

residual disease and then exposed to PTC? These and other questions should provide a hearty agenda for future research.

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## Many are Called but Few are Chosen: Under-utilization of Unrelated Donor Transplantation

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Many within the transplantation community perceive that allogeneic hematopoietic cell transplantation (HCT) is an underutilized approach among appropriate adult patients who potentially may benefit from this procedure. This perception is particularly true for patients who do not have an HLA-identical sibling donor and for whom the graft must come from unrelated donors or umbilical cord blood (UCB) units (henceforth, both are referred to as URD). In this issue, Yao et al. [1] present a study that quantifies this view; after accounting for comorbidities, pretransplantation treatment mortality, and patient preferences, only one quarter of patients in whom URD HCT is indicated actually receive it. The utilization for specific diseases ranged from 11% for myeloma to 54% for chronic myeloid leukemia, 2 diseases for which indications for HCT have dropped. In the present era,

when it appears that nearly all patients can find a suitable donor for transplantation, including haploidentical HCT [2], this low percentage is a staggering statistic. Further, Yao et al. [1] show that among acute leukemia patients, two thirds underwent transplantation only in late stage disease, a point in time when survival outcomes are inferior when compared with earlier use of HCT [3,4].

The National Marrow Donor Program (NMDP) has access to 21 million potential donors worldwide, including 11 million through its Be The Match Registry. This potential graft inventory also includes more than 600,000 cryopreserved UCB units. The likelihood of identifying an adult donor, unfortunately, reflects race, as white patients have a 93% likelihood of finding a match, whereas for minority ethnic and racial groups, the chance is less; the lowest likelihood is for blacks, at 66%. On the other hand, a suitable UCB unit can be found for transplantation for most patients in whom a matched adult donor cannot be found. The NMDP estimates that approximately 12,000 patients in the United States need an URD transplantation each year. An early step in this process is the initiation of a "formal search", which usually indicates a definitive intent on behalf of the transplantation center to move ahead with an URD HCT. In the 2012 fiscal year, a formal search was requested for only 7400 patients, just 62% of the need. Furthermore, only 60% of patients for whom a formal search was initiated actually proceeded to transplantation.

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In an ideal world, the path for a patient in need of transplantation should be straightforward, via a timely and seamless referral to a transplantation center. In real life, however, a “funnel effect” occurs, in which patients successively lose the opportunity to get to transplantation as they go through different phases of their treatment. This phenomenon occurs for both related and URD HCT, but is much more prominent for the latter. Many factors contribute to this funneling of URD HCT. Patients may not be referred to a transplantation center for a consultation, or they may be referred at an advanced disease stage, when transplantation is no longer feasible or effective. First and foremost, however, is the absence or late referral of patients to transplantation centers by our hematology-oncology colleagues. Mawad et al. [5] from Seattle recently reported encouraging results of using allogeneic HCT to treat first complete remission acute myeloid leukemia patients. They employed several novel approaches including alternative donors (some of whom were HLA-mismatched), diverse graft types (such as UCB units), relaxed selection criteria, and less intensive pretransplantation conditioning regimens (as opposed to more conventional intensity). Their data demonstrated that a strong resolve and various creative approaches facilitated many subjects to proceed to potentially curative therapy.

Despite such examples illustrating an improvement in the transplantation rate for eligible patients and improved patient outcome, referring physicians may not refer patients because of their negative perceptions about risks, efficacy, and toxicity of URD HCT, especially in older patients [6].

Although HCT still is associated with mortality, Gooley et al. [7] found that over the past decade, the hazard of death related to allogeneic HCT has been reduced substantially and long-term survival rates have increased because of reductions in organ damage, infection, and severe acute graft-versus-host disease. Undoubtedly, several patient-related barriers to access exist, such as disparities in socioeconomic status, insurance coverage, distance from transplantation center, and cultural preferences [8–10]. Transplantation centers may contribute to this issue, as these institutions may not have the infrastructure and capacity to accommodate the growing demand for transplantation in their area, or they may not have experience in conducting certain types of transplantation, ie, UCB HCT. In some instances, restrictions placed by public and private payers also may prevent patients from receiving a transplant (eg, lack of Medicare coverage for allogeneic HCT for lymphoma and myeloma patients, and until recently, myelodysplastic syndromes). Issues with donor availability, such as attrition or donor medical issues, occasionally can delay transplantation.

How can we close this gap? Most importantly, we need more investigative efforts to understand patient, provider, and healthcare system barriers to URD HCT and to develop interventions to mitigate them. Until research findings become available, we can continue to build the evidence base for the efficacy of HCT and maintain institutional and group (eg, Center for International Blood and Marrow Transplant Research and Blood and Marrow Transplant Clinical Trials Network) efforts to improve patient outcomes further through innovative preclinical research and clinical trials. We need to support and augment the efforts of transplantation centers, the American Society of Blood and Marrow Transplantation and the NMDP to continue to educate our non-transplantation colleagues about the importance of timely

referral for a transplantation consultation. The NMDP, in collaboration with the American Society of Blood and Marrow Transplantation and other stakeholders, has conducted a comprehensive evaluation of personnel and infrastructure challenges to HCT and several projects from this initiative will address these capacity issues [11,12]. Health care disparities need to be addressed, and although more research is conducted specifically for HCT recipients in this area, we can translate knowledge gained from the cancer disparities literature to our patients. The NMDP continues to invest heavily in technology, processes, and infrastructure to shorten the time from initiation of donor search to transplantation. We also need to continue studies that show the value of URD HCT as a treatment modality for various diseases and age groups.

Findings by Yao et al. highlight the significant amount of work that still needs to be done to address several obstacles to URD HCT. The onus to address these barriers rests mainly on us, the transplantation community. We need to serve as better advocates for our patients so that HCT can be made available to all patients who can potentially benefit from this life-saving treatment.

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