CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Lessons Learned From the CAPTIVATE Trial of Ibrutinib Plus Venetoclax in CLL

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

SO CAPTIVATE is a phase 2 trial in patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). All patients were younger than 70 years and received 3 months of standard-dose (420 mg) ibrutinib (Imbruvica, Pharmacyclics/Janssen) followed by 12 cycles of fixed-duration ibrutinib plus venetoclax (Venclexta, AbbVie), with venetoclax ramped up to the standard dose (400 mg). The idea behind the ibrutinib lead-in, which has become standard in randomized trials of combination treatment in CLL, is to debulk the tumor, thereby reducing the risk for tumor lysis during the venetoclax ramp-up.

After the initial 15 months of treatment, 164 patients in the first cohort—called the minimal residual disease (MRD) cohort—were tested for MRD. Those who had confirmed undetectable MRD assessed at a limit of detection of 10^{-4} were randomly assigned in a double-blind fashion to ibrutinib or placebo, and those who did not have confirmed undetectable MRD were randomly assigned in a 1:1 ratio to open-label ibrutinib or continued ibrutinib plus venetoclax. The primary endpoint was 1-year disease-free survival (DFS) after randomization. Dr William Wierda presented the results of the MRD cohort at the 2020 virtual annual meeting of the American Society of Hematology.

In the second cohort, called the fixed-duration cohort, 159 patients received no further treatment after the initial 15 months of treatment. Dr Paolo Ghia presented these results at the 2021 virtual annual meeting of the American Society of Clinical Oncology.

H&O Could you describe the results of CAPTIVATE?

SO One finding was that the 3 cycles of ibrutinib worked as expected to reduce the risk for tumor lysis syndrome. After the ibrutinib lead-in, the risk of 90% of the patients whose risk for tumor lysis syndrome was high at baseline shifted to a medium or low risk, underscoring that this is a highly effective strategy for reducing the risk for tumor lysis.

In the MRD cohort, the rates of MRD undetectability were very high after 12 cycles of venetoclax, at 75% in the peripheral blood and 72% in the bone marrow. This was a notable finding. Among the 86 patients with undetectable MRD, the study showed no statistically significant difference between the 1-year rate of DFS in the placebo group and that in the ibrutinib group, at 95% vs 100%, respectively. Although the DFS rates were very dramatic and impressive in both groups, the patients with undetectable MRD did not benefit from continued ibrutinib. Among the 63 patients who did not have undetectable MRD at randomization, the rates of undetectable MRD improved to 57% in the peripheral blood and 54% in the bone marrow, and the rates were higher with ibrutinib plus venetoclax than with ibrutinib alone. The 30-month rates of progression-free survival (PFS) were at least 95% in all groups, regardless of subsequent randomized treatment.

In the fixed-duration cohort, the overall response rate after 15 months of treatment was very high, at 96%. The rates of MRD undetectability were also high, at 77% in the peripheral blood and 60% in the bone marrow. Patients with the del(17p)/*TP53* mutation had similarly high rates

of MRD undetectability, at 81% in the peripheral blood and 41% in the blood marrow. The 24-month PFS rates were similar in the overall cohort and in the del(17p)/*TP53* mutation cohort, at 95% vs 84%, respectively. The rates of complete response or incomplete response (55% vs 56%) and the overall response rates (96% vs 96%) also were similar in the overall cohort and the del(17p)/*TP53* mutation cohort, respectively.

If we combine the data from the MRD cohort and the fixed-dose cohort, they show very high rates of MRD undetectability after 15 months of ibrutinib/venetoclax treatment in more than 300 patients.

H&O What side effects were increased with the use of venetoclax and ibrutinib in combination?

SO Combining the drugs did not lead to an increase in side effects beyond what we expect with the agents when used individually. Most of the side effects were grades 1 and 2; the most common grade 3 and 4 adverse events in the fixed-duration cohort were neutropenia in 33%, infections in 8%, hypertension in 6%, and a decreased neutrophil count in 5%. Adverse events led to the discontinuation of ibrutinib in 4% of patients and of venetoclax in 2%, so the ability to complete treatment was excellent in this study. The rate of atrial fibrillation was low, with any-grade atrial fibrillation affecting just 4% of patients in the fixed-duration cohort. More than half of the patients experienced diarrhea, which is seen more frequently with ibrutinib than with venetoclax, whereas neutropenia generally occurs with venetoclax but not ibrutinib.

H&O Do venetoclax and ibrutinib have a synergistic effect when used together?

SO They may. We know that ibrutinib drives lymphocytes out of their protective niches in the bone marrow, which is why we see lymphocytosis as the initial response to treatment with single-agent ibrutinib. Shifting lymphocytes from the bone marrow to the circulation could theoretically make them more susceptible to BCL2 inhibition, which might produce synergy. We do not see ibrutinib alone leading to MRD undetectability, however, and we do not have any data on frontline venetoclax as a single agent. The closest data we have are from the CLL14 trial, in which venetoclax and obinutuzumab (Gazyva, Genentech) were used as frontline therapy in 432 patients. The MRD undetectability rates in that trial were comparable with those seen in CAPTIVATE. Could we see a longer durability of remissions in CAPTIVATE than we saw in CLL14? We are measuring MRD undetectability only to 10^{-4}. MRD undetectability in large numbers of patients at 10^{-5} or 10^{-6} could lead to more durable remissions. In any case, the jury is out as to whether synergy exists between ibrutinib and venetoclax.

H&O Are any trials comparing doublet with triplet therapy in CLL?

SO The one that I am aware of is ACE-CL-311 (NCT03836261). This phase 3 trial, which is planning to enroll 780 patients, is randomly assigning frontline patients to 1 of 3 arms: acalabrutinib (Calquence, AstraZeneca) plus venetoclax (AV), acalabrutinib plus venetoclax and obinutuzumab (AVO), and chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR). The trial is designed to compare the AV and AVO arms with the chemoimmunotherapy arm. It may not be designed to detect a difference between the AV and AVO arms, but it will be interesting to see if the results show a statistically significant difference. Even when a trial is not powered to show a difference between 2 groups, we sometimes begin to see the Kaplan-Meier curves split over time—as we did in the ELEVATE TN trial of chlorambucil/obinutuzumab vs acalabrutinib/obinutuzumab vs acalabrutinib alone. Both acalabrutinib curves were significantly better than the chlorambucil curve, but with 4 years of follow-up, the acalabrutinib curves were different from each other, although no *P* value is available.

H&O Are any trials besides CAPTIVATE looking at the upfront use of small molecules in CLL?

SO Many of them are. As for available data, in addition to CAPTIVATE, we have a phase 2 study from MD Anderson and a registration trial called GLOW. The design of the study from MD Anderson is similar to that of CAPTIVATE, in that it begins with a 3-month lead-in with ibrutinib followed by combination therapy with ibrutinib and venetoclax in 80 frontline patients. After 12 months of the combination, the MD Anderson study is different because patients continue to receive therapy until they have undetectable MRD. The MD Anderson study also focused on high-risk and older patients. In a recent publication in *JAMA Oncology*, Dr Nitin Jain and colleagues reported a 3-year PFS rate of 93% and a 3-year overall survival rate of 96% with ibrutinib plus venetoclax.

In the GLOW trial, 211 patients aged 65 years or older were randomly assigned to receive frontline fixed-duration ibrutinib/venetoclax or chlorambucil/obinutuzumab. As expected, PFS was better with ibrutinib/venetoclax than with chlorambucil/obinutuzumab. Although the patients were considerably older in GLOW than in CAPTIVATE, both trials used a fixed duration of therapy. We now have data from 3 different trials in which

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ibrutinib and venetoclax were used, and all of them are producing high rates of MRD undetectability.

H&O What questions remain to be answered?

SO One question that will be difficult to answer is whether using small molecules in combination rather than sequentially will increase PFS or OS. That said, our goal as clinical researchers is to cure patients with CLL, and I do not believe we will be able to do that with sequential single agents. MRD undetectability—which we may be able to achieve with small molecules, with or without antibodies—is necessary to produce a cure, but may not be sufficient. Going forward, I believe that some of the current questions, such as whether the use of antibodies can add to the efficacy of small-molecule combinations, will be answered more quickly by measuring deeper levels of MRD (the current standard is 10^{-4}) than by waiting years for PFS data.

Disclosure

Dr O'Brien has served as a consultant for Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc, Vaniam Group LLC, AbbVie, Alexion, Verastem, Juno Therapeutics, Vida Ventures, Autolus, Johnson & Johnson, Merck, Bristol Myers Squibb, NOVA Research Company, and Lilly; has received research support from Kite, Regeneron, Acerta, and Caribou; and has served as a consultant for and received research support from Gilead, Pharmacyclics, TG Therapeutics, Pfizer, and Sunesis.

Suggested Readings

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