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Discussion: The above results suggest that inhibition of NFATc2 signaling in CD34+ HSC using CSA results in more rapid differentiation towards the myelomonocytic and erythroid lineage (as seen by flow cytometry) without affecting cell proliferation. These results need to be further validated by RNAi mediated NFATc2 knock out in HSC's in vitro. These studies will lead to better understanding of regulation of HSC differentiation and may have implications for routine CSA administration in patients undergoing allogeneic transplantation.

Acknowledgment: Farrow Fellowship Award.

HISTOCOMPATIBILITY/ALTERNATIVE STEM CELL SOURCES

172

EVALUATION OF TRANSPLANT CENTER UNRELATED DONOR SEARCH STRATEGY PROFICIENCY

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The National Marrow Donor Program (NMDP) evaluated the proficiency of U.S. transplant centers (TC) in selecting unrelated donors (URD) for hematopoietic cell transplantation. The study identifies TC specific and individual search specific factors that influence the likelihood of the best matched donors being selected for further typing. We also evaluated changes in search proficiency since a comparable study in 2005.

Methods: Up to five random new patient searches of the Be The Match Registry® were evaluated for each TC from June – September 2011; 25% accrued less than five. All searches were evaluated by HLA experts for three search proficiency characteristics: patient HLA typing (loci/resolution), search strategy approach (select best potential HLA match), and number of donors selected for further typing - each were given a score from 0-3. A total score was calculated per search and stratified into high (perfect) and low (not perfect) proficiency groups. Five factors were evaluated for correlation to proficiency: use of NMDP search services - Search Strategy Advice or Custom Search Support (CSS), presence of Certified Hematopoietic Transplant Coordinator (CHTC) staff, URD procurements (FY 2010), and difficult search (Yes/No).

Results: 566 patient searches from 130 TCs were included in the current study; 76% rated in the high proficiency group and 24% in the low. Univariate and multivariate analysis concurred that searches which received CSS, were performed at TCs with CHTC staff, or were not difficult were more likely to have a high proficiency rating (Table 1). Searches that received CSS were more than four times as likely to have the highest proficiency rating. Similarly, searches at TCs that had CHTC staff were about two times as likely to be high proficiency while searches that were not difficult were about 1.5 times as likely. The majority of searches in the low proficiency group did not select an adequate number of donors.

Conclusions: U.S. TCs have improved their search proficiency from 52% in the high proficiency group in 2005 to 76% in 2011. During this time, NMDP initiatives which may have influenced TC proficiency include publications (NMDP matching guidelines), a new search service (CSS), HapLogic predictions and donor list sorting, and network education. The most frequent characteristic of searches in the low proficiency group was selecting an inadequate number of donors for extended typing which can delay a search.

Table 1. Logistic Regression Results for Search Proficiency Rating

Factor	N	OR	(95% CI)	p-value	Favorable characteristic
Procurement Level				0.073	Not significant
Low	81	1.00			
Medium	350	1.89	(0.84-4.25)	0.127	
High	135	1.05	(0.45-2.46)	0.907	
CSS sent to TC before formal					CSS sent to TC before formal
Yes	71	4.13	(1.39-12.28)	0.011	
No	495	1.00			
SSA sent to TC before formal					Not significant
Yes	32	1.13	(0.47-2.74)	0.781	
No	534	1.00			
At least 1 CHTC on staff					Had at least 1 CHTC staff
Yes	239	2.07	(1.22-3.50)	0.007	
No	327	1.00			
Difficult search					Not difficult
Yes	226	0.63	(0.42-0.93)	0.020	
No	340	1.00			

OR indicates odds ratio; CI indicates confidence interval

173

EXPANSION OF T-CELLS FROM THE CORD BLOOD GRAFT AS A PREDICTIVE TOOL FOR COMPLICATIONS AND OUTCOME OF CORD BLOOD TRANSPLANTATION

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We have previously successfully expanded functional T-cells in vitro from cord blood grafts used for clinical transplantation, with the aim of creating donor lymphocyte infusions to treat e.g. malignant relapse. Here we show that the T cell expansion in addition might work as a prognostic tool for in vivo complications after transplantation. We used multi-color flow cytometry to correlate in vitro phenotypical data from 33 expansions to the clinical outcome post-transplantation. Higher levels of CD69+ activated T-cells in the expansion were associated with prolonged survival of the patient. In addition, we found a correlation between T-cell expansions containing relatively high levels of effector memory T-cells and transplant-related complications. Our data suggest that expansions of cord blood T-cells from the graft might not only be used as donor lymphocyte infusions, but also as in vitro indicators that could give essential information on how to manage cord blood transplanted patients.

174

EFFECTIVENESS OF UNRELATED DONOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: RESULTS OF A DONOR VS. NO DONOR ANALYSIS

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In a consecutive series of unrelated donor searches conducted from March, 2006 through December, 2009 at Moffitt Cancer Center, we studied the following: (1) likelihood of finding a suitable (7-8/8) high-resolution matched unrelated donor; (2) factors associated with reaching transplant (HCT) among those with a donor; and (3) the effect of unrelated donor vs. no donor status on survival by intention to treat (ITT) analysis. Those with a fully HLA-A, -B, -C, and –DRB1 (8/8) matched or single locus (7/8) mismatched unrelated donor were defined as donor (n = 448), while those without were no donor (n = 83). Median time from search initiation to donor identification was 21 days; 95% of these values were within 59

days. While race/ethnicity ($p<0.0001$) and disease ($p = 0.01$) were associated with finding a donor, other variables (age, gender, CIBMTR risk, CMV, KPS, socio-economic status) were not. Among those with a donor, logistic regression modeling identified increasing age ($p = 0.02$), non-Caucasian race/ethnicity ($p = 0.002$), and high CIBMTR risk ($p = 0.007$) as associated with decreased odds for reaching HCT. Among 448 patients in the donor group, 239 underwent HCT. Of those in the no donor group, a total of 14 underwent double umbilical cord blood transplant (dUCBT). In the primary ITT analysis, we studied outcome according to donor vs. no donor status from time of search initiation using a time-dependent Cox model. Compared to no donor, donor status had reduced hazard for mortality (HR of 0.85, 95% CI 0.63 -1.2, $p = 0.3$). Accounting for interaction, those with KPS 90-100 and donor had significantly reduced hazard (HR 0.59, 95% CI 0.38 - 0.90, $p = 0.02$) compared to no donor. Secondary analyses examined outcome by treatment received: Those who received the intended HCT in the donor group had significantly reduced hazard (HR 0.64, 95% CI 0.46 – 0.89, $p = 0.009$) compared to no donor. In a separate analysis, donor, dUCBT, and no donor/no UCBT were treated as time-varying covariates, demonstrating significantly reduced hazard for donor vs. no donor (HR 0.57, 95% CI 0.43-0.76, $p = 0.0001$). No significant effect of matching (7/8 vs. 8/8) was detected in any analyses. In total, these data provide new insight into factors associated with unrelated donor identification according to high-resolution typing methods, identify factors relevant to reaching HCT among those with a suitable donor, and speak to the efficacy of unrelated donor HCT.

175

UNRELATED CORD BLOOD TRANSPLANTATION (CBT) OF 101 HEMOGLOBINOPATHY (HGB) PATIENTS

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Unrelated cord blood transplantation (CBT) is not widely used to treat hemoglobinopathies (HGB) despite being the fastest growing stem cell source for unrelated hematopoietic cell transplantation (HCT). Published series show unfavorable disease-free survival (Ruggeri et al. BBMT 2011) or were single institution efforts (Jaing et al. BMT 2011). We analyzed the clinical outcome for 101 HGB patients following CBT. The combination approach to optimize nucleated cell (NC) dose of choosing CB products manufactured by plasma depletion/reduction to maximize NC recovery, double grafts (whenever single CB had insufficient NC dose), and post-thaw direct infusion were used by the 5 Asian transplant centers (TCs) in this series that performed most of the CBT. A CIBMTR on site-audited analysis was performed on 91 thalassemia and 10 sickle cell disease (SCD) patients transplanted between 1999 and 2011 at 25 TCs in 6 countries using 114 CB products processed by plasma depletion/reduction (88%) and 15 CB units processed by red cell reduction. 84% of the CB were infused directly without post-thaw wash/reconstitution and 19% of the transplants employed double CB grafts. Most TCs reported usage of no-TBI preparative regimens or ones that included Bu/Cy/ATG. Graft failure rate at some TCs declined after switching from oral busulfan to IV formulations, and 7 patients received a second CBT. 24% of the transplants (24 patients/25 CB) were performed at 18 U.S. TCs with the remainder (77 patients/104 CB) at 7 international TCs. 75% of the patients were Asian. Median follow-up time was 711 days (range 2-2,877 days). Transplant characteristics: median age 5.6 years (range 0.3-20); median patient weight 18.8 kg (range 4-80); male 45%; HLA matches (intermediate resolution HLA-A and -B and high resolution HLA-DRB1) of the CB used in these patients: 6/6-23; 5/6-45; 4/6-54; 3/6-3; median pre-freeze TNC dose 9.4 $x10^7$/kg; median pre-freeze $CD34^+$ dose 3.2 $x10^5$/kg. The median times to myeloid and platelet engraftment were 17 days and 47 days, respectively. Of the 101 patients, 21 expired before 180 days (20.8%); 26 prior to 1 year (25.7%) and 27 total deaths (26.7%). To our knowledge, the current multi-center study with 101 patients is the largest unrelated CBT series for HGB or thalassemia. The data appear to support the notion that in the setting of optimal cell dose, favorable overall and disease-free survival may be achieved for unrelated CBT of HGB/thalassemia.

Table. Summary of Patient, CB and Transplant Characteristics

Patient Characteristics	All Patients (n = 101)	Thalassemia PDR CB (n = 79)	Thalassemia RCR CB (n = 12)	SCD PDR CB (n = 9)	SCD RCR CB (n = 1)
Age yo, Median (Range)	5.6 (0.3-20)	5.3 (0.3-20)	4.0 (0.8-12)	12.4 (4-20)	NA
Weight Kg, Median (Range)	18.8 (4-80)	18.5 (8-45)	15.1 (4-36)	34.0 (17-80)	NA
Male Sex %	46	43	58	44	NA
Asian/Caucasian/ AFA/NA %	75/9/8/9	71/4/0/4	4/5/0/3	0/0/8/1	0/0/0/1
CB Graft Characteristics	**All CB (n = 129)**	**Thalassemia PDR CB (n = 105)**	**Thalassemia RCR CB (n = 13)**	**SCD PDR CB (n = 9)**	**SCD RCR CB (n = 2)**
HLA Match NA,3/6,4/6, 5/6,6/6	4,3,54,45,23	1,3,42,38,21	1,0,8,3,1	0,0,4,4,1	2,0,0,0,0
Pre Freeze TNC dose, Median (Range)	9.4 (2.3-23.7)	9.8 (2.5-23.7)	8.7 (2.3-18.6)	4.4 (2.6-10)	NA
Pre Freeze CD34+ dose, Median (Range)	3.2 (0.4-13.5)	3.6 (0.4-10.3)	1.5 (0.4-13.5)	1.8 (0.8-3.1)	NA
% CB bedside thaw	84	89	77	56	0
% Double CBT	19	20	8	0	100

PDR = Plasma Depleted/Reduced; RCR = Red Cell Reduced; CB = Cord Blood; yo = years old; Asian = Asian/Asian Pacific Islander/Indian; Caucasian = Causian/Middle Eastern; AFA = African American; NA = Not Availlable; TNC = Total Nucleated Cells in 10^7; CD34+ cells in 10^5; beside thaw = direct infusion without post-thaw wash or reconstitution

176

HLA-DPA1 MISMATCH IS ASSOCIATED WITH DECREASED OVERALL SURVIVAL FOLLOWING UNRELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Aim: To investigate the impact of HLA-DPA1 and -DPB1 mismatch on clinical outcomes in a modern era of unrelated hematopoietic stem cell transplantation (HSCT).

Methods: Retrospectively, 380 consecutive patients (median age 39, range 0.5-67 years) who underwent HSCT using HLA -A, -B, and -DRB1 allele level-matched unrelated donors at our centre during 1995-2010, were included in the study. Most patients underwent HSCT in the treatment for hematological malignancies (81%), whereas 7% and 12% of all patients were transplanted in the treatment for non-hematological malignancies and non-malignant disorders, respectively. HLA typing using PCR-SSP (Olerup-SSP) or PCR-SSO on a Luminex platform (One Lambda) was performed and revealed 55 HLA-DP (A1 and B1) matched and 325 mismatched donor pairs. HLA-DPA1 and HLA-DPB1 mismatch was noted in 35% and 85% of all recipient donor pairs, respectively.