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Relationship of Race/Ethnicity and Survival after Single Umbilical Cord Blood Transplantation for Adults and Children with Leukemia and Myelodysplastic Syndromes

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The relationship of race/ethnicity with outcomes of umbilical cord blood transplantation (UCBT) is not well known. We analyzed the association between race/ethnicity and outcomes of unrelated single UCBT for leukemia and myelodysplastic syndromes. Our retrospective cohort study consisted of 885 adults and children (612 whites, 145 blacks, and 128 Hispanics) who received unrelated single UCBT for leukemia and myelodysplastic syndromes between 1995 and 2006 and were reported to the Center for International Blood and Marrow Transplant Research. A 5-6/6 HLA-matched unit with a total nucleated cell count infused of $\geq 2.5 \times 10^7$/kg was given to 40% white and 42% Hispanic, but only 21% black patients. Overall survival at 2 years was 44% for whites, 34% for blacks, and 46% for Hispanics ($P = .008$). In multivariate analysis adjusting for patient, disease, and treatment factors (including HLA match and cell dose), blacks had inferior overall survival (relative risk of death, 1.31; $P = .02$), whereas overall survival of Hispanics was similar (relative risk, 1.03; $P = .81$) to that of whites. For all patients, younger age, early-stage disease, use of units with higher cell dose, and performance status ≥80 were independent predictors of improved survival. Black patients and white patients infused with well-matched cords had comparable survival; similarly, black and white patients receiving units with adequate cell dose had similar survival. These results suggest that blacks have inferior survival to whites after single UCBT, but outcomes are improved when units with a higher cell dose are used.

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INTRODUCTION

Umbilical cord blood (UCB) is an alternative stem-cell source for patients without HLA-matched related or unrelated donors [1-3]. Recent results in children and adults suggest that outcomes with UCB transplantation (UCBT) are similar to those seen in patients receiving fully HLA-matched unrelated donor bone marrow transplantation and may approximate the results seen in HLA-matched related donor transplantation [4,5]. Many of the published studies have

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predominantly included white recipients, despite increased ability to find donors for racial/ethnic minorities being a purported advantage of UCB over adult unrelated bone marrow or peripheral blood stem-cell donors.

Analysis of hematopoietic cell transplantation (HCT) is complex, as variables such as economic status, delay in treatment, donor issues, matching criteria, and biologic issues related to disease or treatment may all be important contributing factors to outcomes. Previous studies have addressed racial disparities after HLA-matched related and unrelated donor HCT [6-9]. However, association between race/ethnicity and UCBT outcomes has not been well described. Two recent reports have suggested that the $CD34^+$ count of the cord blood unit, an important prognostic factor for transplantation outcome, may be lower in units from black mothers than from white mothers [10,11]. Although limited by the small number of patients, retrospective data from 122 patients transplanted with cord blood units from the American Red Cross cord blood banks showed no difference in survival between whites and other groups [12].

In this study, we describe the outcomes of over 800 patients from different racial/ethnic backgrounds receiving single-unit UCBT. These results may have important implications for allocation of precious resources toward UCB banks providing sufficient inventory for patients of diverse backgrounds.

MATERIALS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) comprises a voluntary working group of more than 500 transplantation centers worldwide that contribute detailed data on consecutive HCT to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data and on-site audits of participating centers ensure data quality. The institutional review board and the Privacy Officer of the Medical College of Wisconsin approve observational studies conducted by the CIBMTR with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined.

Patients

The study included patients who received an unrelated single UCBT for acute lymphoblastic leukemia, acute myelogenous leukemia, myelodysplastic syndromes, and chronic myeloid leukemia between 1995 and 2006, and were reported to the CIBMTR. Only patients who underwent transplantation in the United States were included. Pediatric and adult patients, and those treated with myeloablative, reduced-intensity, or nonmyeloablative regimens were all included. Patients receiving multiple UCB units were excluded, as there were too few recipients of double-cord blood transplantation with diverse racial/ethnic backgrounds and sufficient follow-up. Patient and donor race/ethnicity were reported by transplantation centers and cord blood banks, respectively, according to the US Office of Management and Budget Classification as white, black, or Hispanic [13]. Because of their relatively small numbers (N = 22), patients belonging to other (eg, Asian, Native Hawaiian/Pacific Islander) and multiple race groups were excluded from this analysis. All surviving recipients included in this analysis were retrospectively contacted and provided informed consent for participation in the NMDP research program. Informed consent was waived by the NMDP institutional review board for all deceased recipients. Approximately 10% of surviving patients would not provide consent for use of research data. To adjust for the potential bias introduced by exclusion of nonconsenting, surviving patients, a corrective action plan modeling process randomly excluded the same percentage of deceased patients [14]. The final study cohort consisted of 885 patients. The follow-up completeness index from time of HCT, which is the ratio of observed person-time and the potential person-time of follow-up in a study, was 84% for whites, 84% for blacks, and 73% for Hispanics at 3 years after transplantation [15].

Outcomes and Study Definitions

Our primary objective was to evaluate the association of race/ethnicity with 3-year overall survival (OS), leukemia-free survival (LFS), relapse, and treatment-related mortality (TRM). Secondary endpoints included neutrophil recovery (absolute neutrophil count of $\geq 0.5 \times 10^9$/L sustained for 3 consecutive days), platelet recovery (platelet count of $\geq 20 \times 10^9$/L independent of platelet transfusions for 3 consecutive days), and acute and chronic graft-versus-host disease (aGVHD, cGVHD) as assessed by standard criteria [16,17]. All outcomes were assessed from the date of HCT. Disease status was classified as early, intermediate, or advanced [7,9,18]. Preparative regimens were classified as myeloablative, reduced intensity, or nonmyeloablative [19,20]. HLA matching was performed at low resolution for class I and high resolution for class II, consistent with prevalent typing of UCB HCT during the time period covered by this study.

Statistical Analysis

Patient-, disease-, and treatment-related factors were compared using the χ^2 test and the Kruskal-Wallis test, as appropriate. Univariate probabilities of OS and LFS were calculated using the Kaplan-Meier estimator [21]. Probabilities of neutrophil and platelet recovery, aGVHD and cGVHD, TRM, and relapse were generated using cumulative incidence estimates. Survival curves were compared using the log-rank test.

The transplantation groups were compared using proportional hazards regression models. All factors were examined for proportional hazards using a time-dependent covariate approach. The model was stratified on any nonproportional hazards factor. A model was built for the factors using a stepwise regression technique. Each model included a factor for race of the patient. First-order interactions between race and each factor were included in the model. The probabilities of neutrophil recovery at 60 days and platelet engraftment at 6 months were modeled using the pseudovalue approach [22]. The interaction between time and race was also examined. Risk factors with $P < .05$ in univariate analyses were included in the model. Patient-related variables included age, gender, Karnofsky or Lansky performance score, recipient cytomegalovirus status, and weight at HCT. Disease-related variables included diagnosis, disease stage at HCT, and time from diagnosis to transplantation. Treatment-related variables included cell dose infused, HLA match, conditioning regimen intensity, year of HCT, and donor race. For OS, LFS, TRM, and relapse, we performed pairwise comparisons of race and cell dose and race and HLA match; pairwise comparisons were done adjusting for other patient-, disease-, and treatment-related variables. We tested for center effects using a random effects scores test in the final regression model for each outcome [23].

All computations were performed using the statistical package SAS Version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Patient characteristics are outlined in Table 1. Our cohort included 612 white patients, 145 black patients, and 128 Hispanic patients. The median age at transplantation was 8 (range: <1-78), 8 (<1-57), and 6 (<1-56) years, respectively, for the three racial/ethnic groups, as the majority of patients receiving UCBT in this time period were children.

Cord Blood Characteristics

Fewer blacks received well-matched UCB units with a good cell dose compared with whites and Hispanics (Table 1). Sixty-nine percent of whites, 62% of blacks, and 73% of Hispanics received a cell dose $\geq 2.5 \times 10^7$ NC/kg ($P = .08$). HLA match differed among the racial/ethnic groups; a higher proportion of whites (54%) received 5 of 6 or 6 of 6 HLA-A, -B, and -DR matched UCB units compared with 30% for blacks and 48% for Hispanics ($P < .0001$). More whites (40%) and Hispanics (42%) than blacks (21%) received UCB units that were well matched (5 of 6 or 6 of 6 HLA matched) and had a cell dose $\geq 2.5 \times 10^7$ NC/kg ($P = .0002$; Figure 1). The racial distribution of the UCB units indicates that 63% white, 30% black, and 33% of Hispanic patients received UCB units from donors of the same race, although race/ethnicity information was missing for a large proportion of donors.

Association of Race/Ethnicity with Overall Survival

Three-year OS rates for whites, blacks, and Hispanics were 41%, 29%, and 45%, respectively ($P = .008$) (Table 2, Figure 2). In multivariate analyses that considered patient-, disease-, and transplant-related variables (see Methods), blacks had worse OS, whereas Hispanic patients had similar OS compared with whites (Table 3).

In multivariate analysis, we also examined factors other than race for their association with OS. Cell dose was significantly associated with OS, whereas HLA match did not affect OS (Table 3). We tested for and found no significant interaction between race and cell dose and race and HLA match. In addition to cell dose, as expected, younger age, less advanced disease, and performance status ≥80 were independent predictors of improved OS for all patients (Appendix Table 1). Donor race did not affect OS; however, information regarding race of the cord blood donor was missing in a substantial proportion of patients in all three race groups. Data from 90 centers were included in our study. However, four centers contributed >40 transplantations each and collectively contributed to 45% of patients included in our analysis. Hence, we tested for center effect and did not find a significant center effect in our analyses.

We were also interested in evaluating whether patients from the three race groups who received UCB units with good cell dose and well-matched units had comparable OS. In pairwise comparisons that adjusted for other patient, disease, and transplant factors (including HLA match status), we found no significant differences in OS by race among patients receiving the same cell dose. White, Black, and Hispanic patients receiving units with cell dose $\geq 2.5 \times 10^7$ NC/kg had comparable OS (Table 4). Similarly, in pairwise comparisons (that also adjusted for cell dose), we found no significant differences in OS by race among patients receiving well-matched (5 of 6 or 6 of 6 HLA-A, -B,

Table 1. Characteristics of Patients with AML, ALL, CML, or MDS Receiving a Single Unrelated Umbilical Cord Blood Transplantation in the United States between 1995 and 2006 and Reported to the CIBMTR

Variables	White N (%)	Black/African American N (%)	Hispanic/Latino N (%)	*P* Value
Number of patients	612	145	128	
Number of centers[a]	77	45	48	
Patient related				
Age at HCT, years, median (range)	8 (<1-78)	8 (<1-57)	6 (<1-56)	.02
Age				.02
0-9	334 (55)	81 (56)	88 (69)	
10-17	141 (23)	34 (23)	24 (19)	
18-54	113 (18)	29 (20)	15 (12)	
≥55	24 (4)	1 (1)	1 (1)	
Male gender	336 (55)	90 (62)	80 (63)	.12
Karnofsky/Lansky performance score				.07
≥80	553 (90)	129 (89)	115 (90)	
<80	43 (7)	14 (10)	3 (2)	
Missing	16 (3)	2 (1)	10 (8)	
Weight at transplantation, kg, median (range)	29 (5-133)	29 (7-118)	22 (5-114)	.12
Missing	1	0	3	
Recipient CMV status				.01
Negative	328 (54)	64 (44)	54 (42)	
Positive	273 (45)	79 (54)	74 (58)	
Missing	11 (2)	2 (1)	0 (.)	
Disease related				
Disease				.15
AML	255 (42)	55 (38)	46 (36)	
ALL	253 (41)	56 (39)	60 (47)	
CML	30 (5)	14 (10)	11 (9)	
MDS	74 (12)	20 (14)	11 (9)	
Disease stage at HCT[b]				.47
Early	184 (30)	38 (26)	38 (30)	
Intermediate	262 (43)	70 (48)	63 (49)	
Advanced	166 (27)	37 (26)	27 (21)	
Transplantation related				
Time from diagnosis to transplantation				.07
≤12 months	346 (57)	67 (46)	67 (52)	
>12 months	266 (43)	78 (54)	61 (48)	
Cell dose infused				.08
$<2.5 \times 10^7$ NC/kg	157 (26)	50 (34)	26 (20)	
$\geq 2.5 \times 10^7$ NC/kg	420 (69)	90 (62)	93 (73)	
Missing	35 (6)	5 (3)	9 (7)	
$CD34^+$ dose infused				<.0001
$\leq 3.0 \times 10^5$/kg	171 (28)	57 (39)	17 (13)	
$> 3.0 \times 10^5$/kg	87 (14)	17 (12)	12 (9)	
Missing	354 (58)	71 (49)	99 (77)	
HLA match[c]				<.0001
6 of 6 match	96 (16)	6 (4)	12 (9)	
5 of 6 match	230 (38)	37 (26)	50 (39)	
≤4 of 6 match	281 (46)	98 (68)	60 (47)	
Missing	5 (1)	4 (3)	6 (5)	
Gender match (donor/recipient)				.43
Male/male	171 (28)	39 (27)	39 (30)	
Male/female	148 (24)	25 (17)	24 (19)	
Female/male	153 (25)	45 (31)	36 (28)	
Female/female	112 (18)	25 (17)	24 (19)	
Missing	28 (5)	11 (8)	5 (4)	
Year of transplantation				.20
1995-2000	207 (34)	49 (34)	33 (26)	
2001-2006	405 (66)	96 (66)	95 (74)	
Race of cord blood donor				<.0001
White	384 (63)	34 (23)	34 (27)	
African American	15 (2)	43 (30)	2 (2)	
Asian/Pacific Islander	10 (2)	2 (1)	3 (2)	
Hispanic	36 (6)	13 (9)	42 (33)	
Other[d]/unknown/missing	167 (28)	53 (37)	47 (37)	
Conditioning regimen intensity				.04
Myeloablative	431 (70)	98 (68)	103 (80)	
Nonmyeloablative/reduced intensity	181 (30)	47 (32)	25 (20)	
GVHD prophylaxis				.43
Cyclosporine ± other	411 (67)	96 (66)	77 (60)	
Methotrexate + cyclosporine ± other	72 (12)	18 (12)	15 (12)	
FK506 ± other	125 (20)	30 (21)	33 (26)	

(*Continued*)

Table 1. (*Continued*)

Variables	White N (%)	Black/African American N (%)	Hispanic/Latino N (%)	*P* Value
Other	4 (0)	1 (1)	3 (3)	
Median follow-up, months, median (range)	52 (3-149)	37 (4-87)	36 (3-102)	

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myeloid leukemia; CMV, cytomegalovirus; MDS, myelodysplastic syndromes; NC, nucleated cell.
[a]Total numbers of centers: 90.
[b]Early disease included AML and ALL in first complete remission, CML in first chronic phase, and MDS with refractory anemia or refractory anemia with ringed sideroblasts, or bone marrow blasts <5% at HCT; intermediate disease included AML and ALL in second or greater remission or CML in accelerated phase or second or greater chronic phase; advanced disease included AML and ALL in relapse or primary induction failure, CML in blast phase, or MDS with refractory anemia with excess blasts or bone marrow blasts ≥5% at HCT.
[c]HLA match is defined by low-resolution typing at HLA-A and -B, and high-resolution typing at -DRB1.
[d]Includes multiple race and Native American.

or -DR match) UCB units (Table 4). Because of the relatively small number of black and Hispanic patients in our cohort, we could not perform multivariate analyses in the subgroup of patients who received well-matched units with adequate cell dose. However, in unadjusted analyses, black patients receiving HLA 5 of 6 or 6 of 6 matched UCB unit with a cell dose $\geq 2.5 \times 10^7$ NC/kg (N = 26) had similar OS compared with white patients receiving units of similar cell dose and HLA match (Figure 3).

LFS

Three-year LFS for whites, blacks, and Hispanics was 38%, 29%, and 39%, respectively ($P = .04$) (Table 2). In multivariate analyses, there was no significant difference in LFS among racial groups (Table 3). As with OS, cell dose influenced LFS while HLA match status did not (Table 3). As with OS, in pairwise comparisons, there was no difference in LFS among white, Hispanic, and black patients receiving UCB units with similar cell dose and among patients receiving well-matched units (Table 4). For all patients, transplantation for advanced disease, older age at transplantation, and performance status of <80 adversely affected LFS, whereas HCT for myelodysplastic syndromes was associated with better LFS (Appendix Table 1).

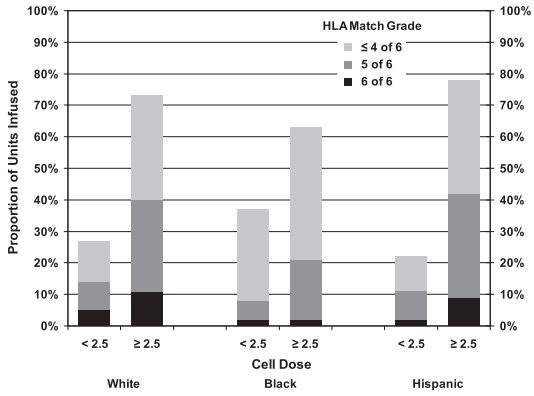

Figure 1. Distribution of UCB units based on race, cell dose, and HLA match.

TRM and Relapse

Table 2 highlights cumulative incidences of TRM and relapse. In multivariate analysis adjusting for other important variables including cell dose and HLA match, race had no influence on risk of relapse or TRM (Table 3).

Cell dose and HLA match status did not significantly affect the risks of relapse (Table 3). There was no difference in relapse risks when we compared white, Hispanic, and black patients who had received units with good cell dose and units with good HLA match (Table 4).

In multivariate analyses, there was no difference in the relative risks of TRM by race (Table 3). Both cell dose and HLA match were significant predictors of TRM. On pairwise comparisons, white, Hispanic, and black patients receiving units with cell dose $\geq 2.5 \times 10^7$ NC/kg had comparable TRM (Table 4). Similarly, white, Hispanic, and black patients who received 5 of 6 HLA-matched units also had similar risks of TRM (Table 4).

Engraftment and GVHD

The median time to neutrophil recovery was 23 (range, 1-104) days, and there was no difference among racial/ethnic groups (Table 2). The median time to platelet recovery was 59 (range, 1-241) days, again with no difference among racial/ethnic groups. In multivariate analysis, race had no independent association with the likelihood of neutrophil engraftment or platelet engraftment. As expected, cell dose was an independent predictor of neutrophil and platelet engraftment. In multivariate analysis, race was not associated with risks of aGVHD or cGVHD.

Causes of Death

Causes of death differed slightly among the different groups. For all patients, relapse was a major cause of death; 37% of white patients (N = 129), 46% of Hispanics (N = 31), and 38% of black patients (N = 38) who died succumbed to relapsed disease. For white (N = 86, 25%) and Hispanic (N = 17, 25%) patients,

Table 2. Univariate Outcomes of Patients with AML, ALL, CML, or MDS Receiving a Single Unrelated Cord Blood Transplantation between 1995 and 2006 and Reported to the CIBMTR

	White		Black		Hispanic		
Outcome Event	N	Probability (95% CI)	N	Probability (95% CI)	N	Probability (95% CI)	*P* Value
Overall survival, 3 years	612	41 (37-45)%	145	29 (22-38)%	128	45 (35-54)%	.008[b]
Leukemia-free survival, 3 years	607	38 (34-42)%	144	29 (22-37)%	127	39 (31-49)%	.04[b]
Relapse, 3 years	607	27 (23-30)%	144	29 (22-37)%	127	31 (23-40)%	.60[a]
Treatment-related mortality, 3 years	607	35 (31-39)%	144	41 (33-50)%	127	30 (22-38)%	.15[a]
Neutrophil engraftment, 60 days	605	86 (83-88)%	145	81 (74-87)%	127	86 (79-91)%	.40[a]
Platelet engraftment, 6 months	602	62 (58-66)%	139	52 (44-61)%	126	67 (58-75)%	.05[a]
Acute GVHD (grades 2-4), 100 days	608	50 (46-54)%	145	50 (42-59)%	127	56 (47-65)%	.42[a]
Chronic GVHD, 2 years	598	24 (20-27)%	143	21 (14-28)%	125	30 (22-39)%	.24[a]

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myeloid leukemia; CI, confidence interval; CMV, cytomegalovirus; MDS, myelodysplastic syndromes.
[a]Cumulative incidence estimate with pointwise *P* value.
[b]Log-rank *P* value.

infection was the second most common cause of death after relapse. For black patients, organ failure (N = 15, 15%) was the second most common cause of death. Death from GVHD was rare in all groups (whites, N = 22 [6%], Hispanics, N = 1 [1%], blacks, N = 8 [8%]).

DISCUSSION

This report examines the association of racial/ethnic background of the recipient with outcomes after UCBT. Results indicate that black patients have inferior OS compared with white patients after single UCB transplantation. This disparity in outcomes is partially a result of the inability to find a well-matched, appropriately sized UCB unit for black patients, as fewer black than white patients received UCB that were 5 of 6 or 6 of 6 HLA matched and had a cell dose of $>2.5 \times 10^7$ NC/kg. In contrast, when the analysis was restricted to patients receiving well-matched units and units with adequate cell dose, there was no significant difference in survival by race. These results suggest that the increased difficulty in finding appropriately matched cord units of sufficient cell dose may be a major obstacle to better outcomes in black patients. Furthermore, the poorer outcomes in black patients may be improved by infusing UCB units with sufficient cell dose. As reported by other investigators, outcomes were better among all patients when transplanted with a higher cell dose. Death from GVHD was low in all groups [24].

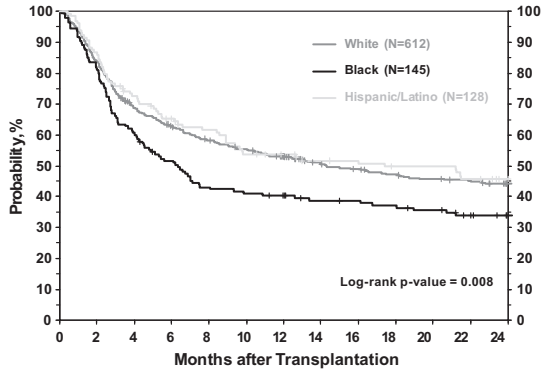

Figure 2. Unadjusted overall survival of white, black, and Hispanic patients receiving single umbilical cord blood transplantation.

This study has some limitations. The majority of patients included in this analysis were children. Geographic variation in distribution of racial/ethnic groups in the United States and extensive UCB transplantation experience could lead to strong center effects. However, transplantation center was not a significant correlate of OS in our analysis. Although use of double cord blood HCT has been increasingly used in adults, too few transplantations in a racially/ethnically diverse population with adequate follow-up were available during the study time period. A future study of racial disparities after double cord blood transplantation is planned. Small patient numbers limited the ability to understand differences in the causes of death. We could not robustly evaluate the impact of using race-matched versus mismatched UCB units on outcomes because these data were missing for a large proportion of donor units. Race/ethnicity was reported by transplantation centers and cord blood banks and was not verified. Furthermore, there may have been differences in access to posttransplantation care or posttransplantation medications among racial/ethnic groups that could not be addressed in this study [3,25]. We could not evaluate the effect of patient socioeconomic status in our study, as zip code data were not available for a large proportion of patients. In a previous study, socioeconomic status estimated by zip code of residence was found to be an independent predictor of OS and TRM following unrelated donor HCT for acute and chronic leukemia [9].

Although there was a difference in OS by race, the risks of LFS, relapse, and TRM were not significantly different among white and black patients. Because of the relatively small number of black patients available for our analysis, our study may have lacked the power to detect any association of race with outcomes other than OS. Studies with a larger number of minority

Table 3. Multivariate Analysis for Outcomes of Single Unrelated Umbilical Cord Blood Transplantation for AML, ALL, CML, or MDS

Endpoint	N	Relative Risk	95% CI		*P* Value
Overall survival[a]					
Race/ethnicity[b]					
White	612	1.00			
Black	145	1.31	1.04	1.66	.02
Hispanic	128	1.03	0.79	1.35	.80
Cell dose infused[b]					
$\geq 2.5 \times 10^7$ NC/kg	603	1.00			
$<2.5 \times 10^7$ NC/kg	233	1.44	1.15	1.80	.001
Missing	49	1.22	0.83	1.80	.31
HLA match[c]					
6/6	114	1.00			
5/6	317	1.01	0.74	1.37	.95
4/6	439	1.25	0.93	1.67	.13
Missing	15	1.77	0.88	3.49	.11
Leukemia-free survival[d]					
Race/ethnicity[b]					
White	607	1.00			
Black	144	1.25	0.99	1.58	.06
Hispanic	127	1.01	0.78	1.31	.95
Cell dose infused[b]					
$\geq 2.5 \times 10^7$ NC/kg	600	1.00			
$<2.5 \times 10^7$ NC/kg	229	1.32	1.11	1.73	.004
Missing	56	1.08	1.09	1.59	.66
HLA match[c]					
6 of 6	113	1.00			
5 of 6	314	1.01	0.75	1.35	.89
4 of 6	436	1.21	0.92	1.61	.18
Missing	22	1.69	0.85	3.37	.14
Relapse[f]					
Race/ethnicity[b]					
White	607	1.00			
Black	144	1.40	0.96	2.03	.08
Hispanic	127	1.13	0.77	1.63	.53
Cell dose infused[b]					
$\geq 2.5 \times 10^7$ NC/kg	600	1.00			
$<2.5 \times 10^7$ NC/kg	229	1.18	0.67	2.08	.56
Missing	49	1.00	0.68	1.46	.99
HLA match[c]					
6 of 6	113	1.00			
5 of 6	314	0.71	0.48	1.04	.08
4 of 6	436	0.77	0.52	1.14	.19
Missing	15	1.40	0.50	4.17	.54
Treatment-related mortality[e]					
Race/ethnicity[b]					
White	607	1.00			
Black	144	1.18	0.87	1.58	.29
Hispanic	127	0.92	0.64	1.31	.63
Cell dose infused[b]					
$\geq 2.5 \times 10^7$ NC/kg	600	1.00			
$<2.5 \times 10^7$ NC/kg	229	1.67	1.26	2.19	.0003
Missing	56	0.92	0.56	1.53	.75
HLA match[c]					
6 of 6	113	1.00			
5 of 6	314	1.52	0.96	2.39	.07
4 of 6	436	2.05	1.33	3.17	.001
Missing	22	2.52	1.00	6.325	.05

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myeloid leukemia; CI, confidence interval; CMV, cytomegalovirus; MDS, myelodysplastic syndromes; NC, nucleated cell.

[a]Other variables significantly associated with overall survival were diagnosis, disease status, age, and performance status score (see Appendix Table 1).

[b]χ^2 test with 2 *df*.

[c]χ^2 test with 3 *df*.

[d]Other variables significantly associated with leukemia-free survival were diagnosis, disease status, age, and performance status score (see Appendix Table 1).

patients and with additional information (eg, socioeconomic status) remain necessary to better understand the reason for differences in survival between white and black patients after UCBT. Nevertheless, an important finding from our study was that white and black patients who received units with adequate cell dose had similar risks of mortality. Similarly, white and black patients who received HLA well-matched units had comparable survival. Hence, survival disparities by race/ethnicity after UCBT could partly be overcome by availability of UCB units with adequate cell dose and HLA match.

Despite extensive recruiting efforts, it remains more difficult for blacks and other racial minorities to find matched adult unrelated donor volunteers via the NMDP. Donor selection using antigen level typing for class I and allele level typing for class II uncovers at least one fully matched adult volunteer donor for 79% of white patients, 40% of black patients, and 57% of Hispanic patients [26]. With more stringent contemporary criteria for HLA matching, the likelihood of finding a well-matched donor for racial minorities is likely even lower. A prospective analysis from Memorial Sloan-Kettering Cancer Center revealed that a 10 of 10 allele level matched adult unrelated donor was identified for 53% of patients with European ancestry and 21% of patients with non-European ancestry [27]. In contrast, 56% of patients receiving a UCB transplantation were of non-European ancestry. However, an early study of five different cord blood banks found no increase in cord blood collections from minorities when compared with bone marrow collections from minorities in the same geographic area [28]. The American Red Cross cord blood banks attempted to increase diversity by establishing banks in different areas of the United States, which resulted in a cord blood donor pool of 64% whites, 16% blacks, 12% Hispanics, 4% Asians, 1% Native Americans, and 3% other [10]. Although the proportion of minority donors may match the distribution of the US population, greater HLA diversity in the black population and a higher proportion of UCB units of low cell dose, may limit the number of high-quality UCB units available to black patients [10,11]. Extensive resources have been allocated in the United States and worldwide to create a large, diverse cord blood donor pool.

Black patients have been reported to have a higher mortality than white patients in both sibling and unrelated donor transplantations [9,29]. However, other studies restricted to HLA matched sibling transplantations showed that Hispanics had a higher risk of overall mortality after transplantation,

[e]Other variables significantly associated with transplantation-related mortality were disease status and age (see Appendix Table 1).

[f]Other variables significantly associated with relapse were diagnosis, disease status, age, performance status score, gender, and time from diagnosis to transplantation (see Appendix Table 1).

Table 4. Pairwise Comparisons of (1) Race and Cell Dose and (2) Race and HLA Match for White, Hispanic, and Black Patients Receiving Single Unrelated Umbilical Cord Blood Units with Adequate Cell Dose and with Adequate HLA Match

Cell Dose						HLA Match[a]					
Race/Cell Dose	N	Relative Risk	95% CI		*P* Value	Race/HLA Match	N	Relative Risk	95% CI		*P* Value
Overall Survival											
White, $\geq 2.5 \times 10^7$ NC/kg	420	1.00				White, 5/6 match	230	1.00			
Hispanic, $\geq 2.5 \times 10^7$ NC/kg	93	0.92	0.65	1.30	.63	White, 6/6 match	96	0.84	0.59	1.35	.32
Black, $\geq 2.5 \times 10^7$ NC/kg	90	1.26	0.93	1.70	.13	Hispanic, 5/6 match	49	0.86	0.55	1.35	.49
						Black, 5/6 match	37	1.22	0.76	1.97	.41
Leukemia-free survival											
White, $\geq 2.5 \times 10^7$ NC/kg	417	1.00				White, 5/6 match	228	1.00			
Hispanic, $\geq 2.5 \times 10^7$ NC/kg	93	0.93	0.68	1.29	.67	White, 6/6 match	95	0.84	0.60	1.13	.31
Black, $\geq 2.5 \times 10^7$ NC/kg	90	1.20	0.89	1.61	.24	Hispanic, 5/6 match	49	0.84	0.55	1.29	.43
						Black, 5/6 match	37	1.10	0.68	1.76	.70
Relapse											
White, $\geq 2.5 \times 10^7$ NC/kg	417	1.00				White, 5/6 match	228	1.00			
Hispanic, $\geq 2.5 \times 10^7$ NC/kg	93	0.98	0.63	1.53	.94	White, 6/6 match	95	1.27	0.81	1.96	.28
Black, $\geq 2.5 \times 10^7$ NC/kg	90	1.30	0.85	2.00	.23	Hispanic, 5/6 match	49	1.02	0.58	1.79	.93
						Black, 5/6 match	37	1.14	0.58	2.24	.71
Treatment-related mortality											
White, $\geq 2.5 \times 10^7$ NC/kg	417	1.00				White, 5/6 match	228	1.00			
Hispanic, $\geq 2.5 \times 10^7$ NC/kg	93	0.89	0.55	1.42	.62	White, 6/6 match	95	0.46	0.27	0.80	.005
Black, $\geq 2.5 \times 10^7$ NC/kg	90	1.16	0.77	1.74	.47	Hispanic, 5/6 match	49	0.65	0.33	1.25	.20
						Black, 5/6 match	37	1.08	0.55	2.10	.82

CI indicates confidence interval.

Analyses were adjusted for other patient-, disease-, and transplantation-related factors (analysis by cell dose also adjusted for HLA match and analysis by HLA match also adjusted for cell dose).

[a]Because of a relatively small number of patients, data on black patients (N = 6) and Hispanic patients (N = 12) who received 6 of 6 HLA matched units are not included in this table.

whereas whites, Asians, and blacks had similar outcomes [7,30]. Black patients are known to have greater genetic diversity and HLA polymorphisms, making matching for minor antigens less likely [31]. Increasing genetic diversity at minor transplantation antigens may affect survival after transplantation, and these differences may be even more important in UCBT given the greater degree of mismatch compared with unrelated donor transplantation [32]. Although this cord blood study has fewer patients than the transplantation studies using sibling or unrelated donors cited previously, we have been able to identify a potential solution to the discrepancy in outcomes, with the use of larger and better matched cord blood units. In addition, because the growth of UCB banks and transplantation was specifically designed to aid populations underrepresented in the traditional transplantation registries, the new information presented here on race/ethnicity and UCBT outcomes is of importance to transplantation physicians, cord blood banks, and policy makers.

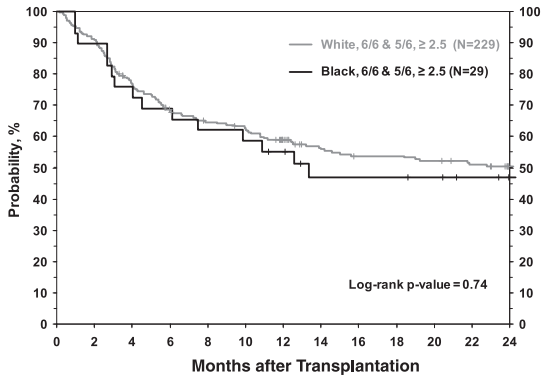

Figure 3. Unadjusted overall survival of white and black patients receiving umbilical cord blood units with 5 of 6 or 6 of 6 HLA match and cell dose $\geq 2.5 \times 10^7$ NC/kg.

This report examines for the first time the outcomes of UCBT for the different racial/ethnic groups. These results suggest that blacks have inferior survival rates to whites after single UCBT. Outcomes for black and white patients are improved when units with higher cell doses are infused. The resources to collect a diverse UCB donor pool and to ensure UCB of high cell dose are extensive, but this report suggests the need to redouble these efforts in order to better meet the needs of the diverse population of transplantation patients.

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AUTHOR CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Appendix Table 1. Factors Other Than Race, Cell Dose, and HLA Match (Shown in Table 3) That Were Significantly Associated with Outcomes of Single Unrelated Umbilical Cord Blood Transplantation for AML, ALL, CML, or MDS

Endpoint/Variable	Relative Risk	95% CI		*P* Value
Overall survival				
Diagnosis				
AML	1.00			<.01
ALL	0.90	0.73	1.10	.29
CML	0.66	0.44	1.00	.05
MDS	0.61	0.45	0.83	<.01
Disease status at HCT				
Early	1.00			<.01
Intermediate	1.01	0.80	1.27	.95
Late	1.80	1.43	2.26	<.01
Age				
<10 years	1.00			<.01
10-17 years	1.07	0.84	1.35	.59
18-54 years	1.47	1.13	1.91	<.01
≥55 years	2.00	1.24	3.22	<.01
KPS score at HCT				
≥80	1.00			<.01
<80	1.60	1.17	2.19	<.01
Missing	0.81	0.47	1.42	.45
Leukemia-free survival				
Diagnosis				
AML	1.00			<.01
ALL	0.88	0.72	1.07	.19
CML	0.76	0.53	1.10	.15
MDS	0.60	0.44	0.81	<.01
Disease status at HCT				
Early	1.00			<.01
Intermediate	0.98	0.78	1.22	.83
Late	1.80	1.43	2.26	<.01
Age				
<10 years	1.00			<.01
10-17 years	0.94	0.75	1.19	.62
18-54 years	1.41	1.10	1.82	<.01
≥55 years	1.85	1.15	2.98	.01
KPS score at HCT				
≥80	1.00			<.01
<80	1.55	1.14	2.10	<.01
Missing	0.97	0.57	1.62	.88
Relapse				
Diagnosis				
AML	1.00			<.01
ALL	0.78	0.57	1.07	.13
CML	0.88	0.50	1.54	.64
MDS	0.34	0.21	0.56	<.01
Disease status at HCT				
Early	1.00			<.01
Intermediate	1.19	0.80	1.77	.39
Late	2.87	2.02	4.09	<.01
Age				
<10 years	1.00			<.01
10-17 years	0.47	0.31	0.73	.06
18-54 years	0.88	0.59	1.31	.52
≥55 years	1.93	0.98	3.82	.06
KPS score at HCT				
≥80	1.00			<.01
<80	2.10	1.34	3.30	<.01
Missing	0.92	0.41	2.10	.84
Sex				
Male	1.00			<.01
Female	1.56	1.20	2.04	<.01
Time from DX to TX				
>12 months	1.00			.03
≤12 months	0.68	0.48	0.96	.03
TRM				
Disease status at HCT				
Early	1.00			.04
Intermediate	1.08	0.82	1.41	.60
Late	1.45	1.07	1.95	.02
Age				
<10 years	1.00			<.01
10-17 years	1.41	1.05	1.90	.02
18-54 years	1.91	1.39	2.63	<.01
≥55 years	1.86	0.95	3.61	.06

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myeloid leukemia; CI, confidence interval; CMV, cytomegalovirus; KPS, Karnofsky performance score; MDS, myelodysplastic syndromes.