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Measurable Residual Disease in Acute Lymphoblastic Leukemia: Techniques and Therapeutic Utility

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H&O Is testing for measurable residual disease (MRD) now a standard component of management of patients with acute lymphoblastic leukemia (ALL)?

LM Measurement of MRD is now a standard test for patients with ALL. An abundance of data and research articles support MRD testing. MRD testing is included in clinical care guidelines across the United States.

H&O What are the techniques for MRD testing in patients with ALL?

LM There are several techniques used in clinical practice. Probably the most common technique in the United States is flow cytometry, which is suitable for almost all patients with ALL. The sensitivity of flow cytometry is based on the quality of the sample obtained and the laboratory performing the study. The sample requires a sufficient number of cells and should be taken from the first pull of bone marrow aspiration. For ALL, it is optimal to send samples for flow cytometry to a laboratory that has a validated MRD assay, with at least 10^{-4} sensitivity for detection in the bone marrow.

Another technique for measuring MRD is polymerase chain reaction (PCR). In the United States, in the setting of ALL, PCR is used most commonly in patients with *BCR/ABL* gene rearrangements or those who are Philadelphia chromosome (Ph)–positive. Commercially available quantitative PCR is widely accessible to test quantitative MRD for *BCR/ABL* rearrangements in patients with Ph-positive ALL. The sensitivity of quantitative PCR is generally higher than for flow cytometry. For disease monitoring, quantitative PCR testing for *BCR/ABL* rearrangements may be performed using peripheral blood with adequate sensitivity.

Another technique often used in ALL is next-generation sequencing (NGS) of immunoglobulin heavy chain receptor rearrangements or T-cell receptors. This technique is the most recent one, but it has been commercially available in the United States for the last few years. The use of NGS for MRD monitoring allows for deeper sensitivity. It also permits MRD monitoring of the peripheral blood. A caveat to the use of this technique is that not every patient will have an initial diagnostic sample for sequencing, and some cases of ALL will not provide a clonal immunoglobulin heavy chain (IGH) or T-cell receptor (TCR) rearrangement that can be subsequently tracked.

H&O How do you select which test to use?

LM Physicians who treat patients with ALL are fortunate to have these tests, which allow us to monitor the disease on a sensitive level. I view the different techniques as complementary. I use different assays in different settings. In some cases, I use more than one assay to gain as much information as possible. Flow cytometry is the only technique that can characterize the immunophenotype, or the antigen profile of the leukemia cells. In the era of targeted

immunotherapy, this information has become important. The use of flow cytometry is a cornerstone for ALL, as it provides important information about the cells.

NGS, especially when used after curative-intent therapy, can provide very sensitive, useful information about emerging disease relapse and the depth of response to treatment. These assays can be complementary.

MRD appears to be the most important factor guiding treatment decisions in ALL.

H&O What factors impact the sensitivity of MRD testing results?

LM In ALL, specimens for MRD assessment are most commonly obtained using bone marrow aspiration. The sensitivity of MRD assays can vary depending on the number of cells in the bone marrow sample. For example, if an aspirate is the third pull of a bone marrow assessment and is hemodiluted, then the flow cytometry result might lack sensitivity and the extent of the disease could be underestimated. This possibility is important to remember. Increasingly, data suggest that peripheral blood may be used as a surrogate for bone marrow when evaluating MRD using NGS or quantitative PCR techniques.

With bone marrow specimens, NGS can reach a sensitivity of 10^{-6}. In the peripheral blood, NGS has a sensitivity ranging from 10^{-4} to 10^{-6}, and results between the blood and bone marrow have shown general concordance.

H&O What is the schedule for MRD testing in patients with ALL?

LM The testing schedule depends on where the patient is in his or her treatment course and which regimen is being utilized. The treatment of ALL in adults encompasses several different approaches that vary according to the patient's age, immunophenotype, and cytogenetic molecular characteristics. In general, MRD testing is performed following induction, after consolidation, and prior to maintenance, as well as prior to transplant. In patients with MRD, ongoing MRD evaluations are necessary to determine whether the burden of disease is rising or clearing.

There is some controversy regarding the ongoing monitoring of MRD among patients who achieve an MRD-negative response. Should testing take place after the completion of therapy, during maintenance therapy, or during long-term follow-up? More research is needed to determine the optimal frequency and duration of ongoing MRD monitoring. With the current ability to use such sensitive tests, increasingly with the peripheral blood, there is an opportunity to refine the testing schedule and incorporate MRD monitoring into the practice schema.

Patients treated with a bone marrow transplant typically undergo MRD assessment before transplant and then at serial time points afterward. I usually assess MRD for at least 2 years after transplant in patients with Ph-negative ALL and often for a longer duration in patients with Ph-positive ALL.

H&O How can MRD testing be used to guide treatment decisions?

LM MRD appears to be the most important factor guiding treatment decisions in ALL. The US Food and Drug Administration granted blinatumomab (Blincyto, Amgen) accelerated approved for CD19-positive B-cell precursor ALL in first or second complete remission based on MRD response rate and hematologic relapse-free survival. Blinatumomab is frequently used for MRD-positive ALL in the frontline setting, and response rates are extremely high. This treatment is an effective bridge to bone marrow transplant.

MRD is used in several other ways. In the frontline setting, MRD is probably the most important consideration when deciding whether to escalate therapy. For example, a patient who is persistently MRD-positive may then receive blinatumomab and undergo a bone marrow transplant. A patient who achieves an early MRD-negative remission is unlikely to undergo transplant in first remission. Future trials will likely also incorporate therapeutic de-escalation based on MRD. In the transplant setting, the reemergence of MRD reflects impending clinical relapse, typically with a period of several weeks to months during which a therapeutic intervention may be attempted.

H&O How well does MRD predict outcome in patients with ALL?

LM This question has been examined by numerous studies in pediatric and adult ALL, as well as in large meta-analyses. Nearly every study has shown that an MRD-negative response to frontline therapy is an independent predictor of overall outcome, whereas persistence of MRD is associated with higher rates of relapse and worse survival.

H&O Do you anticipate that MRD testing will evolve?

LM The current MRD tests are able to quantify residual cells at varying sensitivities. With NGS methods, it is possible to quantify very small amounts of malignant cells. However, these tests do not provide information about the characteristics of the cells, such as the mutational profile. I anticipate that the next generation of MRD tests will go beyond quantification to describe the features of the cells. This information will provide insight into why certain populations are no longer responding to therapy. The current assays also do not focus on quantifying leukemic stem cells.

Another area concerns the lowest threshold of MRD that is clinically relevant. The clinical utility of MRD results below 10^{-4} has varied across studies, and the prognostic significance of very small amounts of residual disease may vary depending on the treatment setting. It may be possible that future assays will have even higher sensitivity, and it will be important to understand whether this may translate into improved prognostic and predictive significance.

MRD testing continues to evolve. Physicians who treat ALL are fortunate to have these technologies commercially available for our patients.

Disclosure

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Suggested Readings

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute lymphoblastic leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Updated April 4, 2022. Accessed April 20, 2022.