CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Managing CLL That Has Progressed After BTK Inhibition

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H&O When patients with chronic lymphocytic leukemia (CLL) progress while on Bruton tyrosine kinase (BTK) inhibitor therapy, what is your next therapy of choice?

LR Because patients can receive BTK inhibitors in a few different clinical scenarios, the answer depends in part on prior therapies. In cases where patients with CLL have progressed on a BTK inhibitor and have not previously received another novel agent, I recommend treatment with a regimen that includes the B-cell lymphoma/leukemia 2 (BCL2) inhibitor venetoclax (Venclexta, AbbVie/Genentech). The US Food and Drug Administration (FDA) has approved the use of venetoclax alone as continuous therapy and in combination with rituximab for a fixed duration of 2 years. There are prospective and retrospective data supporting the use of venetoclax after BTK inhibitor therapy. A phase 2 study of venetoclax monotherapy by Jones and colleagues that was published in 2018 examined patients who had previously received ibrutinib and demonstrated a median progression-free survival (PFS) of approximately 2 years.[1] Notably, the MURANO study by Seymour and colleagues, which served as the basis for FDA approval of the combination of venetoclax and rituximab as a 2-year fixed duration treatment in the relapsed/refractory setting, included relatively few patients who had a prior BTK inhibitor (n=5).[2,3] Retrospective studies have looked at the efficacy of venetoclax following BTK inhibition and have demonstrated efficacy in this setting. Some studies have found that prior BTK inhibitor use does not affect the efficacy of venetoclax,[4-6] whereas other studies have found that prior progression on a B-cell receptor inhibitor adversely affects the duration of response.

The next treatment option for patients who have already received venetoclax depends on the reason for discontinuation. In patients who completed a fixed duration of therapy and were responding at the time that venetoclax was discontinued, retreatment with venetoclax is an option. Patients who have progressed on venetoclax and BTK inhibitors are considered "double progressors" and have limited standard-of-care options. For these patients, enrollment in clinical trials should be strongly considered.

If a patient with CLL has progressed on a covalent BTK inhibitor, such as ibrutinib (Imbruvica, Pharmacyclics/Janssen), zanubrutinib (Brukinsa, BeiGene), or acalabrutinib (Calquence, AstraZeneca), there is no role for a second covalent BTK inhibitor—the mechanisms of resistance are similar for all these agents.

H&O How do you determine when to initiate the next line of therapy?

LR When a patient is progressing on a BTK inhibitor, discontinuation of the BTK inhibitor can lead to a disease flare that is characterized by increasingly symptomatic adenopathy or rapidly worsening cytopenias. Given this, it is often appropriate to continue BTK inhibition until the next line of therapy is initiated. Sometimes, BTK inhibitors and the next line of therapy can even overlap to avoid the disease flare that can occur when BTK inhibitors are discontinued in a patient who is experiencing progression.

When to discontinue the BTK inhibitor depends on the pace of a patient's disease progression. The International Workshop on Chronic Lymphocytic Leukemia

criteria[7] can be used to define disease progression, although disease progression can occasionally be subtle. Transient small increases in the size of lymph nodes while a patient is on BTK inhibitors do not always indicate progression, and patients with these fluctuations can be safely monitored to establish whether the changes are reactive vs representative of progression. If the CLL is progressing slowly, we can closely monitor the patient while planning for the next line of therapy. For example, if a patient's only signs of progression are a slowly increasing white blood cell count or slowly progressive adenopathy, we can monitor that progression for a period while discussing the anticipated need to change therapy. However, if the CLL is progressing rapidly and the patient is experiencing symptoms, switching to another therapy becomes more urgent.

The data to support treatment approaches in the third-line setting are limited, and this remains an area of unmet need.

H&O Do you evaluate measurable residual disease (MRD) to detect early relapse?

LR We are learning more and more about the utility of MRD as both a prognostic tool and a decision-making tool in the clinical trial setting. Many ongoing clinical trials are using MRD as an endpoint for therapy, and some trials are even using MRD progression to prompt retreatment. Although the results of these studies are expected to be highly informative, we currently lack data to suggest that acting on MRD-level relapse meaningfully changes outcomes. Because of this, I do not use MRD status to guide decision-making outside the clinical trial setting. However, MRD can be a helpful prognostic tool, especially for patients who are at the end of time-limited venetoclax-based therapy, because MRD status has been shown to predict PFS. Notably, MRD eradication is rare in patients receiving BTK inhibitors, and has limited usefulness in this patient population.

H&O Are there any prognostic markers of significance that you assess before switching therapy?

LR Any time CLL is progressing, I repeat prognostic testing to evaluate for the evolution of cytogenetic or molecular changes in the disease. Specifically, I repeat cytogenetic testing, including fluorescence in situ hybridization testing and karyotyping as well as testing for mutations in genes, including *TP53.* Although evaluation for BTK inhibitor resistance mutations can be informative, it is not strictly necessary because it does not change decision-making with our currently available therapies. If immunoglobulin heavy chain (*IGHV*) mutational status has already been determined, it does not need to be reassessed at the time of progression because it does not change throughout a patient's disease course. Patients who have mutated *TP53* or del(17p) tend to have a shorter duration of response to novel agents, including venetoclax, so patients should be counseled about this if applicable.

H&O What options are available for patients who are double progressors?

LR The data to support treatment approaches in the third-line setting are limited, and this remains an area of unmet need. According to the CLL treatment guidelines from the National Comprehensive Cancer Network (NCCN), phosphoinositide 3-kinase (PI3K) inhibitors can be used in the double-refractory population, but data supporting their use are very limited.[8] Retrospective data published by Mato and colleagues in 2020 found that PI3K inhibitor use after BTK inhibition and venetoclax therapy is associated with a median PFS of only 5 months.[9] The NCCN guidelines also allow for the option of chemoimmunotherapy, including the use of fludarabine, cyclophosphamide, and rituximab; bendamustine and rituximab; and fludarabine, cyclophosphamide, and ofatumumab (Arzerra, Novartis) based on studies showing their activity in relapsed/refractory disease.[10-14] It is worth noting, however, that none of these studies included any patients with prior novel agent exposure and there are no available prospective data to support the use of chemoimmunotherapy following novel agents. Even retrospective data supporting the use of chemoimmunotherapy in patients previously treated with novel agents are limited. A study examining patients previously treated with B-cell receptor inhibitors (none of whom had received venetoclax) demonstrated that the response rate to chemoimmunotherapy was 25%.[15] A study of patients treated with CD20 monoclonal antibody therapy after venetoclax demonstrated a median PFS of 2 months.[9] This is a setting in which clinical trial enrollment is especially important because multiple effective and promising options are emerging, but none of them are available as a standard of care.

The agent with the most data supporting its use in

Table. Selected Ongoing Studies of Novel Agents in CLL

Class or agent	Identifier
Pirtobrutinib	NCT05254743, NCT04666038, NCT04965493
Other noncovalent BTK inhibitors (nemtabrutinib and AS-1763)	NCT05624554, NCT05673460, NCT05602363
BTK degraders (NX-2127, NX-5948, BGB-16673, and BGB-16673)	NCT04830137, NCT05131022, NCT05294731, NCT05006716
Other small-molecule inhibitors (CG-806, KRT-232, ETH-155008, VIP152, MS-553, TL-895, ONO-7018, ABBV-525, PRT1419, and SGR-1505)	NCT03893682, NCT04502394, NCT04840784, NCT04978779, NCT03492125, NCT05272813, NCT02825836, NCT05515406, NCT05618028, NCT05107856, NCT05544019
Novel targeted antibody therapies (cirmtuzumab, JBH492, belimumab, zilovertamab vedotin, PSB202, and GEN3009)	NCT04501939, NCT04240704, NCT05069051, NCT05458297, NCT05003141, NCT04358458
Bispecific antibodies (mosunetuzumab, epcoritamab, GB261, LAVA-051, NVG-111, JNJ-75348780, odronextamab, and plamotamab)	NCT05091424, NCT04623541, NCT04923048, NCT04887259, NCT04763083, NCT04540796, NCT02290951, NCT02924402

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia.

this setting is the noncovalent BTK inhibitor pirtobrutinib (Jaypirca, Lilly), which is currently FDA approved for use in mantle cell lymphoma but not in CLL. The phase 1/2 BRUIN study, which included many patients with double-refractory CLL, showed that pirtobrutinib is effective in this setting.[16] In the absence of other good options or the ability to enroll in clinical trials, off-label use of pirtobrutinib could be considered an option for these patients.

Further studies of pirtobrutinib are ongoing. Other agents that are being investigated in later-line CLL include other noncovalent BTK inhibitors and BTK degraders, other small-molecule inhibitors, novel targeted antibody therapies, and bispecific antibodies (see the Table). Multiple studies examining chimeric antigen receptor (CAR) T cells are also ongoing. Studies examining the use of novel agents in combination with CAR T-cell therapy are also underway, because these combinations may allow for enhanced efficacy for patients with CLL. Another option for selected young patients who have progressed through 2 novel agents is allogeneic stem cell transplant, which is the only known curative strategy for CLL at this point.

Notably, these recommendations are applicable to patients who have progressed on both BTK inhibition and venetoclax. If a patient had prior intolerance to BTK inhibitors and progresses on venetoclax, the patient may be treated with BTK inhibitors again. With the introduction of BTK inhibitor options that have different toxicity profiles, a patient with previous intolerance to BTK inhibition may be able to tolerate a second-generation BTK inhibitor.[17-20] If a patient previously completed a fixed-duration venetoclax regimen and subsequently progresses, retreatment with venetoclax (including consideration for retreatment with fixed-duration venetoclax and obinutuzumab) should be considered.[21]

Disclosures

Dr Roeker has served as a consultant for AbbVie, Ascentage Pharma, AstraZeneca, BeiGene, Janssen, Loxo Oncology, Pharmacyclics, Pfizer, TG Therapeutics; has served as a CME speaker for DAVA Oncology, Curio Science, Medscape, and PeerView; holds minority ownership interest in Abbott Laboratories; has received travel support from Loxo Oncology; and has received research funding (paid to institution) from Adaptive Biotechnologies, AstraZeneca, Genentech, AbbVie, Pfizer, Loxo Oncology, Aptose Biosciences, Dren Bio, and Qilu Puget Sound Biotherapeutics.

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