RAPID COMMUNICATION


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Allogeneic transplant access can be severely limited for patients of racial and ethnic minorities without suitable sibling donors. Whether cord blood (CB) transplantation can extend transplant access because of the reduced stringency of required HLA-match is not proven. We prospectively evaluated availability of unrelated donors (URD) and CB according to patient ancestry in 553 patients without suitable sibling donors. URDs had priority if adequate donors were available. Otherwise $4/6$ HLA-matched CB grafts were chosen utilizing double units to augment graft dose. Patients had highly diverse ancestries including 35% non-Europeans. In 525 patients undergoing combined searches, 10/10 HLA-matched URDs were identified in 53% of those with European ancestry, but only 21% of patients with non-European origins ($P < .001$). However, the majority of both groups had 5-6/6 CB units. The 269 URD transplant recipients were predominantly European, with non-European patients accounting for only 23%. By contrast, 56% of CB transplant recipients had non-European ancestries ($P < .001$). Of 26 patients without any suitable stem cell source, 73% had non-European ancestries ($P < .001$). Their median weight was significantly higher than CB transplant recipients ($P < .001$), partially accounting for their lack of a CB graft. Availability of CB significantly extends allo-transplant access, especially in non-European patients, and has the greatest potential to provide a suitable stem cell source regardless of race or ethnicity. Minority patients in need of allografts, but without suitable matched sibling donors, should be referred for combined URD and CB searches to optimize transplant access.


KEY WORDS: Unrelated donor, Cord blood, Allogeneic transplantation, Hematologic malignancy

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation may be curative for patients with lethal hematologic malignancies. Thus, it represents 1 of the major achievements of modern hematology [1]. It is therefore imperative that all eligible patients have equal access to this therapy. However, <30% of patients requiring an allograft have a suitable human leukocyte antigen (HLA)-matched sibling donor [1]. Although unrelated donor (URD) registries can supply grafts for those without a suitable sibling donor, the strict HLA-match needed to minimize the chance of lethal or debilitating transplant complications limits the donor pool [2,3]. Patients of racial and ethnic minorities are disadvantaged because of their relatively low numbers in volunteer registries and an increased likelihood that potential donors will be unavailable upon request [4-6]. Highly polymorphic HLA loci pose additional challenges in some groups, such as patients of African ancestry [4].

In 1989, Gluckman and colleagues [7] reported the use of HLA-identical sibling donor cord blood (CB) as a stem cell source for transplantation.
Subsequent series have confirmed the efficacy of unrelated donor CB transplantation [8-13], including leukemia-free survival at least comparable to that provided by 8/8 HLA-matched URD bone marrow transplantation in children [14]. Promising survival has also been reported in adults [15-17], with 2 recent reports suggesting double-unit CB transplantation may be associated with comparable survival to that of HLA-matched sibling donor and URD transplantation in patients with hematologic malignancies [18,19]. A remarkable feature of this neonatal stem cell source is a greatly reduced incidence of graft-versus-host disease (GVHD) for the degree of donor-recipient HLA-mismatch [8-13]. Therefore, public CB banking was originally proposed as a means to provide a stem cell source that could extend transplant access [20]. That CB can extend transplant access to minorities has been suggested, but this hypothesis has never been formally tested and cannot be assumed given the relatively small size of the global CB inventory [21]. Hence, we conducted a prospective study evaluating donor availability according to patient ancestry in the highly diverse population referred to our Center in New York City.

**Patients and Methods**

**Study Population**

Patients were candidates for allogeneic hematopoietic stem cell transplantation for the treatment of high-risk hematologic malignancies or severe aplastic anemia. They had no suitable HLA-matched related donors, were eligible for either URD or CB transplantation, provided informed consent for a formal donor search, and were transplanted or had their search closed during the study period. Institutional review board approval was obtained to analyze patient data including those patients whose preliminary search failed to identify any potentially suitable URD or CB units to request for typing. Adopted patients with unknown ancestry, patients whose searches were ongoing without a donor chosen, and searches for second transplants were excluded. Data on the searches for 553 patients were collected prospectively between October 1, 2005, and December 31, 2009.

**URD and CB Searches**

The majority of patients underwent combined search for both URD and CB units. URD searches and grafts were facilitated by the National Marrow Donor Program (NMDP). CB searches were conducted through the Bone Marrow Donors Worldwide, the NMDP, and the New York Blood Center (NYBC), and both domestic and international units were considered for potential use. Memorial Sloan-Kettering Cancer Center (MSKCC) policy is to type potential URD recipients and their donors at 10 HLA-alleles given the progressive decrease in survival with an allele or antigen mismatch at each of the HLA-A,-B,-C, and -DRB1 loci when transplanting URD grafts, and that HLA-DQ mismatches are detrimental when present with other mismatches [2,3]. Further, our institution is investigating T cell depletion as a means to abrogate severe graft-versus-host disease (GVHD), especially if mismatched. Therefore, adequate donor-recipient HLA-match was defined as ≥8/10 HLA-A, -B, -C, -DRB1, or -DQ for a T cell-depleted graft. Patients requiring unmodified grafts in the setting of very high risk disease or reduced-intensity conditioning (RIC) required ≥9/10 HLA-match for an unmodified URD graft in order to reduce the risk of life-threatening GVHD.

By contrast, adequate CB units were ≥4/6 HLA-A, -B antigen, or -DRB1 allele matched to the recipient with a cryopreserved total nucleated cell (TNC) dose ≥1.5 × 10^6/kg/unit. Double-unit grafts were used to augment engraftment, reduce treatment-related mortality, potentially reduce relapse [22,23], and improve survival in all patients [15-17]. Unit-unit HLA-match was not considered. CB transplant recipients preferably had at least 1 additional backup unit identified before transplant. URDs had priority as the stem cell source. CB was chosen if no suitably HLA-matched URDs were available within the required time period according to physician assessment of transplant urgency. Patients were transplanted with high-dose or RIC according to age, diagnosis, prior therapy, and comorbidities.

**Assessment of Patient Ancestry**

Patient ancestry information was collected by physicians and transplant coordinators using direct patient interview to determine the country of birth of the patient, each parent, and each grandparent for as many generations as known or needed to establish the ancestry. In addition, patients self-identified themselves as Black and/or Hispanic. We used similar categories as previous reports [4,24], but additionally divided patients of European ancestry, however, into northwestern, eastern, southern, and mixed Europeans. Moreover, non-European ancestries were divided into Asian, African (Hispanic and non-Hispanic), White Hispanic, Middle Eastern, and mixed non-European groups. Patients of African ancestry included African-Americans, and immigrants from Africa or the Caribbean. Non-European mixes included any patient with at least partial non-European origins even if partly European (but excluded those who self-identified as Black), and frequently included complex racial mixes. Information concerning the ancestry or race of URDs and maternal donors of CB was incomplete, precluding analyses of recipient-donor ancestral matching.
Statistical Analysis

Tests of association between independent binary variables were performed using Fisher’s exact test; the paired binary data were examined using McNemar’s test. For continuous variables, the test of equality between independent groups was based on the Wilcoxon rank sum test. For multiple observations per subject, the Wilcoxon test incorporating clustering was employed. The time to secure an URD versus a CB graft was not analyzed as URD were given priority, and therefore, URD and CB were not given equal weight at the search initiation. Also, it is already established that cryopreserved CB is available more quickly than URD [25].

RESULTS

Patient Ancestry and Demographics

Our patients had highly diverse ancestries. Only 112 (20%) of the 553 patients were of northwestern European ancestry, whereas 81 (15%) had eastern, 60 (11%) southern, and 105 (19%) mixed European backgrounds. Northwestern Europeans were predominantly of English, Irish, Scottish, German, and/or Scandinavian origins. The majority of southern Europeans originated from southern Italy. European mixes were most frequently a mix of northwestern and southern European (eg, Sicilian Italian-Irish), or northwestern and eastern European (eg, English-Polish) ancestries. Of the 195 (35%) patients of non-European origins, 46 (8%) had Asian, 64 (12%) African (55 non-Hispanic and 9 Hispanic), 51 (9%) White Hispanic, 11 (2%) Middle Eastern, and 23 (4%) mixed non-European ancestries. There were no Pacific Islanders. Ten of the mixed non-Europeans had part Native American ancestry, however. The majority of patients (n = 445, 80%) were born in the United States. Patients had a median age of 47 years (range: 0.9-73 years). Diagnoses included acute leukemia (n = 294; 53%), myelodysplastic syndrome/myeloproliferative disorders (n = 83; 15%), non-Hodgkin lymphoma or chronic lymphocytic/prolymphocytic leukemia (n = 119; 22%), Hodgkin lymphoma (n = 36; 7%), multiple myeloma (n = 12; 2%), aplastic anemia (n = 7; 1%), or other malignancies (n = 2; <1%).

Results of Combined URD and CB Searches

Nearly all patients (n = 525, 95%) had combined URD and CB formal searches that allowed direct comparison of the best matched URD, and best matched and adequately dosed CB units, identified for the same patients (Table 1). The remaining 28 patients had suitably matched URDs and a CB search was not performed. We found that fully matched (10/10) URD were identified for the majority of those with northwestern (62%) or eastern European (59%) backgrounds, and half of those with mixed European

<table>
<thead>
<tr>
<th>Patients of European Ancestries</th>
<th>Northwestern European (n = 104)</th>
<th>Eastern European (n = 76)</th>
<th>Southern European (n = 60)</th>
<th>European Mix (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best URD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10</td>
<td>64 (62%)</td>
<td>45 (59%)</td>
<td>20 (33%)</td>
<td>51 (50%)</td>
</tr>
<tr>
<td>9/10</td>
<td>28 (27%)</td>
<td>20 (26%)</td>
<td>20 (33%)</td>
<td>31 (31%)</td>
</tr>
<tr>
<td>8/10</td>
<td>12 (12%)</td>
<td>11 (14%)</td>
<td>20 (33%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Best CB*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/6/6</td>
<td>88 (85%)</td>
<td>62 (82%)</td>
<td>36 (60%)</td>
<td>84 (83%)</td>
</tr>
<tr>
<td>4/6</td>
<td>15 (14%)</td>
<td>12 (16%)</td>
<td>15 (25%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>No CB</td>
<td>2 (2%)</td>
<td>2 (3%)</td>
<td>9 (15%)</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients of Non-European Ancestries</th>
<th>Asian (n = 42)</th>
<th>African (n = 61)</th>
<th>White Hispanic (n = 48)</th>
<th>Middle Eastern (n = 10)</th>
<th>Non-European Mix (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best URD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10</td>
<td>8 (19%)</td>
<td>5 (8%)</td>
<td>10 (21%)</td>
<td>6 (60%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>9/10</td>
<td>6 (14%)</td>
<td>20 (33%)</td>
<td>14 (29%)</td>
<td>1 (10%)</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>8/10</td>
<td>28 (67%)</td>
<td>36 (59%)</td>
<td>24 (50%)</td>
<td>3 (30%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Best CB*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/6/6</td>
<td>36 (86%)</td>
<td>35 (57%)</td>
<td>33 (69%)</td>
<td>8 (80%)</td>
<td>19 (83%)</td>
</tr>
<tr>
<td>4/6</td>
<td>6 (14%)</td>
<td>14 (23%)</td>
<td>10 (21%)</td>
<td>2 (20%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>No CB</td>
<td>0</td>
<td>12 (20%)</td>
<td>5 (10%)</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

URD indicates adult unrelated volunteer donor; CB, cord blood. *Best CB units were defined according to HLA-match but also had to have an adequate total nucleated cell (TNC) dose of at least 1.5 \( \times \) \( 10^7 \)/kg/unit.
Ancestries (50%). However, a 10/10 HLA-matched URD was identified in only 33% of southern European patients ($P = .001$). Furthermore, although 60% of patients with Middle Eastern ancestry had 10/10 HLA-matched URD identified, this was only the case for 19% of Asian, 8% of African, and 21% of White Hispanic patients. By contrast, CB extended stem cell availability to patients of both European and non-European origins.

Overall, the difference in URD and CB availability according to European versus non-European ancestry in patients undergoing combined searches is summarized in Table 2. European ancestry patients were more likely to have a fully matched URD identified than those of non-European origins (53% versus 21%, $P < .001$). In addition, Europeans were more likely to have 5-6/6 HLA-matched CB units (identified in 79%) than to have 10/10 HLA-matched URD (identified in 53%, $P < .001$). In non-European patients, CB units matched at 5-6/6 HLA loci were also more frequently identified than fully matched URDs (71% versus 21%, $P < .001$).

### Table 2. Summary Comparison of URD and CB Availability for Patients Undergoing Combined Searches According to European versus Non-European Ancestry: European Patients Were More Likely to Secure a 10/10 HLA-Matched URD Than Non-Europeans, Whereas 5-6/6 CB Were Available for Both Groups

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>URD</th>
<th>CB</th>
<th>No Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europeans (n = 341)</td>
<td>10/10: 218 (63%), 9/10: 122 (36%)</td>
<td>6/6: 74 (22%), 5/6: 50 (15%)</td>
<td>No CB: 15 (4%)</td>
</tr>
<tr>
<td>Non-Europeans (n = 184)</td>
<td>10/10: 38 (21%), 9/10: 50 (27%)</td>
<td>6/6: 34 (18%), 5/6: 40 (22%)</td>
<td>No CB: 19 (10%)</td>
</tr>
</tbody>
</table>

URD indicates adult unrelated volunteer donor; CB, cord blood.

### Transplant Analysis

Of the 553 study population, 359 (65%) underwent transplantation. Three-quarters (n = 269, 75%) used URDs (median age 48 years, range: 1-73 years), whereas 25% (n = 90) required CB (median age 37 years, range: 1-68 years). Twenty-six patients (5% of the total study population) were not transplanted specifically because of a lack of a suitable URD or CB graft. The remaining 168 patients (30% of the total) were not transplanted with URD or CB for other reasons, predominantly because of refractory disease or treatment complications (n = 110). The proportions of patients of European (n = 103, 29%) and non-European (n = 65, 33%) backgrounds that could not be transplanted for reasons other than not having a graft were similar ($P = .240$).

### URD Transplant Recipients

Notably, URD transplant recipients were predominantly European (n = 208, 77%), with the largest subgroup having northwestern European ancestry (Table 3 and Figures 1 and 2). Non-European patients combined (n = 61) comprised only 23% of URD transplants. The majority (n = 163, 61%) of the 269 URD transplant recipients received 10/10 HLA-matched grafts, whereas 81 (30%) received 9/10, and 25 (9%) received 8/10 HLA-matched grafts. The percentage of north-western Europeans that received 10/10 URD grafts (n = 49, 68%) was similar to that of other Europeans (n = 87, 64%, $P = .646$), but significantly higher than non-Europeans (n = 27, 44%, $P = .008$). Among non-European patients, although 9 (69%) Asian patients received 10/10 URD, this was only the case in 3 (14%) African, and 6 (40%) white Hispanic patients. URD grafts were obtained from North America (n = 175, 65%), Europe (n = 74, 28%), and elsewhere (n = 20, 7%), with no relationship between patient ancestry and need for a non-American donor.

### CB Transplant Recipients

In marked contrast to URD transplant recipients, only 6 (7%) CB transplant recipients had north-western European ancestry. Notably, over half (n = 50, 56%) of the CB recipients had non-European origins, and included 19% Asian, 17% African, 11% White Hispanic, 3% Middle Eastern, and 6% non-European mix patients (Table 3 and Figures 1 and 2). Thus, compared to URD transplants, CB transplant recipients were more likely to have non-European origins (56% versus 23%, $P < .001$). The majority of CB transplant recipients received CB because they did not have any suitable URDs. Of patients eligible for transplant (ie, those in Table 3 that excludes those not able to be transplanted because of refractory disease or treatment complications), the availability of CB extended transplant access to 8% of northwestern
European, 16% of eastern European, 25% of southern European, and 19% of mixed European patients. For patients of non-European ancestry, the availability of CB had a greater impact by extending access to 57% of Asian, 30% of African, 34% of white Hispanic, 38% of Middle Eastern, and 38% of mixed non-European patients. Units were obtained from domestic \( (n = 129, 72\%) \) or international \( (n = 51, 28\%) \) banks, with no relationship between European versus non-European ancestry and need for international units.

The median infused TNC doses of the double unit grafts were \( 2.56 \times 10^7/\text{kg} \) (range: 1.42-12.79) for the larger and \( 1.94 \times 10^7/\text{kg} \) (range: 0.91-7.09) for the smaller unit. To compare the TNC doses available to patients according to ancestry but independent of the patient’s weight, the TNC/kg were back-calculated to give the total TNC/unit. We found European patients received units with a higher median total TNC postthaw of \( 1.60 \times 10^9/\text{unit} \) (range: 0.64-2.97). This compared with \( 1.40 \times 10^9/\text{unit} \) (range: 0.49-4.07) in non-European patients \( (P = .018) \).

The donor-recipient HLA-match of the 90 CB grafts (180 units) was 5/6 in 58% \( (n = 105) \), and 4/6 in 42% \( (n = 75) \). European patients were not more likely to receive 5/6 HLA-matched units. Fifty \( (63\%) \) of 80 units European patients received, and 55 \( (55\%) \) of 90 units given to non-European patients, were 5/6 HLA-matched \( (P = .362) \).

Patients without URD or CB Grafts

Of the 26 patients (median age 51 years, range: 14-68 years) not transplanted because of lack of any stem cell source, most \( (n = 19, 73\%) \) had non-European origins \( (P < .001) \), with 50% of these patients having African ancestry \( (Table 3 \text{ and Figures 1 and 2}) \). Of the total study population, 1 of 112 (<1%) northwestern, 0 of 81 (0%) eastern, 4 of 60 (7%) southern, and 2 of 105 (2%) mixed European patients had no graft. This compared with 0 of 46 (0%) Asian, 13 of 64 (20%) African, 4 of 51 (8%) White Hispanic, and 2 of 23 (9%) mixed non-European background patients. Thus, patients of African ancestry had the greatest difficulty securing an adequate URD or CB graft. Notably, the median 82-kg (range: 50-151) weight of “no-graft” patients was higher than the 66 kg (range: 7-119) of CB transplant recipients \( (P < .001) \).

**DISCUSSION**

New York City (NYC) has 1 of the most diverse populations in the world. For example, in the Borough...
of Queens alone an estimated 170 foreign languages are spoken [26]. The NYC population, therefore, generates patients with highly diverse ancestry and thus varying and unique racial [4,27] and ancestral [28] HLA haplotypes. This has allowed our Center to directly compare the ability of the global inventory of URDs and CB units to provide suitable grafts to a variety of European, Asian, African, and White Hispanic patients. To study donor availability, we used similar ancestry categories as previous reports [4,24], but distinguished European subgroups, African Hispanics from White Hispanics, and non-European mixes. This considerably broadens the reporting of patient origins beyond “White” versus “non-White.” Although the attribution of ancestry remains complex, our study has the advantage that our physicians and dedicated transplant coordinators took a personal family history of the birthplace of the patients and their ancestors rather than relying on staff assessment of presumed race or ethnicity.

We demonstrate that despite the 6.7 million URDs registered with the NMDP, and an additional 5 million donors in affiliated registries worldwide [29], URD transplantation predominantly serves patients of northwestern, eastern, and mixed European ancestry. However, southern European, Asian, African, White Hispanic, and mixed non-European patients were much less likely to secure a suitable URD. These groups together constituted 46% of our patients. Furthermore, patients of non-European backgrounds, especially African ancestries, were more likely to receive a mismatches URD transplant, with a higher chance of compromising transplant outcome [2,3]. We, therefore, show that URD registries predominantly serve patients of European origins, with the exception of southern Europeans, and confirm the suggestion of the 2002 General Accounting Office Report to the U.S. Congress that “equal access to a match may not be attainable” according to race. From a practical standpoint our findings demonstrate that transplant centers should be mindful of the patient’s ancestry during URD searches given the decreased likelihood of search success for patients with southern European and non-European origins.

CB can be available substantially faster than URDs [25], an advantage for patients requiring urgent transplantation. We now show for the first time that, because of the relative tolerance of HLA-disparity, CB has a further advantage: despite a relatively small global inventory of approximately 400,000 public units [21], CB significantly extends transplant access to all patients, especially those of southern European and non-European ancestry. This is in marked contrast to URD transplantation, and is despite the median weight of 66 kg (range: 7-119) in our CB transplant recipients. Because of the addition of CB as an alternative stem cell source, only 5% of our diverse patient population undergoing URD searches could not be transplanted because of lack of a graft. Furthermore, given that approximately one-quarter of allograft referrals have a sibling donor, the addition of CB to volunteer donors means that the lack of a suitable stem cell source is now a rare barrier to transplant. An additional finding at the opposite end of the donor availability spectrum is striking: Europeans who had 10/10 HLA-matched URD were even more likely to have 5-6/6 HLA-matched CB units, with 22% of European patients having 6/6 HLA-matched CB units, for example. This is relevant given the reporting of higher leukemia-free survival after 6/6 HLA-matched CB transplantation compared with 8/8 HLA-allele matched URD bone marrow transplantation in children [14]. Thus, a randomized study between 5-6/6 matched CB and 10/10 URD may be feasible in the future.

However, despite an encouraging extension of access, CB had limitations. Independent of recipient weight, patients of non-European origins were more likely to receive units with a lower TNC dose. Further, although no Asian patient lacked a suitable CB graft, one-fifth of African ancestry patients, and a significant number of patients with southern European, White Hispanic, and mixed non-European ancestries, did not have suitable CB units. These groups likely have a lesser representation in the global CB inventory. Such patients, especially those with an adult weight, are less likely to identify an adequately HLA-matched and dosed CB graft, even when utilizing double units. Therefore, based on these findings, prior reports suggesting that only a small inventory of CB units should be adequate [30,31] are not correct. An increased inventory of adequately dosed and high-quality units from racially diverse populations is required to rectify this inequity. Units collected from African births have lower TNC counts [32], contributing to a lower inventory of adequately dosed units for African ancestry patients. This is a particular challenge that must be addressed.

We can now demonstrate that CB is extending transplant access to racial and ethnic minorities. Given the recent promising survival after pediatric and adult CB transplantation for hematologic malignancies, this is a major advance in the field. It is known that increasing URD registry size will not result in an appreciable increase in donor availability for populations such as African-Americans because of their varied genetic composition [4,6]. Extending search time also does not increase the likelihood of securing a suitable donor [33]. Our study suggests that with adequate funding, CB has the greatest chance of providing a stem cell source regardless of race or ethnicity. This is compelling support for increased funding of public CB banks and should prompt studies to estimate the size of the CB inventory needed to provide stem cells to all. Furthermore, patients from racial and
ethnic minorities in need of allografts, but without suitable matched sibling donors, should be promptly referred for combined URD and CB searches to optimize identification of a suitable donor and timely transplantation.

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REFERENCES

Americans from the general European American population. 


