



# Biology of Blood and Marrow Transplantation

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## The Art of Transplantation: Conditioning Intensity for Allogeneic Hematopoietic Stem Cell Transplantation

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### A B S T R A C T

The search for the optimal conditioning regimen before allogeneic hematopoietic stem cell transplantation (HCT) for acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) has been ongoing for decades. In this issue, Solh et al present an original analysis evaluating the impact of conditioning intensity on different disease risk index (DRI) groups of patients with AML and MDS. An impressive difference was observed in outcomes between reduced-intensity conditioning and myeloablative conditioning (MAC) regimens in the low/intermediate-risk disease groups, supporting the use of MAC in this population. Further prospective trials in this population are encouraged.

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The search for the optimal conditioning regimen before allogeneic hematopoietic stem cell transplantation (HCT) for acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) has been ongoing for decades [1,2]. Early conditioning regimens consisted of high-dose chemotherapy and radiation, now characterized as myeloablative conditioning (MAC), to achieve the aspired outcome of eliminating malignant disease with concomitant restoration of normal hematopoiesis. With experience and improved understanding of the graft-versus-leukemia effect, investigators began to lower the intensity of conditioning regimens.

With the advent of reduced-intensity conditioning (RIC) regimens, HCT has become an available modality to treat a significantly underserved population of patients of advanced age with MDS/AML and complex comorbidities. Once RIC regimens were being used successfully in practice, determining which patients might benefit most from the use of a less intensive regimen became paramount. Several prospective and retrospective studies have compared RIC and MAC conditioning regimens before HCT for AML and MDS, and there has been a significant effort to determine which intensity yields better outcomes while accounting for disease and patient characteristics.

In this issue, Solh et al [3] present an original analysis evaluating the impact of conditioning intensity on different disease risk index (DRI) groups of patients with AML and MDS. Although this is the first retrospective analysis to evaluate

outcomes based on the DRI, numerous other investigations have addressed how best to use MAC versus less intensive conditioning strategies, with somewhat conflicting results [2,4–10]. Solh et al sought to determine whether the conditioning regimen intensity impacted outcomes in patients when stratified by the DRI. For patients classified by the DRI as low/intermediate risk, compared with recipients of RIC, recipients of MAC had significantly better 3-year overall survival (OS) and disease-free survival (DFS), a lower relapse rate, and similar nonrelapse mortality (NRM). These findings are thought-provoking, and the authors propose a plausible biological cause, even though previously published evidence supports non-HCT treatment modalities over HCT in low/intermediate 1-risk MDS and cautious patient selection for HCT in intermediate-risk AML [11,12]. For high/very high-risk patients, there was no difference in OS, DFS, relapse, or NRM between patients receiving RIC and those receiving MAC.

Several recent studies exploring high-risk populations support those findings [8,10], including a recent analysis by Veltri et al [13] evaluating HCT in high-risk AML patients age  $\geq 65$  years. A recent analysis by Gilleece et al [14] confirmed no difference between MAC and nonmyeloablative (NMA) conditioning/RIC, except in AML patients age  $< 50$  years with positive minimal residual disease (MRD), a population that benefited from MAC over RIC/NMA. Solh et al did not comment on MRD status pre-HCT, although this is known to be an important variable that can have a major impact on outcomes post-HCT. There are also recent conflicting data regarding patients with secondary AML, a known high-risk population, in whom MAC was determined to be superior to RIC based on improved OS and decreased cumulative incidence of relapse [15].

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Before these findings can be widely adopted in practice, several factors must be considered. A significant issue in the evaluation of conditioning regimen intensity is the variety of conditioning regimens used, which may be better classified along a spectrum of intensity rather than grouped as RIC or MAC, particularly when assessed in a retrospective manner [16,17]. In this analysis, several different MAC and RIC regimens were evaluated, and it is conceivable that not all regimens classified as RIC or MAC are of equal intensity. Furthermore, how a moderate-intensity strategy might compare to MAC in the low/intermediate-risk population is also of interest.

Because most readers tend to acknowledge the results that he or she most agrees with, the reader is left with the assurance that using a less intensive strategy for a high-risk population can be pursued without compromising outcomes. And although there did appear to be an impressive difference in outcomes between RIC and MAC regimens in the low/intermediate-risk disease groups, supporting the use of MAC in this population, further prospective trials in this population are encouraged. The bottom line is that the quandary regarding the best choice of conditioning intensity remains, regardless of disease risk, and that even with scientific guidance for selecting conditioning regimen intensity, the art of transplantation is such that conditioning intensity remains a personalized, patient-specific decision at the discretion of the treating physician.

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