children post-AlloHCT is not well defined. We studied the impact of mean tacrolimus levels and number of days with subtherapeutic tacrolimus levels on the incidence of aGVHD. One-hundred eight patients received tacrolimus/ mycofenolate mofetil (MMF) for aGVHD prophylaxis between March 2005 and April 2012. Median age, 8 yrs; 37F/71M, malignant (n=61) and nonmalignant (n=47) disorders. Stem cell source: 18 peripheral blood stem cell donors, 49 bone marrow donors, and 41 unrelated cord bloods. Patients were conditioned with myeloablative (45.4%), reduced toxicity (28.7%), or reduced intensity (25.9%) regimens. Additionally, 30 patients received alemtuzumab (27.8%) and 54 patients received rabbit-ATG (50%). Tacrolimus was initiated at 0.03 mg/kg/d via continuous IV infusion or 0.12mg/kg/d PO, and dose was adjusted to maintain daily steady state concentration or trough levels within 10-20 ng/mL.

The overall incidence of aGVHD was 45.4%. Age, gender, ethnicity, non-malignant/malignant diseases, related/unrelated donors, HLA matching, donor source, conditioning regimen, alemtuzumab, r-ATG, and mean tacrolimus levels <15 ng/mL during each of 4 weeks post-AlloHCT, were examined as potential risk factors for aGVHD. Malignant disease was the only significant risk factor observed (OR 5.41, 95% CI 2.31-12.67, p =0.0001).

Mean weekly tacrolimus levels < 15 ng/mL were not significantly associated with incidence of aGVHD (p=0.705, p=0.879, p=0.952, p=0.524) and mean levels < 10ng/mL as suggested by Ram et al. (BBMT, 2012) were also not significant. The number of days with subtherapeutic tacrolimus levels (< 10 ng/mL) during the first 4 weeks post-AlloHCT (median = 10d) revealed no significant association between > 10d of subtherapeutic tacrolimus levels and incidence of aGVHD (p=0.49). Further analysis of patients with subtherapeutic levels > 3 days per week or > 14 days over 4 weeks were also not significant. Risk factor analysis for subtherapeutic tacrolimus levels demonstrated that an increase in serum creatinine levels by 50% during the 3rd and 4th weeks post-AlloHCT was significantly associated with > 10 days of subtherapeutic tacrolimus levels (p=0.005, p=0.01), as doses were lowered in response to impending renal insufficiency.

Our results suggest that while prophylactic tacrolimus /MMF is effective in preventing aGVHD, maintaining levels as high as 10-20 ng/mL may not be necessary. It may be possible to tolerate more subtherapeutic days in the first month post-AlloHCT without increasing the risk of aGVHD. Further studies are necessary to determine an appropriate lower target range for tacrolimus to reduce incidence of aGVHD while preventing additional immune-suppression and other toxic effects.

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Epidemiology of Chronic Graft-Versus-Host Disease in the Pediatric Recipients of Hematopoietic Stem Cell Transplantation

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Most studies into the epidemiology of chronic graft-versus-host- disease (cGVHD) have focused on adult hematopoietic stem cell transplant (HSCT) recipients. To determine whether the clinical factors that contribute to the development of cGVHD in pediatric HSCT recipients differed from those implicated in adult HSCT recipients, we undertook a cross-sectional, single institution study of pediatric HSCT recipients who were more than one year following their myeloablative HSCT. Pediatric recipients were transplanted between 1998 and 2011. Thirty-one (31) recipients with either active (14) or resolved (17) cGVHD were identified and compared to 47 pediatric HSCT recipients without cGVHD [40 recipients with no history of acute GVHD (Grade II-IV) and 7 recipients with a history of only acute GVHD]. All clinical records were re-evaluated by a single observer and graded for the severity of both acute and cGVHD using the NIH Consensus Scoring Criteria. Recipients' clinical characteristics were determined. Among the variables that did not differ significantly between HSCT recipients with and without cGVHD were: recipient age, donor age (of bone marrow donors), use of TBI containing preparative regimes, malignant versus non-malignant diseases, and female donor/ male recipient. The use of bone marrow as the HSC source, matched related donors, and the absence of acute GVHD were all associated with a decreased probability of cGVHD. No significant differences were identified between the patients who had active cGVHD and those who had resolved cGVHD.

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High Day 28 ST2 Biomarker Levels Predict Severe Day 100 Acute Graft-Versus-Host Disease and Day 180 Transplant-Related Mortality after Double-Unit Cord Blood Transplantation

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Background: Cord blood transplantation (CBT) is a proven therapy for high-risk hematologic malignancies. However, severe grade III-IV acute graft-versus-host disease (aGVHD) is a significant source of morbidity and mortality and most commonly targets the gastrointestinal (GI) tract after CBT. We evaluated whether plasma biomarkers predict aGVHD severity and transplant-related mortality (TRM) after CBT.

Methods: Plasma biomarkers were measured 28 days after unrelated donor double-unit CBT in 113 consenting patients (median age 41 years, range 1.7-69) transplanted at a single center between 5/2006 and 5/2012. Conditioning was myeloablative (n = 37), reduced intensity (n = 47), or non-myeloablative (n = 29), and CB units were 4-6/6 HLA-matched to the recipient. The median follow-up was 44 months (range 14-84). Batched samples blinded to transplant outcomes were analyzed by ELISA for levels of suppressor of tumorigenicity 2 (ST2), IL-2Rα, TNFR1, HGF, IL-8, elafin, and REG3α. Patients were grouped according to being above or below the median biomarker value. Patients who had aGVHD onset prior to day 28 (n = 7) were excluded from aGVHD evaluation.

Results: We found significant associations between day 28 plasma biomarkers and grade II-IV aGVHD and/or 6-month TRM (Table). IL2Rα, elafin, and HGF were not significant. ST2 was the only biomarker associated with both day 100 aGVHD and TRM. Patients with high day 28 ST2 had significantly increased day 100 grade III-IV aGVHD of 27% (95% CI:16-40) versus 11% (95%CI:4-20) in patients with low ST2

Table

Biomarker (ng/ml)	Day 100 Grade II-IV aGVHD (95%CI)	p-value	6-month TRM (95% CI)	p-value
ST2 $\leq$ 33.9	48% (35-61)	0.045	5% (1-13)	0.001
ST2 $>$ 33.9	64% (49-76)		23% (13-35)	
TNFR1 $\leq$ 4792	57% (42-69)	0.660	5% (1-13)	0.005
TNFR1 $>$ 4792	54% (40-67)		23% (13-35)	
IL8 $\leq$ 51	56% (41-68)	0.652	5% (1-13)	0.005
IL8 $>$ 51	56% (41-68)		23% (13-35)	
REG3$\alpha \leq$ 42	57% (42-69)	0.938	5% (1-13)	0.032
REG3$\alpha >$ 42	55% (40-67)		24% (13-36)	

levels, $p = 0.025$. High ST2 was also associated with increased 6-month TRM, and GVHD was the most common cause of transplant-related death. High concentrations of TNFR1, IL-8, and REG3a were significantly associated with 6-month TRM and the most common cause of death in these patients was GVHD or lung toxicity.

Conclusions: This is the first biomarker analysis conducted in CBT recipients. As with adult donor allografts (*NEJM*, 2013), high day 28 ST2 levels is associated with a subsequent increased risk of grade II-IV and III-IV aGVHD, and 6-month TRM. GVHD onset is after day 28 in the majority of the patients which would permit potential therapeutic intervention. Thus, our findings have significant practical implications. Our results warrant further prospective evaluation with the ultimate aim of future interventions to ameliorate severe aGVHD and improve CBT survival.

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Intensified Mycophenolate Mofetil (MMF) Dosing Is Safe from the Standpoint of Engraftment and Reduces Severe Acute Graft-Versus-Host Disease (aGVHD) after Double-Unit Cord Blood Transplantation (DCBT): An Analysis of 173 Patients

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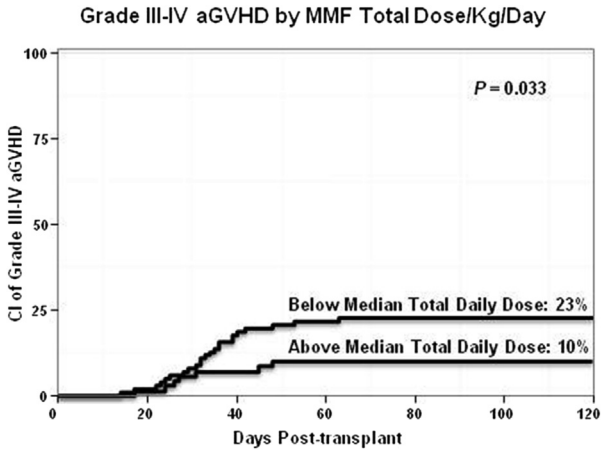

Background: Calcineurin-inhibitor/MMF based prophylaxis in DCBT is frequently associated with aGVHD. MMF dosing in CBT has traditionally been every 12 hours (q12). We increased MMF dosing to 1 gm every 8 hours (q8) to potentially ameliorate severe aGVHD. However, the toxicity and efficacy of intensified dosing is not established.

Methods: We evaluated 173 4-6/6 HLA-matched DCBT recipients (median age 39 years) transplanted for hematologic malignancies 10/2005-5/2013. Patients received calcineurin-inhibitor/MMF from day -3 without ATG. Before 9/2009, 83 patients (48%) received 1 gm MMF IV q12 (if $\leq$12 years 15 mg/kg/dose). From 9/2009, 90 patients (52%) received 1 gm MMF IV q8 (15 mg/kg/dose if $>$12 years and $<$50 kg, or 20 mg/kg/dose if $\leq$12 years).

Results: The median infused CD34+ cell doses of the dominant CB unit were similar in the groups. There were no differences in the speed or success of engraftment, day 180 TRM, or 1-year PFS (Table). Day 100 grade II-IV aGVHD were similar in the groups (46% vs 53%), and decreased day 100 grade III-IV aGVHD in the q8 group was suggested. As all patients $>$50 kg received 1 gm/dose, we then analyzed the effect of the total daily MMF dose/kg (regardless of dosing interval) in all 173 patients. A total daily dose/kg above the median was associated with a significant reduction in severe aGVHD [(23% (95%CI: 15-31) vs 10% (95%CI: 4-18), p=0.033, Figure].

Conclusions: Intensified q8 MMF dosing is safe from the standpoint of engraftment, TRM and relapse. While the reduction in severe aGVHD incidence in q8 MMF DCBT recipients did not reach significance, a total daily MMF dose/kg above the median significantly reduced severe aGVHD risk.

Outcome	MMF q12 Hour (n = 83)	MMF q8 Hour (n = 90)	P value
Neutrophil Engraftment:			
Myeloablative	93% (95%CI: 82-98) Median 23 days (range 12-43)	96% (95%CI: 87-99) Median 24 days (range 12-40)	0.692
Non-myeloablative	96% (95%CI: 38-99) Median 9 days (range 7-36)	93% (95%CI: 17-99) Median 12.5 days (range 8-46)	0.343
+180 Platelet Engraftment:			
Myeloablative	82% (95%CI: 69-90) Median 50 days (range 29-162)	88% (95%CI: 77-94) Median 45 days (range 29-137)	0.137
Non-myeloablative	87% (95%CI: 62-96) Median 34 days (range 9-59)	73% (95%CI: 40-90) Median 34 days (range 26-77)	0.229
+100 Grade II-IV aGVHD	46% (95%CI: 35-56)	53% (95%CI: 42-63)	0.505
+100 Grade III-IV aGVHD	22% (95%CI: 14-31)	13% (95%CI: 7-21)	0.166
+180 TRM	19% (95%CI: 12-28)	20% (95%CI: 13-29)	0.332
1-year PFS	63% (95%CI: 51-72)	61% (95%CI: 50-70)	0.760