

CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Optimizing CLL Treatment After Covalent BTK Inhibition



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H&O What is the standard covalent Bruton tyrosine kinase (BTK) inhibitor regimen for chronic lymphocytic leukemia (CLL)?

CC I typically use covalent BTK inhibitors as monotherapy, either acalabrutinib (Calquence, AstraZeneca) or zanubrutinib (Brukinsa, BeiGene). I do not have a strong preference for either one overall, but in some situations, I prefer one over the other. I like to use acalabrutinib if a patient has hypertension that is difficult to control, and I am especially enthusiastic about the use of zanubrutinib in patients with del(17p) or *TP53*-mutated CLL. Although we can add obinutuzumab (Gazyva, Genentech) to acalabrutinib, I rarely do that. Even though it can improve progression-free survival (PFS), it adds a layer of inconvenience.

H&O How often is therapy discontinued because of adverse events or relapsed/refractory disease?

CC Therapy is inevitably discontinued for one reason or another. It is hard to put an exact number on intolerance, but the rate of intolerance in clinical trials is approximately 10% to 15% and goes up with longer follow-up. We also know, by extrapolating from studies that included primarily ibrutinib (Imbruvica, Pharmacyclics), that the rates of discontinuation are higher in the real-world population than in trial populations because trial populations tend to have fewer comorbidities and receive closer monitoring. I do think that acalabrutinib and zanubrutinib are better tolerated than ibrutinib, but patients do not always stay on them. In rare cases, they stop treatment because of profound intolerance. Other patients may stop taking

their medication for financial reasons, because they do not like the idea of continuing to take a pill for their cancer, or because they think they no longer need to remain on medication.

Although progression is inevitable with enough time on a covalent BTK inhibitor, the median follow-up in frontline trials with acalabrutinib and zanubrutinib still has not been met after 6 years. I predict that these covalent BTK inhibitors will work for an extremely long time, as has been seen on 10-year follow-up with frontline ibrutinib, which showed a median PFS of 8.9 years.¹ Although early progression events do happen, they are not common when the drugs are being used in the frontline setting.

H&O What treatment options are available after covalent BTK inhibition, and how do you decide between them?

CC For a long time, our main option after covalent BTK inhibition was therapy based on venetoclax (Venclexta, AbbVie/Genentech). More recently, pirtobrutinib (Jaypirca, Lilly) has become a second option. I still use a venetoclax-based regimen more often than pirtobrutinib as second-line therapy. Venetoclax is typically used in combination with obinutuzumab in the United States and in combination with rituximab elsewhere in the world, on the basis of results of the phase 3 MURANO trial.² Venetoclax-based therapy is typically used for 2 years, and we expect to see quite a bit of time before inevitable relapse. We do not have great prospective data looking at venetoclax-based regimens following a covalent BTK inhibitor, so how long treatment lasts is a little unclear. There are not many second-line studies, and a lot of the real-world data are from patients who received a venetoclax-based

regimen in the third or fourth line.

Venetoclax-based regimens have several advantages. First, treatment is time-limited. Second, patients who have a good response can potentially be re-treated. Third, oncologists have a lot of experience with venetoclax-based regimens.

The main advantage of pirtobrutinib is convenience. Patients simply take a pill that does not require any ramp-up. Pirtobrutinib also has an excellent safety profile. That said, safety issues with venetoclax are not a major concern. Monitoring for tumor lysis syndrome (TLS) is more of a nuisance than anything. I have rarely seen TLS occur with venetoclax plus obinutuzumab, and when it does occur, it is usually during treatment with obinutuzumab. Another potential concern is myelosuppression, which tends to be worse with venetoclax than with pirtobrutinib.

H&O Does prior BTK inhibitor resistance mutation status change your choice of next therapy?

CC Not right now, although that might be something to think about in the future. The reason is that I have not had many patients go from the sequence of acalabrutinib or zanubrutinib to pirtobrutinib; it has mostly been post-ibrutinib patients who have gone on to pirtobrutinib. There is a theoretical possibility of cross-resistance for some of the non-C481 mutations that might arise in patients whose disease has progressed on zanubrutinib or acalabrutinib. I have sent patients for resistance mutation testing after explaining that the test might or might not inform what we do. I have only infrequently seen these non-C481 mutations, but their presence raises a concern that patients will have a less-than-optimal response to pirtobrutinib. Studies of pirtobrutinib resistance have often found these mutations at very low levels, even before a patient goes on to pirtobrutinib. The response rate is generally the same for patients with these mutations, but the longevity of the response is potentially shorter because of the outgrowth of resistance clones. We will eventually have more information, but for now, we do not need to have patients tested for BTK inhibitor resistance mutation status.

H&O How do *TP53* mutations and del(17p) status factor into your second-line decision?

CC *TP53* mutations and del(17p) status are important. Just because a patient did not have either of these in the frontline setting does not mean that they have not acquired them in the relapsed setting, so that is a reason to recheck general molecular cytogenetics for clonal evolution. The reason that it might affect the next therapy is

that patients with *TP53* aberrations or del(17p) tend to have a shorter response to time-limited therapies. Having this information can add to our discussion regarding the relative benefit of a time-limited venetoclax-based regimen. Time-limited venetoclax-based regimens tend to work better in patients without del(17p), which can help align expectations. Having a better idea of what to expect can also help us think ahead to third-line and later therapy, especially when it comes to younger patients.

H&O What role does fixed-duration vs continuous therapy play in your sequencing strategy?

CC Fixed-duration therapy is nice because it offers time off therapy and the potential for re-treatment. Continuous is nice because it can be very convenient; it generally does not require ramp-up or intravenous therapy. The problem with continuous therapy is that resistance is pretty much inevitable. If the patient's disease progresses on a continuous agent, we cannot use that agent or a similar one again—we cannot simply switch from acalabrutinib to zanubrutinib, for example, to address progression.

H&O How have the data from BRUIN CLL-322 changed your approach?

CC BRUIN CLL-322 was a phase 3 trial that randomly assigned 639 patients with previously treated CLL to pirtobrutinib plus venetoclax/rituximab (PVR) or to VR alone.³ The 2-year results of this landmark trial showed that 24-month PFS was significantly longer with PVR than with VR, at 87% vs 72%, respectively. The difference between the 2 groups was most impressive in the del(17p) patients. As a result, I am open to using PVR for patients who are in that exact situation. A lot of questions remain to be answered, however. Although the study showed that PVR was better than VR, we no longer use VR—we use venetoclax plus obinutuzumab (VO). As a result, it is unclear whether the triplet is better than the current dual therapy we are using. We also do not know whether the rituximab is even necessary—would a PV doublet work? Or should we swap out the rituximab for obinutuzumab? I am unlikely to do either of these until we have more data. A phase 2 study from MD Anderson is looking at PVO in the recurrent setting (NCT06967610); the results have not yet been reported. My main concern with PVO is that it is extremely myelosuppressive, and patients with relapsed disease tend to be especially vulnerable. Another comment about BRUIN CLL-322 is that the median follow-up is still relatively short, at 27 months. PVR is a 28-month regimen and VR is a 2-year regimen,

so when we see progression events, we are seeing the bad actors—the disease that has progressed while the patient is still on therapy. I wonder if the results could shift in one way or another with longer follow-up. I will be very eager to see further updates of this study.

H&O What is your measurable residual disease (MRD) testing strategy once a patient starts a B-cell lymphoma 2 (BCL2)–based regimen?

CC I do order MRD status for all my patients, although I do not think it is mandatory for community-based oncologists. There are arguments for and against getting this status, but I like to get it because MRD status can be prognostic for both PFS and overall survival. The prognostic value is regimen-dependent; we have seen that MRD status is valuable in the context of the venetoclax/anti-CD20 regimens, including VR (as in MURANO) and VO (as in the CLL14⁴ and CLL13⁵ trials). We do not have that same granularity of data regarding acalabrutinib plus venetoclax. After a patient has received venetoclax plus an anti-CD20 agent, I like to know if the patient is positive for MRD because I will watch that patient more closely during the off-treatment period. I also need to plan what I will be doing next. I do not use the information to prolong therapy, however.

H&O How do you manage TLS risk when initiating venetoclax after BTK inhibition?

CC When someone's disease is progressing on a BTK inhibitor, it is important that we not abruptly withdraw the drug because progression of disease can be exacerbated. I overlap the new treatment with the BTK inhibitor until I have evidence that the disease is being controlled with the next therapy. I typically use VO, with the obinutuzumab started before the venetoclax. Oncologists sometimes think that we do not need to worry about TLS with obinutuzumab, but the obinutuzumab phase is when we usually see the TLS. As a result, I conduct baseline laboratory testing, make sure that patients stay hydrated, and start them on allopurinol at least 3 days before they start obinutuzumab. I usually request laboratory tests at the end of the first day if the white blood cell count is very high, I always request them on the second day, and I sometimes request them on the third day, depending on how high the white blood cell count is. We need to think about the immense bulk of disease that obinutuzumab is obliterating to understand why TLS is not rare. I have seen TLS a handful of times in my practice, but luckily it has never had adverse clinical consequences. TLS has not been seen during venetoclax ramp-up in clinical trials that included obinutuzumab lead-in, but I am still cautious

and follow the package insert guidance to conduct monitoring during venetoclax administration.

H&O What is still missing from the data to guide optimal third-line sequencing?

CC It is not feasible to conduct studies in which we would compare a regimen such as a covalent BTK inhibitor followed by venetoclax followed by pirtobrutinib with a different regimen, such as venetoclax followed by re-treatment with venetoclax followed by a covalent BTK inhibitor followed by pirtobrutinib. CLL is a chronic disease, and it would take decades upon decades to conduct such studies. So I do not think we can ever determine the optimal sequence, although real-world data can help us make informed decisions. We are seeing fewer patients die of their CLL, so the bottom line is that many sequences can lead to effective control of CLL.

Our goals are to prevent death from the CLL, prevent fatal complications of therapy, and maintain quality of life, so we need to be cautious about piling on too many extra drugs that can add to toxicity.

I advise against using pirtobrutinib too early (that is, before a covalent BTK inhibitor) in younger patients because of the potential for cross-resistance. In the absence of data regarding whether covalent inhibitors work after pirtobrutinib, caution is warranted.

Disclosures

Dr Coombs has received honoraria from or served as a consultant for AbbVie, Allogene Therapeutics, AstraZeneca, BeOne Medicines, BMS, Genentech, Invivyd, Janssen, Johnson & Johnson, Lilly, Octapharma, and Pharmacyclics; has served on speakers' bureaus for AbbVie, AstraZeneca, BeOne, and Lilly; owns stock in Autolus Therapeutics and Geron; and has received research funding (paid to institution) from AbbVie, AstraZeneca, BeOne, Carina Biosciences, and Lilly.

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