Can measurable residual disease assessment be reliably used to defer allogeneic stem cell transplant in patients with intermediate-risk acute myeloid leukemia?

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Received: May 22, 2023.
Accepted: June 16, 2023.
Early view: June 22, 2023.

https://doi.org/10.3324/haematol.2023.283120

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 adopted to assess measurable residual disease (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 stem cell transplant (allo-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 has not yet been 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 (C2) of treatment in responders. One hundred and 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 allo-SCT even though the HO132 trial recommended non-allo-SCT 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 (Hazard Ratio [HR]: 1.24; 95% Confidence Interval [CI]: 0.75-2; *P*=0.42), and the 3-year EFS was 47% and 54%, respectively. Similarly, there was no significant difference in overall survival (OS) (HR: 1.50; 95% CI: 0.85-2.64; *P*=0.16), with 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 allo-SCT could be safely deferred in some patients without adversely affecting 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 had not been 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 allo-SCT 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 approximately 32% in the midostaurin and 40% in the placebo arms. Similarly, in transplanted patients, the 3-year CIR (with non-AML death as a competing risk) was approximately 22% in the midostaurin and 32% in the placebo arms.[9] This highlights the potential benefit of consolidation allo-SCT to improve outcomes in specific molecular subsets of AML. Recently, quizartinib in combination with intensive chemotherapy was evaluated in the phase III QuANTUM-First trial.[10] This trial used a *FLT3*-ITD-specific PCR-NGS technique, which has a sensitivity of 10^{-4}-10^{-5}, for MRD assessment.[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.[10] Schlenk and colleagues reported that patients treated with quizartinib followed by allo-SCT at CR1 had a significantly longer OS (HR: 0.424; 95% CI: 0.301 - 0.597; P<0.0001) than their counterparts treated with placebo, regardless of pre-allo-SCT MRD status.[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-allo-SCT 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 these patients had inferior survival outcomes with a 3-year CIR of approximately 70%.[13] Intriguingly, the 3-year CIR was approximately 20% when *FLT3*-ITD PCR-NGS variant allele frequency (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 using such highly sensitive tests.[14] These data further support the importance of assessing MRD by a sensitive assay, but do not yet support the decision to abandon allo-SCT in specific subsets.

There is no precise optimal timing of MRD assessment in AML. In the HO132 trial, MRD assessment was performed after C2, whereas in other trials, such as the QuANTUM-First trial, MRD assessment was made after the induction cycle. In the retrospective study by Australian colleagues,[13] MRD was assessed after C2 of chemotherapy. Clearly, standardization and harmonization of MRD assays, as well as the timing of testing, will be desirable in order to arrive at definitive recommendations for the use of MRD testing in selecting post-remission therapy.

The use of an 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 become available in the near future. While allo-SCT is preferred in some molecular subtypes of AML, the higher transplant-related mortality (TRM) (5-35%) makes it less favored in others.[15] Therefore, it is essential to identify patients in whom allo-SCT is beneficial. However, several questions must be addressed before this becomes an accepted approach. First, the ideal timing of the MRD assessment still has 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 allo-SCT. 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 allo-SCT 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 see our approach towards consolidating remission in patients with AML evolve further.

Disclosures

MS and FR have no relevant conflicts of interest to disclose.

Contributions

MS and FR wrote and revised the manuscript.

References

1. Bradstock KF, Papageorgiou ES, Janossy G, et al. Detection of leukaemic lymphoblasts in CSF by immunofluorescence for terminal transferase. Lancet. 1980;1(8178):1144.
2. Grimwade D, Freeman SD. Defining minimal residual disease in acute myeloid leukemia: which platforms are ready for "prime time"? Blood. 2014;124(23):3345-3355.
3. Pui CH, Pei D, Coustan-Smith E, et al. Clinical utility of sequential minimal residual disease measurements in the context of risk-based therapy in childhood acute lymphoblastic leukaemia: a prospective study. Lancet Oncol. 2015;16(4):465-474.
4. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2013;14(3):199-209.
5. Short NJ, Ravandi F. How close are we to incorporating measurable residual disease into clinical practice for acute myeloid leukemia? Haematologica. 2019;104(8):1532-1541.
6. Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021;138(26):2753-2767.

7. Tettero JM, Ngai LL, Bachas C, et al. Measurable residual disease-guided therapy in intermediate-risk acute myeloid leukemia patients is a valuable strategy in reducing allogeneic transplantation without negatively affecting survival. Haematologica. 2023;108(10):2794-2798.
8. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
9. Larson RA, Mandrekar SJ, Huebner LJ, et al. Midostaurin reduces relapse in FLT3-mutant acute myeloid leukemia: the Alliance CALGB 10603/RATIFY trial. Leukemia. 2021;35(9):2539-2551.
10. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10388):1571-1583.
11. Levis MJ, Erba HP, Montesinos P, et al. QuANTUM-First trial: FLT3-ITD-specific MRD clearance is associated with improved overall survival. Blood. 2022;140(Suppl 1):546-548.
12. Schlenk R, Montesinos P, Romero-Aguilar A, et al. Impact of allogeneic hematopoietic cell transplantation in first complete remission plus FLT3 inhibition with quizartinib in acute myeloid leukemia with FLT3-ITD: results from QuANTUM-First. EHA: 2023 5/11/23. https://library.ehaweb.org/eha/2023/eha2023-congress/387837/richard.schlenk.impact.of.allogeneic.hematopoietic.cell.transplantation.in.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dimpact+allogeneic+hematopoietic+cell+transplantation+complete+remission+plus+flt3+inhibition+quizartinib+acute+myeloid+leukemia+flt3-itd%3A+results+quantum-first.
13. Loo S, Dillon R, Ivey A, et al. Pretransplant FLT3-ITD MRD assessed by high-sensitivity PCR-NGS determines posttransplant clinical outcome. Blood. 2022;140(22):2407-2411.
14. Dillon LW, Gui G, Page KM, et al. DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant. JAMA. 2023;329(9):745-755.
15. Loke J, Malladi R, Moss P, Craddock C. The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: a triumph of hope and experience. Br J Haematol. 2020;188(1):129-146.
16. Ghobadi A, Slade M, Kantarjian H, et al. The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis. Blood. 2022;140(20):2101-2112.