Table 2
Transplant Outcomes for MMUD vs MUD Grafts

Outcome	Group	N	1-yr CI	2-yr CI	p-value
	MUD	169	0.72 (0.64-0.79)	0.60 (0.51-0.67)	-
	8/10 Loci	31	0.57 (0.38-0.73)	0.43 (0.25-0.60)	0.04
OS	9/10 Loci	105	0.71 (0.61-0.79)	0.56 (0.45-0.65)	
	Single DQB1	18	0.78 (0.51-0.91)	0.72 (0.45-0.87)	0.44
	Single C	26	0.68 (0.46-0.83)	0.45 (0.25-0.64)	0.07
	Single class 1 or DRB1	87	0.70 (0.59-0.79)	0.522 (0.41-0.63)	0.17
	MUD	169	0.65 (0.57-0.72)	0.54 (0.45-0.62)	-
	8/10 Loci	31	0.47 (0.29-0.64)	0.40 (0.23-0.57)	0.04
DFS	9/10 Loci	105	0.65 (0.55-0.74)	0.50 (0.40-0.60)	
	Single DQB	18	0.78 (0.51-0.91)	0.72 (0 45-0.87)	0.29
	Single C	26	0.56 (0.35-0.73)	0.37 (0.18-0.56)	0.14
	Single DQB1	87	0.64 (0.53-0.73)	0.47 (0.36-0.58)	0.42
	MUD	169	0.09 (0.04-0.14)	0.13 (0.08-0.19)	-
	8/10 Loci	31	0.07 (0.01-0.19)	0.13 (0.40-0.28)	0.36
aGvHD (Gr 2-4)	9/10 Loci	105	0.14 (0.08-0.22)	0.21 (0.14-0.30)	
	Single DQB1	18	0.17 (0.04-0.37)	0.17 (0.04-0.37)	0.21
	Single C	26	0 04 (0.00-0.17)	0.23 (0.09-0.41)	0.62
	Single class 1 or DRB1	87	0.14 (0.08-0.22)	0.22 (0.14-0.32)	0.21
	MUD	169	0.05 (0.02-0.09)	0.10 (0.05-0.16)	-
	8/10 Loci	31	0.03 (0.00-0.15)	0.03 (0.00-0.15)	0.14
cGvHD	9/10 Loci	105	0.03 (0.01-0.08)	0.03 (0.01-0.08)	
	Single DQB1	18	0.06 (0.00-0.25)	0.06 (0.00-0.25)	0.67
	Single C	26	0.05 (0.00-0.20)	0.05 (0.00-0.20)	0.41
	Single class 1 or DRB1	87	0.03 (0.00-0.08)	0.03 (0.00-0.08)	0.06

*As appropriate, logrank or Gray's test p-value comparing outcomes for single DQB1, Single C and Single class 1 or DRB1 to MUD transplants. Similarly, outcomes were compared across 8/10 loci, 9/10 loci and 10/10 loci MUD transplants.

& sheep RBC rosetting (sRBCr) and for PB by automated CD34+ selection +/- sRBCr. Conditioning regimens were ablative and all included ATG. Patients were in remission or had a low volume of disease. No pharmacologic GvHD prophylaxis was given. For different levels of mismatch, overall (OS) and disease-free survival (DFS) were compared using Kaplan-Meier curves and the logrank test. Cumulative incidence functions and Gray's test compared the incidence of grade 2-4 aGvHD and cGvHD. Results were compared with 169 TCD HLA matched unrelated donor (MUD) grafts during the same period.

Results: Table 1 lists demographics. Several subgroups had limited numbers of patients. Table 2 shows cumulative incidence (CI) for outcomes, and Figure 1 survival curves to 5 yrs. There was no difference in outcomes for 1 loci MMUD vs. MUD grafts. There was no statistical difference in outcomes for a single C vs. any single non C mismatch. Nearly all acute GVHD was 2-3, and there were only 4 limited chronic GVHDs. OS and DFS were lower for >1 loci MMUD transplants.

Conclusion: These results support the use of TCD MMUD grafts as alternatives for patients lacking a MUD or ineligible for a CB graft.

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Hemophagocytic Syndrome after Cord Blood Transplantation; Possible Implication of Severe Pre-Engraftment Immune Reactions

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Aims: We reported the impact of hemophagocytic syndrome (HPS) on engraftment failure in cord blood transplantation (CBT). The aim of this study was to explore pathogenesis underlying HPS.

Methods: We retrospectively reviewed 351 patients who underwent single CBT using fludarabine-based regimens at our institute from January 2002 to July 2011 consecutively.

Results: Median age was 58 years (range, 17-82).Diagnoses were AML/MDS (n=209), ALL/ML (n=103), and others (n=36). Tacrolimus plus MMF (TAC+MMF) were used in 196 cases as GVHD prophylaxis, while TAC alone in 155. HPS developed in 33 patients at a median of 19 days post-CBT. The cumulative incidence of HPS was 9.4%. Development of HPS had a negative impact significantly on neutrophil engraftment (33.3% with HPS vs 83.3% without HPS, $p=<0.01$), which resulted in inferior overall survival rate. Majority of the HPS patients (25/30) showed donor-dominant chimerism at the diagnosis of HPS. Patients with severe form of pre-engraftment immune reactions (sPIR) showed significantly higher incidence of HPS than those without PIR (51.9% vs 6.6% $p=<0.01$). Patients who received cord blood unit with higher degree of HLA antigen mismatch in GVH direction (2 vs 0-1) also showed higher incidence of HPS (11.5% vs 4.8% $p=<0.04$). TAC+MMF decreased the incidence of sPIR and HPS compared to TAC alone (2.8% vs 15.3% $p=<0.01$ and 4.6% vs 15.5% $p= <0.01$, respectively), which had a trend toward higher engraftment rate (83.7% vs 72.3% $p=0.07$). In multivariate analysis, GVHD prophylaxis using TAC alone, lower number of $CD34^+$ cells infused ($>0.8x10^5$/kg vs $<0.8x10^5$/kg) and higher degree of HLA antigen mismatch in GVH direction were significantly associated with HPS development.

Conclusion: HPS was closely associated with engraftment failure in our CBT cohort. sPIR plays an crucial role of developing HPS and was possibly controlled by intensification of GVHD prophylaxis.

IMMUNE RECONSTITUTION

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Baseline Thymopoietic Function and Post-Transplant Immune Recovery after Adult Cord Blood Transplantation

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We previously published data from a group of 32 heavily treated adult cord blood transplant (CBT) recipients and

found that their post-transplant immune recovery was characterized by a failure to recover early thymopoiesis and impairment of functional T cell recovery, compared to other recipients of autologous or allogeneic transplants (Komanduri et al., Blood, 2007). We now report a more extensive study of adult CBT recipients in whom thymopoiesis was prospectively assessed by measuring T cell receptor excision circles (TRECs) in the peripheral blood. Thymic function was assessed prior to CBT, and at varying intervals thereafter. A total of 71 adult CBT recipients were assessed prior to CBT and also assessed at least once within the first 180 days after CBT. Of these recipients, 44 of 71 had detectable thymopoiesis prior to the start of conditioning (62%), while baseline thymopoiesis was undetectable in others (38%). In CBT recipients with detectable thymopoiesis at baseline, 32% had at least one sample demonstrating detectable thymopoiesis by six months post-transplant. In contrast, only 4% of subjects with a negative baseline had any detectable thymopoiesis by six months. These results suggest that the recovery of early thymopoiesis within the first six months of CBT in adults may be dependent on functional thymopoiesis at baseline. Univariate landmark of a subset of these CBT recipients (n=41) stratified by the recovery of thymopoiesis at six months after CBT demonstrated that recovery of thymopoiesis was positively associated with overall survival (HR=0.2, 95% confidence interval 0.1-0.7, P=0.01), and also with decreased non-relapsed mortality (HR=0.2, 95% confidence interval 0.1-0.9, p=0.04). Larger studies of baseline thymopoiesis prior to hematopoietic transplantation will be helpful to confirm these findings and ascertain how and why thymopoiesis is preserved in a subset of patients, and to determine more precisely the relationship of baseline function and post-CBT outcomes.

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Phenotypic and Functional Characteristics of NK Cells Associated with Cytomegalovirus (CMV) Reactivation after Allogeneic Hematopoietic Stem Cell Transplantation (HCT)

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Cytomegalovirus (CMV) infection represents a major complication in hematopoietic stem cell transplantation (HCT). There is accumulating evidence that immune responses to CMV infection involve the expansion of specific subsets of NK cells largely driven by the activating receptor NKG2C.

Under an IRB approved protocol (COH 09038), we prospectively examined the reconstitution of NK cells post-HCT (days 21, 30, 45, 80 and 120) with regards to their immunophenotypes and functions. A total of 111 patients are enrolled (median age: 54, range 19-70) who underwent HCT from related (n=49) or unrelated donors (n=62) after either fully ablative (n=36) or reduced-intensity (n=75) conditioning. Donor (D)/Recipient (R) serostatus was D+/R+ in 69, D-/R+ in 33, and D+/R- in 6 pairs. Acute GVHD grade II-IV was observed in 49 patients (47%). CMV reactivations were seen in 26 patients (23.4%) with the median time of reactivation on day 49, including 2 cases of CMV disease.

	Days post HCT	CMV reactivation (n=26)	No CMV reactivation (n=85)	p-values
%NK (median)	45	13.3%	17.2%	p=0.035
	80	7.0%	11.3%	p=0.0015
%NK/PD-1 (median)	45	0.59%	0.42%	ns
	80	0.96%	0.37%	p=0.0003
%NK/IFN-γ (median)	45	2.7%	1.2%	p=0.03
	80	1.8%	1.2%	p=0.03
%NK Perforin (median)	45	60.2%	39.2%	p=0.04
	80	25.4%	41.8%	ns
%NK/Granzyme (median)	45	91.3%	85.7%	p=0.02
	80	89.8%	86.2%	p=0.04

CMV reactivation was significantly associated with increased %NK cells expressing PD-1, IFN-gamma, perforin, and granzyme B (Table 1). More focused analysis on available day 80 samples (n=75) demonstrated a significant increase in NK cells expressing NKG2C in patients with CMV reactivations (24.2%, n=17) compared with no reactivations (13.2%, n=58, p=0.018), consistent with published reports. Among NKG2C+NKcells, CMV reactivation was associated with increased granzyme B (85.4% vs. 56.9%, p=0.003) and Ki67 expression (7.0% vs. 2.9%, p=0.03).

We further explored NK responses to CMV antigen by co-culturing PBMC (day 80 samples) and pp65 peptide mix for 24 hours. There was no significant change in %NKG2C+NK cells before and after pp65 stimulation. Interestingly, NKG2C-NK cells showed a response to pp65 stimulation in their expression of CD137 (pre: 0.06% vs. post: 0.23%, p=0.005) and IFN-gamma (pre: 1.6% vs. post: 2.1%, p=0.03 in CMV reactivators), suggesting a potential role of NKG2C-NK cells in CMV infections.

In summary, our data support that CMV reactivation is associated with expansion (Ki67) and cytotoxic functions (perforin, granzyme, IFN-gamma) of NK cells expressing NKG2C following allogeneic HCT.

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Maintenance of Naïve T Cells and a Diverse TCR Repertoire Are Critical for Reconstitution of EBV-Specific Immunity after Double Cord Blood Transplantation

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Poor reconstitution of T cell immunity after umbilical cord blood transplantation (UCBT) results in susceptibility to viral infections that require intact T cell immunity. Epstein Barr