EDITORIAL

(Donor) age is more than just a number…

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In this issue of Blood and Marrow Transplantation, Nagler et al. provide a timely analysis of registry data from the EBMT regarding outcomes of alternative donor transplantation for patients with acute myeloid leukemia (AML) in first remission in the era of post-transplantation cyclophosphamide (PTCy)-based graft versus host disease (GVHD) prophylaxis [1]. The authors compare outcomes in patients receiving grafts from younger (<35 years) haploidentical donors with those receiving transplants from older (≥ 35 years) mismatched unrelated donors. Alternatively, they also compared outcomes in patients with older haploidentical donors versus younger mismatched unrelated donors. In both comparisons, selection of a younger donor was associated with a significantly lower risk of grade II-IV acute GVHD, although it appears this is largely a consequence of a reduction in grade II acute GVHD. For patients receiving grafts from younger mismatched unrelated donors, this also translated into a lower likelihood of non-relapse mortality compared with those transplanted from older haploidentical donors. Importantly, in both analyses there were no differences in overall survival within two years post-transplantation, which one might speculate relates to the fact that grade II acute GVHD is relatively unlikely to result in life-threatening complications. Another important finding in this study, consistent with data from other analyses [2, 3], is that infections were a more frequent cause of death among patients receiving haploidentical grafts, regardless of donor age, suggesting that immune reconstitution after haploidentical transplantation is less functionally robust during the early post-transplant period.

The effect of donor age on recipient outcomes has been subject to study for several decades, and this analysis serves to reinforce existing data. The National Marrow Donor Program incorporates donor age into unrelated donor selection guidelines, as large retrospective studies have previously demonstrated improved survival, in addition to lower rates of grade III or IV acute GVHD and chronic GVHD, with younger donors [4]. More recent studies have supported the prioritization of younger donors in haploidentical transplantation with posttransplant cyclophosphamide [5]. In patients with AML age ≥ 50 years undergoing HSCT, the use of younger matched unrelated donors was associated with decreased relapse risk and improved disease-free survival compared to older matched sibling donors [6]. A recent study from the ALWP of the EBMT concluded that unrelated donor age may even supersede one allele mismatch for patients with AML undergoing HSCT with PTCy [4]. This study by Nagler et al. is important because it explores the question specifically among patients who lack an HLA matched donor, and points to the importance of donor age in the setting of PTCy prophylaxis.

Although this article does not explore the mechanisms by which donor age impacts outcomes in HSCT with PTCy, multiple recent publications have speculated that enhanced immune reconstitution (perhaps due to increased proportion of naïve T-cells in younger people), improved functionality of donor-derived T- and NK-cells, increased hematopoietic stem cell number and fitness, and lower risk of transfer of clonal hematopoiesis may all contribute to superior outcomes when younger donors are utilized.

PTCy has revolutionized HSCT by reducing transplant-related mortality and GVHD and offers the possibility of potentially curative therapy for a wider spectrum of patients in need, particularly those in racial and ethnic groups not well represented in the registries [7]. This article is one of the first to investigate outcomes in AML with both mismatched unrelated and haploidentical donors incorporating the PTCy platform. While this publication includes patients with AML, comparisons between mismatched unrelated and haploidentical donors with PTCy in other hematologic malignancies remains an area of active research. Notably, a recent study examining alternative donor selection in patients with acute lymphoblastic leukemia (ALL) in CR using PTCy-based GVHD prophylaxis also showed higher rates of grade II acute GVHD after haploidentical versus mismatched unrelated transplants, but otherwise similar outcomes for the two donor types including grades III-IV acute GVHD, chronic GVHD, non-relapse mortality and overall survival [8].

This analysis leaves many important unanswered questions: What is the best strategy for a patient with an available young haploidentical donor and a younger mismatched unrelated donor? Is there an age "cutoff" that we should think about as clinicians for defining optimal donor age, or as other data suggests, should we think about donor age as a continuous variable? How might reduced-dose PTCy dosing regimens, which may decrease post-transplant complications and improve immune reconstitution, influence outcomes with different donor types? And finally, how do alternative GVHD prophylaxis regimens such as graft engineering strategies and abatacept-based regimens fit into our armamentarium of GVHD prophylactic approaches for different donor types in the modern era?

Colin Vale[1] and Amelia A. Langston[1]✉

[1]*Winship Cancer Institute, Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA.*

✉*email: alangst@emory.edu*

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AUTHOR CONTRIBUTIONS

Both CV and AAL contributed to conceptualization and writing of this editorial.

COMPETING INTERESTS

The authors declare no competing interests.