CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Use of Zanubrutinib in Chronic Lymphocytic Leukemia

Danielle M. Brander, MD
Assistant Professor of Medicine
Division of Hematologic Malignancies and Cellular Therapy
Duke Cancer Institute
Durham, North Carolina

H&O What makes the various Bruton tyrosine kinase (BTK) inhibitors different from one another?

DB A variety of BTK inhibitors have been approved for use in the treatment of hematologic malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). The agents that are furthest in development, with approved indications, are the covalent, or irreversible, BTK inhibitors. These include ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene). Noncovalent, or reversible, BTK inhibitors are also being developed and are in various stages of clinical trials.

Ibrutinib is considered a first-generation irreversible BTK inhibitor, and acalabrutinib and zanubrutinib are considered second-generation irreversible BTK inhibitors. Acalabrutinib and zanubrutinib are more selective than ibrutinib for BTK, with fewer off-target kinase effects. Other differences include those in administration and in interactions with other medications. We cannot directly evaluate acalabrutinib and zanubrutinib against each other in terms of side effects and tolerability because they have not been compared in head-to-head, randomized trials. However, 2 different randomized trials have looked at acalabrutinib vs ibrutinib and at zanubrutinib vs ibrutinib in patients with relapsed or refractory CLL.

Acalabrutinib has US Food and Drug Administration (FDA) approval in CLL/SLL and is also indicated in MCL under accelerated approval. Zanubrutinib is approved in WM, with accelerated approval for MCL and MZL. Although it has not been approved for use in CLL/SLL, the National Comprehensive Cancer Network guidelines include zanubrutinib under preferred therapy for patients with CLL/SLL.

H&O Could you describe the randomized studies of acalabrutinib and zanubrutinib in patients with previously treated CLL?

DB ELEVATE-R/R was a phase 3 randomized study in which 533 patients with relapsed or refractory CLL or SLL were assigned to acalabrutinib at 100 mg twice a day or ibrutinib at 420 mg once daily continuously until progression or discontinuation for other reasons. The primary outcome was noninferior progression-free survival (PFS) as determined by an independent review committee. Patients were required to have high-risk CLL as defined by the presence of a 17p deletion (del[17p]), an 11q deletion (del[11q]), or both. PFS was 38.4 months with both treatments. Acalabrutinib was noninferior to ibrutinib in efficacy and was associated with fewer toxicities, including those of special interest for BTK inhibitors, such as atrial fibrillation/atrial flutter and other atrial arrhythmias. Overall, fewer patients discontinued acalabrutinib than ibrutinib because of adverse events (14.7% vs 21.3%, respectively). Byrd and colleagues published the results of this trial in the *Journal of Clinical Oncology* in 2021.

ALPINE is a similar randomized phase 3 study comparing zanubrutinib vs ibrutinib in 652 patients with relapsed or refractory CLL or SLL. The primary endpoint is noninferiority of zanubrutinib vs ibrutinib according to overall response rate (ORR) as determined by investigator assessment. Unlike the patients in ELEVATE-RR, those in ALPINE are not required to have high-risk

CLL (del[11q] or del[17p]). Dr Peter Hillmen presented interim results from the first 415 patients enrolled in this trial at the 2021 annual meeting of the European Hematology Association (EHA).

Both trials have found the second-generation BTK inhibitor to be noninferior to ibrutinib, with fewer adverse events (eg, bleeding and infection) and fewer discontinuations owing to toxicities. The ALPINE trial did find a slightly higher rate of neutropenia with zanubrutinib than with ibrutinib, at 28.4% vs 21.7%, but the rate of grade 3 infections was lower with zanubrutinib than with ibrutinib, at 12.7% vs 17.9%.

These studies both concluded that second-generation BTK inhibitors reduce the risk for BTK inhibitor adverse events of special interest, which include atrial fibrillation and hypertension. For example, the rate of all-grade atrial fibrillation or flutter in ELEVATE-R/R was 9.4% with acalabrutinib vs 16.0% with ibrutinib. In ALPINE, the rate of atrial fibrillation or flutter also was significantly lower with zanubrutinib than with ibrutinib, at 2.5% vs 10.1%, respectively.

Finally, as already mentioned, discontinuation rates owing to adverse events were much lower with the second-generation inhibitors than with ibrutinib. For example, the discontinuation rate owing to adverse events in ELEVATE-R/R was 14.7% in the acalabrutinib group and 21.3% in the ibrutinib group, and in ALPINE it was 7.8% in the zanubrutinib group and 13.0% in the ibrutinib group. This lower discontinuation rate is especially important because BTK inhibitors are given every day or continuously until patients experience intolerable adverse events or disease progression.

H&O Could you discuss the ORR primary endpoint in ALPINE, and how the results changed when they included partial response with lymphocytosis (PR-L)?

DB The primary endpoint in ALPINE was ORR. At a median follow-up of 15 months, the ORR was significantly higher in the zanubrutinib arm than in the ibrutinib arm, at 78.3% vs 62.5%, respectively (*P*=.0006). When the analysis included patients with PR-L, the response rates increased to 88.4% vs 81.3%, respectively. It makes sense that the response rate would improve with the inclusion of patients with PR-L because lymphocytosis is expected with BTK inhibitors even if other clear evidence of a response is present. For example, BTK and other pathway inhibitors are thought to "marginalize" or redistribute the CLL lymphocytes from the lymph nodes and/or spleen to the blood. With time, these lymphocytes usually are cleared from the body, and the lymphocyte count decreases. The speed of that decrease varies among patients, and it can take months or even years for the lymphocyte count to normalize. The lymphocyte count never completely normalizes in some patients, but they are still experiencing a response and benefiting from treatment. The most recent consensus guidelines of the International Workshop on Chronic Lymphocytic Leukemia recognize that lymphocytosis due to redistribution of the CLL lymphocytes can occur and is not progression, given the mechanism of action of BTK and other inhibitors. PR-L is now appropriately being included as a response in many trials of patients with CLL/SLL. The important point is for patients to stay on the medication for as long as they can benefit, regardless of any residual lymphocytosis in the peripheral blood.

H&O What other studies have looked at the use of zanubrutinib in CLL?

DB The randomized phase 3 SEQUOIA study included patients with previously untreated CLL/SLL. Because patients with del(17p) do not respond well to chemotherapy, SEQUOIA had a separate cohort for these patients to receive zanubrutinib monotherapy rather than including them in the randomized study.

In SEQUOIA, 479 patients without del(17)(p13.1) were randomly assigned to either continuous zanubrutinib (n=241) or bendamustine/rituximab (n=238) for up to 6 cycles as frontline therapy. The primary endpoint was PFS in the intention-to-treat population as determined by an independent review committee. At a median follow-up of 26.2 months, PFS—although not reached in either group—was significantly better in the zanubrutinib group than in the bendamustine/rituximab group. The estimated 24-month PFS rate was 85.5% in the patients treated with zanubrutinib vs 69.5% in those treated with bendamustine/rituximab. Zanubrutinib also was well tolerated, with adverse events similar to those seen in previous studies.

Using bendamustine/rituximab as the comparison chemoimmunotherapy in SEQUOIA was notable because other CLL/SLL frontline studies compared BTK inhibitors with less-intensive chemotherapy regimens, such as those based on chlorambucil or chlorambucil combined with obinutuzumab (Gazyva, Genentech). Bendamustine/rituximab was a standard treatment for older or unfit patients with CLL, so it is helpful to use it as a control treatment.

H&O Can you discuss the dosing schedules for zanubrutinib?

DB In the randomized phase 3 studies of patients with CLL/SLL that we just discussed, patients received 160 mg of zanubrutinib twice daily. For the currently approved indications for zanubrutinib—relapsed or refractory MCL or MZL, and WM—dosing is listed as 160 mg twice a day, with 320 mg once daily as an alternative. The alternative

stems from early-phase studies that included some patients treated with once-daily dosing, although those numbers were limited. The conclusion from the analysis and modeling of these studies by Ou and colleagues was that the BTK target occupancy and trough levels were not significantly different. In a small study by Shadman and colleagues of patients with BTK inhibitor intolerance treated with the alternative dosing of zanubrutinib, a possible difference in efficacy but also in toxicity of the dosing was noted, as pointed out by one author. However, the number of patients was small and the follow-up was short, at less than 1 year, as pointed out in a commentary by D'Sa. Postmarketing or real-world studies would likely be helpful in determining if efficacy or side effects are affected by the difference in dosing, but such studies would take time.

H&O When are dose reductions possible?

DB Dose reduction is needed for some patients undergoing BTK inhibitor treatments. For each BTK inhibitor, dosing guidelines in the prescribing information indicate when to interrupt treatments and when to reduce the total daily dose of medication. In many cases, even if an interruption is necessary because of toxicity, resumption of treatment at the full dose is recommended in the case of a first interruption. Because the dosing is BTK-inhibitor specific and depends on the severity or grade of the toxicity, prescribers should refer to the dosing guidelines for the specific medication.

It should be noted that dose reductions for side effects or toxicities are different from dose reductions for drug-drug interactions, in which other medications or supplements that the patient is taking concurrently can affect dosing of the BTK inhibitor. It is important for all patients to maintain an updated list of their current medications, so that possible interactions can be identified when they meet with their oncologist and pharmacist and a plan can be put in place. Sometimes a medication that might interact with the BTK inhibitor must be changed to an alternative and sometimes the starting dose of the BTK inhibitor must be changed; the approach is patient-specific.

We do not have complete data regarding the long-term effects of BTK inhibitor dose reductions or interruptions, and the available data that have been published are inconsistent. Some studies suggest that interruptions or reductions lead to inferior responses or PFS, whereas other studies suggest that when BTK inhibitors are put on hold for certain reasons—such as before surgery because of the risk for bleeding——outcomes are unlikely to be affected. It is difficult to make accurate determinations based on observations because patients who require a dose reduction or interruption may be more likely have comorbidities, or other confounding factors may be present.

H&O What are the options for patients who must stop a BTK inhibitor because of nontolerance?

DB In short, it depends on the reason why the BTK inhibitor must be stopped. Some rare but serious side effects, such as major bleeding and hemorrhage, are less common with a second-generation BTK inhibitor than with ibrutinib, but side effects are still a risk with any BTK inhibitor. Therefore, if a patient on ibrutinib has had a major bleeding event without any other clear cause, for example, it would be difficult to choose another BTK inhibitor (eg, acalabrutinib or zanubrutinib) when the risk for bleeding is still present if other treatment options are available (eg, venetoclax; Venclexta, AbbVie/Genentech) that do not carry an increased risk for bleeding. However, for many other adverse events, switching the BTK inhibitor may be a good option.

Two notable trials in CLL specifically included a population of patients who could not tolerate one BTK inhibitor and switched to a second-generation BTK inhibitor. In an early study by Awan and colleagues, 33 patients with ibrutinib intolerance received treatment with acalabrutinib. Most of these patients, 64%, did not experience a recurrence of the adverse event that led to ibrutinib cessation. If the adverse event did recur, it appeared to be at a lower grade.

Recently, results were published of a phase 2 study by Shadman and colleagues of zanubrutinib treatment for 67 patients with B-cell malignancies (CLL/SLL, MCL, or MZL) who had previously been intolerant of a BTK inhibitor. Of these patients, 57 had been intolerant of ibrutinib and 10 had been intolerant of acalabrutinib or acalabrutinib plus ibrutinib. In most of these patients, the toxicity that caused them to stop the prior BTK inhibitor did not recur while they were on zanubrutinib, although the follow-up was relatively short and the duration of zanubrutinib treatment was also relatively short.

As discussed, the head-to-head CLL studies ELEVATE-R/R and ALPINE indicate that second-generation BTK inhibitors are better tolerated than ibrutinib. A similar finding was reported in the ASPEN study by Tam and colleagues, which compared zanubrutinib vs ibrutinib for WM. Tolerability in these trials, however, in which patients were previously unexposed to BTK inhibition, cannot be compared with tolerability in the trials in which the entire population was already intolerant of a prior inhibitor.

H&O What are the most important studies of zanubrutinib in combination with other agents for patients with CLL/SLL?

DB Numerous studies have looked at BTK inhibitors in combination with other agents—including the anti-apoptotic BCL2 inhibitor venetoclax—in an effort to deepen

responses in patients with CLL or SLL. When this combination is used, a few cycles of the BTK inhibitor are often initiated without venetoclax, which lowers the burden of CLL and therefore lessens the risk for tumor lysis syndrome, which can be a concern with venetoclax. Many of these combinations are taken for a certain number of months or cycles, whereas BTK inhibitor monotherapy is taken continuously unless progression or intolerance occurs.

The phase 2 BOVen trial looked at the combination of zanubrutinib, the anti-CD20 antibody obinutuzumab, and venetoclax as frontline treatment in CLL/SLL. Treatment, which began with a lead-in of 2 cycles of zanubrutinib and obinutuzumab to reduce disease bulk, was administered in 28-day cycles and was discontinued after 8 to 24 cycles if patients met the criteria for undetectable measurable residual disease (MRD) in the blood and bone marrow. The primary endpoint of the study was achievement of undetectable MRD, with the authors assessing whether earlier cessation of treatment affected outcomes. This is important because if BTK inhibitors are given as monotherapy or with an anti-CD20 antibody, they are typically given until progression or intolerance, whereas the standard frontline combination of obinutuzumab and venetoclax is given for 12 cycles of venetoclax regardless of MRD status.

In results that Soumerai and colleagues published in 2021 in *Lancet Oncology*, 33 of 37 patients (89%) in BOVen had undetectable MRD in both bone marrow and blood, meeting the prespecified criteria for cessation of treatment, after a median of 10 cycles. With ongoing post-treatment surveillance, 31 of the 33 patients (94%) still had undetectable MRD at a median of 15.8 months. The most common adverse events were thrombocytopenia, fatigue, neutropenia, and bruising, and 18% of patients experienced grade 3 or worse neutropenia. These were encouraging results, although it has not yet been established that undetectable MRD is an acceptable or necessary reason to stop treatment in CLL. In addition, combinations of a BTK inhibitor plus venetoclax are unlikely to be the best choice for all patients, especially those who are older or less fit, because combinations of agents have the potential to increase toxicities. Therefore, the big questions are these: which patients are most likely to benefit from combination treatment, and when should treatment with these novel agents be stopped?

BTK inhibitors, whether used alone or in combination with other agents, have dramatically changed the treatment landscape for patients with CLL and SLL. However, we still have a lot to learn if we are to optimize treatment for every patient who receives a BTK inhibitor. For example, how do certain side effects—such as risk for hypertension over time—affect a patient's health and other comorbidities, even if they do not lead to treatment discontinuation? Finally, we look forward to learning more about the noncovalent BTK inhibitors that are being studied in ongoing clinical trials but are not yet approved. These agents seem very promising, with favorable toxicity profiles and meaningful sustained responses even in patients whose disease has become resistant to the covalent BTK inhibitors.

Disclosures

Dr Brander has served as a consultant or advisor to AbbVie, Genentech, Pharmacyclics, Pfizer, TG Therapeutics, and Verastem Oncology; has received institutional funding from AbbVie, ArQule, Ascentage Pharma Group, AstraZeneca, BeiGene, DTRM Biopharma, Genentech, Juno/Celgene/BMS, Loxo Oncology, MEI Pharma, Novartis, Pharmacyclics, and TG Therapeutics; and has served as a National Comprehensive Cancer Network panel member.

Suggested Readings

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