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

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Contributors

ME, JPK and VR contributed equally to study design, interpretation of data and had primary responsibility for drafting the manuscript. JPK did the statistical analysis. SS reviewed donor-recipient HLA typing and assignment and contributed to interpretation of data and manuscript preparation. GH assembled donor-recipient HLA typing for review and assignment for MB and SS. GFS, AR, CA, REC, JG-L, GH, MJL, GM, SKN, FOS, MMH and EG contributed to interpretation of data and manuscript preparation. All authors approved the final report.

Conflict of interest statement

Authors declare none.

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Abstract

Background—The importance of matching at the human leukocyte antigen (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 at DRB1. We aimed to determine the relative importance of matching at HLA-C in addition to current selection criteria.

Methods—We used Cox regression to retrospectively examine for the effect of donor-recipient HLA matching on outcomes of 803 single umbilical cord blood transplantations for leukemia (N=727) and myelodysplastic syndrome (N=76). The primary endpoint was transplant-related mortality. HLA typing was performed using molecular techniques with a minimum of intermediate resolution for HLA-A, -B and -C and allele-level for DRB1.

Findings—Compared to transplantations matched at HLA-A, -B, -C, -DRB1 (N=69; HR 1.00), transplant-related mortality risks were higher after transplantations matched at HLA-A, -B, -DRB1 and mismatched at HLA-C (N=23; HR 3.97, 95% CI 1.27 – 12.40, p=0.018). Transplant-related mortality risk were also higher after transplantations with a single mismatch at HLA-A or -B, or -DRB1 and mismatched at HLA-C (N=234; HR 1.70 95% CI 1.06 – 2.74, p=0.029) compared to transplantations matched at HLA-C with a single mismatch at HLA-A, -B, or -DRB1 (N=127; HR 1.00). Examining for an overall effect of HLA disparity on transplant-related mortality, risks were higher with units mismatched at two (N=259; HR 3.27 95% CI 1.42 – 7.54, p=0.006), three (N=253; HR 3.34 95% CI 1.45 – 7.71, p=0.005) or four (N=75; HR 3.51 95% CI 1.44 – 8.58, p=0.006) loci compared to matched units (N=69; HR 1.00).

Interpretation—These data suggest that we re-evaluate the current strategy for umbilical cord blood unit selection, by considering matching at HLA-C for units that are matched at HLA-A, -B, -DRB1 or in the presence of a single locus mismatch at HLA-A, -B or DRB1 to minimize mortality risks.

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Introduction

Several reports demonstrate the importance of donor-recipient matching at the various human leukocyte antigen (HLA) loci in the success of adult unrelated donor hematopoietic 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 may benefit from this treatment option lack a suitably matched (mismatch at no more than one locus) unrelated adult donor. This has led to increasing use of unrelated umbilical cord blood units as an alternative graft. Several groups, including ours, have demonstrated comparable leukemia-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}

Among patients undergoing adult unrelated donor bone marrow transplantation, several studies report more acute graft-versus-host and/or higher mortality after transplantations mismatched at HLA C.^{1–3,10,11} The relative hazard ratios for risks of transplant-related and overall mortality are 1.40 and 1.22, respectively, after transplantations mismatched at HLA-

C compared to 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, -DRB1, using high resolution typing for all loci.¹² In the absence of a matched sibling, most transplant centers search for an unrelated adult donor matched to the recipient at HLA-A, -B, -C, -DRB1. When a matched unrelated adult donor is lacking donor options include adult unrelated donors mismatched at a single locus or umbilical cord blood. The current standard for selecting umbilical cord blood units uses lower resolution matching approaches and does not typically consider matching at HLA-C. Units are selected on total nucleated cell dose (e.g., $>2.5 \times 10^7/\text{kg}$ at cryopreservation), and donor-recipient matching at HLA-A and -B (antigen-level) and -DRB1 (allele-level).¹³

Transplant-related mortality after umbilical cord blood transplantation remains an important obstacle and several strategies are being explored to address this. Efforts thus far focus on delivering higher total nucleated cell doses to facilitate hematopoietic recovery^{14–18} and the benefit of closer HLA matching particularly matching at HLA-C is not known. The present analysis focused on two questions: first, what is the impact on outcomes if matching at the HLA-C locus is considered as an additional factor to current selection algorithm which considers matching at HLA-A, -B, -DRB1; second, how different are the outcomes 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?

Patients and methods

Patients

Data for transplantations in the United States were obtained from the Center for International Blood and Marrow Transplant Research and for transplantations in Europe, from Eurocord-Netcord. All patients received a single unrelated umbilical cord blood unit after myeloablative transplant conditioning regimens for treatment of leukemia or myelodysplastic syndrome (MDS). All transplantations occurred in 1996 to 2008. All patients consented for research. The Institutional Review Boards of the Medical College of Wisconsin, the Eurocord-Netcord scientific committee and the National Marrow Donor Program approved this study.

HLA typing

Donor and recipient HLA typing at -A, -B and -C loci was performed using molecular techniques with a minimum of antigen-split level resolution for HLA-A, -B and -C and allele-level resolution at -DRB1. HLA-matching was scored at the antigen level for HLA-A, -B and -C and allele level for HLA-DRB1. For transplantations in the United States, donor-recipient HLA typings were available from the transplant center or from a centralized confirmatory typing laboratory or, for transplantations performed 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 centers.

Outcomes

The primary outcome was transplant-related mortality defined as the time from transplantation to death not related to disease recurrence or progression. Other outcomes evaluated were: neutrophil recovery defined as achieving an absolute neutrophil count $\geq 0.5 \times 10^9/\text{L}$ for three consecutive measurements on different days, grade 2–4 acute graft-versus-host disease,¹⁹ chronic graft-versus-host disease,²⁰ leukemia or MDS recurrence and overall mortality, defined as death from any cause.

Statistical methods

Median values and ranges are reported for continuous variables and percentages for categorical variables. The probabilities of neutrophil recovery, graft-versus-host disease, transplant-related mortality and relapse were calculated using the cumulative incidence estimator.²¹ Death was the competing risk for neutrophil recovery and graft-versus-host disease. For transplant-related mortality, relapse was the competing risk and for relapse, transplant-related mortality was the competing risk. The probability of overall survival was calculated using the Kaplan-Meier estimator.²¹ 95% confidence intervals (CI) were calculated with log transformation.

To analyze the association between clinical outcomes and donor-recipient HLA-matching, multivariate pseudo-observation models²² were built for neutrophil recovery at day-28, and Cox regression models²³ were built for acute and chronic graft-versus-host disease, transplant-related mortality, relapse and overall mortality. The pseudo-observations enable us to estimate the likelihood of an event for each individual at a given time point for censored data.

Donor-recipient HLA match was examined in five separate models: 1) the first model examined HLA-match at HLA-A, -B, -C, -DRB1 (8/8 vs. 7/8 vs. 6/8 vs. 5/8 vs. 4/8 match); 2) the second model examined HLA-C match vs. HLA-C mismatch in donor-recipient pairs either matched, 1-locus mismatched, 2-loci mismatched or ≥ 3 -loci mismatched at HLA-A, -B or -DRB1; and, 3) three additional models, similar to model two but considering the individual effect of HLA-A, -B or -DRB1 rather than HLA-C. Donor-recipient HLA match categories used for constructing these models are shown in Table 1.

Donor-recipient matching defined in one of the five ways was the main effect term, and was held in all steps of model building. Other variables tested (for all outcomes of interest) included age (≤ 16 vs. > 16 years), recipient sex (female vs. male), leukemia type (acute myeloid leukemia vs. acute lymphoblastic leukemia vs. chronic myeloid leukemia vs. MDS), disease status at transplantation (1st complete remission, 1st chronic phase [early stage] vs. 2nd or greater complete remission, 2nd chronic phase, accelerated phase [intermediate stage] vs. not in remission, blast phase, refractory anemia with excess blasts or blasts in transformation [advanced stage]), total nucleated cell dose pre-cryopreservation (≤ 3 vs. $> 3 \times 10^7/\text{kg}$), recipient CMV serostatus (negative vs. positive), conditioning regimen (TBI-containing vs. non-TBI regimens), graft-versus-host disease prophylaxis (cyclosporine alone or with steroids vs. cyclosporine + methotrexate vs. other regimens), donor-recipient sex match (female donor/male recipient vs. others [chronic graft-versus-host disease model] and male donor/female recipient vs. others [neutrophil recovery model]), year of transplant (≤ 2004 vs. > 2004) and region (Europe vs. U.S.). The optimal cut-point for pre-cryopreservation total nucleated cell dose of $3 \times 10^7/\text{kg}$ for treatment related mortality was determined using the sieve method.²⁴ The sieve method is a standard statistical method applied to discretize a continuous covariate in a regression model. Models were built with the use of forward stepwise selection procedure and confirmed with the use of backward selection procedure. Proportional hazards assumption was tested for each co-variate individually and all co-variables met this assumption. We tested for interactions between each co-variate and the main effect term and found none. All p-values are two-sided and p-values ≤ 0.05 were considered statistically significant. We looked for a transplant center effect on overall survival and found none.²⁵ Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Role of the funding source

The funding sources had no role in the study design, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

Results

Patient, disease and transplant characteristics

Table 2 describes patients, and their disease and transplant characteristics. The median age of the study population was 10 years (range <1 – 62) and 552 of 803 (65%) of patients were 16 years or younger at transplantation. Patients had acute myeloid or lymphoblastic leukemia, chronic myeloid leukemia or MDS; 276 of 803 patients (34%) had early stage disease, 321 patients (40%) intermediate stage and 206 patients (26%), advanced stage at transplantation. Twenty-eight of 803 (4%) of transplantations were in 1995 – 1999, 250 of 803 (31%) were in 2000 – 2004 and 525 of 803 (65%) were in 2005 – 2007. The median total nucleated cell dose at cryopreservation was $4.9 \times 10^7/\text{kg}$ (range 1 – 50) and the median follow-up of surviving patients, 25 months (range 3 – 154). Only 69 of 803 (9%) of donor-recipient pairs were matched at HLA-A, -B, -C and -DRB1. Five hundred and fifty of 803 (68%) of donor-recipient mismatches involved the HLA-C locus and the remaining 184 (22%) donor-recipient pairs were matched at HLA-C. Isolated mismatch at HLA-C was present in only 4% of donor-recipient pairs (23 of 550). Twenty-nine percent (159 of 550) of donor-recipient pairs mismatched at HLA-C also had an additional mismatch at HLA-B, 50 of 550 (9%) at HLA-A and 51 of 550 (9%) at HLA-DRB1; 102 of 550 (19%) had additional mismatches at HLA-B and -DRB1; 48 of 550 (9%) at HLA-A and -DRB1 and 117 of 550 (21%) at HLA-A and -B. Of the 184 of 803 remaining donor-recipient pairs, 8% (62 of 803) donor-recipient pairs had an isolated mismatch HLA-A, 3% (24 of 803) at HLA-B and 6% at HLA-DRB1 (51 of 803). Twenty-two of 803 (3%) donor-recipient pairs were mismatched at HLA-A and -DRB1, 2% (15 of 803) at HLA-A and -B and 1% (10 of 803) at HLA-B and DRB1.

Transplant-related mortality

The risk of transplant-related mortality was associated with the overall degree of HLA-disparity. Risks were higher after transplantations mismatched at two or more loci compared to transplantations matched at HLA-A, -B, -C, -DRB1 and transplantations mismatched at 1-locus (Table 3). When the risks associated with specific loci were examined, transplant-related mortality was significantly higher with HLA-C mismatching when there were no mismatches at HLA-A, -B, -DRB1 or when there was a single HLA-A, -B or -DRB1 mismatch (Table 3; Web figure 1). The three-year probabilities of transplant-related mortality were 9% (95% CI 4–17) and 19% (95% CI 12–27) for units matched at HLA-C and matched at other loci or with an additional mismatch at a single locus, respectively. Corresponding probabilities for units mismatched at HLA-C were 26% (95% CI 11–45) and 31% (95% CI 25–38). Additionally, among transplantations mismatched at a single HLA-A, -B or -C locus, transplant-related mortality risks were significantly higher with an additional mismatch at HLA-DRB1 (Table 3; Web figure 1). A single mismatch at HLA-DRB1 and HLA-C (matched at HLA-A and -B) was associated with higher transplant-related mortality compared to pairs mismatched at HLA-DRB1 and matched at HLA-C, -A, -B (HR 3.20, 95% CI 1.48–6.93, $p=0.003$). Graft failure, infections and organ failure were more frequent in patients who received HLA-C mismatched transplantations compared to those who received HLA-C matched transplantations. Transplant-related mortality was not statistically worse with single mismatches at HLA-A or HLA-B and HLA-C compared to pairs matched at HLA-C (data not shown). Among transplantations mismatched at two or more loci, an

additional mismatch at HLA-C or HLA-DRB1 was not associated with higher transplant-related mortality.

The effect of donor-recipient HLA-match is adjusted for age, cytomegalovirus serostatus and disease status at transplantation the other factors significantly associated with transplant-related mortality. Risks were higher in patients aged >16 years compared to those aged ≤ 16 years (HR 1.69, 95% CI 1.26 – 2.26, $p=0.0005$), patients who are seropositive for cytomegalovirus compared to seronegative (HR 1.61, 95% CI 1.21 – 2.14, $p=0.001$) and those transplanted with advanced stage disease (HR 1.64, 95% CI 1.17 – 2.31, $p=0.005$) but not with intermediate stage disease (HR 1.27, 95% CI 0.91 – 1.79, $p=0.164$) compared to those transplanted with early stage disease.

Overall survival

Overall degree of HLA disparity at HLA-A, -B, -C, -DRB1 was not significantly associated with overall mortality risk (Table 3). The three-year probabilities of overall survival for patients transplanted in early stage are 61% (95% CI 41–76), 73% (95% CI 57–84) and 44% (95% CI 35–52) with units mismatched at zero, one and two or more HLA-loci, respectively. Corresponding probabilities for transplantations in intermediate stage are 37% (95% CI 9–67), 36% (95% CI 19–53) and 43% (95% CI 36–51) and, in advanced stage are 44% (95% CI 17–68), 30% (95% CI 15–46) and 26% (95% CI 16–31). When the mortality risks associated with mismatching at specific loci were examined, the only statistically significant association was with mismatching at HLA-C in the setting of a single additional HLA-A, -B or -DRB1 locus mismatch (Table 4; Web figure 2). The 3-year probability of overall survival after transplantation of umbilical cord blood units matched at HLA-C and mismatched at a single locus (HLA-A, -B or -DRB1) was 51% (95% CI 41 – 60) compared to 37% (95% CI 30 – 45) for transplantations mismatched at HLA-C and a single locus mismatch at HLA-A, -B or -DRB1. A single mismatch at HLA-DRB1 and HLA-C (matched at HLA-A and -B) was associated with higher overall mortality compared to pairs mismatched at HLA-DRB1 and matched at HLA-C, -A, -B (HR 2.95, 95% CI 1.67–5.20, $p=0.0002$).

The effect of donor-recipient HLA-match is adjusted for age and disease status at transplantation the other factors significantly associated with overall mortality. Risks were higher in patients aged >16 years compared to those aged ≤ 16 years (HR 1.27, 95% CI 1.03 – 1.57, $p=0.029$) and patients transplanted with advanced (HR 2.13, 95% CI 1.67 – 2.74, $p<0.0001$) and intermediate stage disease (HR 1.33, 95% CI 1.04 – 1.71, $p=0.024$) compared to those transplanted with early stage disease.

Mismatching at one or two HLA-C and transplantation outcomes

Thirty-five of 234 donor-recipient pairs mismatched at one HLA-A or -B or -DRB1 locus were mismatched at both HLA-C loci. To ensure the observed adverse effect of mismatching at HLA-C was not influenced by the double mismatch at this locus, subset analysis limiting to donor-recipient pairs mismatched at one HLA-C locus was performed. Consistent with the main analysis, risks of transplant-related mortality (HR 1.76, 95% CI 1.08 – 2.88, $p=0.022$) and overall mortality (HR 1.42, 95% CI 1.03 – 1.96, $p=0.030$) were higher after transplantations mismatched at one HLA-C locus compared to those matched at HLA-C.

Hematopoietic recovery

The likelihood of neutrophil recovery at day-28 was associated with the overall degree of HLA-matching (Table 5). Although recovery rates at day-28 were similar after transplantations mismatched at zero, one or two HLA-loci, rates were significantly lower

after transplantations mismatched at three or four HLA-loci. The day-28 probabilities of neutrophil recovery after transplantations mismatched at zero, one or two HLA-loci were 70% (95% CI 57 – 79), 64% (95% CI 55 – 71) and 64% (95% CI 57 – 69), respectively. Corresponding probabilities for transplantations mismatched at three and four HLA-loci were 54% (95% CI 48 – 60) and 44% (95% CI 32 – 55). When the impact of mismatching at specific HLA-loci was examined, mismatching at HLA-DRB1 the presence of mismatches at any other two HLA-loci and mismatching at HLA-A in the presence of mismatching at three or four loci HLA-loci were associated with statistically significant reductions in neutrophil recovery rates (Table 5; Web figure 3). The effect of donor-recipient HLA-match on neutrophil recovery is adjusted for disease status at transplantation the only other factor significantly associated with neutrophil recovery. The likelihood of neutrophil recovery was lower for patients transplanted with intermediate (OR 0.69, 95% CI 0.49 – 0.97, $p=0.031$) and advanced stage disease (OR 0.63, 95% CI 0.43 – 0.93, $p=0.019$) compared to early stage disease.

Graft-versus-host disease

The risks of acute grade 2 – 4 graft-versus-host disease were not significantly associated with HLA-matching, whether considered as overall degree of HLA-disparity or mismatching versus matching at specific loci (data not shown). Results were similar for chronic graft-versus-host disease except for increased risk associated with HLA-A mismatching in the setting of transplantations mismatched at three or four other HLA-loci (Web table 1).

Relapse

Relapse risks were lower after transplantations mismatched at one or more loci compared to transplantations matched at HLA-A, -B, -C and -DRB1 (Web table 2). We did not observe differences in relapse risks by number of loci mismatched, i.e. the risk was similar whether one, two, three or four loci were mismatched.

Discussion

The current analysis focused on whether transplant-outcomes would be different if umbilical cord blood unit selection considered matching at HLA-C in addition to HLA-A, -B and -DRB1, as is the practice when selecting an unrelated adult donor. We report three major findings that are novel and to our knowledge not reported previously: 1) mismatching at HLA-C is an independent risk factor for transplant-related mortality when transplants are matched at HLA-A, -B, -DRB1 or mismatched at a single HLA-A, -B or -DRB1 locus; 2) mismatching at HLA-DRB1 when transplants are mismatched at a single HLA-A, -B or -C locus is an independent risk factor for transplant-related mortality; and 3) mismatching at any one or more loci considering matching at HLA-A, -B, -C, -DRB1 is an independent risk factor for transplant-related mortality. The observed effect of mismatching at HLA-C and -DRB1 are independent of patient age, cytomegalovirus serostatus and disease status at transplantation, the other significant factors associated with transplant-related mortality. We did not observe significant differences in transplant-related mortality rates between transplantations mismatched at two, three and four HLA-loci suggesting the absence of an additive adverse effect of mismatching beyond two-loci. The absence of an additive effect on mortality for transplantations mismatched at two or more HLA-loci has been described after adult unrelated donor transplantation.²

Mismatching at one or multiple loci was associated with lower risks of relapse with no evidence that incremental increases in HLA disparity had a significant impact on relapse as reported by others.²⁶ Consequently, higher transplant-related mortality after mismatched transplantations was offset by lower relapse risks resulting in overall survival rates that were

not significantly different except for patients who received umbilical cord blood units mismatched at the HLA-C locus and a single mismatch at the HLA-DRB1 locus. The absence of a statistically significant effect on overall mortality despite higher transplant-related mortality risks after transplants with a single mismatch at HLA-C or HLA-DRB1 may also be attributed to the relatively small subgroups: only 20 donor-recipient pairs were mismatched at one HLA-C locus and 46 donor-recipient pairs, mismatched at one HLA-DRB1 locus compared to 69 donor-recipient pairs matched at HLA-A, -B, -C, -DRB1.

In contrast to that reported after mismatched adult unrelated donor transplantation,^{2,10} HLA disparity was not associated with higher risks of acute or chronic graft-versus-host disease except for umbilical cord blood transplantations mismatched at two or more HLA-loci with a mismatch at HLA-A. Graft-versus-host disease rates are low after mismatched umbilical cord blood transplantation^{8,9} and any differences with multiple mismatching may be negligible except when one of the disparities occurs at HLA-A. Mismatching at three or four HLA-loci had an adverse effect on neutrophil recovery consistent with other reports.^{27,28} In the current analysis, 65% of patients were aged ≤ 16 years and 75% of umbilical cord blood units contained $>3 \times 10^7$ total nucleated cells per kilogram patient weight. The use of larger units for transplantation may have negated the adverse effects of mismatching at one or two HLA-loci.^{27,28} We tested for an effect of donor sex on hematopoietic recovery and chronic graft-versus-host disease and found none.

In the report by Koegler and colleagues on 122 donor-recipient pairs, the only other report that examined extended HLA typing for umbilical cord blood transplantation, there was no significant association between graft failure, graft-versus-host disease and mortality.²⁹ We hypothesize the apparent discrepancy between our results and those of Koegler and colleagues is related to study power rather than the biology of HLA disparity.

This report includes 803 donor-recipient pairs but there are a number of limitations. First, the statistical power to evaluate the impact of mismatching at specific loci and in some subgroups with limited number of events was low. Second, we did not consider allele-level HLA typing at HLA-A, -B or -C. This was not available for all patients. Among those for whom these data were available, about half of donor-recipient pairs were mismatched at three or more HLA-loci, which prevented us from exploring further. Our findings suggest that altering current selection strategies for umbilical cord blood units may ameliorate some of the excess transplant-related mortality associated with umbilical cord blood transplantation. If a unit matched at HLA-A, -B, -C and -DRB1 is not available, selecting a unit matched at HLA-C is preferred; in particular avoiding a mismatch at HLA-C in the presence of a single mismatch at HLA-DRB1 significantly lowers mortality risks. Changing current selection standards would also allow us to address the effect of matching at the allele-level in the future. However, changing the current selection strategy requires that cord blood banks have HLA-C typing in addition to HLA-A, -B, and -DRB1 for units available for search. Donor-recipient pairs mismatched at HLA-C are likely to be mismatched at HLA-B as there is a high degree of linkage disequilibrium between these loci.³⁰ Therefore, until HLA-C typing is available at search, selecting units matched at HLA-B will increase the likelihood of a match at HLA-C for most but not all cases and HLA-C typing can be performed at time of confirmatory testing. Despite the substantial investment from governments to develop public cord blood banks, our findings support the need for even greater investment. The additional burden of HLA-C typing and the need to build an even larger inventory of cord blood units that will allow for matching at HLA-C will add to the existing financial burden of the public cord blood banks.

Panel: Research in context**Systematic review**

The medical literature was searched in 2009 and 2010 for articles on umbilical cord blood transplantation using Medline. Search terms included HLA-match, unrelated donor transplantation and umbilical cord blood. Several reports on the association between HLA-matching and survival after adult unrelated donor transplantation show higher survival rates after transplantations matched at HLA-A, -B, -C and -DRB1.^{1-3, 11, 12} Transplant-related mortality after umbilical cord blood transplantation with myeloablative transplant conditioning regimens is high and remains an important obstacle to a successful outcome. There are several strategies being explored to address this with all efforts thus far focused on delivering higher total nucleated cell doses to facilitate hematopoietic recovery.¹⁴⁻¹⁸ Literature review identified a single publication²⁹ that examined for an association between closer HLA matching and transplant-outcomes.

However, this report included only 122 donor-recipient pairs. Therefore, our aim was to test whether closer HLA-matching of donor-recipient pairs by considering matching at HLA-A, -B, -C and -DRB1 would improve transplant-related mortality. Current accepted criteria for umbilical cord blood unit selection considers total nucleated cell dose and donor-recipient matching at HLA-A, -B and -DRB1. Therefore, we focused on two questions: first, what is the impact on outcomes if matching at the HLA-C locus is considered as an additional factor to current selection algorithm which considers matching at HLA-A, -B, -DRB1; second, how different are the outcomes 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?

Interpretation

We observed higher transplant-related mortality for transplantations matched at HLA-A, -B, -DRB1 or mismatched at a single HLA-A, -B or -DRB1 locus and mismatched at HLA-C and transplantations mismatched at a single HLA-A, -B or -C locus and mismatched at HLA-DRB1. Consideration of matching at HLA-C in addition to HLA-A, -B and -DRB1 is warranted in some situations; avoiding a mismatch at HLA-C in the presence of a single mismatch at HLA-DRB1 minimizes mortality risks. These data suggest that we re-evaluate the current strategy for umbilical cord blood unit selection and support the need for even greater investment in public cord blood banks because of the importance of HLA matching on transplant-related mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Donor-recipient HLA-match categories

Variable	Number (%)
Total number	803
Donor-recipient HLA-match I	
HLA-A, -B, -C, -DRB1 match	69 (9%)
1-locus HLA-A, -B, -C, -DRB1 mismatch	147 (18%)
2-loci HLA-A, -B, -C, -DRB1 mismatch	259 (32%)
3-loci HLA-A, -B, -C, -DRB1 mismatch	253 (32%)
4-loci HLA-A, -B, -C, -DRB1 mismatch	75 (9%)
Donor-recipient HLA-match II	
HLA-A, -B -DRB1 match + C match	69 (9%)
HLA-A, -B -DRB1 match + C mismatch [*]	23 (3%)
1-locus HLA-A, -B -DRB1 mismatch + C match	127 (16%)
1-locus HLA-A, -B -DRB1 mismatch + C mismatch [†]	234 (29%)
2-loci HLA-A, -B -DRB1 mismatch + C match	57 (7%)
2-loci HLA-A, -B -DRB1 mismatch + C mismatch [‡]	293 (36%)
Donor-recipient HLA-match III	
HLA-A, -B -C match + DRB1 match	69 (9%)
HLA-A, -B -C match + DRB1 mismatch ^{**}	51 (6%)
1-locus HLA-A, -B, -C mismatch + DRB1 match	101 (12%)
1-locus HLA-A, -B, -C mismatch + DRB1 mismatch ^{††}	77 (10%)
2-loci HLA-A, -B, -C mismatch + DRB1 match	181 (23%)
2-loci HLA-A, -B, -C mismatch + DRB1 mismatch ^{‡‡}	119 (15%)
≥3-loci HLA-A, -B, -C mismatch + DRB1 match/mismatch [§]	205 (26%)
Donor-recipient HLA-match IV	
HLA-B, -C -DRB1 match + A match	69 (9%)
HLA-B, -C -DRB1 match + A mismatch	62 (8%)
1-locus HLA-B, -C -DRB1 mismatch + A match	88 (11%)
1-locus HLA-B, -C -DRB1 mismatch + A mismatch	78 (10%)
2-loci HLA-B, -C -DRB1 mismatch + A match	181 (22%)
2-loci HLA-B, -C -DRB1 mismatch + A mismatch	140 (17%)
≥3-loci HLA-B, -C -DRB1 mismatch + A match/mismatch ^{§§}	185 (23%)
Donor-recipient HLA-match V	
HLA-A, -C -DRB1 match + B match	69 (9%)
HLA-A, -C -DRB1 match + B mismatch	24 (3%)
1-locus HLA-A, -C -DRB1 mismatch + B match	125 (16%)
1-locus HLA-A, -C -DRB1 mismatch + B mismatch	153 (19%)
2-loci HLA-A, -C -DRB1 mismatch + B match	112 (14%)
2-loci HLA-A, -C -DRB1 mismatch + B mismatch	193 (24%)
≥3-loci HLA-A, -C -DRB1 mismatch + B match/mismatch ^{§§§}	127 (16%)

* 3 of 23 donor-recipient pairs mismatched at HLA-C were mismatched at both loci

† 35 of 234 donor-recipient pairs mismatched at HLA-C were mismatched at both loci

† 75 of 293 donor-recipient pairs mismatched at HLA-C were mismatched at both loci

** 5 of 51 donor-recipient pairs mismatched at HLA-DRB1 were mismatched at both loci

†† 4 of 77 donor-recipient pairs mismatched at HLA-DRB1 were mismatched at both loci

†† 2 of 119 donor-recipient pairs mismatched at HLA-DRB1 were mismatched at both loci

\$ 168 donor-recipient pairs were matched at HLA-DRB1 and 37 were mismatched at a single DRB1 locus

\$\$ 151 donor-recipient pairs were matched at HLA-A and 34 were mismatched at a single A locus

\$\$\$ 70 donor-recipient pairs were matched at HLA-B and 57 were mismatched at a single B locus

Table 2**Patient, Disease and Transplant Characteristics**

Variables	Number (%)
Total number	803
Sex, male	430 (54%)
Age, years	
≤ 10	392 (49%)
11 – 20	180 (22%)
21 – 30	86 (11%)
31 – 40	69 (9%)
41 – 50	55 (7%)
51 – 62	21 (3%)
Recipient cytomegalovirus serostatus	
Seropositive	421 (52%)
Seronegative	374 (47%)
Not reported	8 (1%)
Disease	
Acute lymphoblastic leukemia	383 (48%)
Acute myeloid leukemia	299 (37%)
Chronic myeloid leukemia	45 (6%)
Myelodysplastic syndrome	76 (9%)
Disease status at transplantation	
<i>Acute leukemia</i>	
1 st complete remission	247 (31%)
2 nd complete remission	316 (39%)
Relapse	119 (15%)
<i>Myelodysplastic syndrome</i>	
Refractory anemia	6 (<1%)
Refractory anemia with excess blasts/transformed	70 (9%)
<i>Chronic myeloid leukemia</i>	
1 st chronic phase	23 (3%)
2 nd chronic phase / accelerated phase	5 (<1%)
Blast phase	17 (2%)
Conditioning regimen	
Total body irradiation + cyclophosphamide ± other	396 (49%)
Total body irradiation + other agents	54 (7%)
Busulfan + cyclophosphamide ± other	203 (25%)
Busulfan + thiotepa ± other	88 (11%)
Busulfan + melphalan ± other	62/ (8%)
Graft-versus-host disease prophylaxis	
Cyclosporine + steroid	649 (81%)
Cyclosporine + methotrexate ± steroid	132 (16%)

Variables	Number (%)
Other agents	22 (3%)

Table 3

Results of multivariate analysis for transplant-related mortality

	N1/N2	Hazard Ratio 95% CI	P- value
Mismatch at HLA-C vs. match at HLA-C*			
Zero mismatch at HLA-A, -B, -DRB1	6/23 vs. 6/69	3.97 (1.27 – 12.40)	0.018
1-locus mismatch at HLA-A or -B or -DRB1	66/234 vs. 23/127	1.70 (1.06 – 2.74)	0.029
2-loci mismatch at HLA-A and/or -B and/or -DRB1	101/293 vs. 17/57	1.25 (0.74 – 2.09)	0.404
Mismatch at HLA-A vs. match at HLA-A*			
Zero mismatch at HLA-B, -C, -DRB1	10/62 vs. 6/69	1.94 (0.70 – 5.35)	0.201
1-locus mismatch at HLA-B, or -C or DRB1	21/78 vs. 18/88	1.11 (0.59 – 2.10)	0.743
2-loci mismatch at HLA-B and/or -C and/or -DRB1	47/140 vs. 53/181	1.07 (0.72 – 1.58)	0.752
≥3-loci mismatch at HLA-B and/or -C and/or -DRB1	15/34 vs. 49/151	1.36 (0.76 – 2.43)	0.307
Mismatch at HLA-B vs. match at HLA-B*			
Zero mismatch at HLA-A, -C, -DRB1	4/24 vs. 6/69	2.66 (0.74 – 9.50)	0.133
1-locus mismatch at HLA-A, or -C or DRB1	40/153 vs. 23/125	1.57 (0.93 – 2.63)	0.088
2-loci mismatch at HLA-A and/or -C and/or -DRB1	61/193 vs. 39/112	0.90 (0.60 – 1.35)	0.613
≥3-loci mismatch at HLA-A and/or -C and/or -DRB1	20/57 vs. 26/70	0.80 (0.44 – 1.43)	0.444
Mismatch at HLA-DRB1 vs. match at HLA-DRB1*			
Zero mismatch at HLA-A, -B, -C	10/51 vs. 6/69	1.95 (0.71 – 5.28)	0.198
1-locus mismatch at HLA-A or -B or -C	33/77 vs. 17/101	2.63 (1.46 – 4.74)	0.001
2-loci mismatch at HLA-A and/or -B and/or -C	40/119 vs. 44/181	1.26 (0.82 – 1.94)	0.288
≥3-loci mismatch at HLA-A and/or -B and/or -C	13/37 vs. 56/168	1.03 (0.56 – 1.88)	0.931
Zero, single or multiple loci mismatches			
HLA-A, -B, -C, -DRB1 match [§] [◇]	6/69	1.00	
1-locus HLA-A, -B, -C, -DRB1 mismatch	27/147	2.02 (0.83 – 4.91)	0.12
2-loci HLA-A, -B, -C, -DRB1 mismatch	75/259	3.27 (1.42 – 7.54)	0.006
3-loci HLA-A, -B, -C, -DRB1 mismatch	83/253	3.34 (1.45 – 7.71)	0.005
4-loci HLA-A, -B, -C, -DRB1 mismatch	28/75	3.51 (1.44 – 8.58)	0.006

N1=number of events; N2=number evaluable

* The relative hazards ratio of transplant-related mortality associated with a single HLA-A mismatch, HLA-B mismatch, HLA-C mismatch or HLA-DRB1 mismatch versus a match at that locus (HR 1.00) in the presence of 0, 1, 2, ≥3 mismatches at other loci. Matching at HLA-C was examined in the presence of 0, 1 or 2 mismatches.

[§]The relative hazard ratio considering 1, 2, 3 or 4 mismatches at any loci vs.0 mismatch

[◇] Pair-wise test

2-loci mismatch vs. 1-locus mismatch: HR 1.62, 95% CI 1.04 – 2.52, p=0.032

3-loci mismatch vs. 1-locus mismatch: HR 1.65, 95% CI 1.07 – 2.57, p=0.024

4-loci mismatch vs. 1-locus mismatch: HR 1.74, 95% CI 1.02 – 2.97, p=0.042

3-loci mismatch vs. 2-loci mismatch: HR 1.02, 95% CI 0.75 – 1.40, p=0.884

4-loci mismatch vs. 2-loci mismatch: HR 1.07, 95% CI 0.69 – 1.67, p=0.748

4-loci mismatch vs. 3-loci mismatch: HR 1.05, 95% CI 0.68 – 1.62, p=0.826

Table 4

Results of multivariate analysis for overall mortality

	N1/N2	Hazard Ratio 95% CI	P-value
Mismatch at HLA-C vs. match at HLA-C*			
Zero mismatch at HLA-A, -B, -DRB1	10/23 vs. 29/69	1.22 (0.63 – 2.34)	0.559
1-locus mismatch at HLA-A or -B or -DRB1	130/234 vs. 57/127	1.42 (1.05 – 1.91)	0.023
2-loci mismatch at HLA-A and/or -B and/or -DRB1	163/293 vs. 29/57	1.17 (0.80 – 1.72)	0.424
Mismatch at HLA-A vs. match at HLA-A*			
Zero mismatch at HLA-B, -C, -DRB1	10/62 vs. 6/69	0.99 (0.60 – 1.54)	0.863
1-locus mismatch at HLA-B, or -C or DRB1	21/78 vs. 18/88	1.29 (0.85 – 1.95)	0.233
2-loci mismatch at HLA-B and/or -C and/or -DRB1	47/140 vs. 53/181	0.92 (0.69 – 1.23)	0.568
≥3-loci mismatch at HLA-B and/or -C and/or -DRB1	15/34 vs. 49/151	1.03 (0.64 – 1.65)	0.919
Mismatch at HLA-B vs. match at HLA-B*			
Zero mismatch at HLA-A, -C, -DRB1	4/24 vs. 6/69	1.42 (0.70 – 2.86)	0.331
1-locus mismatch at HLA-A, or -C or DRB1	40/153 vs. 23/125	1.29 (0.91 – 1.83)	0.147
2-loci mismatch at HLA-A and/or -C and/or -DRB1	61/193 vs. 39/112	0.90 (0.66 – 1.24)	0.526
≥3-loci mismatch at HLA-A and/or -C and/or -DRB1	20/57 vs. 26/70	0.78 (0.49 – 1.23)	0.278
Mismatch at HLA-DRB1 vs. match at HLA-DRB1*			
Zero mismatch at HLA-A, -B, -C	22/51 vs. 29/69	0.66 (0.39 – 1.11)	0.119
1-locus mismatch at HLA-A or -B or -C	45/77 vs. 44/101	1.36 (0.91 – 2.11)	0.129
2-loci mismatch at HLA-A and/or -B and/or -C	67/119 vs. 98/181	0.91 (0.67 – 1.24)	0.560
≥3-loci mismatch at HLA-A and/or -B and/or -C	23/37 vs. 90/168	1.10 (0.70 – 1.73)	0.675
Zero, single or multiple loci mismatches			
HLA-A, -B, -C, -DRB1 match [§] [◇]	29/69	1.00	
1-locus HLA-A, -B, -C, -DRB1 mismatch	65/147	1.06 (0.68 – 1.65)	0.801
2-loci HLA-A, -B, -C, -DRB1 mismatch	142/259	1.38 (0.92 – 2.07)	0.118
3-loci HLA-A, -B, -C, -DRB1 mismatch	136/253	1.33 (0.88 – 2.01)	0.171
4-loci HLA-A, -B, -C, -DRB1 mismatch	46/75	1.33 (0.83 – 2.15)	0.242

N1=number of events; N2=number evaluable

* The relative hazards ratio of overall mortality associated with a single HLA-A mismatch, HLA-B mismatch, HLA-C mismatch or HLA-DRB1 mismatch versus a match at that locus (HR 1.00) in the presence of 0, 1, 2, ≥3 mismatches at other loci. Matching at HLA-C was examined in the presence of 0, 1 or 2 mismatches.

[§]The relative hazard ratio considering 1, 2, 3 or 4 mismatches at any loci vs. 0 mismatch

[◇] Pair-wise test

2-loci mismatch vs. 1-locus mismatch: HR 1.30, 95% CI 0.97 – 1.75, p=0.078

3-loci mismatch vs. 1-locus mismatch: HR 1.26, 95% CI 0.93 – 1.69, p=0.133

4-loci mismatch vs. 1-locus mismatch: HR 1.26, 95% CI 0.86 – 1.84, p=0.243

3-loci mismatch vs. 2-loci mismatch: HR 0.96, 95% CI 0.76 – 1.22, p=0.759

4-loci mismatch vs. 2-loci mismatch: HR 0.96, 95% CI 0.69 – 1.35, p=0.827

4-loci mismatch vs. 3-loci mismatch: HR 1.01, 95% CI 0.77 – 1.40, p=0.998

Table 5

Results of multivariate analysis for neutrophil recovery

	N1/N2	Odds Ratio 95% CI	P- value
Mismatch at HLA-C vs. match at HLA-C*			
Zero mismatch at HLA-A, -B, -DRB1	19/23 vs. 63/69	1.01 (0.34 – 2.98)	0.982
1-locus mismatch at HLA-A or -B or -DRB1	208/234 vs. 117/127	1.10 (0.69 – 1.74)	0.692
2-loci mismatch at HLA-A and/or -B and/or -DRB1	248/293 vs. 46/57	0.75 (0.42 – 1.36)	0.344
Mismatch at HLA-A vs. match at HLA-A*			
Zero mismatch at HLA-B, -C, -DRB1	58/62 vs. 63/69	0.63 (0.30 – 1.34)	0.231
1-locus mismatch at HLA-B, or -C or DRB1	66/78 vs. 78/88	0.76 (0.40 – 1.44)	0.396
2-loci mismatch at HLA-B and/or -C and/or -DRB1	123/140 vs. 158/181	0.63 (0.40 – 1.01)	0.056
≥3-loci mismatch at HLA-B and/or -C and/or -DRB1	26/34 vs. 129/151	0.37 (0.17 – 0.82)	0.014
Mismatch at HLA-B vs. match at HLA-B*			
Zero mismatch at HLA-A, -C, -DRB1	21/24 vs. 63/69	0.89 (0.32 – 2.51)	0.828
1-locus mismatch at HLA-A, or -C or DRB1	137/153 vs. 114/125	1.60 (0.95 – 2.70)	0.078
2-loci mismatch at HLA-A and/or -C and/or -DRB1	170/193 vs. 92/112	0.87 (0.54 – 1.40)	0.559
≥3-loci mismatch at HLA-A and/or -C and/or -DRB1	46/57 vs. 58/70	0.93 (0.46 – 1.88)	0.837
Mismatch at HLA-DRB1 vs. match at HLA-DRB1*			
Zero mismatch at HLA-A, -B, -C	45/51 vs. 63/69	0.71 (0.32 – 1.57)	0.402
1-locus mismatch at HLA-A or -B or -C	63/77 vs. 93/101	0.62 (0.33 – 1.15)	0.129
2-loci mismatch at HLA-A and/or -B and/or -C	100/119 vs. 159/181	0.57 (0.35 – 0.93)	0.024
≥3-loci mismatch at HLA-A and/or -B and/or -C	30/37 vs. 148/168	1.54 (0.74 – 3.23)	0.250
Zero, single or multiple loci mismatches			
HLA-A, -B, -C, -DRB1 match [§]	63/69	1.00	
1-locus HLA-A, -B, -C, -DRB1 mismatch	134/147	0.73 (0.39 – 1.38)	0.37
2-loci HLA-A, -B, -C, -DRB1 mismatch	223/259	0.80 (0.44 – 1.45)	0.46
3-loci HLA-A, -B, -C, -DRB1 mismatch	222/253	0.54 (0.30 – 0.98)	0.004
4-loci HLA-A, -B, -C, -DRB1 mismatch	59/75	0.32 (0.16 – 0.65)	0.002

N1=number of events; N2=number evaluable

* The relative odds ratio of neutrophil recovery associated with a single HLA-A mismatch, HLA-B mismatch, HLA-C mismatch or HLA-DRB1 mismatch versus a match at that locus (OR 1.00) in the presence of 0, 1, 2, ≥3 at other loci. Matching at HLA-C was examined in the presence of 0, 1 or 2 mismatches.

[§]The relative odds ratio considering 1, 2, 3 or 4 mismatches at any loci vs.0 mismatch