CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Is MRD Testing Ready for General Use in Chronic Lymphocytic Leukemia?

Carolyn Owen, MD
Associate Professor
Cumming School of Medicine, Department of Oncology
University of Calgary
Calgary, Alberta, Canada

H&O What are the potential uses of measurable residual disease (MRD) testing in patients with chronic lymphocytic leukemia (CLL)?

CO The most important use of MRD testing is for prognosis—to identify patients who have had a suboptimal response to fixed-duration therapy. Fixed-duration therapies are so effective now that by the end of the planned treatment, most patients no longer have detectable MRD. These patients are likely to experience a long remission and prolonged survival. However, some patients still have subclinically detectable disease in the form of MRD, and we know that these patients do not do as well as those without detectable disease. A positive MRD test result alerts us that we need to watch these patients more closely and consider altering our plans by changing or extending therapy.

Another proven use of MRD testing in CLL is to evaluate patients who have had a stem cell transplant. These cases are rare because transplant is rarely used in CLL. But when patients do have detectable MRD after a stem cell transplant for acute leukemia or CLL, the treating physician will typically alter treatment by removing immune suppression to get more of a graft-versus-tumor effect or by infusing donor lymphocytes.

We have less evidence to support additional uses of MRD testing, but one possibility is earlier identification of disease relapse. It is not clear whether earlier identification of relapse is helpful in a disease that is not particularly aggressive and that typically is left untreated when patients have low levels of disease. Researchers are currently investigating MRD for this use, however.

H&O How does the therapy being used affect the usefulness of MRD testing in CLL?

CO We know that MRD is valuable for predicting survival and duration of remission after fixed-duration therapy. Fixed-duration therapy over recent years has included a monoclonal antibody such as rituximab or obinutuzumab (Gazyva, Genentech) plus chemotherapy (which we no longer use in CLL) or a monoclonal antibody plus venetoclax (Venclexta, AbbVie/Genentech).

However, when it comes to the newer treatment regimens, such as a BTK inhibitor plus venetoclax or BTK inhibitor monotherapy, MRD testing does not have the same clear prognostic relevance. Because monotherapy with a BTK inhibitor continues indefinitely, the patient does not need to achieve undetectable MRD to have a good outcome. Indeed, most people do not achieve undetectable MRD with BTK inhibition alone, so it is not particularly useful there. When we combine BTK inhibition with venetoclax, many patients do achieve undetectable MRD, but it not clear if that result is as predictive as the genetic features of the CLL that existed before treatment started.

H&O What are some of the studies looking at MRD testing in CLL?

CO Most recent clinical trials include MRD testing in CLL. I would argue that none of these studies is designed to answer the question that matters most here, which is whether outcomes are better when MRD testing is used to direct therapy than when it is not used. The CAPTIVATE trial,[1] for example, would have

been very useful if it had been powered to compare the fixed-duration cohort with the MRD-directed cohort. If the patients in the MRD-directed cohort lived longer overall, this would show that using MRD made patients do better. However, the study was not planned that way. It was planned with 2 different cohorts, and not enough patients were enrolled to allow a meaningful comparison of outcomes between the 2 cohorts. The researchers altered therapy duration according to the results of MRD testing in the MRD-directed cohort, but they are not investigating whether MRD testing itself improves outcomes overall.

Several studies are of particular interest, however. The phase 3 FLAIR study from the United Kingdom directed time on therapy on the basis of MRD[2]; the phase 3 MAJIC study is looking at extending therapy in patients who have detectable MRD at the end of therapy (NCT05057494); and the phase 2 HOVON 141/VISION study is looking at the use of MRD to direct restarting therapy (NCT03226301).

H&O How widely used is MRD testing at this point in patients with CLL?

CO MRD testing is used in routine practice only in academic centers in the United States and in some well-funded European centers. Here in Canada, we do not use MRD testing at all in CLL outside clinical trials. I believe that MRD testing should be incorporated into clinical trials as much as possible to assess whether it improves outcomes so that we can determine if and when it should be used in routine clinical practice.

H&O What factors are limiting the use of MRD testing in CLL?

CO Several factors are limiting the use of MRD testing in CLL. In the United States, just one commercial test has received US Food and Drug Administration (FDA) approval. This test is expensive, although many health insurance companies will cover it. Another option is for hospital laboratories to develop their own tests, validate them, and process samples. The biggest limitation, however, is the lack of strong data suggesting that MRD testing improves patient outcomes. Without improvements in outcomes, it is difficult to get our laboratories to agree to fund an expensive test just for prognosis.

H&O What testing method have you been using in clinical trials?

CO The method depends on the trial, but we most often use flow cytometry because every center has a flow cytometry machine. The technique is not complex, although more time on the flow cytometry machine is required for MRD testing of the sample than for the usual clinical use of flow cytometry of diagnosing CLL. The standard definition of undetectable MRD is less than 1 in 10,000 cells, so that 2,000,000 cells must be examined.

Another option is polymerase chain reaction (PCR)–based assessment, which allows batch testing and has the potential for sensitivity greater than that of flow cytometry. PCR testing requires a pretreatment sample, however, and the technique sometimes fails to work because of amplification issues.

We typically test both peripheral blood and bone marrow when we are assessing response in clinical trials. For sequential testing, we usually test only peripheral blood so that patients do not need to have bone marrow tests repeatedly. The frequency of sequential testing varies by study, but testing typically is conducted no more often than every 3 months.

H&O What questions remain to be answered regarding MRD testing in CLL?

CO The biggest question is whether MRD can do anything in CLL beyond prognostication. Those who are currently using MRD to direct therapy are doing so without knowing whether they are improving patient outcomes, so it is very important that we continue to gather information and use the data to decide how best to apply MRD testing.

Disclosures

Dr Owen has no disclosures relevant to MRD testing or analysis. She has received honoraria for consulting/advisory board participation from AbbVie, AstraZeneca, BeiGene, Janssen, Merck, Lilly, Incyte, and Roche.

References

1. Wierda WG, Jacobs R, Barr PM, et al. Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): up to 5.5 years of follow-up in the phase 2 CAPTIVATE study [ASCO abstract 7009]. *J Clin Oncol.* 2024;42(16)(suppl).
2. Munir T, Cairns DA, Bloor A, et al; National Cancer Research Institute Chronic Lymphocytic Leukemia Subgroup. Chronic lymphocytic leukemia therapy guided by measurable residual disease. *N Engl J Med.* 2024;390(4):326-337.