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Can Measurable Residual Disease (MRD) assessment be reliably used to defer allogeneic stem cell transplant in patients with intermediate-risk acute myeloid leukemia?

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Efforts to detect minute numbers of leukemic blasts and differentiate them from normal cells date back to the 1980s.(1) Immunofluorescence microscopy was the first method used to assess MRD, but it is no longer commonly used. More modern assays such as multicolor flow-cytometry (MFC), real-time quantitative polymerase chain reaction (RT-qPCR), next-generation sequencing (NGS), and PCR-NGS are significantly more sensitive tools to detect residual leukemic cells that are conceptually the cause of future relapse.(2) MRD is now routinely used in clinical practice as a guide to select post-remission therapies, including allogeneic hematopoietic stem cell transplant (AH SCT), especially in pediatric patients with acute lymphoblastic leukemia (ALL).(3, 4) Similarly, MRD is shown to be highly prognostic in specific subsets of acute myeloblastic leukemia (AML), such as acute promyelocytic leukemia (APL), core-binding factor leukemia, and NPM1 mutated AML.(5) This has led to significant recent interest in considering MRD detection as a potential endpoint in clinical trials. The European LeukemiaNet (ELN) has established guidelines for MRD assessment in specific subsets of AML.(6) However, the role of MRD testing in ascertaining the type of post-remission therapies remains to be fully characterized.

In this issue of the journal, Tettero et al. report the outcome of patients with intermediate-risk AML treated in the HOVON-SAKK132-trial (HO132, conducted from 2014 - 2017) who received MRD-guided post-remission therapy.(7) The study included a comparator arm of patients with intermediate-risk AML treated in other HOVON-SAKK trials (conducted from 2006 – 2013) who received post-remission treatment without planned MRD guidance. Both groups of patients were compared using propensity score match analysis. MRD was assessed by MFC and/or RT-PCR for NPM1 mutations after cycle 2 of treatment in responders.
One hundred fifty-three patients with intermediate-risk AML received MRD-guided post-remission therapy. Among them, 110 became MRD-negative, and 43 had persistent detectable MRD. Forty-four percent of MRD-negative patients received AHSC T even though the HO132 trial recommended non-AHSC T consolidation. Of note, half of these patients had a complex karyotype (46%), and a third achieved complete remission only after two courses of treatment. There was no difference in the event-free survival (EFS) of patients with MRD-positive and MRD-negative status (HR – 1.24; 95% CI, 0.75 – 2; p=0.42), and the 3-year EFS was 47% and 54%, respectively. Similarly, the overall survival (OS) was not significantly different (HR – 1.50; 95% CI, 0.85 – 2.64; p=0.16), with the 5-year OS of 54% and 65%, respectively. The observations were similar in the comparator arm, which included patients who received non-MRD-adapted consolidation therapies. The subgroup analysis comparing the outcomes of MRD-negative patients in both groups showed that the MRD-adapted consolidation approach did not significantly influence the survival (3-year EFS (HR – 0.86; 95% CI, 0.56 – 1.33; p=0.50) and 5-year OS (HR – 0.84; 95% CI, 0.5 – 1.4; p=0.50)) suggesting that AHSC T could be safely deferred in some patients without adversely effecting outcomes.

This study has a few limitations that need to be addressed. Firstly, intermediate-risk AML is a diverse population. Patients with FLT3, IDH, and RAS pathway mutations are categorized as intermediate-risk AML by the ELN 2022 AML risk stratification if they do not have favorable or adverse-risk characteristics. The study had 42 patients and 50 patients with FLT3 mutations in the MRD-guided and MRD-unguided groups, respectively. These patients did not receive FLT3 inhibitors as midostaurin was not approved at the time of treatment. Currently, the standard therapy for these patients involves the combination of midostaurin with intensive chemotherapy. The RATIFY trial demonstrated a longer median OS in patients who underwent AHSCT at first complete remission (CR1).(8) However, no MRD information was available from the RATIFY trial. Nevertheless, the post hoc analysis of patients treated on the trial showed that the 3-year cumulative incidence of relapse (CIR) in responders (with non-AML death and transplant as competing risks) was ~32% in midostaurin and 40% in the placebo arm. Similarly, in transplanted patients, the 3-year CIR (with non-AML death as a competing risk) was ~22% in midostaurin and 32% in the placebo arm.(9) This highlights the potential benefit of
consolidation ASHCT for improved outcomes in specific molecular subsets of AML. Recently, quizartinib in combination with intensive chemotherapy was evaluated in a phase 3 QuANTUM-First trial.\(^\text{(10)}\) FLT3-ITD-specific PCR-NGS technique, which has a sensitivity of \(10^{-4}-10^{-5}\), was used for MRD assessment in the trial.\(^\text{(11)}\) The investigators reported that the 3-year CIR was 34\% (95\% CI, 26 – 42 months) in the quizartinib arm as compared to 45\% (95\% CI, 37 – 53 months) in the placebo arm.\(^\text{(10)}\) Schlenk and colleagues reported that patients treated with quizartinib followed by AHSCT at CR1 had a significantly longer OS (HR, 0.424; 95\% CI, 0.3010.597; p <0.0001) than their counterparts treated with placebo, regardless of pre-AHSCT MRD status.\(^\text{(12)}\) This further signifies the importance of adding a FLT3 inhibitor in patients with FLT3-mutated AML receiving intensive chemotherapy. Other investigators have reported the outcomes of patients with FLT3-ITD mutated AML based on the pre-AHSCT MRD, assessed by FLT3-ITD PCR-NGS. They showed that 81\% of patients, who were FLT3-ITD MRD-negative by capillary electrophoresis, were MRD-positive by PCR-NGS. All those patients had inferior survival outcomes with a 3-year CIR of \(~70\%\).\(^\text{(13)}\) Intriguingly, the 3-year CIR was \(~20\%\) when FLT3-ITD PCR-NGS VAF was \(<0.001\%\) compared to 70\% in VAF \(<0.1\%\). The latter emphasizes the importance of a sensitive MRD assay and the prognostic significance of such highly sensitive assays.\(^\text{(14)}\) These data further support the importance of assessing MRD by a sensitive assay but do not yet support the decision to abandon AHSCT in specific subsets.

The optimal timing of MRD assessment in AML is not precise. In the HO132 trial, MRD assessment was performed after course 2. Whereas in other trials, such as the QuANTUM-First trial, MRD assessment was after the induction cycle. In the retrospective study by Australian colleagues,\(^\text{(13)}\) MRD was assessed after course 2 of chemotherapy. Clearly, standardization and harmonization of MRD assays as well as the timing of testing will be desirable to arrive at definitive recommendations for the use of MRD testing in selecting post-remission therapy.

MRD-adapted approach to select post-remission therapy is a compelling concept, especially in intermediate-risk AML, where alternative options for consolidation or maintenance may be coming available in the near future. While AHSCT is preferred in some molecular subtypes of AML, the higher transplant-related mortality (5 to 35\%) makes it less favored in others.\(^\text{(15)}\) Therefore, it is essential to identify patients in whom AHSCT is beneficial.
However, several questions must be addressed before this becomes an accepted approach. First, the ideal timing of the MRD assessment remains to be defined; this may also be influenced by the intensity of the induction regimen. Second, with the development of small molecule inhibitors, such as venetoclax and other targeted inhibitors, it may be possible to improve outcomes in patients with MRD-negative disease with non-intensive maintenance strategies rather than with consolidation AHSCT. Finally, highly sensitive MRD assays are required to identify patients with a very low risk of relapse who could then avoid a higher TRM.

We have witnessed this in patients with Philadelphia chromosome-positive ALL, where historical reliance on AHSCT for long-term remission has progressively diminished with the introduction of more effective agents. (16, 17) Furthermore, there are ongoing efforts to develop therapeutics that could eradicate MRD in AML, as has been seen with blinatumomab in patients with ALL. This is likely to further evolve our approach to consolidating remission in patients with AML.

Reference:


