The ABCs of donor selection: Availability Before Compatibility?

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In this issue of *Hematologica*, Sanz and colleagues report outcomes in patients with acute lymphoblastic leukemia (ALL) that underwent human leukocyte antigen (HLA)-matched and -mismatched unrelated donor (URD) allogeneic hematopoietic cell transplantation (alloHCT) with post-transplant cyclophosphamide (PTCy)-based graft-*versus*-host disease (GvHD) prophylaxis.[1] The aim of this study, which leveraged data reported to the European Society for Blood and Marrow Transplantation (EBMT), was to examine donor parameters predictive of outcomes in this population. The authors reach the provocative conclusion that HLA-matched and HLA-mismatched URD recipients had similar outcomes, and that non-HLA parameters such as donor age, cytomegalovirus serology matching, and donor sex should be prioritized when selecting URD for HCT. These results echo findings from a similar EBMT analysis in patients with acute myelogenous leukemia (AML), but both are in opposition to a larger EBMT study that demonstrated inferior survival in HLA-mismatched URD recipients even when PTCy was used.[2,3] What should the practising clinician then conclude is the current standard of care when selecting an URD for patients with ALL?

Historical GvHD prevention platforms typically included a calcineurin inhibitor (CNI) combined with short-course methotrexate, with or without other agents such as anti-thymocyte/lymphocyte globulin (ATG). Registry-based studies have demonstrated inferior outcomes after HLA-mismatched compared to HLA-matched URD recipients when a CNI-based approach is used.[4] For this reason, selection of URD was heavily informed by HLA matching, a practice that limited access to HCT in persons of non-European ancestry, where the likelihood of an existing matched URD in international registries is lower (Figure 1).[5] The advent of PTCy disrupted this paradigm, first by demonstrating favorable outcomes after HLA-haploidentical donor HCT, followed by a similar improvement in outcomes in HLA-mismatched URD recipients from both retrospective and prospective studies (Table 1).[6-8] Importantly, two recent, large-scale

Table 1. Retrospective and prospective studies examining outcomes in HLA-mismatched unrelated donor allogeneic hematopoietic cell transplantation recipients using post-transplant cyclophosphamide.

Reference	Study population	Key findings
Sanz *et al.*[1]	EBMT, ALL recipients of matched and mismatched URD with PTCy-based prophylaxis.	HLA-matched and -mismatched URD recipients had similar OS.
Sanz *et al.*[2]	EBMT, AML recipients of matched and mismatched URD with PTCy-based prophylaxis.	Younger donor age was more prognostic of leukemia-free survival than HLA matching.
Arrieta[3]	Pan-EBMT analysis (>17,000 patients) receiving either CNI or PTCy-based GvHD prophylaxis.	HLA Class I mismatching worsened survival regardless of GvHD prophylaxis approach.
Shaffer[6]	CIBMTR, including AML, ALL, MDS. Recipients of matched and mismatched URD HCT with CNI and PTCy-based prophylaxis.	HLA 7/8 and HLA 8/8 matched URD recipients had similar OS with PTCy.
Al Malki[7]	Prospective study of 4-7/8 matched URD with PTCy, using mobilized blood-derived grafts.	1-year OS was 83.8% in recipients of myeloablative conditioning and 78.6% in recipients of reduced/non-myeloablative conditioning.

ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; CIBMTR: Center for International Blood and Marrow Transplant Research; CNI: calcineurin inhibitor; EBMT: European Society for Blood and Marrow Transplantation; GvHD: graft-*versus*-host disease; HCT: hematopoietic cell transplantation; MDS: myelodysplastic syndromes; OS: overall survival; PTCy: post-transplant cyclophosphamide; URD: unrelated donor.

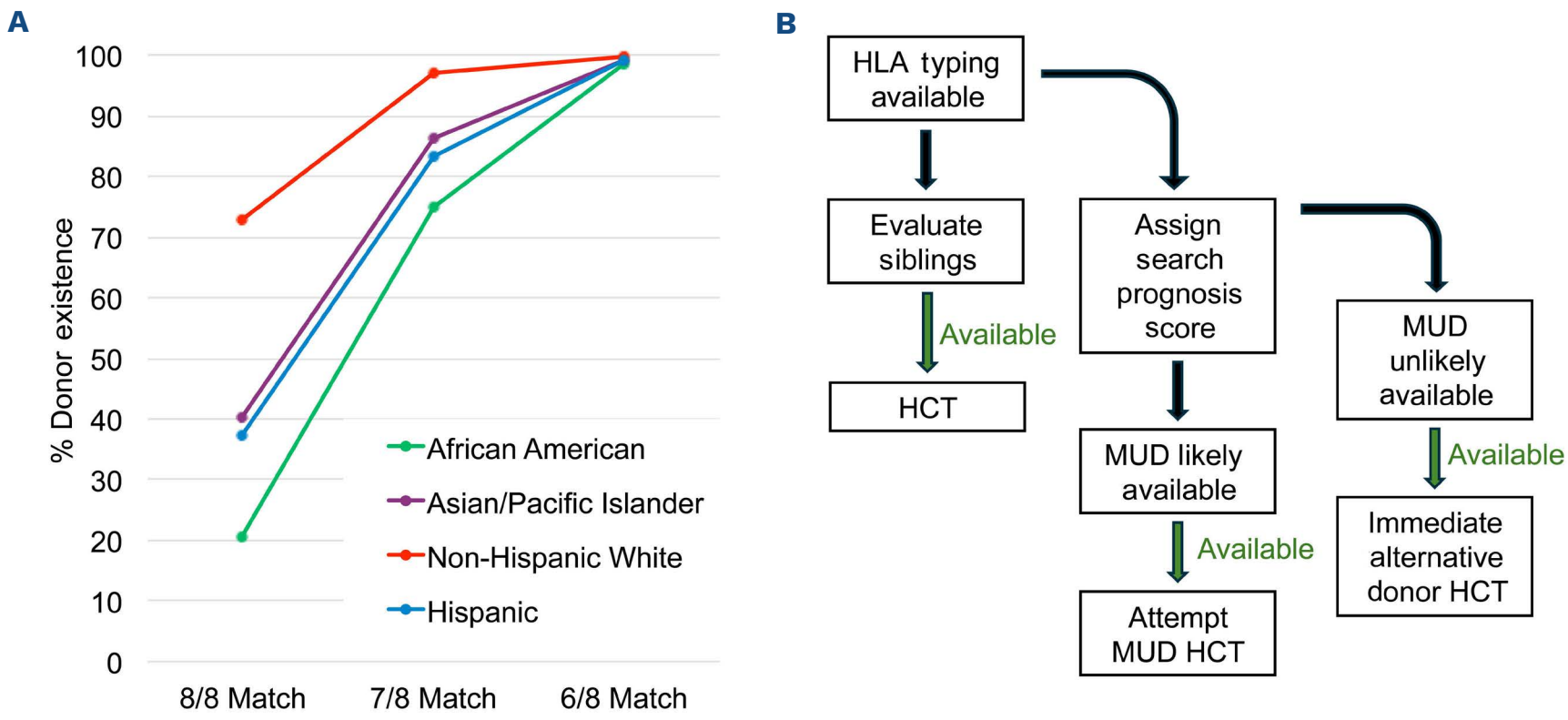

Figure 1. Existence of unrelated donors varies based on patient self-reported race and ethnicity. (A) Percentage of likelihood of donor existence in the NMDP Registry based on HLA matching and patient ancestry. Consideration of more highly mismatched unrelated donors results in near universal donor existence for patients regardless of ancestry. (B) Adaptive search approach. Use of a prognostic tool to determine patients that are at risk of having a poor unrelated donor search identifies patients that benefit from an alternative donor search early in the overall process.

analyses derived from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT, respectively, reached different conclusions with respect to whether an HLA-7/8 matched URD resulted in similar survival to a matched URD (Table 1).[3,6] The CIBMTR study included more recent HCT recipients and lower use of ATG compared to the EBMT study and reported no significant clinical differences in recipients of HLA-8/8 URD recipients *versus* HLA-7/8 URD recipients with PTCy. On the other hand, the EBMT study found a significant decrease in survival after HLA-mismatched donor (8-9/10) in recipients that received CNI-based or PTCy-based prophylaxis, suggesting that the use of PTCy does not completely normalize outcomes between these two donor sources.

The CIBMTR and the EBMT studies highlight the strengths and weaknesses of registry-based retrospective studies. These data are a critical tool to compare real-world outcomes among HCT recipients; however, the uncontrolled nature of the data allows the potential for selection and other forms of bias. These problems may be particularly acute when examining new or emerging technological platforms such as the use of PTCy in unexplored donor types. A key question in the current work by Sanz *et al*. is whether the relatively smaller sample size in this study diminishes the statistical power to detect a real difference in outcomes between the two groups, as was observed in the larger EBMT study. Exacerbating this problem is significant heterogeneity in the cohort (different conditioning programs, PTCy-backbones, and remission status). Given this, the reader should exercise some caution in applying these findings immediately into clinical practice. A reasonable interpretation may be that outcomes after HLA-mismatched URD are at least similar enough to HLA-matched URD recipients that the former should be considered when their use improves access to HCT.

An important consideration in HCT for ALL (and AML) is the question of whether URD are available in a timeframe that is compatible with the patient's plan of care. The window of remission in this disease is often limited and HCT planning can be urgent. A recent prospective study demonstrated that early consideration of alternative donors in patients who are unlikely to have a matched URD improves access to HCT without impacting survival;[9] such an approach is illustrated in Figure 1. To apply this study to practice, a universal and validated search prognosis algorithm is needed to rapidly identify patients that will require an HLA-mismatched donor. Such a tool will allow for a more universal application of this approach in the clinic. Perhaps a key takeaway from the current report by Sanz *et al*. is that it is reasonable to consider a partially HLA-matched URD in patients that do not have readily available, younger, 8/8 matched URD in international donor registries, particularly in patients that may require urgent HCT.

A wider message from this study and others is that the advent of PTCy requires us to re-think how best to prioritize URD selection. It is at least feasible that the 'ideal' URD for patients with ALL (and other highly proliferative hematologic malignancies) is the person that is available to donate when the patient is ready for HCT. An excessive focus on HLA matching can potentially limit or delay access

to HCT, thereby worsening outcomes. For the time being, an HLA-matched donor should be sought when readily available, but Sanz and colleagues inform us that alternative donors could be considered early when one is not. A key priority then for international registries is to provide guidance with respect to best practices in this adaptive search paradigm. The widespread use of PTCy has resulted in an URD search rubric that is both complicated and simple. Perhaps the best approach is to remember your ABCs: Availability Before (HLA) Compatibility.

Disclosures

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