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Should all unrelated donors for transplantation be matched?

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Abstract

Previous analyses have suggested that hematopoietic cell transplantation (HCT) from an unrelated donor results in better survival if the patient is younger and, more importantly, if the donor is also 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 significance, however, is that the best donor is HLA-compatible, healthy, promptly available, and willing to give the requested product for HCT.

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 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.

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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 addressed the importance of antigen (low resolution molecular matching) vs. allele (high resolution molecular matching) at specific loci. Additionally, specific mismatches at one or combinations of loci were compared to fully matched pairs. In this large data set with numerous endpoints being examined, the importance of multiple testing was recognized, and stringent statistical criteria were used to determine important conclusions.

The quality of HLA-matching in the 3,800 pairs was variable. Approximately 50% were allele matched at 5 loci (HLA-A, B, C, DR, DQ) while over 900 had single allele mismatches, nearly 700 had 2 allele mismatches, and only 300 had 3 allele mismatches amongst those 5 loci. However, single mismatches at either HLA-B or DRB1 were uncommon and thus only limited analyses could address the importance of those single locus mismatches. The rarity of the specific mismatch combinations was due both to the phenotypic heterogeneity of HLA-typing amongst the donor-recipient pairs and transplant center strategies for choosing donors. This limits the ability to probe the clinical importance of specific mismatches, even in this largest to date, well-typed array of transplant pairs.

A single mismatch at any specific locus among HLA-A, B, C, and DR was clinically important and associated with statistically significant worsened survival, disease-free survival, transplant-related mortality, and more frequent acute GVHD. A single locus mismatch did not significantly affect relapse, engraftment, or chronic GVHD. For each of these endpoints at the 4 loci examined, there was no statistically significant difference between an antigen or allele level mismatch on survival, disease-free survival, treatment-related mortality, relapse, and acute or chronic GVHD. There was a trend, but not independent significance, for worsened outcomes (particularly engraftment) for antigen mismatch at HLA-C vs. allele level mismatch at HLA-C. A larger, independent data set would be required to confirm this suggestion.

An important clinical question is, if an 8 of 8, fully matched donor at A, B, C, or DR, was not available, then does mismatch at any specific locus confer worse clinical outcome? Mismatch at HLA-A was associated with statistically significant worsened survival, treatment-related mortality, and acute GVHD. Mismatch at HLA-C led to worsened treatment-related mortality and more frequent acute GVHD. Mismatch at HLA-B was associated with more frequent acute GVHD. Mismatch at any specific single locus did not yield differences in engraftment, relapse, or chronic GVHD, but these analyses are limited by the infrequency of pairs with an isolated mismatch at HLA-B or HLA-DR. As expected, the addition of a second mismatch at HLA-A, B, C, or DRB1 were all associated with statistically significant worse survival and thus should be avoided if possible. While mismatch at HLA-DQ did not alter these clinical outcomes, mismatch at HLA-DQ was associated with worse survival if another mismatch was present.

These patients had a 52% 5-year survival for 10 of 10 matched donor-recipient pairs, while single locus mismatch (9 of 10 matched) had a 45% 5-year survival, and 8 of 10 matching yielded a 37% 5-year survival. Approximately 7–8% lower overall survival was associated with each additional HLA-mismatch, whether it was an allele- or antigen-level mismatch at either HLA-A, B, C, or DR. This association of poorer survival with HLA-mismatch was most prominent in patients with early disease stage, where single locus mismatch in patients showed 41% survival (vs. 50% for 10 of 10) and 2 locus mismatch, 34% 5-year survival. The differences were present, but of marginal clinical importance in advanced disease patients where 18%, 14%, and 11% 5-year survival was seen in the 3 HLA-match groups, respectively (Figure 1).

NON-HLA FACTORS INFLUENCING OUTCOME

In this large and comprehensive data set, other clinical factors were examined for their influence on HLA-matching and survival. Donor age, donor CMV serology, donor gender (or gender match), or donor parity had no independent significance beyond HLA in affecting survival, which was different than earlier reports. Those with CML and MDS had better survival compared to patients with acute leukemia, and, as expected, early disease stage led to improved survival, independent of HLA. CMV seropositive recipients, older patient age, and black recipient race were each associated with adverse impacts on survival, independent of HLA.

This analysis emphasized that allele matching at HLA-A, B, C, and DRB1 were associated with the best survival while mismatch isolated to HLA-DQ or HLA-DP did not lead to worse survival. A single locus mismatch at either the allele or antigen level conferred similarly potent adverse impacts on survival. Mismatch at HLA-A may be worse than mismatch at either HLA-B or HLA-C. A second mismatch at HLA-A, B, C, DRB1 (or DQ) worsened outcomes and a second mismatch at any of these loci results in equally adverse outcome. Each locus mismatch yields approximately 7–8% decrease in survival, primarily in early stage disease. However, age of the recipient (not the donor) and the CMV serostatus of the recipient as well as their diagnosis and disease stage also impacted survival. These effects were all somewhat stronger and perhaps of greater clinical importance than the impact of limited HLA-mismatch.

CONCLUSIONS

These analyses emphasize that clinical factors as well as HLA-matching are important for the outcome of unrelated donor HCT. In examining the impact on survival however, only HLA-match (based upon the donor choice) and the timing of transplant are modifiable factors. Patients' disease, CMV serostatus, age, and other covariates are not modifiable when a patient is referred to consider transplant therapy. It emphasizes that extending a donor search to identify an optimally matched donor while a disease progresses from early to intermediate or advanced stage is unwise. The impact of advanced disease is substantially more risky than a limited HLA-mismatch in a promptly available and suitable donor. Alternative treatments or alternative donors (including umbilical cord blood) which might offer expeditious means of effecting successful transplant therapy should be strongly considered in patients who have no well-matched donor available after the initial phases of donor searching.

Generally, extended donor searches fail to find an ideal donor and, as a consequence, fail to improve donor outcome. Refined algorithms for seeking the best partially matched donor can use NMDP tools such as Haplogic or formal immunogenetic consultation based on understanding HLA frequencies to optimize donor searching and improve patient outcome. These approaches might conclude that further donor searching is fruitless and choosing from the partially matched donors at hand might be the wisest clinical option. Improvements in transplant technique and the more widespread application of cord blood transplants may further improve clinical options and give more patients a good chance at long-term survival.

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Figure 1.

The probability of overall survival by HLA matching 5 years after transplant

The probability of 5-year survival based on HLA matching for early disease stage (dark) and advanced disease stage (light) is shown. Survival is significantly better with a 10/10 vs. 9/10 or 8/10 allele matched donor in early disease ($p < .0001$) and in advanced disease ($p .02$).