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Research Paper

Optimizing the Management of Acute Leukemias Through Measurable Residual Disease Detection: An Integrated Approach

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Abstract
The detection of measurable residual disease (MRD) is revolutionizing the management of acute leukemias by providing a cutting-edge prognostic and therapeutic tool. Utilizing advanced techniques such as flow cytometry, real-time quantitative PCR, droplet digital PCR, and next-generation sequencing, MRD assessment enables evaluation of treatment response with sensitivities reaching 10^{-6}. This article examines the latest methodological advancements, clinical implications, and future perspectives of MRD in the personalization of treatment, relapse prediction, and optimization of therapeutic strategies, including hematopoietic stem cell transplantation.

Keywords: *measurable residual disease, acute leukemias, detection techniques, treatment personalization, prognosis.*

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I. Introduction

In a context where acute leukemias remain a major cause of morbidity and mortality, the emergence of measurable residual disease (MRD) as both a prognostic and therapeutic biomarker has transformed the management of these malignant hematologic disorders [1,2]. By enabling the detection of persistent leukemic cells at submicroscopic levels, MRD offers unprecedented sensitivity, surpassing traditional morphological methods, and guiding clinical decisions with increasing precision [3]. As of May 22, 2025, technological advancements in flow cytometry, quantitative PCR, and next-generation sequencing (NGS) have made the optimization of therapeutic strategies a top priority [4,5]. This paper aims to explore MRD detection methods, assess their impact on prognosis and treatment personalization, and propose future directions for their integration into a comprehensive approach to the management of acute leukemias, based on the latest available evidence

Clinical Context and Relevance

Measurable residual disease (MRD) detection is emerging as a cornerstone in the management of acute leukemias, including both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). By identifying residual leukemic cells at submicroscopic levels post-treatment, MRD outperforms traditional morphological assessments and informs therapeutic decisions [1,2]. Recent advances, notably the use of regimens such as RFC (rituximab, fludarabine, cyclophosphamide), have enabled MRD levels below 10^{-4}, associated with improved progression-free survival (PFS) and overall survival (OS) [6,7]. However, variability in detection methods and the need for standardization remain major challenges [3].

II. Advanced MRD Detection Methods

2.1 Molecular Approaches

- **Real-Time Quantitative PCR (qPCR):** The reference technique for molecular markers in AML, with sensitivity ranging from 10^{-4} to 10^{-6} depending on the targeted transcripts (e.g., MLL/HRX) [4]. DNA-based qPCR is recommended for gene junction detection [4].

- **Droplet Digital PCR (ddPCR):** Ideal for rare mutations such as NPM1, with promising results in a study at Lille University Hospital involving 40 patients [8]. It also targets IDH1/IDH2, DNMT3A-R882, among others [4].
- **Next-Generation Sequencing (NGS):** Offers high sensitivity but is limited by cost and DNA quality. Markers such as TET2, ASXL1, and IDH1/2 require combined analysis for optimal interpretation [4].

2.2 Multiparametric Flow Cytometry (MFC)

Flow cytometry detects blast cells based on abnormal protein expression (atypical markers, asynchronous patterns) [9]. Two main strategies are used:

- **LAIP (Leukemia-Associated Immunophenotype):** Tracks diagnostic immunophenotypic profiles.
- **dFN (Different-from-Normal):** Compares immunophenotypes to normal hematopoietic profiles.

Recent advancements now allow for the simultaneous analysis of up to 14 markers, though treatments such as immunotherapy may alter phenotypes [9]. A combined LAIP/dFN approach is preferred to maximize sensitivity [4].

III. Clinical Applications and Prognostic Impact

3.1 Assessment of Therapeutic Response

MRD levels measured between 2 and 6 months after treatment correlate with both progression-free survival and overall survival. An MRD level $<10^{-2}$ after immunochemotherapy improves OS, while MRD $<10^{-4}$ prolongs PFS [3]. Ultra-sensitive techniques like duplex sequencing detect persistent mutations, which are associated with higher relapse rates in AML [10,11].

3.2 Guiding Therapeutic Strategies

MRD status helps guide treatment intensification for MRD-positive patients in clinical remission or enables early intervention in those who relapse at the molecular level [12]. It also influences decisions regarding hematopoietic stem cell transplantation, optimizing outcomes for high-risk patients [12].

3.3 Predicting Relapse and Personalization

MRD kinetics can predict the timing of relapse, supporting the implementation of adapted maintenance therapies [8]. The integration of immune parameters further enhances prognostic precision and understanding of tumor dynamics [13].

IV. Challenges and Future Perspectives

Despite its high sensitivity, MRD assessment has limitations: a negative MRD result does not entirely exclude residual leukemic cells, as testing only covers a small fraction of total leukocytes [4]. Standardization of thresholds and protocols remains a major hurdle, requiring international harmonization [1]. Optimizing detection methods and integrating immune profiling could enhance the utility of MRD in both clinical trials and routine clinical practice [13].

V. Conclusion

MRD detection is reshaping the management of acute leukemias by enabling a personalized approach grounded in precise prognostic and therapeutic insights. Flow cytometry and molecular techniques (qPCR, ddPCR, NGS) serve as complementary tools, though their optimization and standardization are crucial. Integrating MRD into clinical trials and therapeutic decision-making may improve remission and survival outcomes, paving the way for precision medicine in hematology.

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