ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Noncovalent BTK Inhibitors in B-Cell Lymphoma

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H&O What are the limitations of standard (covalent) BTK inhibitors in B-cell malignancies?

CC The 2 major limitations of covalent Bruton's tyrosine kinase (BTK) inhibitors are intolerance and resistance. The most common reason for discontinuation of these drugs in the frontline setting is adverse events, which occur in a significant proportion of patients who receive covalent BTK inhibitors. These side effects can range from bothersome and affecting quality of life to severe and life-threatening. Recent updates from the RESONATE-2 trial demonstrated that 24% of patients discontinued ibrutinib (Imbruvica, Pharmacyclics/Janssen) owing to adverse events. Looking at real-world practices, Mato and colleagues, for example, found (in a study published in *Haematologica* in 2018) that a significant proportion of patients with chronic lymphocytic leukemia (CLL) given ibrutinib eventually discontinued therapy, most commonly owing to side effects, which is a major barrier to its long-term use.

The good news is that we now have 2 second-generation covalent BTK inhibitors with improved tolerability compared with ibrutinib. These are acalabrutinib (Calquence, AstraZeneca), which is approved by the US Food and Drug Administration (FDA) for the treatment of mantle cell lymphoma (MCL) and CLL or small lymphocytic lymphoma (SLL), and zanubrutinib (Brukinsa, BeiGene), which is FDA-approved for the treatment of marginal zone lymphoma, Waldenström macroglobulinemia (WM), MCL, and (as of January 19 of this year) CLL or SLL. Nonetheless, issues with tolerability may still limit the long-term use of these drugs and lead to early discontinuation.

The second limitation of covalent BTK inhibitors is resistance. The most common mechanism of resistance is through the acquisition of C481 mutations. All covalent BTK inhibitors are very similar with respect to their mechanism of action. They require a wild-type C481 residue, in which they form their covalent bond and have their optimal activity. Thus, a patient's resistance is oftentimes through the acquisition of a mutation at that residue, to where the drug can no longer form its covalent bond and have activity to prevent cancer growth.

Unfortunately, if someone progresses on ibrutinib, for example, we cannot switch that person to acalabrutinib or zanubrutinib because all the drugs share the same mechanism of resistance. If someone has intolerance to ibrutinib, however, acalabrutinib or zanubrutinib may be an effective approach.

H&O What is the pharmacologic rationale for pursuing noncovalent BTK inhibitors in B-cell cancers?

CC Three effective covalent inhibitors are available. All of these have the same binding mechanism, which requires wild-type C481. The pharmacologic rationale for developing a noncovalent BTK inhibitor is to have a unique mechanism of binding the BTK protein that is not dependent on the presence or absence of this resistance

mutation. Therefore, one can have a drug that effectively inhibits BTK, despite the acquisition of a resistance mutation to the traditional covalent class of BTK inhibitor.

The other potential benefit noncovalent inhibitors may have over covalent inhibitors is that their inhibition of BTK is not affected by rapid cell turnover. In more aggressive B-cell malignancies, new proteins may be generated that may not be effectively inhibited by an irreversible (covalent) inhibitor. The reversible or noncovalent BTK inhibitor pirtobrutinib, also known as LOXO-305, should not be affected in these scenarios of rapid B-cell turnover. This mechanism may be important in the more rapidly proliferative B-cell malignancies, such as Richter transformation, which is one of the newer ways that the drug had been studied.

Outcomes for patients with Richter transformation—when CLL undergoes transformation to a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL)—are profoundly poor, with overall survival of less than a year. The BRUIN phase 1/2 study has shown efficacy in this group, but follow-up was short. Dr Nirav Shah presented updated data by Wierda and colleagues from the Richter's cohort of BRUIN at the 2022 American Society of Hematology (ASH) annual meeting that demonstrated an overall response rate (ORR) of 52%, with median PFS of 3.7 months and median OS of 13.1 months. To have a drug that not only works but also has improved tolerability and minimizes potential complications associated with chemoimmunotherapy is very exciting.

H&O What is the design of the phase 1/2 BRUIN study?

CC The BRUIN phase 1/2 trial is examining the use of pirtobrutinib monotherapy in individuals with B-cell malignancies (NCT03740529). The phase 1 portion followed a standard 3+3 dose-escalation design in 28-day cycles, with a few unique aspects. Dose level expansion was permitted once a dose was cleared with respect to safety, and intrapatient dose escalation was also permitted. For example, if patients started at the lowest dose of 25 mg daily, they were allowed to increase their dose once the subsequent dose level had been deemed safe.

Intrapatient dose escalation is particularly relevant because the goal is to be able to obtain effective inhibition of the target, and that was seen more effectively at doses higher than 25 mg daily. Ultimately, 200 mg daily was determined to be the recommended phase 2 dose. It is interesting to note that a maximum tolerated dose was not reached—that dose was selected in the event of potential added toxicity for future combination trials—and patients were treated safely with up to 300 mg daily.

The phase 2 portion of BRUIN continued to enroll patients to one of 7 cohorts depending on tumor histology and prior treatment history to provide a better analysis of efficacy. At ASH in 2021, we presented safety data on 618 patients enrolled in the study, of whom 96% were treated at the recommended phase 2 dose of 200 mg daily or higher. In total, the largest patient population of BRUIN had CLL/SLL followed by MCL. The study also included patients with other B-cell malignancies, such as WM, follicular lymphomas, prolymphocytic leukemia, DLBCL, and Richter transformation.

H&O What are some recent findings from the phase 1/2 BRUIN study?

CC The most recent CLL data from BRUIN, which Dr Anthony Mato presented at the 2022 ASH annual meeting, focused specifically on a subset of 247 patients with CLL who had been failed by a prior BTK inhibitor. When we look at the waterfall plot, which measures how much lymph node reduction patients had upon exposure to pirtobrutinib, nearly all patients had some degree of lymph node reduction.

When applying the International Workshop on Chronic Lymphocytic Leukemia criteria, the overall response rate was 82%, wherein the majority of patients who responded achieved partial remission or partial remission with lymphocytosis. The ORR notably has increased with this longer period of follow-up. Responses were seen regardless of what prior therapies patients had and whether they had discontinued their prior BTK inhibitor owing to intolerance, which applied to 23% of cases, or prior progressive disease, which applied to 77% of cases. A substantial number of patients had prior venetoclax, and responses were also seen in that subgroup. The drug appears to work regardless of these clinical factors and regardless of cytogenetic risk factors, such as the presence of deletion 17p, the presence of the BTK mutation, and so on.

Median PFS was 19.6 months for all patients with prior BTK inhibition (median, 3 prior therapies) and 16.8 months for the subgroup of patients with prior BTK inhibition and BCL2 inhibition (primarily venetoclax; median, 5 prior therapies). Follow-up ranged from 18.2 to 19.4 months for these groups.

H&O What are some of the adverse events in the phase 1/2 BRUIN study?

CC One of the most favorable aspects of pirtobrutinib is its toxicity profile in comparison to the covalent BTK inhibitors. Depending on the length of follow-up, between 10% to 25% of patients who received a covalent BTK inhibitor discontinue the drug owing to side

effects. With extended follow-up from the BRUIN trial, we see that the safety profile remains very favorable for pirtobrutinib, with only 2.6% of patients discontinuing the drug owing to treatment-related adverse events. The side effects that occurred were mostly low-grade and manageable to the point where the patient was able to stay on the drug.

Few incidences of atrial fibrillation occurred, which is encouraging because this is a common side effect with the covalent BTK inhibitors. At least a few of the atrial fibrillation cases were in patients who already had a history of the condition and consequently were not clearly drug-related. Across side effects, few grade 3 or higher events occurred. Neutropenia, which occurred in 20% of patients (deemed treatment-related in 11.5%), was the only grade 3 adverse event that was reported in more than 10% of patients. Again, the most common side effects in the phase 1/2 BRUIN study are lower-grade events.

> The phase 1/2 BRUIN trial demonstrated a promising progression-free survival of 16.8 months for pirtobrutinib in patients who had been failed by both a covalent BTK inhibitor and venetoclax.

H&O What are the mechanisms of resistance to noncovalent BTK inhibitors?

CC The mechanisms of resistance were recently elucidated by Wang and colleagues from the Memorial Sloan Kettering Cancer Center, which enrolled the largest number of CLL/SLL patients in the BRUIN trial. They were able to bank pretreatment specimens and post-progression specimens for genomic analysis. Of 55 patients, 13 progressed, of whom 9 had pretreatment and post-progression samples, which enabled comparison of mutations that those patients had prior to exposure to pirtobrutinib and then at time of progression. The study demonstrated that the most common mechanism of resistance to pirtobrutinib is through acquisition of new (non-C481) BTK mutations.

One concern based on these findings is whether the new mutations would confer resistance even to the covalent BTK inhibitors. Results of binding tests suggest there may be some cross-resistance. However, it is difficult to conclude how to sequence our therapies based on these 9 patients, because they all had prior treatment with ibrutinib, and they had many lines of prior therapy. With subsequent lines of therapy, patients with CLL have significant genomic instability and are more prone to development of mutations. What occurred in these refractory patients may not necessarily be reflected if pirtobrutinib was used in earlier lines of therapy.

H&O How are the unmet clinical needs for patients with B-cell malignancies being addressed?

CC An overarching goal should be to have effective drugs that treat the disease while minimizing unnecessary toxicity so patients can maintain their quality of life. For a subset of patients, disease progression occurs despite our 2 most effective classes of drugs, covalent BTK inhibitors and the BCL2 inhibitor venetoclax. Unfortunately, these patients have limited options outside of investigational approaches, pirtobrutinib being one.

Other promising approaches include chimeric antigen receptor T-cell therapies; other noncovalent inhibitors, such as nemtabrutinib (MK-1026, formerly known as ARQ 531); bispecific antibodies; and BTK degraders. The most widely studied chimeric antigen receptor T-cell therapy in CLL/SLL is lisocabtagene maraleucel (Breyanzi, Bristol Myers Squibb), though it does not yet have FDA approval for this use. Because not everyone has access to an academic center or to clinical trials, having something available for patients in the community who are unable to access these novel therapies, especially in the third-line or even second-line settings, would be helpful. Taking venetoclax, for instance, which necessitates a 5-week ramp-up and frequent lab checks, can be challenging for patients who lack easy access to a cancer center. Although there have been major improvements, a lot of work is needed to optimize CLL patient outcomes.

H&O How will the results of phase 3 studies of pirtobrutinib that are in progress add to the BRUIN study's results?

CC Several phase 3 trials are evaluating pirtobrutinib. The BRUIN CLL-314 study is comparing pirtobrutinib head-to-head with ibrutinib in the CLL/SLL setting; the study is including both frontline and relapsed/refractory patients (NCT05254743). In the BRUIN-MCL-321 study, patients with MCL are being randomly assigned to

either pirtobrutinib or investigator's choice of a covalent BTK inhibitor: ibrutinib, acalabrutinib, or zanubrutinib (NCT04662255). The BRUIN CLL-321 study is comparing LOXO-305 as a monotherapy with an investigator-choice option of either idelalisib (Zydelig, Gilead)/rituximab or bendamustine/rituximab (NCT04666038). BRUIN CLL-313 is comparing pirtobrutinib with bendamustine/rituximab (NCT05023980). I suspect that this trial will primarily enroll patients outside of the United States, in places where bendamustine/rituximab is still considered a standard of care. Finally, BRUIN CLL-322 is evaluating pirtobrutinib plus venetoclax and rituximab compared with venetoclax and rituximab in previously treated patients with CLL/SLL (NCT04965493).

The BRUIN CLL-321 enrollment criteria require that patients have had exposure to at least a covalent BTK inhibitor; prior venetoclax is not required, although it is likely that some patients may also have prior venetoclax exposure. In the real-world setting, phosphoinositide 3-kinase inhibitors, such as idelalisib, are used less often. Phosphoinositide 3-kinase inhibitors are still considered after the use of both covalent BTK inhibitors and venetoclax, however, or occasionally prior to venetoclax if access is limited. However, few data exist on their efficacy in the post-BTK inhibitor setting. The phase 1/2 BRUIN trial demonstrated a promising progression-free survival of 16.8 months for pirtobrutinib in patients who had been failed by both a covalent BTK inhibitor and venetoclax. If positive, the BRUIN CLL-321 trial could potentially give pirtobrutinib enough data to support its regulatory approval for patients following therapy with a covalent BTK inhibitor. However, pirtobrutinib could fill the biggest unmet need in patients in the third-line setting whose disease has progressed on venetoclax.

Disclosure

Dr Coombs has served on the speakers' bureau of AbbVie and Genentech, steering committees for AbbVie and Loxo Oncology, and independent review committees for AbbVie and Octapharma; has consulted for/received honoraria from AbbVie, AstraZeneca, BeiGene, Genentech, Loxo Oncology, MEI Pharma, Novartis, and TG Therapeutics; is a CTI Biopharma and Bluebird Bio shareholder; and has received research funding (paid to institution) from AbbVie and Loxo Oncology.

Suggested Readings

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