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14. ABSTRACT

This is the final report summarizing all of the activity and ongoing activity. The funding of this project has now created a consortium of robust collection sites that will be focused on the procurement of high quality cord blood units (CBU) for stem cell transplantation. The educational process and expansion of collection sites has given us a steady supply of cord blood for clinical use; and now we have the operational nucleus of several collection sites that is self-perpetuating a continual drive to expand to affiliated institutions. The greatest benefit of this project is the demonstration of how we solved the problem of increasing the overall yield of the cord blood units. We convincingly demonstrate that putting resources into individual patient education and prenatal visits is not likely to increase the cell yield and thus will not likely increase the number of bankable cord blood units for transplantation. With these findings, we then initiated a program of educating the birth-care providers and public in several newly recruited institutions and we are now able to collect increasing high-quality cord blood units. Furthermore, we have also implemented a quality improvement program within the institution. We have data to show that through direct feedback to the birth-care providers of their performance in procuring high-quality units, we were able to improve the yield for each birth-care provider. Finally, we extend the observation of transplant outcomes of the African/American CBU recipients compared with other racial groups at Karmanos Cancer Center.

15. SUBJECT TERMS
Cord blood, transplantation, minority, African/American, stem cell, donor

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INTRODUCTION

Cord blood is an increasing important source of stem cells used in clinical transplantation. At the inception of this technology, cord blood stem cell transplantation was being used when the search for adult stem cell donor had been exhausted. The disadvantage of a cord blood stem graft is the lower content of hematopoietic stem cells and the limitation of use in recipients with body weight of 70 kg or lower. However, the cord blood stem cell graft also has other potential advantages such as allowance of greater HLA disparity between donor-recipient pair, shorter time to identify a suitable donor, lower potential of transmitting viral infection to recipients and no risk to the donor since the umbilical cord and placenta is normally discarded as medical waste products.[1] A lower risk of graft-versus-host disease, thus allowing use of mismatched cord blood units for transplantation, is an important advantage for minority groups especially among African-Americans who are not able to find a suitable living adult donor.[2] The clinical application of cord blood transplantation has now been extended to adult recipients and has been shown to have a comparable outcome as those recipients of a bone marrow graft.[3,4] Recently, transplantation with 2 partially matched cord blood units in adult patients has been shown to be feasible.[5,6] If this approach is confirmed, it would markedly increase the use of cord blood in transplantation and the demand for cord blood would increase.

With the advancement of clinical science in the application of unrelated cord blood transplantation, we must develop and keep up with the infrastructure to support this form of therapy. Inventory of high-quality cord blood units with genetic diversity is crucial to the long-term success of this therapy. Furthermore, we must also bear in mind the cost and practicality of the harvest process to ensure the participation of the birth-care providers, and finally, to continue to maintain an optimal size inventory.

BODY

a. Collection, Processing of Cord Blood Units

Following the demonstration of the feasibility study that we can expand the collection of cord blood units (CBUs) to the community using an *in utero* collection technique (St John Hospital as the model), we then approached Providence Hospital in Southfield and then St Joseph Mercy Hospital in Ann Arbor in March 2008. In November of 2008, we added Providence Hospital in Novi as an additional collection site. We currently have 3 active collection sites who are all operating the *in utero* collection model. The units we store are of high quality in terms of cell dose, timeliness of data submission for search through the National Marrow Donor Program and most important of all, we are still collecting a high percentage of African-American units and other racial minorities. Most importantly, there is a higher percentage of CBUs shipped for transplantation from our cord blood bank than from any cord blood bank of similar size – direct evidence that we have targeted collections to the most desirable group of donors. The momentum of cord blood collection will continue as long as we have the capability of storing the CBUs in our facility. The long-term health of JP McCarthy Cord Stem Cell Bank will now have to rely on the availability of federal funding (e.g. through Health Resource and Service Administration) to continue supporting the laboratory operation of the bank.

In order to gear up towards CBUs collection at these sites, we spent several months of in-service training of the medical and nursing staff in each Labor & Delivery Unit. We set up the cord blood storage, transportation and processing of these CBUs according to the good tissue practice with the purpose of registering these units in the Cord Blood Registry of the National Marrow Donor Program. At the same time, we continue to accept CBUs donated to us through the former collection site at the adjacent Hutzel Hospital.

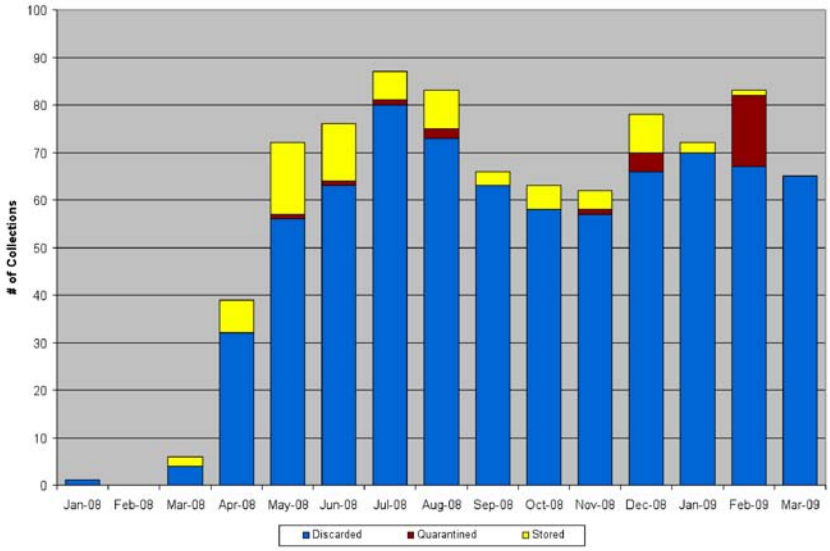


Figure 1. This graph depicts the collection activity from 2 main collection sites: Providence Hospital (Southfield and Novi) and St Joseph Mercy Hospital in Ann Arbor. The level of collection at Hutzel Hospital is minimal. For the entire period shown on this graph only 3 units were collected from Hutzel. Quarantine units are those awaiting further testing and other quality checks; once completed the units will be moved to permanent long term storage.

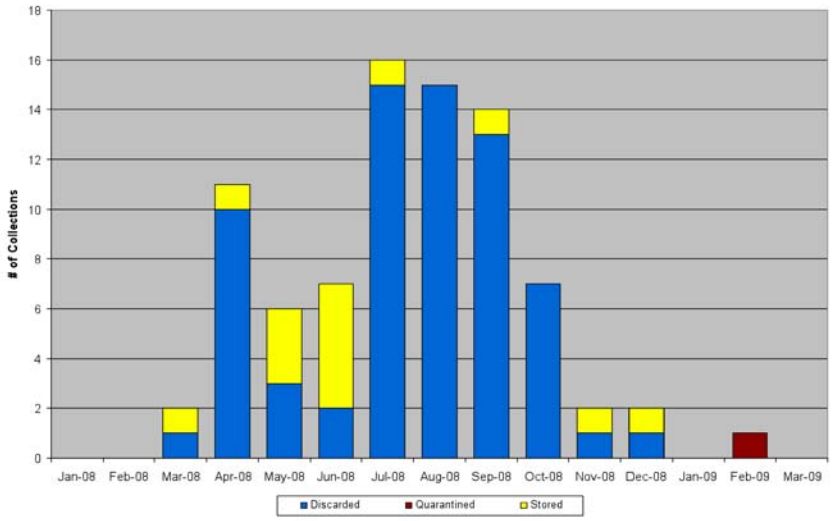


Figure 2 The number of African-American CBUs collected, processed, quarantined and stored. The drop in African-American CBUs collected from October 2008 was due to resources being shifted towards the opening of new collection sites (Henry Ford Hospital at Wyandotte and Sinai-Grace Hospital in Detroit. The latter has the largest percentage of African-American births in Southeastern Michigan.

b. Quality Indicators of Cord Blood Collection at JP McCarthy Compared to Other Cord Blood Banks Listing with the National Marrow Donor Program (Data provided by the NMDP)

Table 1 below shows the racial distribution of the CBUs in the JP McCarthy Cord Stem Cell Bank in comparison to all other cord blood banks registered with the National Marrow Donor Program. Our cord blood bank still has a far greater percentage of African-American CBUs than the average of the entire inventory – 46.8% vs. 6.8%. Although there is only an incremental increase of 2% from the prior year, this reflects the difficulty in accessing the African-American community to educate them about cord blood donation. We know that this cannot be accomplished within the period of the grant but we are continuing the effort to increase the inventory of ethnic minority groups, specifically the African-American donors.

Table 1.

	Cord Blood Bank Data					All Cord Blood Bank Data				
	2008		As of 12/31/2007	Increase From Prior Period		2008		As of 12/31/2007	Increase From Prior Period	
CBU Inventory by Broad Race:	Qty	%	Qty	Qty	%	Qty	%	Qty	Qty	%
Total	1,296		1,213	83	6.8%	98,315		73,360	24,955	34.0%
Caucasian (non-Hispanic ethnicity)	497	38.3%	444	53	11.9%	52,453	53.4%	39,302	13,151	33.5%
Hispanic/Latino (old His race + Cau, Unk, Dec race w/His ethnicity)	38	2.9%	36	2	5.6%	17,068	17.4%	11,960	5,108	42.7%
Asian/Pacific Islander (His and non-His ethnicity)	19	1.5%	15	4	26.7%	7,079	7.2%	4,466	2,613	58.5%
Black (His and non-His ethnicity)	606	46.8%	594	12	2.0%	6,717	6.8%	4,789	1,928	40.3%
Hawaiian (His and non-His ethnicity)	1	0.1%	1	-	0.0%	89	0.1%	74	15	20.3%
Am. Indian/Alaska Native (His & non-His ethnicity)	2	0.2%	2	-	0.0%	202	0.2%	161	41	25.5%
Multiple Race (His & non-Hispanic ethnicity)	133	10.3%	121	12	9.9%	9,930	10.1%	7,891	2,039	25.8%
Unknown (non-Hispanic ethnicity)	-	0.0%	-	-	NA	4,367	4.4%	4,313	54	1.3%
Decline (non-Hispanic ethnicity)	-	0.0%	-	-	NA	268	0.3%	265	3	1.1%
Other	-	0.0%	-	-	NA	142	0.1%	139	3	2.2%

c. CBUs from JP McCarthy Shipment to Transplant Centers

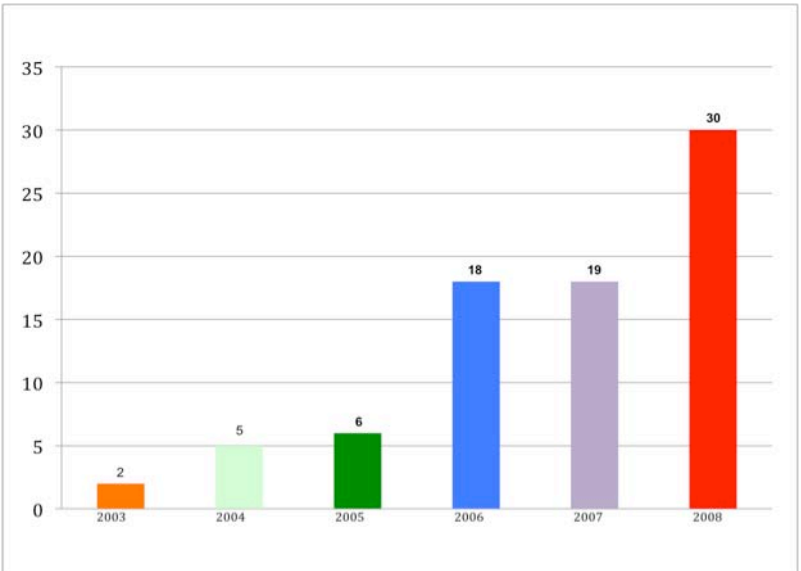
In 2008, we shipped 30 CBUs to transplant centers worldwide for allogeneic stem cell transplantation. Criteria for cord blood unit selection is based on the degree of matching. The landmark study of Cord Blood Transplantation Study (COBLT) has provided us with a guideline for cord blood selection that is based on the degree of HLA matching. In most cases, CBUs are matched at HLA-A and HLA-B at intermediate resolution and HLA-DR at the allele level.[7] Although our inventory has 46.8% African-American CBUs, the number of African-American CBUs shipped was 56.7% which is greater than the percentage in our inventory despite the lower average cell dose of 155 x 10^7 compared to 170 x 10^7 in the pooled data of the entire registry. This finding underscores the urgency to increase African-American CBUs for the entire registry. The lower number of cell dosage shipped from our bank also points toward the demand for African-American CBUs that results in a closer racial HLA match for the recipient. Thus, the transplant physician may need to sacrifice the cell dose that is noted to be inherently lower in African-American CBUs. Other evidence of favorable search outcomes for our bank is the lower ratio of confirmatory typing requests per CBU shipped – 1.2:1 vs. 2:1 for all cord blood banks.

Table 2.

	2008 CBB				2008 All CBB's			
	Ratio				Ratio			
CT:Shipment Ratio	1.2:1				2:1			
CBU Shipment Data:			TNC x 10^7				TNC x 10^7	
	Qty	%	Range	Median	Qty	%	Range	Median
Total Shipments	30		90-313	155	1154		25-489	170
CBU Broad Race:								
Caucasian	10	33.3%			578	50.1%		
Asian/Pacific Islander	0	0.0%			26	2.3%		
Black or African American	17	56.7%			87	7.5%		
Hawaiian	0	0.0%			1	0.1%		
Hispanic/Latino	1	3.3%			179	15.5%		
American Indian/Alaska Native	0	0.0%			2	0.2%		
Multiple Race	2	6.7%			74	6.4%		
Unknown	0	0.0%			202	17.5%		
Decline	0	0.0%			3	0.3%		
Other	0	0.0%			2	0.2%		
Recipient Broad Race:								
Caucasian	8	26.7%			537	46.5%		
Asian/Pacific Islander	2	6.7%			53	4.6%		
Black or African American	9	30.0%			111	9.6%		
Hawaiian	0	0.0%			2	0.2%		
Hispanic/Latino	3	10.0%			133	11.5%		
American Indian/Alaska Native	0	0.0%			7	0.6%		
Multiple Race	0	0.0%			0	0.0%		
Unknown	8	26.7%			305	26.4%		
Decline	0	0.0%			3	0.3%		
Other	0	0.0%			3	0.3%		

Figure 3

As of 12/31/08, the JP McCarthy Cord Stem Cell Bank had distributed 79 CBUs to transplant centers worldwide. The distribution of the CBUs shipped by year is shown in Figure 3. The total number of units shipped is 80, however, one of the unit's arrived at the destination thawed and this unit could not be used clinically.



d. Transplant Outcome at Karmanos Cancer Center

Karmanos Cancer Center is unique because we are one of the top ten stem cell transplant centers in the country with an operating cord blood bank. Only a few cancer centers have the dual role as supplier and user of the cord blood unit. This is pivotally important in a national emergency situation where we can mobilize to performance transplantation as well as supplying donors through readily available shipments of CBUs to transplant centers.

Table 1 below shows the outcomes of 28 cord-blood transplantations performed at our center. This analysis was covered under the IRB-approved protocol D2928 (IRB approval and continuation approval is attached). These patients were candidates for allogeneic stem cell transplantation but no suitable adult stem cell donors were identified in the donor registry. Therefore, allogeneic stem cell transplantation using cord blood was considered the last option for these patients. There is no change in the demographic information but there is one additional death due to relapse of acute lymphocytic leukemia in an adult patient who received a second cord blood transplantation due to lack of an adult donor. The survival curve and comparison was made using the same statistical tools.

Table 1 Demographics and outcome of cord blood stem cell transplantation at Karmanos Cancer Center

Data Category	African/American	Others	P value
Race			0.68
Male	3	11	
Female	5	9	
Median age (range)	11 (5-43)	19 (0.5-61)	
Acute GVHD	4	3	0.14
Chronic GVHD			0.22
None	7	15	
Limited	0	2	
Extensive	1	3	
Diagnosis			0.27
Aplastic anemia	2	0	

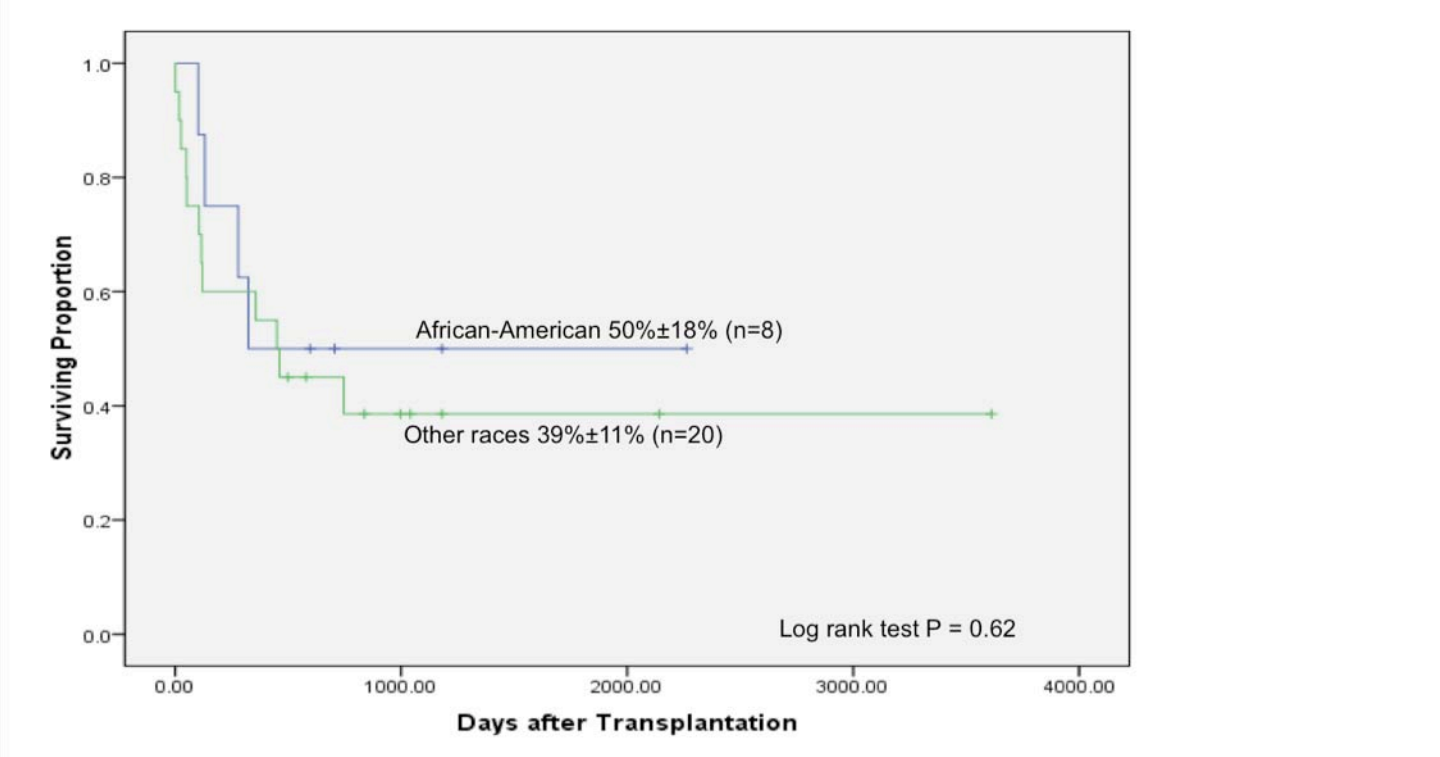
Acute lymphoid leukemia	3	5	
Acute myeloid leukemia	2	7	
Acute Biphenotypic leukemia	0	1	
Juvenile myelomonocytic leukemia	0	2	
Myelodysplastic syndrome	0	1	
Myeloma	1	0	
Non-Hodgkin lymphoma	0	2	
Osteopetrosis	0	1	
Severe combined immunodeficiency	0	1	
Preparative Regimens			0.53
Busulfan, cyclophosphamide, ara-C	4	2	
Busulfan, cyclophosphamide	0	1	
Busulfan, cyclophosphamide, melphalan	0	2	
Busulfan, fludarabine	0	1	
Busulfan, fludarabine, TBI	1	4	
Cyclophosphamide, ATG	1	0	
Cyclophosphamide, fludarabine, TBI	0	1	
Cyclophosphamide, TBI	1	4	
Fludarabine, melphalan, TBI	1	1	
R-BEAM	0	1	
TBI, VP-16	0	2	
None*	0	1	
Causes of Death			1.0
Graft failure	0	1	
Bleeding	0	1	
Bacterial infection	1	1	
Fungal infection	0	1	
Recurrent/persistent disease	3	5	
Secondary malignancy	0	1	

* One patient did not receive the conditioning regimen due to critical clinical condition. Patient had severe combined immune deficiency on a respirator with multisystem organ failure.

There was no difference in the distribution of demographic characteristics of African/American patients and other racial groups.

There were 4 patients who had 2 transplants at the time of their demise; one had 2 cord blood transplantations, 2 patients had prior autologous transplantations with progressive malignancy, the remaining one relapsed after a sibling donor transplant then received a second transplant with an unrelated cord blood unit. Overall survivals were calculated according to the Kaplan-Meier product limit estimated from the time of transplantation to the last date of contact shown in Figure 4. The estimated 3 –year survival for African/American patients was 50%±18% and for other races was 39%±11% (log rank P = 0.62). Thus, there was no difference of survival between African/American vs. other racial groups.

Figure 4



KEY RESEARCH ACCOMPLISHMENTS

1. There is no evidence that improvement of prenatal care will result in a higher number of nucleated cells. Increased availability of CBUs from African-American donors will need to be achieved via increasing awareness, education and collection access to the areas with the greatest concentration of African-American donors.
2. We implemented the expansion of collection sites (St John Hospital) and we were able to show that increased awareness can increase the number of collections.
3. We demonstrated the reproducibility of expansion to other collection sites via community education and we are now recruiting new collection sites – 3 collection sites are now actively collecting cord blood.
4. We have shown that African-American patients can achieve similar survival using cord blood transplantation despite the small inventory. Thus, the expansion of inventory will be crucial to improve access of this stem cell source.

REPORTABLE OUTCOMES

See KEY RESEARCH ACCOMPLISHMENTS above.

CONCLUSION

Over the first year of this project, we have shown that the only maternal variable associated with total nucleated cell yield in cord blood procurement is maternal race. African/American donors had a lower nucleated cell yield and this did not appear to correlate with the frequency of prenatal clinic visits. The lower nucleated cell count in the CBUs from African-American donors is the inherent biologic characteristic shared by Asian donors as well.[8] It is not likely that any operational or clinical maneuver will change the yield among these two racial groups.

In the second year we focused our effort on the expansion of the program to increase the participation of African/American donors in cord blood donation. This was carried out at one site for the ease of monitoring. Through greater participation of the potential donors, we were able to increase the collection of African/American CBUs. At the same time (in the second year and continuing into the third year), we implemented a long-term strategy to involve the Wayne State University medical students as volunteers to help with the education of potential cord blood donors and to obtain informed consent for cord blood donation. We are hoping that the education of future practitioners will increase the awareness of the importance of cord blood procurement and will ensure continuation of cord blood procurement into the future. Finally, we then opened 3 new sites at St Joseph Mercy Hospital in Ann Arbor, Providence Hospital in Southfield and Novi. The expansion strategy has been very successful in that the expansion is now self-propelling with Henry Ford Hospital in Wyandotte, Sinai-Grace Hospital (majority of births are African-American) and 2 other hospitals in Toledo Ohio (with very diverse racial distributions). These sites are getting ready to participate in the next few months.

The last focus is on this Center's transplant outcome and we presented the update of the survival analysis of 28 cord blood transplants conducted at Karmanos Cancer Center. We demonstrated the practicality of the cord blood stem cell transplantation in African/American patients in the absence of other stem cell source adult donors. Cord blood stem cell transplantation can produce a comparable outcome in African/American patients in comparison to other racial groups.

This funding has produced an impressive start-up for cord blood collection in the inner city hospitals that will be productive for many years to come. JP McCarthy Cord Stem Cell Bank is now providing highly desirable CBUs for those patients who cannot find a suitable adult living stem cell donor.

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APPENDIX I

A listing of personnel receiving pay from the research effort:

Personnel

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