ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Update on the CAPTIVATE Trial of Ibrutinib Plus Venetoclax

Tanya Siddiqi, MD
Associate Professor
Medical Director, Division of Lymphoma, City of Hope Orange County
Director, Chronic Lymphocytic Leukemia
Department of Hematology/HCT
City of Hope
Duarte, California

H&O Could you describe the impetus for and design of the CAPTIVATE trial?

TS The large, multicenter, phase 2 CAPTIVATE trial focused on patients with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) who had never received treatment. This study involved the combination of ibrutinib (Imbruvica, Pharmacyclics/Janssen) and venetoclax (Venclexta, AbbVie), with 2 separate cohorts under investigation. One cohort was studying fixed-duration treatment, where every patient would receive treatment for 15 months and then stop, followed by monitoring. The other cohort was studying measurable residual disease (MRD) and treated patients the same way for 15 months but would then assign them to a group for randomization based on whether MRD-detectable disease was present or not. This was a double-blinded, placebo-controlled randomization. If MRD-undetectable disease was confirmed, patients would be randomized to either single-agent ibrutinib or observation. If MRD-positive disease was detected, we refrained from abruptly stopping treatment and instead randomized patients to either continue both medicines together vs ibrutinib alone. This aspect of the study was not blinded, providing clarity for patients. Although this may sound complicated, the MRD portion allowed for longer treatment, akin to a maintenance phase, whereas the fixed-duration cohort stopped treatment for all participants at 15 months.

The impetus for doing this study was to determine if it was possible to achieve deep and durable remissions with the combination of ibrutinib and venetoclax with all oral therapy. Oral treatments offer the greatest convenience for patients. The goal was to provide patients with a successful treatment hiatus for a while, similar to how we use chemotherapy but with longer periods without side effects. Of note, all drugs used in this study were nonchemotherapy agents. Thus, the core impetus was to see if this specific trial could achieve deep and lasting remissions.

H&O What were the initial findings of the trial, and how have they changed over the past 5 years?

TS The 2 different cohorts both showed very deep remissions in all patients, whether they had high-risk features of disease or not. There were approximately 200 patients in each cohort, making it one of the largest frontline CLL studies. Looking at the fixed-duration part, most patients achieved complete remission (CR) or had undetectable MRD (uMRD). In the MRD cohort, patients were in very good remission at the end of the initial 15 months. Those with MRD-positive disease went on to receive either ibrutinib alone or a combination of both medications and continued to do well. There was an increase over time in conversions to uMRD status among patients who continued both medications together. On the other side, those in an uMRD state for 15 months were randomized

between placebo vs ibrutinib maintenance. No significant progression-free survival differences were observed between the 2 blinded maintenance arms.

The bottom line of the whole study after 15 months of treatment and subsequent annual follow-ups was the durable and deep remissions. Progression-free survival (PFS) was greater than 90% at both 3 years and 4 years, essentially across all arms. We hope to share similar 5-year data at the American Society of Hematology (ASH) 2023 Annual Meeting. Patients are continuing to fare extremely well. There have been a handful of cases of CLL relapse along the way. However, these patients can be successfully retreated, often with ibrutinib alone. We will also be presenting some data at ASH on patients who underwent retreatment and the subsequent outcomes. It is worth noting that patients with CLL have shown positive responses to fixed-duration ibrutinib and venetoclax combination therapy, and if they can go 3 to 5 years without needing treatment again, that is a very good clinical benefit. This translates to a good quality of life, where patients are thriving without the need for ongoing treatment. This is a substantial achievement.

Patients with CLL have shown positive responses to fixed-duration ibrutinib and venetoclax combination therapy, and if they can go 3 to 5 years without needing treatment again, that is a very good clinical benefit.

H&O Were there any major adverse events or toxicities?

TS Although much of this study took place during the COVID pandemic, patients have done extremely well. There were some patients, particularly those who were slightly older, who experienced more side effects in terms of infections and low white blood cell counts. In such cases, the dose of venetoclax was adjusted down to 300 mg, as well as administering antibiotics and granulocyte colony-stimulating factor, when needed. A subset of patients was more prone to infections, requiring dose adjustments and the administration of intravenous immunoglobulin, among other measures. Although infection was the primary area we had to watch out for, infectious complications were not a widespread occurrence. There were no significant grade 3 or serious adverse events, likely because of the absence of infusions and associated reactions.

H&O Could you elaborate more on the role of MRD in the context of this trial and CLL/SLL treatment in general?

TS MRD is a moving target nowadays in CLL. Some trials have shown that achieving a uMRD status, particularly at a level of less than 10^{-4}, may lead to delayed relapses and improved PFS. The precise application of MRD in CLL is still under investigation.

With the availability of MRD assessment in clinical trials, we are also trying to use it more in the routine care of patients, especially at bigger institutions like ours. We are not supposed to make treatment-stopping decisions based solely on MRD status, but it does help inform our decision. For instance, if I am planning on stopping a patient's treatment after a full course, I like to assess MRD to see if it is undetectable. This allows me to tell the patient that they may not require treatment for several years. If MRD is still detectable, I tell them they may need treatment again in a year or 2, but at least in the meantime, they will have had time without treatment.

H&O What do you anticipate as the next steps for this combination therapy?

TS That is a great question that poses some challenges for me to answer definitively. This combination has already been approved in certain European countries, but the US Food and Drug Administration (FDA) has not opted to move it forward as an approved combination in the United States. This raises the question for clinicians on how we can proceed with using it in our patients, especially when insurance providers might decline coverage, given these treatments can be quite costly even when fixed-duration therapy is used. Additionally, we are seeing a decrease in the use of ibrutinib in favor of newer agents with fewer side effects. The combination also works very well in patients who have relapsed after prior chemoimmunotherapy as well. In addition, ongoing trials are looking at combinations of more novel BTK inhibitors, like acalabrutinib (Calquence, AstraZeneca) and zanubrutinib (Brukinsa, BeiGene) in combination with venetoclax to see if that might yield fewer side effects and even more benefit.

H&O How does the combination compare with the other existing treatment options for patients with CLL/SLL?

TS We thankfully have a lot of good treatment options in CLL right now, especially in the frontline setting. Typically, I prefer to initiate treatment with a combination of venetoclax plus obinutuzumab (Gazyva, Genentech). The CLL14 trial showed great benefit with this regimen. It is noteworthy for being the shortest fixed-duration treatment, spanning just 1 year. Even if patients have high-risk disease features, they might relapse faster than others, but that still gives them a period of treatment-free time, which is valuable.

BTK inhibitors tend to work more slowly than venetoclax and are to be continued indefinitely. Discontinuation might not be feasible, especially for those with high-risk features like *TP53* mutation, since the depth of remission is not enough to allow long-term treatment-free intervals. In such instances, we continue the BTK inhibitor continuously until it demonstrates efficacy unless it is not well tolerated. Additionally, we are seeing promising results from newer trials with innovative drugs, including chimeric antigen receptor (CAR) T cells, BTK degraders, and bispecific antibodies, among others. There is a wealth of exciting developments in CLL treatment, but the top 2 standard options are still BTK inhibitors and venetoclax, with or without obinutuzumab.

H&O In addition to the CAPTIVATE trial, are there any other real-world studies or data that support the efficacy and safety of the ibrutinib and venetoclax combination?

TS The GLOW study specifically targeted older patients, the reasoning being that they might not be suitable candidates for more intensive chemotherapy regimens, like FCR (fludarabine, cyclophosphamide and rituximab) or BR (bendamustine and rituximab). Nowadays, we have moved away from using chemotherapy, but at the time the trial was designed, the standard option for older patients included chlorambucil (Leukeran, Aspen Global) plus obinutuzumab, which is a lower-intensity therapy than FCR or BR. They compared this regimen in a 1:1 fashion with the combination of ibrutinib plus venetoclax to see if this 2-pill nonchemotherapy combination could offer superior outcomes in an older patient population compared with the lower-intensity chemoimmunotherapy option. The study did show that ibrutinib plus venetoclax was more effective, but since the patient population is older and frailer, there was some concern about toxicities and 80% of patients completed the full regimen. This combination potentially may be good for younger patients as well and better tolerated. However, in the United States, we face challenges in using this combination because of the lack of FDA approval.

Other studies in the relapsed setting (MD Anderson, the United Kingdom, and Stanford/City of Hope trials) are exploring ibrutinib plus venetoclax combination therapy. Even in this scenario where patients had prior chemotherapy and were now seeking retreatment, we observed excellent outcomes.

H&O So what do you think is ahead for the future of the CLL treatment landscape in general?

TS There is a big wave of new treatments on the horizon. The top options thus far remain BTK inhibition and venetoclax, with or without obinutuzumab. Many new drugs are coming for patients who have experienced relapse after BTK inhibitor and venetoclax use. I have been involved with research on CAR T-cell therapy, and several centers are actively investigating BTK degraders. Additionally, there is a growing interest in bispecific antibodies. All in all, there is a wealth of promising developments coming down the line.

H&O Is there anything else you would like to add?

TS I would like to emphasize to the readers that finding a cure for this disease will take a collective effort. We are aiming to reach a cure for a disease that historically has been deemed largely incurable, except for a subset of young, fit patients with good risk features who have done well for over 10 years after FCR chemoimmunotherapy. Based on the E1912 cooperative group trial, we know that ibrutinib plus rituximab yields better outcomes than FCR but with ongoing ibrutinib. Improvements and cures can only be achieved through the timely completion of clinical trials testing novel drugs and novel combinations. To do this, we need patients referred for trials in a timely fashion. It is not just about advancing research, but also about benefiting the patients by providing access to newer drugs and combinations, even before the FDA approves them. Nowadays, trials are studying highly promising drugs and combinations, some of which may have already received separate FDA approvals for other diseases. So, it is not entirely uncharted territory, which I know can be a concern for many patients.

My plea is always 2-fold: firstly, consider trials and encourage patients to participate in clinical trials. Secondly, if you have a patient already struggling with CLL, meaning they have progressed on a BTK inhibitor and are not responding well to venetoclax, consider an early

consultation for CAR T-cell therapy or any of our novel trials. This way, we can avoid trying numerous interventions that may not yield the desired results before patients come for trials that may not work in that multiply refractory situation. Early referral for these novel therapies is crucial. If a patient is not responding well to 1 novel agent, it indicates a more challenging disease course.

Disclosure

Dr Siddiqi is a member of advisory boards for BeiGene, Bristol Myers Squibb, AstraZeneca, Gilead/Kite, and AbbVie; is a speaker for BeiGene, Bristol Myers Squibb, and AstraZeneca; and has received research funding from Bristol Myers Squibb.

Suggested Reading

Al-Sawaf O, Robrecht S, Zhang C, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6 year-results of the randomized CLL14 study [EHA2023 abstract S145]. *HemaSphere*. 2023;7(suppl 3).

Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomized, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.

Barr PM, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study [ASCO abstract 7535]. *J Clin Oncol*. 2023;41(16)(suppl).

Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.

Kater AP, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evid*. 2022;1(7). doi:10.1056/EVIDoa2200006.

Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. *Blood*. 2022;139(22):3278-3289.

Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. *J Clin Oncol*. 2021;39(34):3853-3865.