Although it should be too early to refer long term outcome, unmanipulated haploSCT could be considered as an option to fight against refractory diseases.

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DONOR DAY 7 CD3 CHIMERISM IS PREDICTIVE OF THE LONG-TERM ENGRAFTING UNIT FOLLOWING MYELOABLATIVE DOUBLE CORD BLOOD TRANSPLANTATION (dCBT)

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Background: After myeloablative dCBT, one unit typically persists as the engrafting unit responsible for long-term hematopoiesis. It has been postulated that unit-versus-unit immune interactions contribute to the emergence of single donor dominance; however, there is currently no reliable method of determining the winning unit. We evaluated the role of donor day 7 CD3 peripheral blood (PB) chimerisms on predicting the engrafting unit.

Methods: In this prospective single-center analysis, PB was flow sorted into cell fractions, and DNA chimerism analysis was performed by amplified fragment length polymorphism. Chimerism detection sensitivity was 1-5%, with a range of accuracy +/- 5%. A logistic regression model was used to determine the correlation between a higher CD3 chimerism and the likelihood of being the predominant unit, and a t-test was applied to compare the mean CD3 chimerism of the winning versus losing unit.

Results: Between 10/2007-7/2010, 29 patients aged 12-63 years underwent myeloablative dCBT for AML (n = 14), ALL (n = 8), CML (n = 2), MDS/MPD (n = 4), and CLL (n = 1). 17 patients received 13.2 Gy TBI, 120 mg/kg cytoxan, and 75 mg/m^2 fludarabine; 12 patients received treosulfan 42 gm/m^2, fludarabine 150 mg/m^2, and 2 Gy TBI. GVHD prophylaxis was cyclosporine and MMF. The median infused cell doses were: 3.5 $\times$ 10^7 TNC/kg, 0.16 $\times$ 10^6 CD34/kg, and 10.7 $\times$ 10^6 CD3/kg. Day 7 CD3 chimerisms were evaluable in 25/29 patients. We found no correlation between engrafting unit and infused TNC, CD34, or CD3 dose, nor unit viability or HLA disparity. In 21/25 patients (Group A), the unit with higher CD3 chimerism on day 7 became the engrafting unit [OR 27.5 (95% CI: 6.0-125.0), p = 0.0001]. Furthermore, the mean day 7 CD3 chimerism was significantly different between the winning and losing units in this group (p < 0.0001). CD3 chimerism from the non-engrafting unit was higher at day 7 in only 4 patients (Group B).

Conclusions: Donor day 7 CD3 peripheral blood chimerism is highly predictive of the long-term engrafting unit in the setting of myeloablative dCBT. These results further support the hypothesis that single-donor dominance is immune-mediated by graft-graft interactions, and may provide insight into basic principles of transplant immunology. Importantly, the ability to predict the long-term engrafting unit at day 7 would allow for early selection of the cord blood unit to be used for adoptive immunotherapy post transplant.

Table 1. Patient Characteristics

	All Cohort (n=29) N(%)	Group A (n=21) N(%)	Group B (n=4) N(%)	p value
Median age in years (range)	31.6 (12.9-63.3)	33.3 (12.9-63.3)	24.9 (17.7-56.3)	0.76
Gender				0.93
Female	15 (52)	10 (47)	2 (50)	
Male	14 (48)	11 (53)	2 (50)	
HLA disparity*				0.20
4/6	19 (66)	14 (67)	1 (25)	
5/6	8 (27)	6 (29)	2 (50)	
6/6	2 (7)	1 (4)	1 (25)	
CMV serostatus				0.65
Positive	18 (62)	13 (62)	2 (50)	
Negative	11 (38)	8 (38)	2 (50)	
Transplant type				0.50
Flu+Cy+TBI (13.2 Gy)	17 (81)	12 (57)	3 (75)	
Flu+Treosulfan	12 (19)	9 (43)	1 (25)	
GVHD prophylaxis	CSA+MMF	-	-	-
Median weight in Kg (range)	76.1 (45.5-114.4)	76.1 (47.7-114.4)	72.2 (66-78.4)	0.57
Disease				0.96
AML	14 (48)	11 (52)	2 (50)	
ALL	8 (28)	5 (24)	1 (25)	
CML	2 (7)	1 (5)	-	
MDS/MPD	4 (14)	3 (14)	1 (25)	
CLL	1 (3)	1 (5)	-	
Median TNC infused x10^7/Kg (range)**	3.5 (1.8-6.4)	3.3 (2.3-6.4)	3.3 (2.6-4.0)	0.61
Median CD34 infused x10^6/Kg (range)**	0.16 (0.08-0.66)	0.14 (0.08-0.66)	0.26 (0.20-0.31)	0.23
Median CD3 infused* x10^6/Kg (range)**	10.7 (6.9-18.5)	10.8 (6.9-18.5)	10.4 (9.4-16.4)	0.92
Viability* % (range)**	75 (60-87)	74 (60-87)	78 (72-79)	0.33

*For dCBT, HLA disparity reflects the lower match of the 2 units.
**Post thaw.
***Post wash.

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SCORING HLA MISMATCHES BY HistoCheck DOES NOT PREDICT CLINICAL OUTCOME IN HCT

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High resolution HLA matching at HLA-A, B, C and DRB1 has proven critical for optimal outcomes following unrelated donor (URD) hematopoietic stem cell transplantation (HCT). Approximately 30% of URD HCT facilitated through by the National Marrow Donor Program (NMDP) are mismatched (MM) at one or more loci. Currently, no rating system exists to reliably predict which HLA MM URD should be selected for patients who do not have an HLA allele matched donor. In 2002, Elsner and Blasczyk suggested that a rating system, HistoCheck, might be used to identify acceptable MM. This algorithm is based on the functional similarity of amino acids weighted based on the position of the disparity in the HLA molecule to yield a Dissimilarity Score (DSS).

We evaluated the ability of DSS to predict the risk associated with HLA disparity in a population of 744 single allele or antigen HLA-A, B, or C MM myeloablative URD HCT for AML, ALL, CML or MDS facilitated through the NMDP from 1988-2003. All pairs in the study were retrospectively high resolution typed for HLA-A, B, C, DRB1, DQB1 and DPB1. Multivariate models were used to adjust for other significant clinical risk factors. A threshold of p < 0.01 was used to define significance due to multiple comparisons. HLA MM were scored using the HistoCheck web-based tool and the patients divided into 4 quartiles: DSS 1.04-2.84 (allele MM), 2.84-13.75 (allele and antigen MM), 13.75-19.385 (antigen MM) and 10.385-36.62 (antigen MM). Using the lowest scoring quartile as the reference, the DSS groups were evaluated for an association with relapse, transplant related mortality (TRM), acute and chronic GVHD, leukemia free survival (LFS), and overall survival in the entire cohort and in subset analyses by disease and disease stage.

No significant associations were found between DSS and any outcomes in the overall cohort using the quartile categories or treating DSS as a continuous variable. Higher DSS scores were associated with decreased engraftment in early stage disease (p = 0.0003) but not in other disease stages. In disease subset analyses, DSS score was associated with TRM, LFS and OS in MDS. However, the MDS subgroups were very small (n = 10-21) diminishing confidence in the association.

In summary, DSS does not correlate with transplant outcome, and the HistoCheck scoring system does not provide an effective strategy to rank HLA MM. The dataset used in this study is available to evaluate new algorithms developed for donor selection.