REGULAR ARTICLE

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Racial disparities in access to HLA-matched unrelated donor transplants: a prospective 1312-patient analysis

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Key Points

- 8/8 HLA-matched URD access has only modestly increased recently and marked racial disparity persists despite increasing registry size.
- The majority of southern European and non-European patients do not have access to 8/8 HLA-matched URDs.

Availability of 8/8 HLA-allele matched unrelated donors (URDs) is a barrier for ethnic and racial minorities. We prospectively evaluated receipt of 8/8 HLA-allele matched URD or either 7/8 URD or cord blood (CB) transplants by patient ancestry from 2005 to 2017. Matched URDs were given priority if they were available. Of 1312 patients, 723 (55%) received 8/8 URD, 219 (17%) 7/8 URD, 319 (24%) CB, and 51 (4%) had no 7/8 or 8/8 URD or CB graft. Europeans were more likely to receive an 8/8 URD transplant than non-Europeans (67% vs 33%) and less likely to have no URD or CB graft (1% vs 9%). Southern Europeans received 8/8 URD transplants (41%) at rates similar to those of Asians (34%) and white Hispanics (35%); Africans were the least likely (18%) to undergo 8/8 URD transplantation. CB and 7/8 URDs extended transplant access to all groups. In 742 recent patients, marked racial disparity in 8/8 URD access between groups observed in earlier years persisted with only a modest increase in the percentage of 8/8 URD transplants. Of 78 recent African patients, 46% received a CB transplant and 14% had no 7/8 or 8/8 URD or CB graft. Increasing registry size has not resolved the racial disparity in URD access, which emphasizes the importance of alternative graft sources.

Introduction

Eight HLA-allele matched unrelated donors (URDs) are widely considered the optimal hematopoietic stem cell (HSC) source in the absence of a suitable HLA-matched sibling.[1-7] Access to HLA-matched URDs, however, is a major barrier to transplantation, especially for ethnic and racial minorities.[8-11] Speed of donor availability is an additional limitation.[8,12-14] Increasing registry size and efforts to improve donor availability have been pursued to improve access to transplants. But whether access to 8/8 HLA-allele matched URD is improving has not been established.

Methods

We evaluated access to 8/8 HLA-allele matched URD transplants in patients without suitable HLA-matched related donors by recipient ancestry between 2005 and 2017. Throughout the study period, 8/8 URDs were given priority for all patients regardless of age and diagnosis in the absence of a suitable HLA-identical sibling donor. All consecutive patients age 70 years old or younger with hematologic malignancies or severe aplastic anemia who had an indication for allogeneic transplantation and underwent searches for a URD at Memorial Sloan Kettering Cancer Center during this time period were included in the study. Ancestry data were prospectively collected by detailed family history at the beginning of the URD search, and patients were divided into European and non-European subgroups as previously described[9] and as listed in Table 1 and Figure 1.

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Table 1. Transplant type (or no 7/8 or 8/8 URD/CB transplant) by recipient ancestry divided into recent (January 2012-November 2017) vs earlier (October 2005-December 2011) periods

	Transplant type, n (%)				
Patient ancestry group	**8/8 URD***	**7/8 URD**	**CB**	**No URD or CB**	**Total patients, N (%)**
Early patients	273 (48)	127 (22)	138 (24)	32 (6)	570 (100)
European (not Southern)	203 (63)	68 (21)	48 (15)	3 (1)	322 (100)
Northwestern European	77	21	10	1	109
Eastern	62	18	15	0	95
Mixed European	64	29	23	2	118
Southern European	20 (36)	13 (24)	17 (31)	5 (9)	55 (100)
Non-European (not African)	41 (33)	28 (22)	51 (40)	6 (5)	126 (100)
Asian	11	11	23	0	45
White Hispanic	14	12	16	4	46
Middle Eastern	6	1	4	0	11
Mixed non-European	10	4	8	2	24
African	9 (13)	18 (27)	22 (33)	18 (27)	67 (100)
Recent patients	450 (61)	92 (12)	181 (25)	19 (3)	742 (100)
European (not Southern)	319 (78)	38 (9)	54 (13)	0 (0)	411 (100)
Northwestern European	121	13	13	0	147
Eastern	93	9	17	0	119
Mixed European	105	16	24	0	145
Southern European	34 (44)	14 (18)	28 (36)	2 (3)	78 (100)
Non-European (not African)	80 (46)	26 (15)	63 (36)	6 (3)	175 (100)
Asian	21	4	24	1	50
White Hispanic	20	11	16	4	51
Middle Eastern	9	3	7	0	19
Mixed non-European	30	8	16	1	55
African	17 (22)	14 (18)	36 (46)	11 (14)	78 (100)
All patients	723 (55)	219 (17)	319 (24)	51 (4)	1312 (100)

Africans included African Americans or African ancestry patients from the Caribbean or Africa. Non-European mixes had at least partial non-European origins excluding those who self-identified as black.

*Statistical comparisons of receipt of 8/8 HLA-allele matched URD transplants in recent vs early periods: 61% in all recent period patients vs 48% in early patients ($P < .001$). In ancestry subgroups, the comparisons were European patients (not southern) 78% in recent patients vs 63% in early patients ($P < .001$), Southern European patients 44% vs 36% ($P = .511$), non-Europeans (not African) patients 46% vs 33% ($P = .029$), and African patients 22% vs 13% ($P = .275$).

Within the patient cohort, we also evaluated the ancestry distribution of those without an 8/8 URD who received a 7/8 HLA-allele matched URD or a ≥4/6 HLA-A, -B antigen, or -DRB1 allele matched cord blood (CB) transplant or who had no 7/8 or 8/8 URD or CB grafts. During the study period, either 7/8 URDs or CB grafts were chosen for patients without an 8/8 HLA-matched URD, with an increasing preference for CB grafts over mismatched URDs at our center in recent years. URD grafts were secured via the National Marrow Donor Program, and searches routinely included affiliated international registries. CB searches made use of the inventories of the National Marrow Donor Program, the National Cord Blood Program of the New York Blood Center, and international banks accessed via Bone Marrow Donors Worldwide. Acceptable CB grafts usually consisted of 2 units (total nucleated cell count dose ≥1.5 × 10^7/kg per unit and ≥4/6 donor-recipient HLA match).[15-17]

At our center, haploidentical donors were only recently introduced as an alternative treatment option. Therefore, their availability could not be analyzed throughout the study period. Patients who were evaluated for URD and CB graft availability but had neither of these and who subsequently proceeded to haploidentical transplantation were represented in this analysis (included in the no 7/8 or 8/8 URD or CB graft group). However, patients who underwent haploidentical transplants as a result of physician preference without undergoing formal URD and/or CB searches were excluded because they were not formally evaluated for 7/8 or 8/8 URD or CB graft availability. Institutional review board approval for the study was obtained.

Results

Patient demographics

Patients (n = 1312; median age, 51 years [range, <1-70 years]) most commonly had acute leukemia (n = 696 [53%]). Other diagnoses included myelodysplasia or myeloproliferative disorders (n = 207 [16%]), lymphomas (n = 390 [30%]), or aplastic anemia (n = 19 [1%]). Patients had highly diverse ancestries: 866 (66%) were European (256 northwestern, 214 eastern,

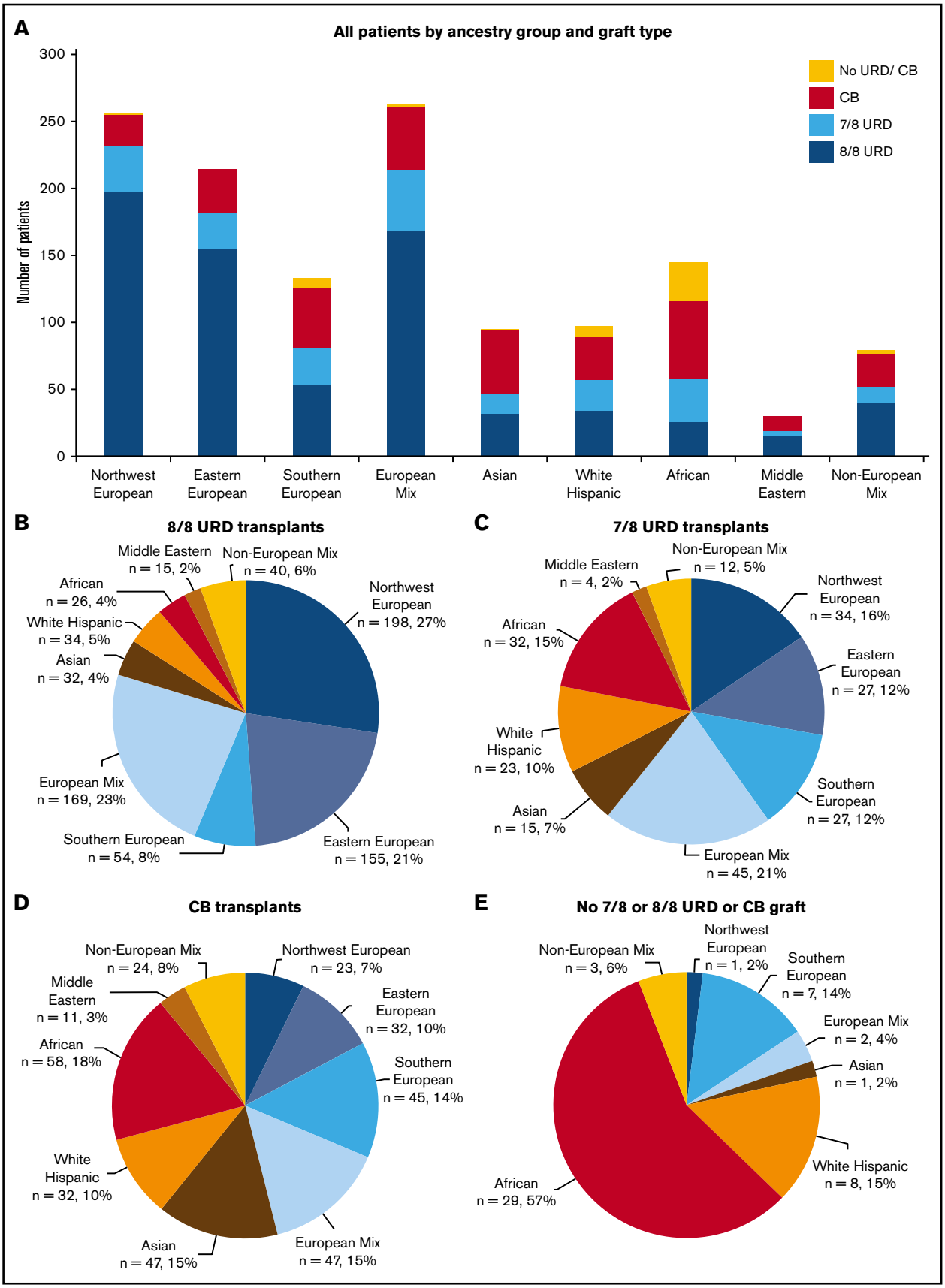
A
All patients by ancestry group and graft type
No URD/ CB
CB
7/8 URD
8/8 URD
Number of patients
300
250
200
150
100
50
0
Northwest European
Eastern European
Southern European
European Mix
Asian
White Hispanic
African
Middle Eastern
Non-European Mix
B
8/8 URD transplants
Middle Eastern n = 15, 2%
Non-European Mix n = 40, 6%
African n = 26, 4%
Northwest European n = 198, 27%
White Hispanic n = 34, 5%
Asian n = 32, 4%
European Mix n = 169, 23%
Southern European n = 54, 8%
Eastern European n = 155, 21%
C
7/8 URD transplants
Non-European Mix n = 12, 5%
Middle Eastern n = 4, 2%
Northwest European n = 34, 16%
African n = 32, 15%
Eastern European n = 27, 12%
White Hispanic n = 23, 10%
Southern European n = 27, 12%
Asian n = 15, 7%
European Mix n = 45, 21%
D
CB transplants
Non-European Mix n = 24, 8%
Northwest European n = 23, 7%
Middle Eastern n = 11, 3%
Eastern European n = 32, 10%
African n = 58, 18%
Southern European n = 45, 14%
White Hispanic n = 32, 10%
Asian n = 47, 15%
European Mix n = 47, 15%
E
No 7/8 or 8/8 URD or CB graft
Non-European Mix n = 3, 6%
Northwest European n = 1, 2%
Southern European n = 7, 14%
European Mix n = 2, 4%
Asian n = 1, 2%
White Hispanic n = 8, 15%
African n = 29, 57%

Figure 1.

263 mixed, 133 southern), and 446 (34%) were non-European (95 Asian, 97 white Hispanic, 30 Middle Eastern, 79 mixed non-European, 145 African).

Transplant distribution by ancestry

Of 1312 patients, 723 (55%) received 8/8 URD, 219 (17%) 7/8 URD, and 319 (24%) CB transplants, whereas 51 (4%) had no 7/8 or 8/8 URD or CB grafts (Table 1). URD grafts came from US centers (n = 573 [61%]), Germany (n = 235 [25%]), or other countries (n = 134 [14%]). All but 5 CB transplant (CBT) recipients received double-unit grafts. Of 633 CB units infused, the majority (n = 447 [71%]) originated from US banks, whereas 186 (29%) came from international banks. The majority of CB units (96 [84%] of 114) for 58 African patients were domestic.

The transplant distribution (or no 7/8 or 8/8 URD or CB graft) by each ancestry group is shown in Figure 1A. Europeans were more likely to receive an 8/8 URD transplant than non-Europeans (576 [67%] of 866 vs 147 [33%] of 446; $P < .001$) and much less likely to have no 7/8 or 8/8 URD or CB graft (10 [1%] of 866 vs 41 [9%] of 446; $P < .001$). Southern Europeans received 8/8 URD transplants (54 [41%] of 133) at rates similar to those of Asians (32 [34%] of 95) and white Hispanics (34 [35%] of 97). Africans were the least likely to receive an 8/8 URD transplant (26 [18%] of 145). Mismatched URDs and CB extended transplant access to all groups.

Figure 1B-E shows the patient ancestry distribution within each transplant type. Overall, there was marked disparity in the proportion of Europeans within each transplant group ($P < .01$). Eight-allele matched URD transplants predominantly served Europeans (576 [80%] of 723 of 8/8 URD transplants were European and 147 [20%] of 723 were non-European; Figure 1B). More 7/8 URD recipients were non-European (Figure 1C). CB extended transplant access to all (Figure 1D) with the majority of CB recipients (172 [54%] of 319) being non-European. Of the 51 patients not transplanted with a 7/8 or 8/8 URD or CB graft, most were non-European (41 [80%] of 51 non-European vs 10 [20%] of 51 European). The majority were of African descent (Figure 1E).

Donor access by time period

To determine whether donor access has improved, we analyzed transplant type by ancestry in recent (January 2012 to November 2017 [n = 742]) vs earlier years (October 2005 to December 2011 [n = 570]). Because southern Europeans have lower URD match rates than other Europeans and because Africans have worse access than other non-Europeans, patients were analyzed in 4 cohorts (Table 1). Overall, the percentage of patients who underwent an 8/8 HLA-allele matched URD transplant increased in recent years (61% of 742 recent patients vs 48% of 570 early patients; $P < .001$). However, in recent patients, the marked racial disparity in 8/8 URD access between ancestry groups that was observed in earlier years persisted (Table 1). Importantly, the majority of recent patients other than northwestern, eastern, and mixed Europeans had no 8/8 URD. Of 78 recent African patients, 36 (46%) of 78 underwent CBT and 11 (14%) of 78 had no 7/8 or 8/8 URD or CB graft. Of the 19 recent patients without a 7/8 or 8/8 URD or CB graft, 9 received transplants (6 haploidentical, 3 autologous) and 10 received non-transplant therapies.

Discussion

This study demonstrates marked racial disparity in 8/8 HLA-matched URD access. Despite increasing registry size (currently estimated at 19 million US donors and 30 million donors worldwide), this inequality in 8/8 HLA-matched URD access persists. In addition, if required HLA match incorporating additional HLA alleles were more stringent, availability of volunteer donors who were considered a match would likely decrease. The advantage of this study is that it analyzed a large number of diverse patients by using prospective ancestry data collection. Because an 8/8 URD has been our center's priority throughout the study regardless of patient age or diagnosis, the analysis provides an accurate evaluation of not only the likelihood of identifying an 8/8 URD but also of actually receiving the transplant. This is in contrast to studies that have used population-based genetic models to estimate the likelihood of identifying a URD on the basis of projected registry size[8,18] or studies that did not account for URD attrition.[11]

An additional finding is the marked differences in securing an 8/8 URD, even within European patients, with the percentage of southern Europeans receiving an 8/8 URD transplant being no better than that of Asians or white Hispanics. Furthermore, the increase in 8/8 URD transplants within each ancestry group has been modest, thus emphasizing the need for alternative donors. This is especially true for Africans; recently, only 22% received an 8/8 URD transplant. These findings are important because most centers consider 8/8 URDs as the standard HSC source in the absence of an HLA-matched sibling. They also underscore that increasing the URD inventory will not address the limitation to URD access for many patients.[8,18] Efforts to improve minority recruitments and donor availability are also unlikely to meaningfully address this problem in the United States[18] because the population is becoming more diverse.[19]

Both 7/8 URD and CB extended transplant access in all groups. Given that a survival advantage has been demonstrated with CBT over mismatched URD transplantation,[16,20] CBT has been prioritized over mismatched URD in recent years at our center. More than half the CBT recipients have been non-European and nearly half the recent African patients evaluated for URD transplants have undergone CBT. The dependence of Africans on US CB banks also demonstrates the necessity for ongoing funding of US CB collections. This is important because we previously reported that

Figure 1. Patient ancestry distribution by graft type. (A) All patients (n = 1312) divided by ancestry group and graft type: 8/8 URD (n = 723), 7/8 URD (n = 219), CB (n = 319), or no 7/8 or 8/8 URD or CB (n = 51). (B) 8/8 URD transplant patients divided by ancestry group (n = 723). In all, 576 (80%) of 723 patients were European and 147 (20%) of 723 were non-European. (C) 7/8 URD transplants divided by ancestry group (n = 219). In all, 133 (61%) of 219 patients were European and 86 (39%) of 219 were non-European. (D) CB transplants divided by ancestry group (n = 319). In all, 147 (46%) of 319 patients were European and 172 (54%) of 319 were non-European. (E) Patients without a 7/8 or 8/8 URD or CB graft divided by ancestry group (n = 51). In all, 10 (20%) of 51 patients were European and 41 (80%) of 51 were non-European.

minority patients, especially African patients, may not have suitable haploidentical donors.[21]

A limitation of this analysis is that, although 8/8 URDs have remained the priority throughout the study period, the sophistication of URD searches has improved. Accordingly, in recent years, the URD search is likely to be abandoned more quickly in patients who are very unlikely to have an 8/8 URD when the search is initiated.[22] However, this should not compromise our ability to accurately evaluate 8/8 URD access, because our recent URD search prognosis algorithm has proven to accurately predict futile URD searches.[22] Another limitation is that the ancestry distribution of haploidentical donor transplant recipients could not be addressed, because these transplants have only recently been used as a treatment alternative at our center. This alters the patient denominator recently evaluated. The time from search initiation to transplant was also not recorded throughout the study period. Only a prospective trial dictating patient triage, donor priority in the absence of 8/8 URDs incorporating all HSC sources, and the conduct of URD searching[22] (defining the maximal time permitted for securing a URD before abandoning the search) could accurately address the speed and success of obtaining all HSC options, including haploidentical donors. A trial of this type has not been performed at any center to date, but it will be important to pursue such a study for the future. Nonetheless, the ongoing ethnic and racial barriers to 8/8 HLA-matched URD access in this study cannot be disputed, which underscores the importance of alternative graft sources to ensure allograft access to all.

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Authorship

Contribution: J.N.B. designed and supervised the research; and all authors contributed to this work and wrote the manuscript.

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