CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Fixed-Duration vs Continuous Treatment for Chronic Lymphocytic Leukemia in the CLL17 Trial

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H&O What was the impetus for the CLL17 trial?

OA Over the past 5 to 10 years, we have seen the evolution of 2 treatment paradigms in chronic lymphocytic leukemia (CLL): continuous treatment and fixed-duration treatment. Continuous treatment is based on Bruton tyrosine kinase (BTK) inhibition, whereas fixed-duration treatment regimens formerly consisted of chemoimmunotherapy but now generally consist of the BCL2 inhibitor venetoclax (Venclexta, AbbVie/Genentech) plus another agent. Continuous BTK inhibition and venetoclax-based therapy were both introduced after they demonstrated efficacy in comparison with chemoimmunotherapy, with these 2 approaches evolving independently of each other. The CLL17 study was designed to answer a basic question: How do continuous treatment and fixed-duration treatment compare with each other? We wanted to know which patients should receive which one of these types of therapy on the basis of robust randomized evidence rather than of cross-trial comparisons and indirect extrapolations.

H&O Could you describe the design of the CLL17 trial?

OA At the time that we designed CLL17, ibrutinib (Imbruvica, Pharmacyclics) was the most-established BTK inhibitor, and venetoclax/obinutuzumab (VO; Venclexta, AbbVie/Gazyva, Genentech) and venetoclax/ibrutinib (VI) were both fixed-duration options that were soon to be approved. We randomly assigned 909 patients with previously untreated CLL to continuous ibrutinib, fixed-duration VO, or fixed-duration VI in a 1:1:1 ratio.[1] Continuous ibrutinib was administered until disease progression or nontolerance, and fixed-duration treatments were administered for approximately 1 year. To make sure that we had a balanced representation of patients across the 3 arms, we stratified patients by tumor protein P53 gene (*TP53*) alteration status, immunoglobulin heavy chain variable region gene (*IGHV*) status, and whether they were fit or unfit. The median age of patients was approximately 66 years. The primary endpoint was progression-free survival (PFS).

H&O Could you describe the results of the trial?

OA Our hypothesis was that the shorter therapies would prove equally as effective clinically as continuous therapy because of their distinct mechanism of action, which relies on producing deep remissions. Indeed, we saw that after a median observation time of 34.2 months, the average 3-year PFS rate was 80% to 81% in all 3 arms, making the fixed-duration treatments noninferior to continuous therapy. The overall survival rate was greater than 90% in all 3 arms, ranging from 92% in the VO arm to 96% in both the VI and ibrutinib arms.

Regarding specific subgroups, the study found that both VO and VI were statistically noninferior to continuous ibrutinib in patients with unmutated *IGHV.* What we cannot be certain about are the data in patients with *TP53* mutations, in which the confidence intervals are still quite wide and the direction into which the data are heading is not clear. So far, we are seeing a signal that VO is less effective than continuous ibrutinib in patients with *TP53*-altered disease. VI, by contrast, has some mixed

patterns but might be even more effective than continuous ibrutinib in patients with *TP53*-altered disease.

H&O How did measurable residual disease (MRD) status relate to the response to treatment?

OA MRD negativity at final restaging was highest with VO, at 73% in peripheral blood and 62% in bone marrow, which is in line with what we have seen in previous phase 3 studies. Approximately half the patients in the VI group and no patients in the continuous ibrutinib group had undetectable MRD. This finding substantiated that only the combination therapies were able to produce deep remissions, which is why we can stop therapy, whereas most or all patients on single-agent ibrutinib are still MRD-positive after 1 or 1 1/2 years. The next question for us to answer is, how much does the MRD status correlate with patient survival? We still need 1 or 2 more years of follow-up to see whether the difference between the MRD rates in the VO and VI arms will translate into meaningful PFS differences.

H&O How did adverse events differ among the 3 groups?

OA Atrial fibrillation occurred in 17% of those taking single-agent ibrutinib, 13% of those taking VI, and 4% of those taking VO, so the typical relationship between BTK inhibitors and cardiovascular side effects was evident. We also saw more severe infections and more cytopenias in the VO arm than in the other arms, with grade 3 to 5 infections affecting more than one-third of patients in the VO arm and neutropenia affecting more than half of the patients in the VO arm.

H&O How did COVID-19 affect the results?

OA We opened enrollment in February 2021, while the pandemic was ongoing and vaccines were not yet available, and finished enrollment in November 2022. Vaccines became available approximately midway through enrollment, with nearly half the patients receiving a vaccine before starting study treatment and most patients being vaccinated at some point during the study. Approximately 40% of the patients had documented COVID infections of any grade. Although fewer than 10% of the patients had severe COVID infections, severe COVID was more likely in the VO arm than in the other 2 arms, presumably because obinutuzumab is an anti-CD20 antibody. We assume that this finding about increased susceptibility to severe COVID with an anti-CD20 antibody would extend to other infections, such as respiratory syncytial virus infection or the flu.

H&O How do the results of CLL17 fit in with what we have learned from other CLL studies, such as AMPLIFY and CLL14?

OA These studies had both similarities to and differences from CLL17. Both AMPLIFY[2] and CLL14[3] were looking at fixed-duration targeted therapies vs chemoimmunotherapy, with AMPLIFY looking at acalabrutinib (Calquence, AstraZeneca)/venetoclax, acalabrutinib plus VO, or chemoimmunotherapy and CLL14 looking at VO vs chlorambucil/obinutuzumab. AMPLIFY enrolled young, fit patients, whereas CLL14 enrolled elderly, unfit patients; CLL17 enrolled a mixture of both. Another difference is that AMPLIFY did not enroll any patients with *TP53* alterations and CLL14 enrolled only a few, whereas approximately 7% to 8% of the patients in CLL17 had a *TP53* alteration. Approximately 45% of the patients in CLL17 fulfilled the inclusion criteria for CLL14, and 55% fulfilled the inclusion criteria for AMPLIFY.

We saw similar efficacy outcomes in CLL17 and CLL14 in terms of PFS when we look at the first 2 or 3 years of data. The data differ more when we compare the VI arm in CLL17 with the acalabrutinib/venetoclax arm in AMPLIFY, in which the MRD rates were very limited in the acalabrutinib/venetoclax arm. The reasons for that may have been the effect of COVID-19 or a different interaction between acalabrutinib and venetoclax than between ibrutinib and venetoclax. It will be interesting to see whether a difference in efficacy remains with longer follow-up, although the difference may be traced to the different patient populations. Taken together, these studies confirm the principle behind fixed-duration therapy.

H&O Is there a concern that this finding could change with longer follow-up?

OA The time from randomization to second objective disease progression or death (PFS2) is a predefined secondary endpoint in CLL17, so we will have data on this with longer follow-up. We do not have a difference in PFS1, so it would be very surprising to see a difference in PFS2. Still, we need to appreciate that the study is not fully powered at this point. The subgroups are small and the follow-up is still short, so we need longer observation to have a clearer picture. As a result, I think it makes sense to continue to follow the continuous BTK inhibitor approach in patients with very high-risk disease.

H&O Can we extrapolate anything from the use of ibrutinib to the use of acalabrutinib or zanubrutinib?

OA Although strictly speaking we cannot say, I think we

can extrapolate to a certain degree regarding efficacy. Both the ELEVATE-RR study,[4] which tested acalabrutinib against ibrutinib, and the ALPINE study,[5] which tested zanubrutinib (Brukinsa, BeiGene) against ibrutinib, enrolled patients with relapsed or refractory disease, so we would expect the results to be different from those of a first-line study. Our efficacy results with ibrutinib are much closer to those seen with ibrutinib in the SEQUOIA study of zanubrutinib[6] and the ELEVATE-TN study of acalabrutinib.[7] Even though the patient populations were slightly different from that in CLL17, these were both first-line studies. As for toxicity, I would expect that if we conducted a version of CLL17 with acalabrutinib or zanubrutinib, we would see a lower risk of atrial fibrillation than we did with ibrutinib because this is much less common with the next-generation BTK inhibitors. This also has the potential to affect the rate of dose reductions and treatment discontinuations, but otherwise I would expect the results to be comparable. I would assume that the treatment with fixed-duration acalabrutinib/venetoclax is noninferior to continuous acalabrutinib, just as it is noninferior to continuous ibrutinib. We also are very likely to see that a fixed-duration combination of the investigational next-generation BCL2 inhibitor sonrotoclax and zanubrutinib is noninferior to continuous zanubrutinib. A combination of sonrotoclax and zanubrutinib vs VO is being studied in the phase 3 CELESTIAL-TNCLL trial of patients with previously untreated CLL (NCT06073821).

H&O What is your takeaway from the CLL17 trial?

OA I would say that fixed-duration treatment should be considered in the first-line setting for any patient who does not have *TP53* alterations. The question comes up regarding how to choose among fixed-duration treatments. For example, I would avoid the use of obinutuzumab in a patient who has a history of repeated respiratory tract infections. For that patient, VI would be a better choice. Although I prefer to recommend fixed-dose treatment, patients who live far away from the clinic or have mobility issues might be better off with a continuous single-agent treatment, which does not require infusions or regular laboratory checks.

H&O What other relevant studies are ongoing?

OA The phase 3 CLL18/MOIRAI study is examining whether efficacy is greater with venetoclax plus pirtobrutinib (Jaypirca, Lilly) until undetectable MRD is achieved than with fixed-duration venetoclax plus either obinutuzumab or pirtobrutinib. This is an attempt to further optimize the use of limited-duration strategies by individualizing the treatment duration.

H&O What additional research would you like to see conducted?

OA Naturally, we want to increase the efficacy further. We now have a 3-year PFS of approximately 80%, which means that some patients still experience progression or even die within the first 3 years of CLL, so there is still room for improvement. In addition to improving efficacy, we need to be more mindful of all the effects that both the therapy and the disease have on patients, especially infections and secondary cancers. CLL17 clearly demonstrates that infections are a major issue for patients with CLL, affecting approximately 80% of them. We have a major need to find ways to restore immune function in patients with CLL. Furthermore, we have been observing an increased rate of secondary cancers among patients with CLL during the last 2 decades, regardless of the therapy we administer. Figuring out what we can do to reduce this risk is an important long-term goal.

Disclosures

Dr Al-Sawaf has done consulting for and received research funding from AbbVie, Janssen, Roche, BeiGene, Genmab, Lilly, and AstraZeneca.

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