 months in the ibrutinib arm.⁶ Patients with *TP53* mutation or 17p deletions did have a shorter PFS, but patients with 11q deletions did not.

The ASCEND trial looked at acalabrutinib in the relapsed setting and compared it with investigator's choice of idelalisib + rituximab or bendamustine + rituximab.⁷ This study, which included patients with high-risk features, found that acalabrutinib prolonged PFS in all groups, including those with high-risk features such as del(17p)/*TP53* mutations and unmutated *IGHV*, confirming acalabrutinib as an effective treatment option for relapsed CLL.

The ELEVATE-RR trial comparing acalabrutinib versus ibrutinib in patients with relapsed/refractory CLL with 17p or 11q deletions showed no difference in efficacy between the 2 BTK inhibitors (hazard ratio, 1.0). However, secondary endpoints revealed a lower incidence of toxicities with acalabrutinib, including atrial fibrillation, hypertension, low-grade bleeding, diarrhea, and arthralgia events.⁸

The ALPINE trial compared zanubrutinib with ibrutinib in an "average-risk" relapsed/refractory population, as the study had no criteria for high-risk disease (ClinicalTrials.gov identifier: NCT03734016). With a primary endpoint of overall response rate (ORR), zanubrutinib led to an ORR of 78%, compared with 62% with ibrutinib.

"Of note, the 17p patients had a much higher overall response to zanubrutinib, at 83% versus 54% with ibrutinib," said Dr. Brown. "Most intriguingly in this study, with a short 12-month follow-up, there was actually a 10% improvement in PFS for zanubrutinib compared with ibrutinib." However, she warned against comparing these trial data with data from ELEVATE-RR, as the patient populations are significantly different, and further follow-up of the ALPINE trial is needed.

"I think we can say that both next-generation BTK inhibitors in head-to-head trials have shown similar efficacy and improved tolerability compared with ibrutinib," she

said. “In my personal practice, I have essentially switched to second-generation BTK inhibitors as my first choice.”

In the MURANO trial, treatment with fixed-duration venetoclax and rituximab led to a PFS benefit as well as an overall survival benefit compared with bendamustine/rituximab in patients with relapsed/refractory disease (NCT02005471). The 5-year study follow-up has confirmed that this benefit was sustained, and no new safety signals have been identified. Undetectable MRD at the end of treatment was also found to be associated with improved PFS in these patients.⁹

When deciding whether to start patients with CLL on a BTK inhibitor or venetoclax in the frontline or relapsed setting, Dr. Brown advises keeping several factors in mind. Factors favoring a BTK inhibitor include longer follow-up data (with ibrutinib), better toxicity profile of next-generation BTK inhibitors, the intense early monitoring needed with venetoclax, and more prospective data with venetoclax after prior therapy with BTK inhibitors. Factors favoring venetoclax include high CR and undetectable MRD rates, fewer long-term side effects, the fact that it is a limited-time therapy, patient preference, lower cost, and the potential for re-treatment.

“This generally leads to a lengthy discussion between the doctor and the patient about the best option,” she said. “We really need more data in that setting.”

For treating relapse after prior therapy, the prospective data for venetoclax in patients who experience disease progression after ibrutinib show lower CR rates than those seen in patients naive to BTK inhibitors.¹⁰ However, BTK inhibitor therapy has been shown to be effective in patients with CLL resistant to venetoclax.¹¹

Combination Therapies

A lower level of residual disease is generally associated with a longer time to disease progression.¹²

“The idea of combinations and the goal of undetectable MRD is that the more you push down the disease burden, the more you’re going to prolong the [time to] relapse,” Dr. Brown said. “If you push it down far enough, maybe it can result in a very, very late relapse or even cure.”

According to Dr. Brown, great interest has been shown in combining BTK and BCL2 inhibitors. In the phase II CLARITY study of ibrutinib and venetoclax in patients with “reasonably” high-risk relapsed/refractory CLL, patients on this combination demonstrated a progressive improvement in undetectable MRD in peripheral

blood and bone marrow over time.¹³ “MRD results kept improving up to about month 26, but adding a third year didn’t really help more,” she noted. “This suggests that, in the relapsed setting, 2 years [of treatment] may result in a plateau in the achievement of undetectable MRD.” Patients on this study also had a 36-month PFS rate of 96%. “This is really quite remarkable,” she added.

In the CAPTIVATE trial, which assessed both MRD-guided discontinuation and fixed-duration therapy with the combination of ibrutinib and venetoclax in patients with treatment-naïve CLL or SLL, the ORR was 96% across the different cohorts, with the CR rate at about 55% (ClinicalTrials.gov identifier: NCT02910583). Undetectable MRD was 77% in peripheral blood and 60% in bone marrow. “This is notable because it’s not very different from venetoclax/obinutuzumab, which had a 75% rate of undetectable MRD in peripheral blood and 57% in bone marrow,” said Dr. Brown. “PFS also looked quite good at 2 years, at 96%.”

Compared with CAPTIVATE, the GLOW trial of ibrutinib and venetoclax showed a significantly higher rate of adverse events, although the study population was older and had a higher disease burden.¹⁴

Research into 3-drug combinations with BTK inhibitors has also shown promise. The 3-year follow-up from a phase II study of combination therapy with obinutuzumab/ibrutinib/venetoclax in CLL showed a PFS of 95%.¹⁵

Looking Forward

Patients who experience disease progression after a BTK and BCL2 inhibitor constitute a new unmet need, for which clinical trials are ongoing. According to Dr. Brown, the most promising options right now include noncovalent BTK inhibitor pirtobrutinib and CAR T-cell therapy, both of which are being evaluated in ongoing clinical trials.

Currently, further investigation is being conducted around a variety of combination therapies including targeted agents, particularly of BTK and BCL2 inhibitors with or without anti-CD20 antibodies.

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