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Should all unrelated donors for transplantation be matched?

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Previous analyses have suggested that hematopoietic cell transplantation (HCT) from an unrelated donor results in better survival if the patient is younger and, possibly also if the donor is younger. Additionally, survival is improved if HCT is performed during early disease stage and if the recipient and possibly the donor are cytomegalovirus (CMV) seronegative. Equivocal data have been published comparing bone marrow vs. (granulocyte-colony stimulating factor) G-CSF-stimulated peripheral blood stem cells for transplantation. A randomized trial is underway by the Blood and Marrow Transplant Clinical Trials Network that is testing the prospective comparison of bone marrow vs. primed peripheral blood grafts from unrelated donors and patients with hematologic malignancies. Of most significance, however, is that the best donor is HLA-compatible, healthy, promptly available, and willing to give the requested product for HCT.

Key words: Allogeneic transplantation; Unrelated donors; HLA-matching.

INTRODUCTION

Issues in donor choice remain, and they involve variables of donor age, donor gender and gender match, prior donor alloimmunization (usually through female parity), and cytomegalovirus (CMV) serostatus. Preferred cell dose, graft source, and composition must be considered along with the optimal HLA-matched donor; and all need to be tempered with consideration of the urgency of a transplant. A patient in advanced remission of acute leukemia has an expected short time until relapse. Thus, the optimal donor may be the one who is satisfactorily matched and most quickly available. Speed of availability is one potential advantage for the choice of umbilical cord blood donor

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units when compared to volunteer adult donors for allotransplantation. Cord blood units are readily available after confirmation of HLA-typing, appropriate cell dose, and clearance of infectious disease markers on the cryopreserved unit. Volunteer donors require the same screening, in addition to a physical evaluation, the consent process, and scheduling issues related to the collection of the volunteer donor graft. Patients with less urgency of transplant may have the luxury of an extended time period to find the best donor, time which would compromise the safety and transplant outcome of those with more urgent medical conditions.

One must consider which factors are critical in donor selection and address how they are modified by patient and disease factors, which also alter HCT outcomes. Such analysis can help devise a practical clinical algorithm for donor selection or alternative therapies when considering candidates for unrelated donor HCT.

EARLIER STUDIES ADDRESSING HLA-MATCHING

A series of previous reports have emphasized the importance of allele-level HLA-matching between donor and recipient.[1–5] They suggested that donor selection by antigen level matching may be associated with worse outcomes, including greater frequencies of graft vs. host disease (GVHD), graft rejection, and poorer survival. A later analysis from the National Marrow Donor Program (NMDP) emphasized that allele-matching results in improved survival if HLA-A, B, DR, and, importantly, HLA-C are matched in choosing the best donor.[6] Matching at HLA-A appeared most clinically important, though the analysis was limited by sizes of subsets where only single loci were mismatched. This analysis did not identify distinctions in outcome between matching at the allele or antigen level at each locus though, again, subsets with specific mismatches were limited in numbers.

Conflicting data on the relative importance of Class I vs. Class II and HLA-DQ matching have been presented.[1,4,5,7,8] These distinctions may be attributable to different data sets with differing frequencies of mismatch at different loci and, importantly, to different ethnic populations. Relative HLA homogeneity in the Japanese populations, for example, may have uncovered the importance of Class I mismatching and poorer outcome, while analysis in a broader, multiethnic population failed to identify these distinctions. Finally the other MHC major locus which has been examined, HLA-DP, is rarely matched and previous studies have shown variable findings. In general, it is not possible to find a HLA-DP-matched donor without sacrificing matching at other loci, and no clear data demonstrates that HLA-DP matching provides any clinical benefit for unrelated donor HCT.[6,9]

A recent analysis readdressed the issue of allele-level typing using data from the NMDP/CIBMTR amongst 3,860 US transplants performed between 1988 and 2003.[10] All patients had acute leukemia, chronic myeloid leukemia, or MDS, and all had received myeloablative conditioning. Most received calcineurin inhibitor (cyclosporine or tacrolimus)-based GVHD prophylaxis and the vast majority of grafts were not ex vivo manipulated to remove T cells. Nearly all were bone marrow grafts. The transplant survivors had a median follow-up of 6 years posttransplant, so the data sets were mature. The donor recipient pairs were all retrospectively typed at high resolution for HLA-A, B, C, DRB1, DQB1, DQA1, DPB1, and DPA1. The fully matched (8/8) reference group was high resolution, allele matched at HLA-A, B, C, and DRB1. The importance of mismatching at different loci and different levels of resolution were compared in relation to other clinical factors that can affect outcomes after transplantation. The analysis was adjusted for important clinical covariates and