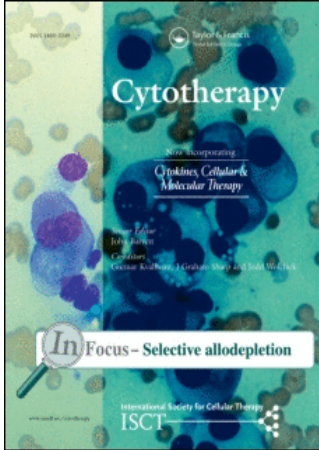


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### Ethnically mismatched cord blood transplants in African Americans: the Saint Louis Cord Blood Bank experience

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# Ethnically mismatched cord blood transplants in African Americans: the Saint Louis Cord Blood Bank experience

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## Background

For ethnic minority patients where a suitably matched BM or peripheral blood donor is frequently unavailable, cord blood offers an opportunity for hematopoietic stem cell transplantation. Focused recruitment of ethnic minorities for cord blood donation has been proposed as the preferred strategy to improve access for minority recipients to cord blood for transplantation. The aim of this study was to evaluate cord blood characteristics for Caucasian and African American donors and the success of ethnically mismatched UC blood transplantation in African American recipients.

## Methods

Retrospective data analysis was performed comparing the characteristics of 556 cord blood units from African American and Caucasian donors. The outcomes of 18 African American ethnically mismatched transplant recipients were compared with a paired sample of 18 ethnically matched Caucasian recipients.

## Results

The fraction of collected units meeting acceptability criteria from African Americans was significantly lower compared with

Caucasians ( $P = < 0.0001$ ). Additionally, African Americans had a significantly lower post-processing total nucleated cell count (TNC) compared with Caucasians ( $P = 0.007$ ) but there were no other significant differences in conventionally measured product characteristics. In the transplant analysis, there was no difference in overall survival at 1 year ( $P = 0.85$ ) or time to neutrophil engraftment ( $P = 0.92$ ) between the two patient populations.

## Discussion

At comparable levels of TNC dose and HLA matching, the use of ethnically mismatched UC blood units as a source for allogeneic unrelated transplant can result in successful transplant outcomes for African American patients.

## Keywords

African American, cord blood, cord blood donation, ethnic mismatch, hematopoietic stem cell transplantation.

## Introduction

UC blood is the preferred graft source for hematopoietic cell transplantation in a significant number of patients. However, in many cases cord blood is utilized as an alternative option for stem cell transplantation when an HLA-matched BM or PBSC cell donor is unavailable. This is often the case for minority populations, including African Americans. According to the National Marrow Donor Program (NMDP), only 30% of patients needing a

marrow or blood cell transplant have a matched related donor [1]. The hope for the remaining 70% of patients rests on the ability to find a suitable unrelated donor. For African Americans, this situation is compounded by the greater diversity of HLA genotypes in this population compared with other ethnic groups (specifically Caucasian). According to the October 2002 General Accounting Office's report to Congress, 'African Americans may never have the same probability of finding matches, and

therefore access to transplants, as Caucasian patients, regardless of the efforts made to recruit them' [2]. Further, African Americans have been shown to be less likely to participate in stem cell donation programs, partly because of a lack of awareness that transplantation can save lives, lack of opportunities to donate, mistrust of the medical community and fear of donating [3,4]. Specific to cord blood, a barrier limiting the ability to store collected products for use in transplant is low yield of nucleated cells, a cord blood product feature that is critical to cord blood unit selection and transplant outcome [5,6]. This study relates the St Louis Cord Blood Bank (SLCBB, St Louis, MO, USA) experience with African American cord blood collection and evaluates the outcome of allogeneic unrelated transplants in African American recipients receiving a single cord blood unit from the SLCBB.

### Methods

Cord blood unit and donor data was gathered from 28 participating collection facilities following SLCBB standard operating procedures. Briefly, cord blood is collected by the donor's obstetrician via cannulation of the umbilical vein into a sterile anticoagulated blood bag during the third stage of labor. Cord blood was collected under IRB approval and donor informed consent. Donors with a medical history that suggested genetic defects or 'high risk behavior' were excluded from the transplantation inventory. Collected cord blood units were shipped at room temperature to a central processing laboratory, with all processing and cryopreservation steps completed within 48 h of collection.

Patient outcome data were provided by transplant centers or donor registries dependent on product procurement method, as required under the SLCBB's Investigational New Drug application on file with the Food and Drug Administration (FDA). Since 2000, measurements of total nucleated cells (TNC) and CD34<sup>+</sup> cells have been made utilizing the Sysmex XE-2100 (Sysmex Corporation, Wakinohama-Kaigandori, Chou-KU, Kobe, Japan) automated hematology analyzer and the Coulter Epics-XL flow cytometer (Beckman Coulter, Inc., Fullerton, California) using a modified ISHAGE protocol with 7-AAD for viability determination, respectively. All cord blood units included in this study were processed in accordance with SLCBB standard operating procedure,

which includes hetastarch sedimentation to reduce red blood cells and plasma depletion. This procedure did not include analysis of CD34<sup>+</sup> subsets [7]. Analysis of the ratio of colony-forming cells (CFC) to CD34<sup>+</sup> cells was performed to provide a 'surrogate' measure of hematopoietic stem progenitor cell content in the CD34<sup>+</sup> cell population. For evaluating mean initial volume (volume prior to processing manipulations) and post-processing cell counts, a random sample of 278 Caucasian cord blood units was generated using GraphPad StatMate Version 1.01i (GraphPad, San Diego, California) to compare with African American cord blood collections ( $n = 278$ ). The analysis period spanned 1996 to 2005.

Retrospective data analysis was performed to evaluate the outcomes of African American patients transplanted between 1996 and 2005. The outcomes of 18 African American ethnically mismatched transplant recipients were compared with a paired sample of 18 ethnically matched Caucasian recipients, to determine the effectiveness of UC blood as a source of hematopoietic stem cell reconstitution for the African American population. Selection of the Caucasian group was performed using GraphPad StatMate Version 1.01i (GraphPad, San Diego, California). Patients were paired based on age, TNC dose post-processing and HLA match. Diagnosis of acute leukemia and administration of a myeloablative conditioning regimen were the inclusion criteria for this analysis. End points included patient survival at 1 year post-transplant and the probability of neutrophil recovery defined as an absolute neutrophil count of  $\geq 500/\mu\text{L}$  for 3 consecutive days. Donor engraftment was confirmed by DNA-based 'chimerism' analysis as per the transplant center protocol. Transplant-related mortality was defined as events related to transplant exclusive of relapse.

### Statistical analysis

Categorical data were compared using Fisher's exact test (two-sided). Continuous variables were analyzed with the Mann-Whitney test (two-tailed). The proportion of cord blood recipients achieving neutrophil engraftment at various time points and overall survival were estimated with the Kaplan-Meier method. All statistical analyses were performed with GraphPad Prism version 3.03 and GraphPad InStat version 3.05 (GraphPad, San Diego, California).

## Results

For the SLCBB, cord blood donors are recruited from a geographic region within a 150-mile radius of the St Louis metropolitan area. To determine the degree to which African American donors are represented in our cord blood inventory, a 3-year period, 2002–2005, was examined to evaluate potential donors, collections and storage rates for African American and Caucasian populations, utilizing estimates of the birth rate for these populations in the St Louis area as reported by the Missouri Hospital Association. This information is summarized in Table 1. Donations to our bank represented only 3.5% of the total African American births during this 3-year period, compared with 17.1% of Caucasians ( $P < 0.0001$ ). The under-representation of African American donors in our inventory is largely because the physicians and their staff who serve as collectors in our program deliver their patients in private hospitals located in the predominantly Caucasian rural and suburban areas surrounding St Louis. Within these regions, African Americans are likely to comprise only 3–5% of the total population. Accordingly, fewer African American mothers are available to donate

within the geographic regions of our donor population. This, compounded with a low willingness to donate, results in difficulty in increasing the number of units from African American donors.

Table 1 also shows the significant difference in storage rate for African American and Caucasian donors. The storage rate is defined as the percentage of collected units that meet minimum criteria for acceptability based on TNC and that are not deferred based on information obtained from the donor questionnaire, family medical history form or results of infectious disease testing. This information is summarized in Table 2.

Between 1996 and 2005, 1288 African American cord blood units were collected by the SLCBB, with 278 meeting storage criteria. Analysis of African American and Caucasian units meeting storage criteria ( $n = 278$  for each population) revealed a significant difference in post-processing TNC count yield ( $P = 0.007$ ). The difference in cellular yield did not result from cell loss during processing, as the median recovery for both groups was 86% ( $P = 0.20$ ). Although the TNC for African American cord blood units was lower compared with that of Caucasians, this trend was not detected for post-processing CD34<sup>+</sup> and initial volume ( $P = 0.07$ ,  $P = 0.79$ ), although CD34<sup>+</sup> counts were approaching significance. Table 3 provides a summary of these variables.

Outcomes for the African American and Caucasian acute leukemia study populations were compared, to determine the effectiveness of ethnically mismatched unrelated UC transplantation for African American patients. Table 4 provides a summary of the demographic and clinical characteristics.

No significant difference in the proportion of patients achieving neutrophil engraftment and time to neutrophil engraftment was detected between the two groups ( $P = 0.92$ ; median African American = 24 days, median Caucasian = 23 days). Survival at 1 year was similar between the two populations ( $P = 0.85$ ). Figure 1 summarizes the engraftment and survival analysis. Further, there was no difference with regard to transplant-related mortality between the groups ( $P = 0.56$ ).

The evaluation of acute GvHD demonstrated no significance with regard to incidence ( $P = 0.47$ ) or severity ( $P = 0.30$ ). Populations were compared for severity in groups of grade  $\leq 2$  and  $> 2$ . A similar analysis was performed for chronic GvHD, assessing incidence and

**Table 1.** Comparison of African American and Caucasian cord blood donations

Race	2003	2004	2005	Total
<b>African American</b>				
Births	5739	6153	6153	18045
Cord Blood Donors	144	190	304	638
Percent Donors	2.5%	3.1%	4.9%	3.5%
Cord Blood Units	27	33	64	124
Stored				
Storage Rate (%)	18.8%	17.4%	21.1%	19.4%
<b>Caucasian</b>				
Births	23579	23412	23011	70002
Cord Blood Donors	3902	3896	4143	11941
Percent Donors	16.5%	16.6%	18.0%	17.1%
Cord Blood Units	1113	1004	1059	3176
Stored				
Storage Rate (%)	28.5%	25.8%	25.6%	26.6%

*Cord blood donation and storage rates differed significantly between the populations (Donation Rate  $p < 0.0001$ ; Storage Rate  $p < 0.0001$ ).*

*\*Birth data provided by Missouri Hospital Association.*

*\*\*Illinois participating centers were not included in this table due to lack of birth data.*

**Table 2.** Summary of cord blood unit deferrals 1996–2005

Deferral Reason	African American	Caucasian	<i>p</i> value
Insufficient Volume	653 (64.7%)	18687 (67.6%)	0.05
Insufficient TNC	215 (21.3%)	4316 (15.6%)	< 0.0001
Infectious Disease	4 (0.40%)	78 (0.28%)	0.72
Response on Medical History	6 (0.59%)	48 (0.17%)	0.008
Other	132 (13.0%)	4505 (16.3%)	0.007
Total	1010 (100.0%)	27634 (100.0%)	

severity, and produced similar results ( $P = 0.65$ ,  $P = 1.0$  respectively). Disease relapse did not differ between populations ( $P = 1.0$ ).

### Discussion

Initiatives have been launched that are aimed at increasing minority cord blood donation. We agree research should be done to determine if there is a benefit for ethnically matched transplants for the African American population. However, we have seen that barriers to donation and storage have persisted, despite efforts to reverse these trends, thus inhibiting the ability to pursue such research. The SLCBB began a partnership in 2003 with the Charles Drew Community Cord Blood Donor Campaign to increase African American cord blood donations. The SLCBB experience indicates that African Americans are significantly less likely to donate than their Caucasian counterparts. However, since the inception of this campaign, we have seen a modest increase in donations, from 2.5% in 2003 to 4.9% in 2005. Although collections have nearly doubled during this period, the rates of donation are still far below those of Caucasians. Currently, there are not enough African American donors to meet the needs of African American patients requiring transplant, should centers seek ethnically matched products. Barriers to donation had been identified previously as lack of awareness of donation programs and lack of understanding of the life-saving potential of UC blood. In addition to the social and cultural problems encountered when recruiting donors, biologic barriers have prevented use of collected units. Our study mirrors the COBLT study conclusion, that African American UC blood units have a significantly lower nucleated cell count compared with Caucasian cord blood units [5,6]. Both nationally and within the SLCBB collection radius, rates for low birth weight deliveries and pre-term labor were higher for African Americans [8], two variables correlated with decreased TNC yield [5]. An

additional factor that may impact cellular characteristics is compliance with prenatal care in the first trimester, which was lower for the African American population [8]. As a result, these units less often meet storage criteria, and those that do are less likely to be selected by transplant centers for transfusion when units are chosen based on nucleated cell dose.

Unique to cord blood is the ability for the graft to function with a greater degree of HLA mismatch. Because donations from African Americans represent only a small proportion of total donations, it is often necessary for ethnically mismatched UC blood units to be considered for use in transplant. Additionally, because of the high variability of HLA alleles within the African American population [9], suitable donors that are ethnically matched can still be difficult to locate. The SLCBB experience shows that, for the 39 cord blood units shipped between 1996 and 2005 for African American patients, 213 potential cord blood units were identified. Of these 213 units, only nine were ethnically matched. Successful dual cord transplantation provides an opportunity to overcome the cell dose limitations associated with African American

**Table 3.** Comparison of cord blood characteristics for units in inventory (median)

Collection Variable	African American	Caucasian	<i>p</i> value
<i>n</i>	278	278	
Post Processing TNC (*10 <sup>6</sup> )	956.5	1036.7	0.007
Percent Recovery	86.0	86.0	0.20
CD34 <sup>+</sup> (*10 <sup>6</sup> )	3.6	4.0	0.07
CFU (*10 <sup>5</sup> )*	7.6	8.0	0.23
Initial Volume	75	77	0.79

\*African American *n* = 211 Caucasian *n* = 216.

**Table 4.** Demographics and clinical characteristics for transplant recipients

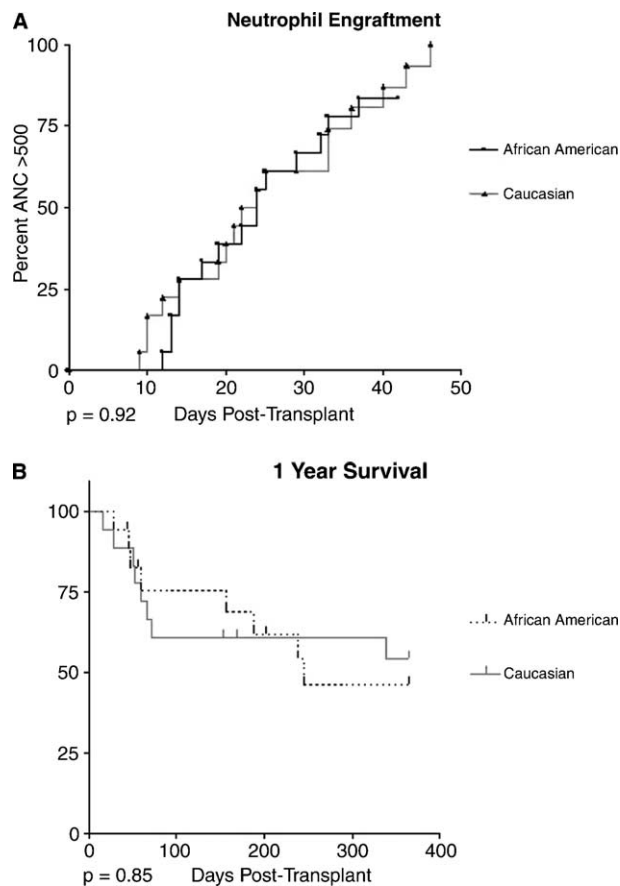
Transplant Variable	African American	Caucasian	<i>p</i> value
Age			
<i>n</i>	18	18	
Median (y)	6.9	7.0	0.99
Prior Transplant*			
<i>n</i>	18	17	
Prior Transplant	2	2	
No Prior Transplant	16	15	1.0
HLA Match			
<i>n</i>	18	18	
< 5/6	14	13	
≥ 5/6	4	5	1.0
TNC Dose			
<i>n</i>	18	18	
Median (*10 <sup>7</sup> /kg)	5.5	5.6	0.96
CD34+ Dose			
<i>n</i>	18	18	
Median (*10 <sup>5</sup> /kg)	0.38	0.32	0.99
CFC/CD34+ **			
<i>n</i>	13	12	
Median	1.02	1.23	0.57
Acute GVHD***			
<i>n</i>	15	16	
Acute GVHD	9	7	
No Acute GVHD	6	9	0.47
Chronic GVHD****			
<i>n</i>	11	11	
Chronic GVHD	5	3	
No Chronic GVHD	6	8	0.65
Relapse			
<i>n</i>	18	18	
Relapse	5	4	
No Relapse	13	14	1.0

\*Prior transplant information not available for one Caucasian patient.

\*\*CFC data on 11 infused units was unavailable for analysis.

\*\*\*Changes in Acute GVHD sample size are a result of nonengraftment for 3 African American and one Caucasian patient, and unavailable information for one Caucasian patient.

\*\*\*\*Changes in Chronic GVHD sample size are a result of early deaths of 3 African American and 5 Caucasian patients, nonengraftment for 3 African American and one Caucasian patient, and unavailable information for one African American and one Caucasian patient.

**Figure 1.** Neutrophil engraftment and survival curves for African American transplants compared with Caucasian transplants.

donations, and therefore increases the potential for ethnic matching.

The results of this study indicate that the use of ethnically mismatched UC blood units as a stem cell source for allogeneic unrelated transplant can result in a successful transplant outcome for African American patients. There was no difference in engraftment kinetics between the ethnically matched Caucasian population and the ethnically mismatched African American population, which is evidence that racial (ethnic) disparity does not compromise cord blood unit function. Overall survival analysis at 1 year did not yield a significant difference between study groups. Further, when evaluating survival at 100 days, a period critical for neutrophil engraftment, graft failure, the development of GvHD and other complications, survival was higher for African Americans (71%) than for Caucasians (61%). However, from the period of day +150 to day +365, survival proportions for the African American group showed a steady decline to 43%, whereas Caucasians remained at 61% survival up to day

+ 365. With no significant difference regarding clinical indicators such as TNC, CD34<sup>+</sup> dose, CFC/CD34<sup>+</sup> ratio, acute and chronic GvHD or relapse rates, a trend that has been identified in BM and PBSC cell transplants as well as in cord blood [10], the disparity in survival could be attributed to variables unrelated to graft performance, such as socio-economic factors. This information was not provided to the SLCBB by the transplant centers, but several studies have attributed outcome disparities to these factors, which may be appropriate to apply to cord blood transplant. In renal transplant outcome studies, African Americans have shown a 1-year graft survival similar to that of Caucasians. However, graft loss at 3 years is significantly higher among the African American population [11,12]. It has been postulated that African American renal transplant recipients require more stringent compliance with regard to medication intake and post-transplant care because of physiologic differences compared with their Caucasian counterparts. Therefore, non-compliance produces a more profound adverse effect in the African American population [12]. Additionally, African Americans have higher rates of co-morbidities, such as diabetes, hypertension and atherosclerosis, which compound the issue of non-compliance as well as independently complicating their post-transplant care [12]. Similarly, in a study comparing outcomes in African American and Caucasian myocardial infarction patients, there was no difference in 30-day mortality rates yet a significant difference beyond 30 days [13]. Transplant and associated care may not be enough to raise survival rates for this population. Improving issues such as compliance, access to care and patient education may also be necessary for a successful outcome [14].

The results of this study are promising; however, we feel that a much larger scale study is required to confirm the effectiveness of this therapy and to identify variables critical to transplant outcome in this population. Although we did not identify significant differences in graft characteristics, we also recommend additional characterization of cord blood products from African American and non-African American donors utilizing flow cytometry with CD34<sup>+</sup> cell subset analysis. Furthermore, engraftment studies in xenotransplant models should be performed to establish whether significant qualitative and quantitative differences exist in the HPC/HSC population in cord blood collected from these different donor populations. Because of the retrospective nature of this

study, the inability to follow patients prospectively post-discharge to analyze variables such as compliance with follow-up care was a major limitation. Also, several recipients were unable to be included in this study because of a lack of reporting on the part of the transplant center. Efforts to acquire these data were unsuccessful. Another limitation to this study was a lack of ethnically matched African American transplant recipients for comparison with the African American ethnically mismatched group. For the SLCBB, African Americans represent less than 6% of our donor population and less than 5% of our recipient population. Thus we would expect that fewer than 1.5% of the total donor–recipient pairs would both be African American. We recommend repeating this study in a more controlled manner with a select group of transplant centers to increase the sample size, improve data management and provide a comparison between ethnically matched and mismatched patients within the African American population.

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