EDITORIAL

Recurrence of minimal residual disease in acute myeloid leukemia: a window of opportunity for intervention

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Measurable residual disease (MRD) assessment has emerged as the most important prognostic marker in the management of acute myeloid leukemia (AML).[1] A meta-analysis of 81 clinical studies with over 11,151 AML patients has shown that MRD-negative response is associated with approximately 50%-60% improved overall and disease-free survival compared to MRD positivity.[2] European LeukemiaNet (ELN) guidelines have recommended MRD monitoring in AML as a standard-of-care practice.[3] Real-world outcomes of MRD surveillance strategies are lacking. In this issue of *Haematologica*, Gong *et al*. analyze the trajectory of MRD recurrence in AML patients who achieved MRD-negative remission following induction chemotherapy.[4]

Starting with 1,744 newly diagnosed AML patients, they restricted their cohort to 767 patients who had achieved MRD-negative remission within two cycles of induction therapy. In this study, they used eight-color multi-parameter flow cytometry with high sensitivity (lower limit of detection 0.004%) and implemented a meticulous monitoring schedule: quarterly for 3 years, then biannually for another 2 years. MRD recurred in 22.3% of patients, with a median MRD level of 0.24%. Importantly, 34.5% of MRD-recurrent events were below the 0.1% threshold conventionally considered positive.[3] Subsequently, temporal patterns in MRD recurrence were identified, revealing that the median duration from MRD-negative complete remission to MRD recurrence was approximately 6 months, with an additional average period of 3.3 months elapsing before morphological relapse occurred. These intervals demonstrated significant variability based on risk stratification. Patients classified as favorable-risk exhibited extended intervals, averaging 7.5 months, whereas those designated as adverse-risk experienced shortened intervals of approximately 3.8 months. This information is critical for informing individualized monitoring strategies - more frequently for those with adverse-risk AML and less frequently for those with favorable-risk AML.

Next, the researchers conducted an analysis of their time-to-event data utilizing time-dependent Cox models to mitigate time-lag bias, as well as competing risk models to consider non-relapse mortality as a competing event when examining the association between MRD recurrence with overall survival and the cumulative incidence of relapse. The reliability of their findings was further enhanced by performing a sensitivity analysis that excluded patients lacking consecutive monitoring. MRD recurrence was an independent predictor of relapse and survival across age and ELN risk strata (overall survival: hazard ratio=7.807, $P \leq 0.001$). Survival for patients with minute MRD recurrence (<0.1%) and overt MRD recurrence (≥0.1%) was comparable.[4] These findings suggest modifications to the ELN-recommended MRD threshold of ≥0.1%,[3] and support redefining MRD positivity to include any detectable level.

Early intervention following MRD recurrence extended the time to morphological relapse from 1.7 to 4.2 months ($P=0.033$). Among patients receiving pre-emptive treatment, 32.1% achieved MRD negativity after one cycle, correlating with reduced relapse rates and prolonged survival. Achieving second MRD negativity after intervention reduced the relapse rate by 50% (37.7% *vs*. 66.0%) compared to that in patients with persistent MRD.

These findings have important clinical implications, described below.

Minimal residual disease cut-offs and standardization of minimal residual disease detection

The equivalence of outcomes between patients with minute or overt MRD recurrence underscores that any detectable MRD should be actionable. While multi-parameter flow cytometry remains the most accessible MRD platform globally, it is not without limitations. Its dependence on antibody panels, operator expertise, and subjectivity in identifying abnormal immunophenotypes makes it less standardized than highly sensitive molecular techniques such as error-corrected next-generation sequencing and

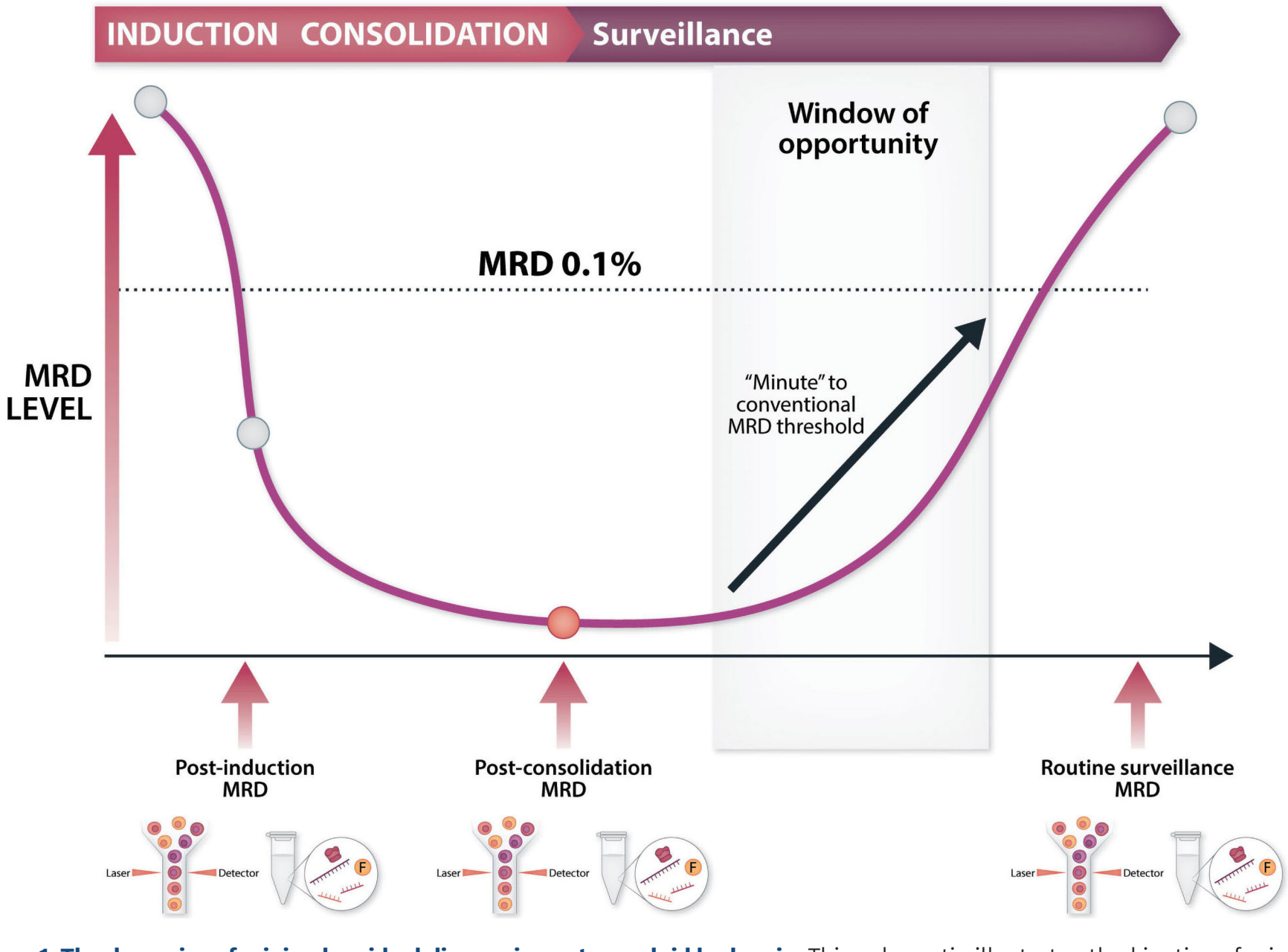

Figure 1. The dynamics of minimal residual disease in acute myeloid leukemia. This schematic illustrates the kinetics of minimal residual disease (MRD) during treatment and follow-up of acute myeloid leukemia. The burden of leukemic cells decreases sharply with induction therapy and is further reduced during the consolidation phase, reaching its lowest point. Following treatment, patients enter a surveillance period. A rise in MRD during this time, progressing from a minute level toward a conventional threshold (e.g., 0.1%), signals an impending relapse. This interval presents a critical "window of opportunity" in which detecting recurrence may allow for pre-emptive intervention before a full clinical relapse occurs.

digital droplet polymerase chain reaction, which can detect MRD levels down to 10^{-6}.[5] Future work should explore the additive prognostic value of the detection of MRD recurrence by multi-omic platforms, potentially integrating flow cytometry, targeted next-generation sequencing, and single-cell technologies. In addition, the best source (bone marrow, peripheral blood, or cell-free DNA) for MRD testing remains to be defined.[6,7] Kinetic modeling of MRD response and molecular relapse probability may refine risk-adapted therapy.[8] Furthermore, the frequency of MRD monitoring should be adapted to risk: more intensive in adverse-risk patients.

Early intervention at recurrence of minimal residual disease creates a therapeutic window

One of the most important take-away points from the study is the timing and trajectory of disease progression following MRD recurrence. The median interval from MRD recurrence to morphological relapse was just 3.3 months, and nearly half of patients who relapsed did so within 90 days. Although narrow, this window enables the implementation of MRD-guided therapy or timely referral for allogeneic hematopoietic stem cell transplantation. While the study by Gong *et al*. supports early therapeutic intervention after MRD recurrence, it does not definitively identify the optimal treatment approach. The use of hypomethylating agents or bridging to allogeneic stem cell transplantation was largely physician-dependent, and outcomes varied widely. Prospective trials are urgently needed to evaluate standardized, MRD-triggered interventions, potentially incorporating targeted agents. Ongoing trials (e.g., NCT06284486) are exploring MRD-targeted strategies, such as combining venetoclax and revumenib in *NPM1*-mutated and *KMT2A*-rearranged AML.[9] Sequential MRD tracking may also expedite drug development by serving as a surrogate endpoint for early efficacy.

Healthcare system readiness

MRD-guided management requires frequent bone marrow assessments and rapid turnaround of results. Institutions must develop infrastructure and protocols to ensure real-time MRD reporting and treatment decision-making within days not weeks of sample collection. As Gong *et al*. noted, interventions were typically initiated within 4 days of detection of MRD recurrence, a benchmark that may be difficult to replicate in less-resourced settings. Implementing frequent, high-sensitivity MRD monitoring with rapid turnaround is resource-intensive. Yet the potential to prevent relapse and facilitate curative therapies such as hematopoietic stem cell transplantation may justify these investments.[10]

In conclusion, Gong *et al*. provide definitive evidence that MRD recurrence, regardless of level, is a powerful predictor of relapse and survival in AML. Their work highlights the importance of high-sensitivity MRD detection, risk-adapted monitoring, and timely therapeutic escalation. As MRD transitions from a research biomarker to a clinical decision tool, it is imperative to redefine MRD thresholds, validate surrogate endpoints, and implement standardized MRD-guided care algorithms.

Disclosures

No conflicts of interest to disclose.

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