Written By: Tara Graff, DO, MS
Institution: Mission Cancer + Blood

Positive Quality Intervention: Advances in MRD Monitoring for Diffuse Large B-Cell Lymphoma (DLBCL)

Description: The purpose of this PQI is to assess an unmet need in the DLBCL patient population by enhancing the ability to evaluate treatment efficacy, monitor disease kinetics and remission, and detect early relapse.

Background: DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL), a malignancy originating in the lymphatic system. The median age at diagnosis is 70 years of age, and patients typically present with rapidly enlarging lymph nodes accompanied by both local and systemic symptoms. With currently available therapies, approximately 60% of patients are cured, and the median overall survival for patients with DLBCL is approximately 8 years. Following first-line (1L) therapy, assessment of disease relapse primarily depends on standard imaging and clinical evaluation. However, there is a growing need for more sensitive and specific testing modalities to detect minimal residual disease (MRD).

In NHL, MRD can be assessed using polymerase chain reaction (PCR) and next-generation sequencing (NGS) technologies that analyze circulating tumor DNA (ctDNA). One such NGS-based MRD assay, clonoSEQ®, is increasingly being adopted at leading cancer centers across the United States. While clonoSEQ is currently FDA-cleared for use in multiple myeloma (MM), B-cell acute lymphoblastic leukemia (B-cell ALL) and chronic lymphocytic leukemia (CLL), it is also CLIA-validated for DLBCL, mantle cell lymphoma (MCL), and other lymphoid malignancies. clonoSEQ received initial regulatory clearance for use in DLBCL in 2018. Most recently, in March 2025, Adaptive Biotechnologies launched an enhanced version of clonoSEQ for MRD detection in DLBCL. This updated assay allows ctDNA extraction from 3 mL to 10 mL of plasma derived from Streck-preserved blood samples, expanding its applicability and sensitivity in clinical monitoring.

The NCCN guidelines now recommend circulating tumor DNA (ctDNA) testing for minimal residual disease (MRD) assessment in DLBCL patients who are PET-positive at the end of frontline therapy. This updated guidance is intended to minimize the need for unnecessary biopsies and guide treatment decisions based on the ctDNA results.

PQI Process: DLBCL is typically identified through imaging and biopsy, along with immunohistochemistry (IHC) and next-generation sequencing (NGS) for more refined classification. Disease response and relapse have conventionally been monitored using imaging. However, measurable residual disease (MRD) testing via NGS now offers an additional method for detecting circulating tumor DNA (ctDNA), providing a more sensitive approach to monitoring. The clonoSEQ assay can be utilized for this purpose.

- A pre-treatment clonality (ID) sample with a high disease burden is required to identify the dominant sequences specific to the patient's tumor. clonoSEQ is a two-part assay: at least one dominant sequence must be identified in the clonality (ID) test before measurable residual disease (MRD) tracking can begin. Once identified, these sequences can be monitored over time using subsequent clonoSEQ tracking (MRD) blood tests.
- At the time of initial diagnosis, nearly all patients will have a lymph node biopsy and in many cases a bone marrow biopsy. Assessment of DLBCL patients can be obtained from a diagnostic specimen, including archived or stored specimen, typically FFPE from lymph node.
- For tracking (MRD) samples, the recommendation is to collect 2 x 10 mL of fresh peripheral blood (20 mL total) in Streck cell-free DNA BCT.

- If same-day shipment is not an option, store specimen at room temperature only (do not refrigerate or freeze).
- ctDNA originates from tumor cells and is released into the bloodstream through cell turnover (e.g., apoptosis, necrosis, shedding).[1-4]
- ctDNA is a subset of cfDNA and refers specifically to fragments of DNA from tumor cells circulating in the blood stream.
- ctDNA counts can be normalized to total cfDNA or plasma volume.[1,2]

MRD Testing can be performed:

- To evaluate disease kinetics, assess treatment response, and/or detect potential relapse early:
  - During frontline therapy (baseline, interim and end of treatment)[1,2,4,6]
  - Post-transplant[3]
  - Post-CAR T-Cell infusion[4] and Bispecific Antibody Therapy[5,7]
  - Periodically during surveillance monitoring[1,2]
- MRD testing can be utilized in conjunction with imaging initially.
  - For example, MRD assessment may be performed alongside interim imaging after a defined number of treatment cycles during first line therapy and at the end of treatment, to demonstrate concordance between the two modalities.
    - Once concordance is established, MRD testing can be employed independently in high-risk patients at intervals offset from imaging schedules or if there is an abnormal imaging finding that may not warrant a biopsy but requires further validation.

Patient-Centered Activities:

Explain MRD testing to the patient and what the utility of this testing is and how it can be applied.

- We are attempting to detect circulating DLBCL tumor DNA, a marker for disease burden, in the blood before it would show up on standard imaging or the patient would present clinically.
- Based on current literature, a negative MRD test does not mean that you can stop all cancer treatment; this decision will be best left to the treating physician
- Explain results to patients clearly, including how to interpret the test results
- Explain the data regarding MRD positive vs. negative status to patients
- Patient Assistance: NCODA Financial Assistance Tool

References:

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