Measurable Residual Disease Testing: Integration Pathway

Advancing Care for Patients with Acute Lymphoblastic Leukemia

From Theory to Practice: The Road to Measurable Residual Disease Testing

While the landscape of B-cell acute lymphoblastic leukemia has changed drastically over the last few decades, the discovery of measurable residual disease is one of the most important advances and has emerged as a powerful prognostic tool for select malignancies. Measurable residual disease, previously known as minimal residual disease, is the low level of leukemic cells remaining in systemic circulation after definitive treatment that is undetectable by conventional cytomorphology.[1] Monitoring measurable residual disease at various points throughout the course of active treatment and into remission provides important, personalized insights into the effectiveness of therapy and may be used as an indicator to predict which patients are at risk of relapse.

Understanding that nearly 85 percent of patients with cancer are treated in either community oncology practices or community-based cancer programs, provider education on emerging technologies like measurable residual disease testing and its specific and complex techniques for application and integration become critical. Moreover, the routine use of measurable residual disease testing continues to be variable at best within community practice settings.

Using acute lymphoblastic leukemia, the first and only disease state with a treatment approved by the U.S. Food and Drug Administration (FDA) that is based on measurable residual disease response rate as the model of measurable residual disease testing at work, different testing methods continue to be studied for their specificity, sensitivity, reproducibility, and cost.

In June 2021, the Association of Community Cancer Centers (ACCC) launched the Measurable Residual Disease Testing Implementation Roadmap for B-cell Acute Lymphoblastic Leukemia, an online learning tool to help multidisciplinary cancer care teams obtain the knowledge they need to implement, expand, and sustain measurable residual disease testing for patients with adult B-cell acute lymphoblastic leukemia. Expert insights from the Advisory Committee provided in the Roadmap give teams a deeper understanding of how measurable residual disease testing can fit into their cancer program. Relevant resources are also included throughout the Roadmap, which are available in a searchable resource library along with additional information related to measurable residual disease testing.

To assess the usability of the Roadmap in practice, ACCC recruited two sites to participate in a pilot program– Inova Schar Cancer Institute in Fairfax, Va. and part of the Inova healthcare system, and Northwell Health Cancer Institute, part of Northwell Health, serving patients in the New York City Metropolitan area and Long Island. Over the course of the pilot, a number of activities were conducted at each site including: identification of all stakeholders involved in measurable residual disease testing; review of current testing methods and infrastructure; identification of associated testing costs/financial responsibilities; creation of algorithms and processes; and identification of opportunities to improve education, communication, and coordination between providers and departments.

The Data Behind the Technology

Historically, complete remission, defined as having fewer than 5 percent blasts in bone marrow, has been the standard goal of treatment. However, up to 50 percent of patients with acute lymphoblastic leukemia who achieve complete remission have residual leukemic cells that can lead to relapse.[2] With the advent of new technology, it is now possible to detect the presence of cancer cells at levels of 1:104 – 1:106 (cancer cells:nucleated cells), compared to 1:20 for conventional cytomorphology. This means that treatment response can now be further refined, rendering traditional definitions of remission insufficient.

Studies suggest that the minimal threshold for measurable residual disease is 0.01 percent, which means one cancer cell is identified per 10,000 normal cells.[3] Achieving measurable residual disease negativity at this threshold has been consistently shown as the most important prognostic factor in the treatment of acute lymphoblastic leukemia. In a meta-analysis of 13,637 pediatric and adult patients with acute

lymphoblastic leukemia, event-free survival (EFS) was strongly associated with measurable residual disease negativity. The 10-year EFS rate for adults who achieved measurable residual disease negativity was 64 percent compared to just 21 percent for those who were measurable residual disease-positive.[4] In one study, following induction chemotherapy, patients with measurable residual disease <0.05 percent at day +35 had substantially longer relapse-free survival (RFS) than patients with higher measurable residual disease levels (42 months vs. 16 months, p = 0.001).[5] Notably, all patients in this study with measurable residual disease >0.1 percent had relapsed within two years.

Measurable residual disease has also been used to guide post-remission therapy in patients with acute lymphoblastic leukemia. In a 2003 United Kingdom childhood acute lymphoblastic leukemia randomized trial, 553 measurable residual disease high-risk (MRD > 0.01 percent at day 29) patients were randomized to receive either standard or escalated post-remission therapy (including additional doses of pegylated asparaginase, vincristine, and dose-escalated methotrexate).[6] After five years, EFS was significantly higher in those who received augmented therapy compared to those who received standard treatment (89.6 percent vs. 82.8 percent, p = 0.04). In patients with measurable residual disease-positive disease (>0.1 percent) after induction and consolidation therapy, blinatumomab was initially tested to determine if it could induce measurable residual disease negativity.[7] Eighty percent of patients in the study achieved a negative measurable residual disease status within four cycles of treatment and RFS reached 61 percent after 33 months of median follow-up. Moreover, six of eleven patients who did not receive subsequent allogeneic stem cell transplantation remained in complete remission at a median follow-up of 31 months. For patients who remain persistently measurable residual disease-positive, treatment with inotuzumab ozogamicin can be considered due to better outcomes compared to salvage chemotherapy.[8]

In the pediatric population, achieving measurable residual disease negativity before transplantation is directly linked to superior outcomes, motivating many experts to use all means to reach measurable residual disease-negative status before sending their patients to transplant.[9] However, measurable residual disease positivity does not preclude patients from stem cell transplantation, and for many measurable residual disease-positive patients, stem cell transplantation is an effective option to attain continuous complete remission and improve survival.[10,11] In the post-transplant setting, measurable residual disease positivity is generally associated with a greater risk of relapse; however, relapse risk is notably reduced in patients who develop acute graft versus host disease. Moreover, measurable residual disease positivity at an earlier time point (i.e., in the first 100 days after transplant) is associated with a lower risk of treatment failure compared to measurable residual disease positivity at a later point in time (i.e., 6 – 12 months after transplant), justifying the need for frequent post-transplant measurable residual disease monitoring.

Methods Used to Quantify Measurable Residual Disease

Studies have shown that bone marrow, as opposed to peripheral blood, provides the best estimate of measurable residual disease; hence, adequate bone marrow sampling is critical to ensuring accurate quantification of measurable residual disease. Hemodiluted samples can be falsely interpreted for a lower residual disease burden. For example, a patient may have a true measurable residual disease of 0.2 percent, but in a hemodiluted sample, the measurable residual disease could be inaccurately quantified as 0.05 percent due to the higher total number of cells in the sample. In order to avoid hemodilution, the sample for measurable residual disease assessment should be taken from the first bone marrow pull and should be limited to 2 – 5 milliliters (mL).[3] Once obtained, the sample should be immediately sent for processing.

There are several methods used to quantify measurable residual disease, including multiparameter flow cytometry (MFC), real-time quantitative polymerase chain reaction (RQ-PCR), and next-generation sequencing (NGS)-based assays.[3] This was an area of particular interest to both pilot program sites. At Inova Schar Cancer Institute, two different interventional radiology sites are used to pull bone marrow. Each site utilizes a different external lab for measurable residual disease testing, but both utilize the flow cytometry method to quantify measurable residual disease. Meanwhile, at Northwell Health Cancer Institute, an external lab has been used for years which utilizes flow cytometry to quantify measurable residual disease, but clinicians are discussing a shift to an FDA-approved NGS method. In fact, one of Northwell's primary goals during the pilot was to utilize the Roadmap to help determine which method of testing should be used for patients with B-cell acute lymphoblastic leukemia moving forward.

MFC is a widely available process that detects cells using fluorescent-labeled antibodies specific to cancer cell antigens.[1] MFC can reach a sensitivity of 0.01 percent or 0.001 percent and is applicable to nearly 100 percent of patients with acute lymphoblastic leukemia. The disadvantages of MFC include lack of standardization and quality control among different laboratories as well as the higher level of technical expertise required to conduct flow cytometry.[12] Additionally, targeted therapy can alter the immunophenotype of leukemic blasts, complicating the interpretation of measurable residual disease in these settings.[13] Thus, labs performing measurable residual disease assessments should be notified if rituximab, blinatumomab, inotuzumab, or tisagenlecleucel have been used.[14] Despite the limitations, flow cytometry is the most common method of measurable residual disease evaluation in the United States.

Molecular techniques for the assessment of measurable residual disease rely on quantification of leukemia-specific immunoglobulin (Ig) and/or T-cell receptor (TCR) rearrangements using RQ-PCR or NGS-based assays. RQ-PCR is routinely used to quantify measurable residual disease for patients with well-defined genetic abnormalities, such as the BCR-ABL1 fusion gene, at a sensitivity threshold of approximately 0.001 percent. However, for those without clearly defined genetic aberrations, leukemia-specific Ig/TCR rearrangements must first be sequenced for each patient with subsequent generation of patient-specific primers for measurable residual disease to be quantitated through RQ-PCR. This is known as allele-specific oligonucleotide (ASO)-based RQ-PCR and while it is applicable to 90 – 95 percent of acute lymphoblastic leukemia cases, it is not commonly used in the U.S. due to its labor-intensive process and high cost.

More recently, the development of NGS has overcome several limitations of RQ-PCR, allowing for highly sensitive analysis without the need to generate patient-specific oligonucleotides. In this method, PCR consensus primers are used to amplify the complete set of Ig or TCR gene sequences in a patient sample. Once amplified, the samples are sequenced by NGS technology, and any leukemia-specific rearrangements can be followed over time to measure disease burden. NGS is currently the most sensitive method for determining measurable residual disease, reaching a sensitivity of 0.0001 percent, and is applicable to 90 percent of acute lymphoblastic leukemia cases. Moreover, it is the only process approved by the FDA for use in acute lymphoblastic leukemia, and is commercially available as the clonoSEQ Assay from Adaptive Biotechnologies.[15] This assay is a send-out test from any medical center in the U.S., making measurable residual disease quantification more readily available regardless of patient location.

Among the three methods, MFC is the only approach that requires a fresh sample for analysis, whereas both fresh and stored samples can be used for RQ-PCR or NGS. Regarding the turnaround time, results are generally available within a few hours for MFC, within one week for RQ-PCR, and usually within two weeks for NGS.[3] As the various methods of measurable residual disease assessment differ in their sensitivities, a negative measurable residual disease status should always be reported with the sensitivity threshold (i.e., MRD less than 0.001 percent) to facilitate appropriate clinical decision making. Based on the differences in clinical utility, there is currently no gold standard method of assessment for measurable residual disease. Ultimately, the best method for measurable residual disease measurement is the method that is readily available to the patient and that can achieve a sensitivity of at least 0.01 percent.

In adult patients with acute lymphoblastic leukemia who are undergoing frontline treatment, measurable residual disease should be assessed after the end of induction, in early consolidation (after three months of therapy), and approximately every three months for at least three years (or five years for patients with Ph+ acute lymphoblastic leukemia who do not undergo stem cell transplantation in first remission). Patients with acute lymphoblastic leukemia who undergo stem cell transplantation should have measurable residual disease measured immediately prior to stem cell transplantation and about every three months after stem cell transplantation. For those with relapsed/refractory acute lymphoblastic leukemia on salvage therapy, measurable residual disease should be evaluated at morphological remission and at the end of treatment.[16]

Implementation of Measurable Residual Disease Testing

As cancer care programs prepare for implementation of measurable residual disease testing for acute lymphoblastic leukemia, the first step is to create a measurable residual disease task force and identify a physician champion, typically a hematologist/oncologist, who will spearhead the organization's efforts to institute testing.[17] Subsequently, it is important to identify all key stakeholders and ensure that they are represented on the task force and throughout operationalization. This should include administrators, clinical staff (e.g., physicians, advanced practice providers [APPs], pharmacists, nurses), laboratory staff (e.g., pathologists, laboratory managers, technicians), social workers, insurance/billing staff, financial navigators, and electronic health record (EHR)/information technology (IT) staff.

Once stakeholders are identified, the measurable residual disease task force should review the organization's options for testing to determine if in-house testing is feasible or if samples should be sent to an outside laboratory for analysis. Within the U.S., there are currently 26 facilities conducting measurable residual disease testing.[18] Generally, cancer centers should plan to send their samples out for testing, as it is usually not feasible for hospitals to set up an measurable residual disease lab, particularly in smaller community practices.

Cancer centers who plan to send patient samples to an external lab should contact multiple labs to identify the best match as a primary reference laboratory. This evaluation should not only review the logistics of sending and processing samples but should also delineate the financial responsibilities of both institutions. Measurable residual disease testing typically requires prior authorization from an insurance provider and send-out samples may result in out-of-network fees for patients. Some labs may cover the cost of testing if it is not covered by the patient's insurance, but it is also not uncommon for community centers to incur these costs. There are various patient assistance programs that can help alleviate cost burdens associated with measurable residual disease testing, which should be pursued by financial navigators or billing staff.[19]

It is important for the cancer center to assess its laboratory infrastructure to determine if it can collect and handle specimens, especially for send-out tests. Pathologists and laboratory personnel should lead the discussion on obtaining the necessary laboratory equipment. To ensure that samples are handled correctly, clinical and laboratory staff must be adequately trained to process and ship samples to the appropriate labs for testing.[20] All specimens should be processed within 24 hours of collection. The samples should be labeled with patient data as well as the specific laboratory analysis requested, and should be packaged in water-tight receptacles with room temperature gel-packs to provide temperature stability during transit.[20] Laboratory staff should have clear guidance on where to send tests if a reference laboratory is being used and should notify the receiving lab when a sample has been sent.

Tools and Resources for Implementation

One of the most important aspects of a successful implementation includes the provision of key tools and useful resources. This was a significant area of interest for Inova Schar Cancer Institute and Northwell Health Cancer Institute, who sought specific guidelines, protocols, and algorithms to guide its care teams through the measurable residual disease testing process.

At Inova Schar Cancer Institute, while most patients receive measurable residual disease testing at diagnosis and/or at some point during treatment, there is no clear protocol as to when testing should be done. One of the biggest challenges related to measurable residual disease testing is that there is currently no order for this type of testing as part of the bone marrow biopsy procedure order in Epic. Furthermore, such incorporation to the software may not happen for another one to two years. At Northwell Health Cancer Institute, there is a lack of clear clinical guidelines by the institute regulating which specific time points measurable residual disease testing should be conducted for patients with B-cell acute lymphoblastic leukemia. Most patients receive measurable residual disease testing after the completion of induction, but there is some variability at other time points due to provider discretion and lack of standardization.

For cancer programs preparing for implementation, the measurable residual disease task force should determine which standard operating procedures are necessary to have in place at the institution for testing and staff training purposes. Algorithms for diagnosis and follow-up are instrumental in guiding clinicians and laboratory staff through the process of testing and sending out samples. Experts recommend including flow cytometry with evaluation for CRLF2, chromosome analysis, FISH for t(9;22) BCR-ABL1, and DNA/RNA extraction and storage into the algorithm for initial workup.[17] The algorithm should highlight the standard set of tubes that need to be collected with every bone marrow collection, such as heparin tubes (for flow cytometry and cytogenetic tests) and EDTA tubes (for molecular tests), to ensure the availability of samples for all tests needed for complete evaluation. It is important to emphasize the proper method for obtaining a high-quality measurable residual disease sample, which consists of the first pull of the marrow aspirate in a 2 to 3-mL sample to avoid hemodilution.[20]

Along with algorithms, the institution's EHR should be optimized to facilitate measurable residual disease testing. Order sets can be developed that incorporate all necessary tests, if the EHR allows for it. Other options include utilizing check boxes or leaving comments in the order to indicate the need for measurable residual disease testing, which would trigger a process to reserve tubes for the testing. Some institutions rely on the clinician to put in the order for testing, resulting in a lab requisition form that the patient takes to the procedure team with clear instructions on what samples to obtain.[17] Each institution should determine the best way to utilize its EHR system to automate measurable residual disease testing as much as possible.

Patient education is a critical component for successful implementation of measurable residual disease testing and should be clearly communicated in various formats, including written documentation with verbal reinforcement. Providers should develop patient education materials that outline the purpose and process of measurable residual disease testing to better prepare patients for the rigors of testing. Trusted caregivers and family members should also be educated to help patients process the information.

Once the testing process has been launched, the measurable residual disease task force will need to re-evaluate the process on a recurring basis to identify issues and devise strategies to modify the workflow. For example, if there are inconsistencies regarding which bone marrow aspirates are used for measurable residual disease testing, then a clearer algorithm should be developed for ordering. As smaller community centers may not routinely conduct evaluations for measurable residual disease, there is a possibility that lab staff may not remember the workflow for how to process and send out samples, emphasizing the need to create detailed training documents and/or videos. As the field of measurable residual disease testing is continually evolving, institutions should be prepared to adapt to changes on a regular basis.

Pilot Program Insights

At Inova Schar Cancer Institute, the overarching goal was to utilize the Roadmap to help assess current processes and practices of measurable residual disease testing in B-cell acute lymphoblastic leukemia in their

outpatient setting. The assessment would then inform future opportunities for quality improvement work. At the end of the pilot, one representative (Jillian Powers, BSN, RN, OCN, and oncology nurse navigator, Malignant Hematology) said in reference to the Roadmap, "For programs starting up measurable residual disease testing or needing more guidance, this would be a great project for them. For us, we were already doing measurable residual disease testing, but it helped us recognize where our gaps are and what we can do in the meantime to make testing a little more efficient so that results are more timely, things are done properly and not missed, and everybody's on the same page."

At Northwell Health Cancer Institute, the goal was to utilize the Roadmap to help determine which method of measurable residual disease testing should be used moving forward for patients with B-cell acute lymphoblastic leukemia (i.e., flow cytometry vs. NGS) and to develop an accompanying protocol/pathway for the practice to follow. Several lessons were learned over the course of the pilot, including the importance of a clinical champion; importance of securing buy-in when switching measurable residual disease testing methods; involving pathology from the outset to explore their resource base and assess feasibility of measurable residual disease testing/testing method; ensuring sufficient training of staff who are pulling marrows and sending samples out; and continuing to educate non-clinical staff about the uniqueness and importance of measurable residual disease testing to further streamline administrative processes.

Both sites found the Roadmap usable and helpful as they worked toward implementing their goals. Sites agreed that the information was presented in an easy-to-follow format and appreciated the expert insights. Powers noted, "I liked the expert insights, it was helpful to see what other people are doing and say, 'oh yeah, we do that too or we don't do that.' But, just having ideas to pull from, or reassurance that we're doing things that other people are doing." David Chitty, DO, MSc, and assistant attending physician, Malignant Hematology at Northwell stated, "In some ways the Roadmap felt to me like an FAQ. If I knew what I was looking for, I would go down and find out what the recommendation, advice, or suggestion was from the expert."

In addition to the expert insights, both sites found the resources beneficial as well. Dr. Chitty said, "It was really helpful to have all of the studies in one place, and I could look at which protocols those studies were using, and if they lined up closer to what we would do and how we could translate it into practice." Moreover, Powers noted, "I think the Roadmap provides a lot of resources, not just research articles and scientific papers, but also Leukemia and Lymphoma Society resources that are available to patients. I would not have thought that the Leukemia and Lymphoma Society had a fact sheet that explains measurable residual disease testing or to even look for that. So, knowing that's there and in simple language that we can just pull off and provide to a patient to help them better understand what we're doing and why—that's helpful."

Both sites identified various opportunities for improvement and/or expansion of the Roadmap, including: additional opinions on when to conduct measurable residual disease testing, even if opinions are differing; a worksheet/flow diagram that outlines the steps one would need to take to set up measurable residual disease testing; key points/summary sentences at the end of each section; and additional algorithms, protocols, and tools to help implement measurable residual disease testing.

The Future

Measurable residual disease testing has become the gold standard for evaluating response in B-cell acute lymphoblastic leukemia. Numerous studies have demonstrated the prognostic significance of measurable residual disease status throughout treatment. Measurable residual disease-negativity has consistently been shown to lead to improved survival, while measurable residual disease-positivity directly correlates with a greater risk for relapse. Not only is measurable residual disease status an important prognostic factor, but it is also a powerful tool in the determination of treatment. The decision to use targeted therapy or to proceed to hematopoietic stem cell transplantation is often dependent on measurable residual disease status.

To optimize care for patients with acute lymphoblastic leukemia, cancer centers should implement measurable residual disease testing in their own capacity to be able to offer this testing to patients as a routine part of their disease management. ACCC's Measurable Residual Disease Testing Implementation Roadmap serves as a vital resource to help multidisciplinary cancer teams integrate and/or improve measurable residual disease testing at their institutions.

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