Principles and Tools for Selection of Umbilical Cord Blood and Unrelated Adult Donor Grafts

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ABSTRACT

An analysis of NMDP data shows that allele-level matching for HLA A, B, C, and DRB1 is preferred in the selection of adult unrelated donors. If mismatching is unavoidable, mismatches at HLA B or C may be better tolerated than those at A or DRB1. Whether mismatches are at the allele level (ie, within an antigen group) or at the antigen level makes no difference in outcome, except at HLA C where allele mismatches are better tolerated. Matching for HLA DQ and DP should be prioritized below matching at the 4 major loci. These findings are compared and contrasted with previous publications.

The impact of HLA matching on major outcomes in umbilical cord blood (UCB) transplantation continues to be refined. Total nucleated cell dose was previously thought to be sole determinant of outcome with partially HLA matched UCB transplantation, but HLA matching, particularly at low total nucleated cell dose, appears to play an important role. Relatively small sample sizes limit the consistency of findings from cord blood studies, but the consensus supports consideration of both total nucleated cell dose and HLA matching in the selection of optimal UCB units. As search considerations for both adult donors and umbilical cord blood units have become more complex, the National Marrow Donor Program has developed software, services and relationships to ease the burden on transplant teams.

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KEY WORDS

Unrelated hematopoietic cell donors ∙ Umbilical cord blood ∙ HLA matching

INTRODUCTION

Hematopoietic cell transplantation (HCT) from adult unrelated donors and unrelated umbilical cord blood (UCB) units can cure patients with malignant and nonmalignant hematologic diseases who lack a suitable family member donor. The National Marrow Donor Program (NMDP) facilitates more than 300 HCT each month. Although most of these are adult donor transplants, UCB HCT comprises nearly 20% of the total and continues to increase. The NMDP registry lists more than 6.7 million adult donors and 68,000 UCB units. An additional 5 million adult donors and 200,000 UCB units are available for search through international collaborations. Selection of the best available adult donor or UCB unit is necessary to maximize the likelihood of successful HCT. The principles of optimal donor/UCB unit selection are continuing to evolve, and the tools for simplifying the process continue to improve.

SELECTING ADULT UNRELATED DONORS

Currently in the NMDP experience, up to 70% of patients undergo unrelated donor transplantation using an HLA-A, B, C, and DRB1 allele-matched unrelated donor, and some have multiple 8/8 allele matched donors identified. For these patients, the question is how to choose a donor among several HLA-matched possibilities based on criteria such as donor age [1]. For the approximately 30% for whom an 8/8 allele-matched donor cannot be identified, how should the best mismatched donor be selected? Recent results from a NMDP analysis are summarized followed by a discussion of relevant previous studies.

HLA-A, B, C, and DRB1

Increasing genetic disparity, particularly for human leukocyte antigen (HLA) molecules, is associated with greater risks of acute graft-versus-host disease
(aGVHD), higher transplant-related mortality, and lower survival in HCT. The NMDP recently analyzed 3857 transplant procedures and reported several key findings [2]: (1) high-resolution DNA matching for HLA-A, B, C, and DRB1 (8 of 8 match) was confirmed as the minimum level of matching associated with the highest survival. A single mismatch detected by low- or high-resolution DNA testing at HLA-A, B, C, or DRB1 (7 of 8 match) was associated with higher mortality (relative risk $1.25$, 95% confidence interval [CI] $1.13-1.38$, $P < .0001$) and 1-year survival of 43% compared to 52% for 8 of 8 matched pairs. Mismatching at 2 or more loci compounded the mortality risk. (2) An allele mismatch was associated with the same statistical decrement in survival as an antigen mismatch, except for HLA-C where the lower survival was primarily associated with antigen mismatches. (3) Single mismatches at HLA-A or HLA-DRB1 appear more poorly tolerated than mismatches at HLA-B or HLA-C (relative risk [RR] $1.18$, 95% CI $1.10-1.38$, $P = .04$) (Table 1). (4) Single mismatches were also associated with treatment-related mortality and aGVHD. There was no statistically significant difference between 7 of 8 (either allele or antigen) and 8 of 8 matched pairs for relapse, chronic GVHD (cGVHD), and engraftment.

Transplant procedures were performed between 1988-2003 using myeloablative conditioning and primarily bone marrow as a stem cell source. Diseases included acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and myelodysplastic syndrome. Pairs mismatched at specific loci were compared with 8 of 8 HLA matched pairs, in contrast to previous studies that relied on multivariable models to adjust for multiple mismatches [3] or grouped different mismatches together before performing subgroup comparisons [4]. Because of multiple testing, a $P$-value $<.01$ was considered statistically significant. Although this approach more precisely estimates the association between specific mismatches and outcomes, limited patient numbers in certain subsets may severely limit the power of the analysis for those subgroups.

### HLA-DQ

In the NMDP analysis discussed above, a single HLA-DQ mismatch was not associated with any adverse outcomes. If a pair is already mismatched at another locus, adding an additional HLA-DQ mismatch was associated with a mortality risk of $1.15$, 95% CI $0.95-1.39$, $P = .14$. Among 6 of 8 matched pairs, the mortality risk associated with an additional HLA-DQ mismatch was $1.20$, 95% CI $0.98-1.46$, $P = .08$. Thus, if a pair is otherwise matched at HLA-A, B, C, and DRB1, the NMDP analysis suggests additional testing for HLA-DQ is not necessary because single HLA-DQ mismatches were not associated with increased mortality. However, if 1 or more other mismatches are present, HLA-DQ matched donors should be favored given the same degree of matching at other loci.

### HLA-DP

HLA-DP locus mismatches were common in otherwise well-matched pairs. There was no association of HLA-DP mismatching with survival or disease-free survival (DFS) in the multivariate analysis. However, increased aGVHD (RR $1.43$, 95% CI $1.16-1.76$, $P = .0009$) and a trend toward a lower relapse rate (RR $0.74$, 95% CI $0.57-0.96$, $P = .02$) was seen with HLA-DP mismatching, consistent with prior reports [5-8].

### Donor Age and Other Characteristics

Multivariate models were constructed to identify factors predictive of patient survival. HLA matching was highly statistically significant, as were patient age, race, disease stage, and CMV status. Donor factors, such as age, parity, CMV status, and gender were not significantly associated with patient survival, suggesting that HLA matching should be the primary determinant in donor selection.

### Current Results in the Context of Past Findings

This section reviews the survival results presented above in the context of other published literature from the NMDP and 2 other groups, the Fred Hutchinson
In 1995, Petersdorf and colleagues [9] at the FHCRC in Seattle analyzed 364 patients and reported that HLA-DRB1 allele mismatching was associated with higher rates of aGVHD and mortality. Subsequently, in 1996, they reported that HLA-DQB1 mismatching was also associated with grade III-IV aGVHD in 449 patients, although survival was not evaluated [10]. The next FHCRC publication in 1998 analyzed 300 CML patients and found that 2 or more class I and combined class I and II allele mismatches were associated with graft failure and mortality [11]. In 2001, they extended this analysis to 471 CML patients and reported that single antigen but not allele class I mismatches were associated with graft failure. Survival at 5 years was not statistically different between single class I allele mismatched pairs, single class I antigen mismatched pairs, and matched patients [5]. Petersdorf et al [12], in 2004, analyzed 948 patients using both HLA-mismatched subset comparisons and multivariate analysis and reported that a single allele or antigen mismatch was associated with higher mortality in early-phase disease, defined as CML in chronic phase within 2 years of diagnosis, but not in patients with more advanced disease. In particular, a single disparity at HLA-C (n = 24) was associated with lower survival as was an HLA-DQ mismatch in combination with other mismatches. They also found that single allele and single antigen mismatched pairs had similar mortality.

The current NMDP study is consistent with the Seattle results in that allele and antigen mismatches are associated with similar adverse outcomes in early-phase disease. However, the NMDP studies have also documented lower survival for single mismatches in patients with advanced disease phases, while conversely, failing to find a statistically significant adverse effect of HLA-DQ mismatching in combination with other mismatches. The larger NMDP sample size and consequent ability to emphasize comparison of single locus mismatched pairs to fully matched pairs may explain some of these differences.

A second set of studies comes from the JMDP. These mostly focus on pairs already serologically matched for HLA-A, B, and DR. In 1998, JMDP reported that HLA-A mismatches were associated with higher grade III-IV aGVHD and mortality. HLA-C mismatches were associated with higher aGVHD and lower relapse, but no difference in survival, and class II mismatches were not associated with either aGVHD or survival. Multivariate modeling, controlling for any additional mismatches present, was used to analyze 440 pairs [13]. In 2002, JMDP updated their analysis, including 1298 pairs. In this report, they performed both multivariate analyses and subset analysis comparing mismatched to fully matched pairs. Because of limited numbers, they analyzed 3 subsets: HLA-A and/or HLA-B, HLA-C, and DRB1 and/or DQB1. All subgroups were associated with grade III-IV aGVHD but only HLA-A and/or HLA-B mismatches were associated with higher mortality and cGVHD [4]. More recently, the JMDP published a study identifying 15 specific allele combination mismatches (at least 1 in each locus) associated with severe grade III-IV aGVHD. Further analysis showed 6 specific amino acid substitution positions in HLA class I were associated with severe aGVHD [14].

The current NMDP study is consistent with JMDP reports in that high-resolution mismatching at HLA-A is associated with increased mortality, but high-resolution mismatching at HLA-C is not. Unlike the JMDP, we also found increased mortality among 104 transplants with a single DRB1 high-resolution mismatch ± a DQB1 mismatch, whereas JMDP found similar nonrelapse mortality among 116 patients with DRB1 and/or DQB1 mismatches compared to fully matched pairs. It is possible that relatively small numbers, rather than the biology of HLA-DR in the 2 ethnic groups, accounts for the different conclusions.

The NMDP has published 2 earlier studies examining HLA matching in adult unrelated donor HCT. In 2001, the NMDP analyzed 831 patients with CML in a chronic or accelerated phase, and reported that HLA-DRB1 allele mismatching was associated with lower relapse-free (RFS) and overall survival (OS) [15]. In 2004, an NMDP study led by Flomenberg analyzed 1874 pairs and reported that low-resolution mismatches at HLA-A, B, C, and DRB1 were associated with similar decrements in survival. In contrast, mismatches detected only with high-resolution typing were not statistically associated with lower survival at $P < .01$. HLA-A mismatches were associated with higher grade III-IV aGVHD and cGVHD. Mismatches at HLA-DQ and HLA-DR were not associated with survival differences [3]. Although patients in the 2004 NMDP study comprised 34% of the pairs in the current study, several findings differed. First, in the current 2007 study, both allele and antigen mismatches were roughly equivalent (except for HLA-C), whereas the 2004 study found that antigen mismatches fared more poorly than allele mismatched pairs. Second, in the 2007 study, HLA-A, HLA-C, and HLA-DR mismatches were associated with higher mortality than HLA-B, whereas the 2004 study concluded that mismatches at these 4 loci were approximately equivalent. These discrepancies may be explained by differences in study population and method of analysis. The 2007 study was limited to patients with AML, ALL, CML, and MDS, and compared outcomes between fully matched patients and defined subsets of patients with specific mismatches, providing independent risk
estimates according to locus and resolution mismatch. The 2004 study included more heterogeneous diseases, including 9% nonmalignant diagnoses, and utilized multivariate modeling to adjust for the presence of additional mismatched loci.

The estimated effect of donor age on survival is controversial. The current 2007 NMDP study did not find a statistically significant association between donor age and patient survival. Using donor age <31 years as the baseline, donor age 31-45 years was associated with a RR 1.05, 95% CI 0.95-1.14, \( P = .38 \) and >45 years, with an RR of 1.06, (95% CI 0.93-1.20, \( P = .42 \)). In contrast, a previous 2001 NMDP study by Kollman found that each decade of donor age was associated with an RR of 1.10 (95% CI 1.06-1.14, \( P < .0001 \)) [16]. The 2001 NMDP study included twice as many patients (N = 6978), used serologic typing for class I loci, had a median follow-up of only 2 years, and included 17% with different diseases than our population.

CONCLUSION

Increasingly large numbers of unrelated donor pairs allow more refined studies of the association between HLA matching and the success of unrelated donor transplantation. However, the constant evolution of graft sources, conditioning regimens, GVHD prophylaxis regimens, and supportive care guarantees that solid data to guide donor selection will always lag behind current practice to some extent. Nevertheless, donor decisions need to be made today, and these data are the best available evidence to help select the optimal donors. Based on the most recent NMDP study, donor selection should be based on high-resolution matching at HLA-A, B, C, and DRB1 so as to maximize the chance for a successful transplant. If a fully allele-matched donor at HLA-A, B, C, and DRB1 is not available and multiple mismatched donors are fully typed, then single mismatches at HLA-B or HLA-C are better tolerated than single HLA-A or DRB1 mismatches in our study. We could not document a difference between the adverse effects of allele and antigen mismatches, except perhaps for HLA-C, where only antigen mismatches were associated with worse outcomes. Although HLA-DQ and HLA-DP matching and younger donor age were not statistically significantly associated with mortality in this study, it is reasonable to prioritize HLA-DQ and HLA-DP matched and younger donors if other HLA considerations are equal and complete high-resolution typing is known.

SELECTING UMILICAL CORD BLOOD UNITS

Since the initial report of the successful use of partially HLA-mismatched unrelated donor UCB as a source of hematopoietic stem cells by Kurtzberg et al [17], in 1996, several studies have shown that the results of HCT using HLA-matched or partially mismatched unrelated donor UCB are comparable to those using unrelated donor bone marrow [18-22]. UCB is now accepted as an alternative source of hematopoietic stem cells for unrelated donor transplantation, with over 8000 UCB transplants performed worldwide [23].

It is important to note that the majority of UCB HCT reported in the literature has utilized matching at the antigen level for HLA-A and HLA-B loci typed either by serology or low- to intermediate-resolution DNA-based methods, and at the allele level for HLA-DRB1 loci. The current standard for UCB unit selection is thus based on HLA matching at low to intermediate resolution for HLA-A and B and allele-level matching for DRB1 with donor-recipient match status categorized as a 6 of 6, 5 of 6, or 4 of 6 match.

Similar to the results of studies in adult unrelated donor HCT, it is likely that allele-level disparity between donor and recipient may also impact transplant outcomes, although the paucity of data in this regard is a limitation in determining the current role of allele-level HLA matching in UCB HCT. Retrospective studies of UCB HCT utilizing allele-level matching data have shown that when the original HLA match is compared to the final one, the HLA match status is demoted in almost a third of donor/recipient pairs [24]. As an example, a study by Kogler et al [25] of 122 donor-recipient pairs showed that over half (9 of 16) of the patients initially thought to be 6 of 6 matched actually had lower levels of match at the allele level.

Impact of HLA Matching on Engraftment after UCB HCT

UCB HCT differs from either unrelated bone marrow or peripheral blood stem cell transplantation in that there is a significant delay in the time to engraftment and the overall probability of engraftment is lower with UCB [18,19,21,22,26,27]. Studies of UCB HCT have shown that the total nucleated cell dose is a critical factor that is strongly correlated with hematopoietic engraftment [28-30]. Other studies suggest that the CD34+ cell dose [31] or the graft progenitor cell content as measured by colony-forming cells [32] may be more important determinants of hematopoietic recovery post-UCB HCT, but the nucleated cell dose is more widely accepted as the criterion by which UCB units are selected because quantification of CD34+ cells or colony-forming cells is difficult to standardize from bank to bank.

In addition to graft cell dose, analyses of outcomes following UCB HCT also suggest an impact of donor-recipient HLA matching on engraftment. In the largest analysis done to date on 562 UCB HCT
Impact of HLA Matching on GVHD

Several analyses of UCB HCT have assessed the impact of HLA matching on GVHD incidence. Analysis of the New York Blood Center’s experience shows a trend, suggesting an impact of matching on risk of severe grade III-IV GVHD with recipients of matched UCB showing a lower GVHD risk compared to recipients of mismatched UCB (P = .06) [29]. The analysis of Eurocord data shows that the risk of grade III-IV GVHD is higher in recipients of UCB where class I and II disparities coexist between donor and recipient [34]. In the COBLT study, multivariate analysis showed that HLA matching impacted grade II-IV aGVHD risk, with a significantly higher risk of aGVHD in recipients of 4 of 6 matched UCB compared to 5 of 6 and 6 of 6 matched UCB (P = .03) [27]. The outcome comparison study of unrelated BM versus UCB by Eapen et al [19] failed to show a correlation between HLA match and aGVHD or cGVHD risk among recipients of UCB transplants.

Role of HLA Compatibility on Survival after UCB HCT

Analyses by Rubinstein et al [29] and Wagner et al [31], have identified a detrimental effect of HLA-A, B, and DRB1 mismatching on survival. In a multivariable Cox model, Rubinstein et al [29] found a higher risk of adverse events (defined as death, autologous reconstitution or second transplant) in 217 UCB HCT with 1 mismatch (RR = 2.0), and 300 UCB HCT with 2 or more mismatches (RR = 2.5) compared with 40 matched UCB transplants. Although the power of the study was limited, there was no significant effect of the number of mismatched loci, type of mismatched locus, and level of typing resolution utilized to define the mismatch at DRB1. Wagner et al [31] found an increased risk of death (RR = 2.4) among 44 recipients of UCB HCT mismatched for 2-3 loci, compared to 58 recipients mismatched for 0-1 locus (P = .01). Eapen et al [19] evaluated treatment failure as the inverse of leukemia-free survival and showed a favorable outcome for matched UCB HCT compared to 1 to 2 antigen mismatched UCB HCT or matched or allele-mismatched UBMT (P = .041). It is to be noted there were only 35 patients in the matched UCB cohort, but suggests that HLA matching may be of strong import in outcome after UCB HCT. In contrast to the above studies, a study of 550 UCB HCT by Eurocord [34] failed to find an effect of HLA disparity on 3-year survival. Although the reasons for the disparate results are not obvious, it is possible that a cell dose interaction may be contributory because it did not enter the multivariable model in the Eurocord study. In this analysis, HLA disparity did impact survival for patients with nonmalignant diseases [23]. Table 2 summarizes the findings of the largest studies to date that have evaluated the role of HLA match on survival following UCB HCT.

In the COBLT study, multivariate analysis using retrospective high-resolution typing data showed that there was a significant increase in the incidence of grades II-IV and III-IV aGVHD (P = .02) and a significant decrease in survival probability when a 2-4 of 6 matched UCB HCT was compared to 5-6 of 6 matched transplants (P = .04) [27]. Although a few other studies have shown a positive effect of high-resolution HLA matching on survival after
UCB HCT, these data should be interpreted with caution because of the small numbers of patients analyzed.

When interpreting all the analyses described above, the following limitations need to be kept in mind. First, only a small proportion of patients have received fully matched UCB transplants. Second, the majority of transplants performed to date have been 1 or 2 antigen mismatched, and larger patient numbers will be required to fully determine the differences between these 2 cohorts. Third, although there are suggestions of an interaction between cell dose and HLA matching, small sample sizes have limited the investigation of this interaction. Patient age and cell dose may also be confounding variables.

Additional factors that may influence how a transplant physician chooses UCB units include the UCB bank, whether the unit was red cell depleted prior to cryopreservation, availability of attached segments for confirmatory typing and infectious disease marker characteristics of the unit. No data currently exist to assist us in evaluating the role of these in engraftment or survival after UCB transplantation.

**CONCLUSION**

UCB graft cell dose is a critical determinant of hematopoietic recovery and survival after UCB HCT, but there is increasing evidence that HLA match is also a key factor in UCB HCT outcome. Current data suggest that HLA match is critically important in the setting of a low cell dose. The complete elucidation of the impact of graft dose and match on UCB HCT outcome will require the analysis of larger cohorts of patients. The impact of a 1 versus 2 antigen mismatch, the “trade-off” between HLA-match and cell dose in unit selection, the importance of allele-level matching at HLA-A and B, the match vector, and whether HLA-C or DQB1 should be considered in the selection of UCB units for transplantation cannot be fully discerned at the current time. Currently available data would consider this to be a unit that has $>2.5\times10^7$ total precryopreserved nucleated cells per kg recipient body weight.

**Tools for Locating the Optimal Adult Donor or UCB Unit**

The process for identifying and ultimately selecting an unrelated donor or UCB is the responsibility of the transplant center. NMDP has published recommendations about how to search for adult bone marrow donors, and a similar set of recommendations concerning UCB units is under consideration [1,35].

NMDP provides software to transplant centers (TRANS Link®) that allows real-time searching of the complete NMDP inventory of adult donors and UCB units. TRANS Link produces a donor/UCB list that is sorted with the best of potential donors/UCB at the top. Within HLA match grades, UCB are prioritized according to total nucleated cell (TNC) content, whereas adult donors are prioritized by HLA matching likelihood alone. An NMDP innovation named HapLogic™ predicts the likelihood of allele-level matching based on calculated HLA haplotype frequencies within major racial and ethnic populations [36]. Currently, HapLogic predicts high-resolution matching at HLA A, B, and DRB1, but a future release in active development will also consider HLA C and DQ. TRANS Link allows the user to further customize the search results by prioritizing specific HLA loci or donor/UCB characteristics (age, sex, CMV status, etc.). Currently, using TRANS Link requires that a software program is installed on the user’s computer that accesses the NMDP databases through the Internet. A future release of NMDP matching software will allow access through a standard WWW browser interface (eg, Internet Explorer, Firefox).

Another NMDP software product is the Multi-Cord Tool. The Multi-Cord Tool evaluates HLA matching between the proposed recipient and the UCB units as well as the matching between UCB units. The tool was developed to simplify the UCB selection process for double cord transplantation. It can operate on the UCB units from the NMDP search, from a Bone Marrow Donors Worldwide (BMDW) search, or those hand-entered by the user. The Multi-Cord Tool is provided at no charge, and access is granted through the NMDP Center for Cord Blood.

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**Table 2. HLA Match: Effect of Mismatching on Survival following Umbilical Cord Blood Transplantation**

<table>
<thead>
<tr>
<th>HLA-A, B, DRB1 match status*</th>
<th>Rubinstein et al [29]</th>
<th>Wagner et al [31]</th>
<th>Gluckman et al [34]</th>
<th>Eapen et al [19]‡</th>
<th>Kurtzberg et al [27]</th>
</tr>
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<tbody>
<tr>
<td>5/6</td>
<td>Decrease</td>
<td>Decrease</td>
<td>No effect†</td>
<td>Decrease</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>≤ 4/6</td>
<td>Decrease</td>
<td>Decrease</td>
<td>No effect†</td>
<td>Decrease</td>
<td></td>
</tr>
</tbody>
</table>

*Mismatch count based on antigen-level match at HLA-A, B, and allele level at HLA-DRB1.
†Cell dose was not considered in the multivariate analysis.
‡Leukemia-free survival.
Although the NMDP lists more than 1.5 million non-U.S. donors and several thousand UCB units in its participating international centers/banks in the upfront TRANS Link search, additional adult donors and UCB units are accessible only through cooperative registry/cord bank agreements. BMDW provides its online search as a convenient way to target registries and banks for further inquiries. The NMDP automatically searches BMDW with every new search submission. Several registries, including NMDP, also automatically exchange donor and UCB search information using the messaging protocol, EMDIS (European Marrow Donor Information System, www.zkrd.de/emdis.html). For registries that have not implemented EMDIS, the searching process is largely manual, involving facsimile transmissions and e-mail messages.

Up-to-date HLA information is available through several Web resources. The NMDP maintains 2 useful Web sites: www.nmdpresearch.org and bioinformatics.nmdp.org. The latter provides links to the IMGT/HLA database, which includes sequence information on all recognized human HLA alleles. The NMDP also provides human resources to assist in the unrelated adult donor and UCB units search process. NMDP HLA consultations are available for any active patient search to provide estimates of the likely best available matches and strategies for conducting complicated or alternative searches. An HLA consultation service is also available through BMDW. In addition, the NMDP has begun to offer Centralized Search Service. With Centralized Search Service the transplant center provides a list of adult donor or UCB unit criteria from which the NMDP will manage the entire search process. The transplant center receives a listing of the best available adult donors or UCB units from which a final selection can be made. Finally, the NMDP Office of Patient Advocacy (OPA) provides a number of services for patients including review of search results and explanations of the search process. The OPA maintains a toll-free telephone access (1-888-999-6743).

**REFERENCES**
