COMMENTARY

Treatment options for adult intermediate-risk AML patients in CR1: Allo-HSCT or chemotherapy?

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Acute myeloid leukemia (AML), which is the most common form of acute leukemia in adults, is a heterogeneous, clonal hematopoietic disorder characterized by the accumulation of immature myeloid progenitors. This heterogeneity is especially obvious in the "intermediate-risk group" as defined by international criteria such as those of the European LeukemiaNet, Medical Research Council (MRC), and National Comprehensive Cancer Network. However, with new molecular markers being identified by polymerase chain reaction, next-generation sequencing (NGS), and other new methods, which could predict the prognosis, patients who were originally classified into the intermediate-risk group are reclassified into the favorable-risk group or the adverse-risk group according to their prognosis. Nevertheless, the intermediate-risk group still accounts for the largest proportion of patients (50%–60%) and is the most heterogeneous subgroup of AML in adults. Thus far, the postremission treatment (PRT) options for these patients remain controversial. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is not presented as an option for most AML patients in the favorable-risk group but is recommended for patients in the adverse-risk group. However, whether allo-HSCT can benefit patients in the intermediate-risk group remains unknown.

Recently, Bornhäuser et al.[1] presented the data from a multicenter study (ETAL-1 trial) in patients with intermediate-risk AML after the first complete remission (CR1), which was the first randomized trial mainly aimed at comparing the clinical outcomes between allo-HSCT and standard consolidation chemotherapy. Allo-HCST was associated with a lower 2-year cumulative incidence of relapse (20% versus 58%, $p < 0.001$) and a better 2-year probability of disease-free survival (DFS) (69% versus 40%, $p = 0.001$); however, the overall survival (OS) (i.e., the primary endpoint) was comparable between the allo-HSCT and conventional consolidation chemotherapy groups. This study presented valuable evidence for PRT options in adult AML patients, and the authors concluded that allo-HSCT may be delayed until first relapse in intermediate-risk AML in CR1.

The biggest benefit of allo-HSCT over chemotherapy is relapse reduction due to the intensive conditioning regimen and the graft-versus-leukemia (GVL) effect. In other words, the goal of treatment for most patients proceeding to allo-HSCT is cure and not temporary disease control. However, in the ETAL-1 trial, the primary endpoint was OS, which may have led to an underestimation of the merits of allo-HSCT.[1] Emerging new drugs (e.g., venetoclax and ivosidenib) have been shown to prolong the life of patients who relapse after previous therapies, but most of them only control the disease temporarily, and the long-term outcomes of patients are still very poor. Clinical trials could help relapsed AML patients benefit from novel drugs; however, few such patients are enrolled owing to stringent inclusion and exclusion criteria. In addition, many relapsed patients cannot afford the economic burden of persistent treatment with new drugs, particularly those patients from developing countries. Thus, in the real-world treatment of AML, relapse often means the failure of treatment, with minimal hope of cure. Therefore, leukemia-free survival (LFS) may be a more appropriate primary endpoint to compare the efficacy of allo-HSCT and chemotherapy. In the ETAL-1 study, 41 patients in the chemotherapy group relapsed and proceeded to allo-HSCT, which may improve the survival outcomes of the chemotherapy group in the intention-to-treat analysis for OS. Considering LFS, allo-HSCT is significantly superior to chemotherapy in intermediate-risk AML patients.

In the ETAL-1 trial, intermediate-risk AML was classified according to the MRC classification, which was proposed in 2010 and is based on cytogenetic abnormalities. While the use of this classification scheme was appropriate at the beginning of the trial, it does not reflect the current guidelines for classifying of AML patients. The study was started nearly 12 years ago (February 2, 2011, to July 1, 2018), and the criteria for AML classification have progressed from ELN 2017 to ELN 2022. An increasing number of molecular markers were identified and used to stratify intermediate-risk patients into subtypes with the widespread use of NGS. Thus, a substantial portion of patients in the study would now be categorized in the adverse-risk group or favorable-risk group based on the ELN 2022 criteria. In fact, nearly one-third of the patients in the study should have been classified as favorable-risk according to the ELN 2017 criteria, and most of them could benefit from standard consolidation chemotherapy alone. Given the evolving risk stratification criteria, the PRT options for intermediate-risk AML patients are complicated and should be continuously updated.

Measurable residual disease (MRD) refers to the detection of malignant cells by a more precise method (i.e., multiparameter flow cytometry [MFC]) in patients without AML blasts on morphological examination. MRD has been considered as one of the most important markers to predict relapse after chemotherapy and can help guide intensive consolidation therapies, including allo-HSCT. MFC and polymerase chain reaction are the most commonly used approaches for MRD monitoring. Recently, NGS-based MRD detection has helped to more accurately identify patients who have a higher risk of relapse.[2] Several studies have reported that intermediate-risk AML patients with persistent MRD positivity may benefit more from allo-HSCT. In the pivotal GIMEMA AML1310 trial, MRD-positive (determined by MFC) intermediate-risk AML patients receiving allo-HSCT had OS and DFS rates similar to those of MRD-negative intermediate-risk patients receiving autologous HSCT, which highlighted the potent antileukemic effect exerted by allo-HSCT in intermediate-risk patients with MRD positivity.[3] In addition, Jentzsch et al.[4] reported that for intermediate-risk AML patients who were MRD positive during the second remission, the posttransplant relapse rate was higher than 80%, and the authors suggested that allo-HSCT should be avoided in these patients. Considering that not all patients can achieve MRD negativity after the first relapse, a substantial portion of them may lose the chance for allo-HSCT. Thus, the conclusion that allo-HSCT can be delayed until first relapse in all intermediate-risk AML-CR1 patients without considering the MRD status may be premature. Furthermore, the randomization did not take MRD status into account, and this may be a potential confounding factor in the final analysis in the ETAL-1 trial. Besides, 27% and 38% of patients in the allo-HSCT and chemotherapy groups, respectively, were MRD negativity and could have achieved persistent survival using consolidation chemotherapy. This fact may explain the comparable OS between the allo-HSCT and chemotherapy groups in this study.

Only HLA-matched sibling donors or unrelated donors were chosen as donors in the ETAL-1 study, which may have partially contributed to the slow accrual of the study. With the application of antithymocyte globulin or posttransplant cyclophosphamide, haploidentical-related donors have become the most important alternative donor, with more than 60% of allo-HSCT procedures employing

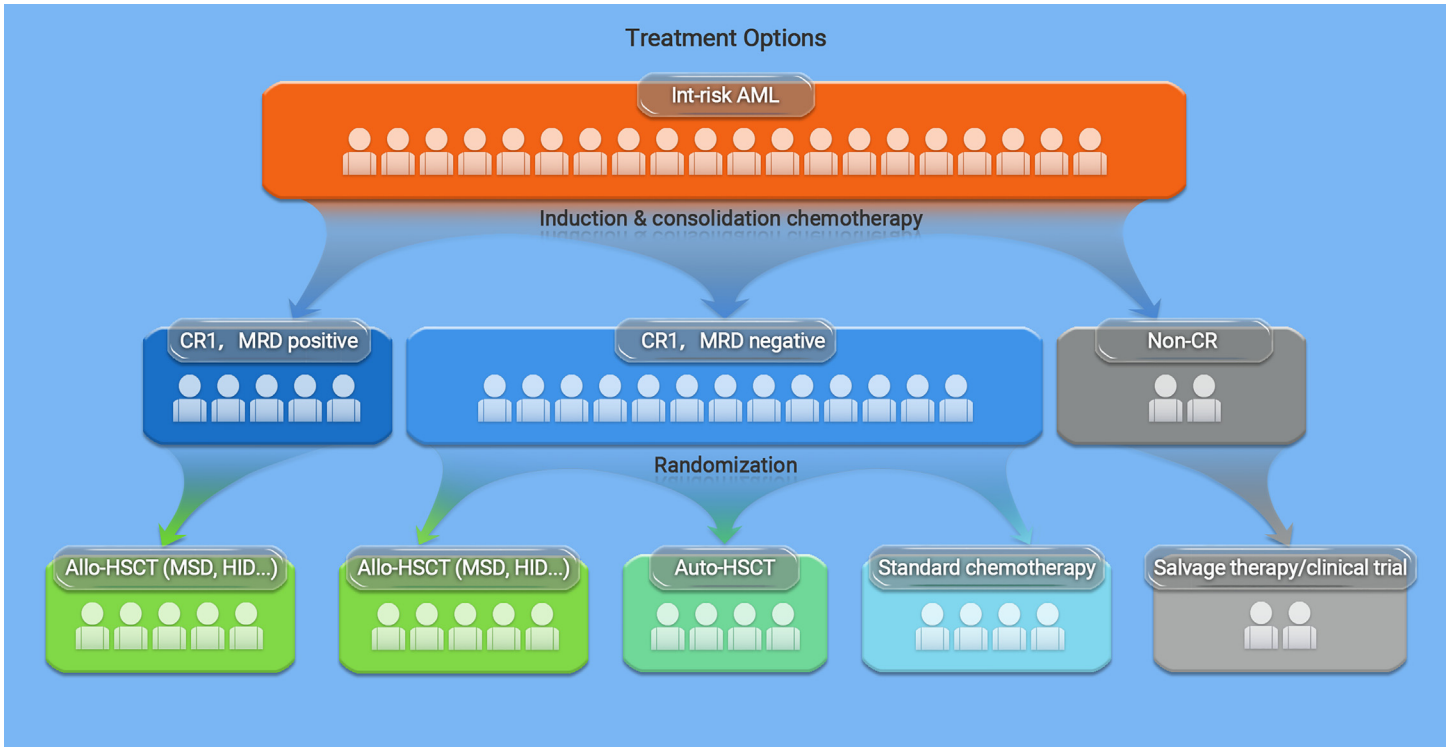

Figure 1. The proposed paradigm of the MRD-directed randomized trial in adult intermediate-risk AML patients

haploidentical-related donors in China since 2019. Allo-HSCT procedures employing such donors show a stronger GVL effect than those employing matched sibling donors, and this may help to overcome the adverse impacts of pretransplant MRD positivity on clinical outcomes in AML patients. The rapid development of haplotype transplantation has ushered in a new era where "everyone has a donor," and haploidentical HSCT is one of the most important strategies for allo-HSCT. Moreover, the accessibility of allo-HSCT in China has increased in recent years because many of the transplant expenses can be covered by social medical insurance. In a prospective study, Lv et al.[5] reported that the OS and LFS of myeloablative haploidentical HSCT were superior to those of chemotherapy as PRT in patients with intermediate-risk AML in CR1. Thus, an allo-HSCT group without cases of haploidentical-related donors is insufficient to compare the efficacy and safety with those of chemotherapy in intermediate-risk AML patients.

In conclusion, although the ETAL-1 trial presented valuable data for PRT options in intermediate-risk AML patients, whether these patients should receive allo-HSCT or standard consolidation chemotherapy is still controversial, and many of them may still need to receive allo-HSCT to achieve persistent LFS. The 2-year nonrelapse mortality incidence of allo-HSCT recipients was only 9% in the ETAL-1 trial, suggesting that the safety of allo-HSCT has been significantly improved and that the benefit of the GVL effect can be maximally restored. Randomized trials using state-of-the-art risk stratification and including post-treatment MRD status may help to further compare the outcomes between allo-HSCT and standard consolidation chemotherapy in intermediate-risk AML patients, and cases employing haploidentical-related donors should be included in the allo-HSCT group (Figure 1).

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DECLARATION OF INTERESTS

The authors declare no competing interests.