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Conditioning for acute myeloid leukemia: looking beyond intensity

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Running Title: Beyond intensity in AML conditioning

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Contributions

JG and FM co-wrote the editorial.

Myeloid neoplasms predominantly affect older adults, many of whom are not candidates for standard myeloablative conditioning (MAC) prior to allogeneic hematopoietic stem cell transplantation (HSCT). Yet HSCT remains the only potentially curative therapy for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), making the choice of conditioning regimen a critical determinant of outcome. Reduced-intensity conditioning (RIC) regimens were introduced to decrease non-relapse mortality (NRM), but this reduction has often been accompanied by higher relapse rates.[1] Identifying a conditioning platform that preserves antileukemic efficacy while minimizing toxicity therefore remains a central challenge in contemporary transplantation.

Treosulfan, a hydrophilic bifunctional alkylating agent, has emerged as an attractive alternative to conventional busulfan-based approaches[2,3]. Its favorable organ toxicity profile, consistent engraftment, and immunosuppressive potency have led to its classification as a reduced-toxicity conditioning backbone, positioned between traditional MAC and RIC platforms[4]. In this context, a multicenter randomized phase 3 non-inferiority trial published in 2020 compared treosulfan (10 g/m² body surface area IV from days −4, to −2) plus fludarabine (treo/flu) with reduced-intensity busulfan (3.2 mg/kg IV days −4, −3) plus fludarabine (bu/flu) in patients with AML or MDS undergoing allo-HSCT who were considered at increased risk for NRM due to age and/or comorbidities.[5] Although designed to demonstrate non-inferiority with respect to 2-year event-free survival (EFS), the study not only met its primary endpoint but showed superiority of treosulfan, with significantly improved EFS and overall survival, largely driven by a reduction in NRM.

In the current issue of Haematologica, Stölzel et al. report a dedicated AML subgroup analysis of the previously published randomized phase 3 trial, focusing on graft-versus-host disease (GVHD) and graft-relapse-free survival (GRFS) among the 352 patients with AML enrolled in the study.[6] Consistent with the primary report, patients receiving treo/flu demonstrated superior 24-month EFS (65% vs. 53%, p=0.01) and overall survival (73% vs. 65%, p=0.03) compared with those receiving bu/flu, with the Kaplan–Meier curves for EFS separating within the first 6–9 months after HSCT.

Non-relapse mortality at 24 months numerically favored treo/flu (8.4% vs. 14.7%), while relapse rates were similar between the two groups, suggesting that the survival advantage was not driven by improved disease control. Acute GVHD occurred at comparable rates in both arms; however, the incidence of extensive chronic GVHD was significantly lower in the treo/flu group (15.1% vs. 28.1%, p=0.01). Importantly, the benefit of treosulfan was particularly pronounced among patients with higher comorbidity burden (HCT-CI >2), in whom both EFS and overall survival differences were magnified. This interaction between baseline vulnerability and conditioning platform strengthens the hypothesis that cumulative organ stress plays a central role in determining transplant outcomes in this population. Collectively, these findings suggest that the survival difference is largely attributable to reduced late toxicity, particularly chronic GVHD, which in turn may contribute to lower NRM and improved long-term outcomes.

Thus, compared with RIC bu/flu, treo/flu appears to confer a clinically meaningful advantage in older or comorbid patients with AML, largely through improved tolerability and a lower burden of chronic GVHD. Busulfan-related toxicities commonly involve the gastrointestinal tract, liver (including sinusoidal obstruction syndrome), and lungs,[7] organs that also represent classic targets of chronic GVHD. In contrast, treosulfan's active metabolite (monoepoxide) achieves relatively low concentrations in these tissues.[8] Although the precise mechanisms linking conditioning regimen to chronic GVHD remain incompletely defined, reduced gastrointestinal injury with treosulfan could theoretically limit exposure of host antigens and attenuate allo-reactive immune activation. One may therefore speculate that, in the busulfan arm, overlapping regimen-related toxicity and chronic GVHD create a cumulative burden that contributes to higher NRM, whereas this "double-hit" effect may be mitigated with treosulfan-based conditioning.

An important and significant caveat of the trial is that it was conducted before the widespread adoption of post-transplant cyclophosphamide (PTCy), which has since become a standard approach for GVHD prophylaxis across donor platforms. The incorporation of PTCy may attenuate differences in chronic GVHD between conditioning regimens and could potentially narrow the survival gap observed between the two arms. Accordingly, future studies integrating contemporary GVHD prophylaxis strategies are essential to determine whether the advantages associated with treosulfan persist in the current transplant landscape.

Beyond GVHD prophylaxis, comparative effectiveness remains an open question. Treosulfan-based conditioning should be evaluated not only against reduced-intensity busulfan, but also against myeloablative platforms and other commonly used reduced-intensity regimens. Given the widespread use of fludarabine/melphalan conditioning, randomized head-to-head comparisons between melphalan- and treosulfan-based regimens are warranted to define the optimal preparative strategy for older or comorbid patients with AML. Dose optimization also warrants further investigation. It is important to note that in the randomized trial and the AML subgroup analysis by Stölzel et al., treosulfan was administered at 10 g/m² per day. Whether alternative dosing strategies could further refine outcomes remains an open question. Higher-dose treosulfan regimens (e.g., 14 g/m²/day for three consecutive days) have demonstrated activity in other settings and may offer additional opportunities to fine-tune the balance between antileukemic efficacy and regimen-related toxicity.[9]

In light of the subgroup analysis presented by Stölzel et al., it may be time to reconsider how we define and prioritize conditioning intensity in older patients with comorbidities with AML. Their findings suggest that the distinction between "reduced-intensity" and "myeloablative" conditioning may be less informative than an assessment of cumulative toxicity and its long-term consequences. Ultimately, optimization of conditioning regimens must account not only for disease eradication and engraftment, but also for the late toxicities that may determine whether the curative intent of transplantation is fully realized.

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