Diagnostic and Monitoring Approaches Focused on Minimal Residual Disease

Miyoung Kim
Department of Laboratory Medicine, Asan Medical Center,
University of Ulsan College of Medicine, Korea

Minimal Residual Disease (MRD), or measurable residual disease, refers to the small fraction of cancer cells (typically $\leq 10^{-3}$) that remain after treatment and are undetectable by conventional microscopic or cytogenetic methods. As a primary driver of relapse, MRD serves as the most potent prognostic indicator in hematologic malignancies. Unlike baseline prognostic factors, MRD reflects a patient's in vivo chemosensitivity and drug metabolism post-intervention.

Effective MRD assessment requires high sensitivity and specificity to distinguish rare malignant cells from their normal counterparts. Clinical requirements for sensitivity vary by disease: $\leq 10^{-4}$ for B-cell acute lymphoblastic leukemia (B-ALL), $\leq 10^{-5}$ for plasma cell myeloma (PCM)—with both ideally reaching $\leq 10^{-6}$—and $\leq 10^{-3}$ for acute myeloid leukemia (AML).

In past, qPCR targeting specific translocations and multi-parameter flow cytometry (MFC) have been the mainstays of detection. qPCR still remains the preferred method when stable translocations are present, though its utility is limited by the low frequency of trackable mutations and a lack of standardized reagents for all variants. Flow cytometry employs two primary strategies. LAIP (Leukemia-Associated Immunophenotype): Identifies patient-specific aberrant markers (e.g., cross-lineage or asynchronous expression). However, it requires customized panels and can be hindered by immunophenotypic shifts during treatment. DFN (Different from Normal) focuses on common deviations from normal maturation patterns seen across most patients, reducing the need for baseline data or patient-specific panels. Recently next-generation sequencing (NGS) emerged as an MRD modality with high sensitivity and specificity. In lymphoid malignancies, NGS monitors clonal IG/TR V(D)J rearrangements. While highly effective for these lineages, NGS targets for other hematologic diseases are currently less standardized.

This lecture explores the evolving landscape of flow cytometry and NGS-based MRD analysis across various hematologic neoplasms.