CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Clinical Use of Measurable Residual Disease in CLL

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H&O What are some of the limitations of the International Workshop on CLL (iwCLL) response criteria for chronic lymphocytic leukemia (CLL) in the era of novel agents?

AD The iwCLL response criteria, which were designed in the era of chemoimmunotherapy, make clear delineations among complete response (CR), partial response (PR), and no response. Patients who experience a CR to chemoimmunotherapy have better outcomes than those who experience a PR, and those who experience a PR have better outcomes than those who experience no response. Although this remains true in the modern era, PR has taken on a new meaning since the introduction of Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib (Imbruvica, Pharmacyclics/Janssen) and acalabrutinib (Calquence, AstraZeneca).

What we have seen is that patients who achieve a PR on BTK inhibitors tend to have better outcomes than those who achieve a CR on chemoimmunotherapy, so we no longer need to aim for a CR. Furthermore, we have learned that BTK inhibitors and other newer agents, such as the phosphoinositide 3-kinase (PI3K) inhibitors idelalisib (Zydelig, Gilead) and duvelisib (Copiktra, Secura Bio), can induce redistribution lymphocytosis. This has confused doctors, particularly those who do not treat CLL regularly, who might misinterpret an increase in the lymphocyte count following treatment as a sign of disease progression. A category of PR with lymphocytosis has been introduced to account for this phenomenon. Finally, the iwCLL response criteria do not account for measurable residual disease (MRD) at this time.

H&O What are the different methods used to detect MRD, and what are the advantages and disadvantages of each?

AD In the United States, the most commonly used method to detect MRD is flow cytometry, followed by next-generation sequencing (NGS). Allele-specific polymerase chain reaction is another method that is used less commonly.

Flow cytometry is a standardized test that requires 1 or 2 tubes of blood and is available in several laboratories in the United States and in Europe. We have a lot of historical data to support this test, and the European Research Initiative on CLL (ERIC) provides guidelines for the use of flow cytometry (Wierda et al, *Leukemia*, 2021). The disadvantages of flow cytometry are that it has a relatively low sensitivity of 10^{-4} when performed as a 4-color assay, which is the most common version, and that it is somewhat labor-intensive, requiring technician time to run the sample. The use of a 6-color or 8-color assay may increase the sensitivity to 10^{-5} or 10^{-6}, but few laboratories are able to carry this out at this time.

NGS is the newest and the most sensitive method, with a sensitivity of 10^{-6}. This test requires a smaller amount of blood than flow cytometry. The clonoSEQ assay from Adaptive Biotechnologies is the first NGS assay for MRD to have US Food and Drug Administration (FDA) clearance. The main disadvantage of this test is that it requires a baseline sample prior to treatment. This test is also more expensive than flow cytometry.

H&O What is the relative benefit of using bone marrow over peripheral blood for MRD testing?

AD Using peripheral blood for MRD testing is the easiest because of accessibility, whereas taking bone marrow is a more invasive procedure. Bone marrow testing is considered the gold standard in terms of accuracy because MRD may remain in the bone marrow even after it has disappeared from the blood, but many patients prefer to avoid it if possible.

Whether peripheral blood is a reasonable alternative to bone marrow depends on the therapeutic regimen. The results with peripheral blood differ from those with bone marrow by approximately 20% to 30% when chemoimmunotherapy is used. The discrepancy is even higher with certain monoclonal antibodies, such as alemtuzumab. In contrast, the discrepancy between the 2 methods is only 10% or 15% with therapy based on venetoclax (Venclexta, AbbVie/Genentech).

H&O Is it better to use bone marrow at every interval?

AD Although the use of bone marrow might be ideal, it is burdensome for the patient. As a result, we usually rely on peripheral blood testing at most intervals with only occasional bone marrow MRD testing.

H&O Does MRD status predict outcome regardless of what therapy is used?

AD Most of our information is derived from the era of chemotherapy, which has produced extensive data showing that undetectable MRD predicts improved progression-free survival (PFS). That relationship holds true regardless of whether patients achieve a CR or a PR. We have some data suggesting that the level of MRD predicts overall survival (OS). We also have extensive data showing that undetectable MRD predicts improved PFS when novel venetoclax-based regimens are used, but we do not know whether it also predicts OS in these patients. As for BTK inhibitors, we rarely see undetectable MRD when these agents are used. Even when undetectable MRD does occur with BTK inhibition plus an anti-CD20 monoclonal antibody, such as rituximab or obinutuzumab (Gazyva, Genentech), we do not have enough data to say that outcomes will be any better.

H&O What data support the use of MRD in clinical decision-making?

AD Several studies are relevant. The best known of these studies is CAPTIVATE, a phase 2 study that is assessing the use of MRD-guided discontinuation of therapy following doublet treatment. In early results that Wierda and colleagues published in the *Journal of Clinical Oncology* in 2021, the rates of undetectable MRD among 164 patients taking ibrutinib and venetoclax for treatment-naive CLL were 75% in peripheral blood and 68% in bone marrow. The data from this study are still immature, however, and we need to wait longer to see whether MRD status can help us determine whether to discontinue therapy. This concern did not come up in the era of chemoimmunotherapy, when the duration of treatment was fixed.

> MRD status is already being used as an endpoint in diseases other than CLL, so it has the potential to become an endpoint in CLL as well.

Another study of interest is CLL14, which Al-Sawaf and colleagues presented at the 2020 American Society of Clinical Oncology (ASCO) annual meeting. In this study, 216 patients with previously untreated CLL were assigned to take venetoclax and obinutuzumab. Eighteen months after the end of treatment, the rate of undetectable MRD in these patients was 47% in peripheral blood.

In the GLOW study, which Munir and colleagues presented at the 2021 American Society of Hematology (ASH) annual meeting, the rates of undetectable MRD among 106 patients with CLL taking ibrutinib plus venetoclax as first-line therapy were 55% in peripheral blood and 52% in bone marrow.

H&O How often is MRD status being used in clinical practice at this time?

AD MRD status still has limited use outside of clinical trials, for numerous reasons. One reason is the low availability of MRD testing, which is easy to perform in some academic centers but not in others. Community practitioners may lack convenient access to these assays.

The second reason is that we still do not have enough information on how the results of this assay should guide our treatment decisions. Although MRD is predictive of outcomes with venetoclax-based regimens, such as in the CLL14 study, no definitive data exist to suggest that we should adjust the treatment regimen based on MRD status.

The third reason is that when it comes to BTK inhibitors, which are the most prescribed oral drugs for CLL in the community, MRD status is even less helpful at predicting outcomes, simply because undetectable MRD rarely occurs. As a result, most MRD use is restricted to clinical trials.

I do use MRD detection in my patients in some special circumstances, such as if I am worried about rapid progression in patients who have in the past rapidly developed debilitating symptoms or autoimmune complications. Otherwise, I rarely use assessment of MRD status outside the clinical trial setting.

H&O Where do you see MRD being used in the future?

AD The hope is to eventually use MRD to guide therapy. We would like to see treatment in CLL be limited in duration, which is becoming possible with regimens such as venetoclax/obinutuzumab and venetoclax plus a BTK inhibitor. MRD status would be helpful if we could use it to determine which patients can stop taking medication, which patients should continue with their treatment, and which ones should switch to a different treatment regimen.

H&O Should undetectable MRD be the goal of therapy?

AD Undetectable MRD is not necessarily the goal of therapy at this point. In the future, however, it could be the goal of therapy when using time-limited regimens.

H&O Should MRD be used as an endpoint for clinical trials and drug approval?

AD Yes, clinical trials are an area where MRD status plays an important role. As far as drug approval is concerned, MRD status is already being used as an endpoint in diseases other than CLL, so it has the potential to become an endpoint in CLL as well.

Disclosure

Dr Danilov has received consulting fees from AbbVie, AstraZeneca, Bayer Oncology, BeiGene, Bristol Myers Squibb, Genentech, Genmab, Incyte, Lilly Oncology, Nurix, Oncovalent, Pharmacyclics, and TG Therapeutics, and receives ongoing research funding from AbbVie, AstraZeneca, Bayer Oncology, Bristol Myers Squibb, Cyclacel, MEI Pharma, Nurix, and Takeda Oncology.

Suggested Readings

Al-Sawaf O, Zhang C, Tandon M, et al. Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial [ASCO abstract 8027]. *J Clin Oncol.* 2020;388(15)(suppl).

Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;131(25):2745-2760.

Munir T, Moreno C, Owen C, et al. First prospective data on minimal residual disease (MRD) outcomes after fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O) for first-line treatment of CLL in elderly or unfit patients: the Glow study [ASH abstract 70]. *Blood.* 2021;138(1)(suppl).

Thompson PA, Srivastava J, Peterson C, et al. Minimal residual disease undetectable by next-generation sequencing predicts improved outcome in CLL after chemoimmunotherapy. *Blood.* 2019;134(22):1951-1959.

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.

Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. *Leukemia.* 2021;35(11):3059-3072.