Effect of donor–recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis

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Lancet Oncol 2011; 12: 1214–21

Published Online
October 7, 2011
DOI:10.1016/S1470-2045(11)70260-1

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Summary

Background The importance of matching at the HLA C locus has not been well defined for unrelated umbilical-cord blood transplantation. The selection algorithm for umbilical-cord blood units generally considers intermediate resolution HLA typing at A and B and allele-level typing at DRB1. We aimed to establish the relative importance of additional matching at HLA C.

Methods We used Cox regression to assess retrospectively the effect of donor–recipient HLA matching on outcomes of single umbilical-cord blood transplantations for leukaemia and myelodysplastic syndrome. Our primary endpoint was transplant-related mortality. HLA typing was done with molecular techniques with a minimum of intermediate resolution for HLA A, B, and C, and at the allele-level for DRB1.

Findings The median age of our study population was 10 years (range <1–62) and 552 (69%) of 803 patients were aged 16 years or younger at transplantation. Compared with transplantations matched at HLA A, B, C, and DRB1 (n=69), transplant-related mortality risk was higher after transplantations matched at HLA A, B, and DRB1 and mismatched at HLA C (n=23; HR 3·97, 95% CI 1·27–12·40; p=0·018). Transplant-related mortality risk was also higher after transplantations with a single mismatch at HLA A, B, or DRB1 and mismatched at HLA C (n=234; 1·70, 1·06–2·74; p=0·029) compared with transplantations matched at HLA C with a single mismatch at HLA A, B, or DRB1 (n=127). Assessing the overall effect of HLA disparity on transplant-related mortality, risks were higher with units mismatched at two (n=259; 3·27, 1·42–7·54; p=0·006), three (n=253; 3·34, 1·45–7·71; p=0·005), or four (n=75; 3·51, 1·44–8·58; p=0·006) loci compared with matched units (n=69).

Interpretation Our data suggest that the present strategy for umbilical-cord blood unit selection should be reassessed; matching at HLA C for units that are matched at HLA A, B, or DRB1 or in the presence of a single locus mismatch at HLA A, B, or DRB1 should be included to minimise mortality risks.

Funding National Cancer Institute, National Heart Lung and Blood Institute, National Institute for Allergy and Infectious Diseases, Leukemia and Lymphoma Society, US Department of the Navy, Children's Leukemia Research Association, and INSERM.

Introduction

Many reports show the importance of donor–recipient matching at various HLA loci in the success of adult unrelated-donor haemopoietic stem-cell transplantation; matching at HLA A, B, C, and DRB1 is associated with lower acute graft-versus-host disease and mortality.[1–3] However, many patients who might benefit from this treatment option lack a suitably matched (mismatch at no more than one locus) unrelated adult donor. This lack of donors has led to a rise in the use of unrelated umbilical-cord blood units as an alternative graft. Several groups, including ours, have shown similar leukaemia-free survival, despite higher transplant-related mortality after transplantation of HLA-mismatched umbilical-cord blood versus HLA-matched adult unrelated-donor bone marrow or peripheral blood-progenitor cell transplantation.[4–9]

Of patients undergoing adult unrelated-donor bone-marrow transplantation, several studies report more acute graft-versus-host toxicity, higher mortality, or both, after transplantations mismatched at HLA C.[1–3,10,11] The relative hazard ratio (HR) for risk of transplant-related mortality is 1·40 (95% CI 1·20–1·64) and for overall mortality is 1·22 (1·06–1·39) after transplantations mismatched at HLA C compared with transplantations matched at HLA C.[2] Consequently, the accepted standard for adult unrelated-donor transplantation requires donor and recipient be fully matched at HLA A, B, C, and DRB1, with high-resolution typing for all loci.[12] In the absence of a matched sibling, most transplant centres search for an

unrelated adult donor matched to the recipient at HLA A, B, C, and DRB1. When there is no matched unrelated adult donor, options include adult unrelated donors mismatched at a single locus or umbilical-cord blood. The present standard for selecting umbilical-cord blood units uses lower-resolution matching approaches and does not typically include matching at HLA C. Units are selected on total nucleated-cell dose (eg, $>2\cdot5\times10^7$ cells per kg at cryopreservation) and donor–recipient matching at HLA A and B (antigen level) and DRB1 (allele level).[13]

Several strategies are being explored to address transplant-related mortality after umbilical-cord blood transplantation. Efforts so far have focused on delivering higher total nucleated-cell doses to facilitate haemopoietic recovery.[14–18] The benefit of closer HLA matching, particularly matching at HLA C, is not known. Our analysis focused on the effect of outcomes if matching at the HLA C locus is included as an additional factor to the present selection algorithm—which considers matching at HLA A, B, and DRB1—and how outcomes differ if a mismatched umbilical-cord blood unit (mismatched at one or more HLA loci) is used instead of a unit that is matched at HLA A, B, C, and DRB1.

Methods

Participants

We obtained data for transplantations between 1996 and 2008 in the USA from the Center for International Blood and Marrow Transplant Research and in Europe from Eurocord-Netcord. All patients received a single unrelated umbilical-cord blood unit after myeloablative transplant conditioning regimens for treatment of leukaemia or myelodysplastic syndrome. All patients provided written informed consent. The institutional review boards of the Medical College of Wisconsin, the Eurocord-Netcord scientific committee, and the National Marrow Donor Program approved this study.

Procedure

Donor and recipient HLA typing at A, B, and C loci was done with molecular techniques with a minimum of antigen-split level resolution for HLA A, B, and C and allele-level resolution at DRB1. For transplantations in the USA, donor–recipient HLA typings were available from the transplant centre or from a centralised confirmatory typing laboratory, or, for transplantations done with incomplete typing, from retrospective typing of stored research samples. For transplantations facilitated by Netcord banks, donor–recipient HLA typings were obtained from the cord blood banks or from transplant centres.

Our primary outcome was transplant-related mortality, which we defined as the time from transplantation to death not related to disease recurrence or progression. The other outcomes we assessed were neutrophil recovery (defined as achieving an absolute neutrophil count of $0\cdot5\times10^9$ cells per L or greater for three consecutive measurements on different days), grade 2–4 acute graft-versus-host disease,[19] chronic graft-versus-host disease,[20] leukaemia or myelodysplastic syndrome recurrence, and overall mortality (defined as death from any cause).

Statistical analysis

We report median values and ranges for continuous variables and percentages for categorical variables. We calculated the probabilities of neutrophil recovery,

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	Number (%)
Total	803
Donor–recipient HLA match (model 1)	
A, B, C, and DRB1 match	69 (9%)
One locus (A, B, C, or DRB1) mismatch	147 (18%)
Two loci (A, B, C, or DRB1) mismatch	259 (32%)
Three loci (A, B, C, or DRB1) mismatch	253 (32%)
Four loci (A, B, C, and DRB1) mismatch	75 (9%)
Donor–recipient HLA match (model 2)	
A, B, and DRB1 match plus C match	69 (9%)
A, B, and DRB1 match plus C mismatch*	23 (3%)
One locus (A, B, or DRB1) mismatch plus C match	127 (16%)
One locus (A, B, or DRB1) mismatch plus C mismatch†	234 (29%)
Two loci (A, B, or DRB1) mismatch plus C match	57 (7%)
Two loci (A, B, or DRB1) mismatch plus C mismatch‡	293 (36%)
Donor–recipient HLA match (model 3)	
A, B, and C match plus DRB1 match	69 (9%)
A, B, and C match plus DRB1 mismatch§	51 (6%)
One locus (A, B, or C) mismatch plus DRB1 match	101 (13%)
One locus (A, B, or C) mismatch plus DRB1 mismatch¶	77 (10%)
Two loci (A, B, or C) mismatch plus DRB1 match	181 (23%)
Two loci (A, B, or C) mismatch plus DRB1 mismatch‖	119 (15%)
Three or more loci (A, B, and C) mismatch plus DRB1 match or mismatch**	205 (26%)
Donor–recipient HLA match (model 4)	
B, C, and DRB1 match plus A match	69 (9%)
B, C, and DRB1 match plus A mismatch	62 (8%)
One locus (B, C, or DRB1) mismatch plus A match	88 (11%)
One locus (B, C, or DRB1) mismatch plus A mismatch	78 (10%)
Two loci (B, C, or DRB1) mismatch plus A match	181 (23%)
Two loci (B, C, or DRB1) mismatch plus A mismatch	140 (17%)
Three or more loci (B, C, and DRB1) mismatch plus A match or mismatch††	185 (23%)
Donor–recipient HLA match (model 5)	
A, C, and DRB1 match plus B match	69 (9%)
A, C, and DRB1 match plus B mismatch	24 (3%)
One locus (A, C, or DRB1) mismatch plus B match	125 (16%)
One locus (A, C, or DRB1) mismatch plus B mismatch	153 (19%)
Two loci (A, C, or DRB1) mismatch plus B match	112 (14%)
Two loci (A, C, or DRB1) mismatch plus B mismatch	193 (24%)
Three or more loci (A, C, and DRB1) mismatch plus B match or mismatch‡‡	127 (16%)

*Three of 23 donor–recipient pairs mismatched at C were mismatched at both loci. †35 of 234 donor–recipient pairs mismatched at C were mismatched at both loci. ‡75 of 293 donor–recipient pairs mismatched at C were mismatched at both loci. §Five of 51 donor–recipient pairs mismatched at DRB1 were mismatched at both loci. ¶Four of 77 donor–recipient pairs mismatched at DRB1 were mismatched at both loci. ‖Two of 119 donor–recipient pairs mismatched at DRB1 were mismatched at both loci. **168 donor–recipient pairs were matched at DRB1 and 37 were mismatched at a single DRB1 locus. ††151 donor–recipient pairs were matched at A and 34 were mismatched at a single A locus. ‡‡70 donor–recipient pairs were matched at B and 57 were mismatched at a single B locus.

Table 1: **Donor–recipient HLA-match categories**