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days post SCT. In summary, NAC and AlloSCT in patients with SCD using both related and unrelated donors has been shown to be well tolerated and effective in inducing a high degree of mixed donor chimerism.

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DONOR CHIMERISM KINETICS IN PEDIATRIC PATIENTS UNDERGOING REDUCED INTENSITY CONDITIONING (RIC) WITH ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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From 9/03–9/07 fifty-three children with malignant (n = 31) and non-malignant diseases (immune deficiencies, metabolic disorders, severe aplastic anemia, n = 22) underwent RIC HSCT; median age at time of HSCT was 8 years (1 month - 17 years). RIC included fludarabine 30 mg/m^2/d × 5 d and targeted (AUC 4000 micorMol*-min) single daily IV busulfanX2d (n = 4), + ATG(n = 34) or 2 weekly treatments of extracorporeal photopheresis (ECP, n = 12). Three received other fludarabine-based regimens. GVHD prophylaxis included CSA±MMF (n = 53), + post-HSCT ECP (n = 12). Neutrophil and platelet recovery were defined as 1st of three consecutive ANC > 500/μl and platelet count > 20,000/μl without transfusion. Lineage specific chimerism assays of total white cells(TW), T-cell (CD3), and myeloid cells (CD33) were monitored serially post-HSCT by variable number tandem repeats(VNTR) assays. Full donor chimerism (FDC) was defined as≥95 + 5%, subsequent loss of full donor chimerism was defined as a drop below 50%. Patients who did not reach 95% were termed mixed chimerism. Neutrophil recovery occured in 94% at a median of 18 days (4–39); one never fell below 500/μl. Platelet recovery was evaluated in 52; 54% did not fall below 20,000/ l, 40% reached 20,000/μl (median 20 days, 9 – 158), and 38% reached 50,000/μl (median 20.5 days, 11–142). Median cell doses per kilogram body weight were as follows: CD34 6.77 × 10^6 (0.12 – 25.8), MNC 4.84 × 10^8 (0.27 – 8.85), and TNC 8.15 × 10^8 (0.41 – 46.1). No correlation between cell dose and neutrophil recovery was seen; significant correlation was seen between cell dose and platelet recovery (CD34, p = 0.009, MNC, p = 0.05, TNC, p = 0.02). Patients who received RIC HSCT (Table 1) for malignant disorders when compared with non-malignant disorders showed a significant difference in achieving FDC in TW (p = 0.0002) and myeloid (p = 0.0002) cell lines. Two lost TW chimerism (malignant n = 1, day 46, non-malignant n = 1, day 340). 17/53 achieved mixed chimerism (malignant n = 4, non-malignant n = 13); those with malignant disease received second HSCT. Non-malignant patients remain free of disease (2nd HSCT n = 7). There is significant difference in achieving FDC in those pts with malignancies which may be attributed to prior therapy. Stable partial chimerism may be sufficient in pts with non-malignant diseases. Chimerism requires frequent monitoring; interventions such as changing immune suppression or donor lymphocyte infusions must be considered.

Table 1.

RIC With Allo-HSCT	FDC TW (%)	Median Time to FDC TW (days)	FDC T-cell (%)	Median Time to FDC T-cell (days)	FDC Myeloid Cell (%)	Median Time to FDC Myeloid (days)
All Patients (n = 53)	68%	48	69%	99	75%	29
Malignant Diseases (n = 31)	87%	33	82%	97	85%	26
Non-Malignant Diseases (n = 22)	41%	383	52%	169	48%	167
		p = 0.0002		p = 0.1		p = 0.0002

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ALTERNATIVE DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA USING CAMPATH IN A MYELOABLATIVE CONDITIONING REGIMEN

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Allogeneic transplantation from a matched sibling donor (MSD) offers curative therapy for pediatric patients with acute lymphoblastic leukemia (ALL); however, less than 30% of patients will have a MSD. Alternative donor (AD) transplantation is a viable option for these patients, but the risk for GVHD remains much higher. From 2001 to present, we have used Campath in the conditioning regimen for AD transplants to achieve *in vivo* T-cell depletion, in an effort to reduce the risk of GVHD. Here we report the outcome of pediatric ALL patients receiving AD transplants using Campath as part of a myeloablative conditioning regimen. Risk assessment is assigned prior to transplant – standard risk (SR) includes patients with ALL in 1st or 2nd complete remission. Since 1997, 39 patients with SR ALL were transplanted with MSD grafts, and since instituting Campath in 2001, 39 patients have received AD grafts. AD patients received bone marrow or peripheral blood stem cell products from up to 1 antigen mismatched related or unrelated donor. Myeloablative conditioning included cyclophosphamide, cytarabine arabinoside and total body irradiation (1200 cGy for MSD and 1400 cGy for AD) in all patients with the addition of Campath in the AD recipients. Additional GVHD prophylaxis consisted of FK506 or cyclosporine with either methotrexate or prednisone. All but one evaluable patient achieved neutrophil engraftment. The 5-year disease-free survival for patients with MSD was 83% compared to 60% for AD recipients. The 100-day mortality was 8% in the AD group and 3% in the MSD group. GVHD was low in the AD cohort – 13% developed grade II-IV acute GVHD and none developed extensive, chronic GVHD. Consistent with other published reports using Campath, we did observe a high incidence of viral infections – 28% developed adenovirus reactivation; 28% developed CMV reactivation; and 3% developed EBV-LPD. We conclude that Campath used with a myeloablative conditioning regimen offers a curative option for pediatric patients with acute lymphoblastic leukemia requiring alternative donor transplantation with a low incidence of GVHD.

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OUTCOMES OF UNRELATED UMBILICAL CORD BLOOD TRANSPLANTATION IN PEDIATRIC PATIENTS WITH MYELODYSPLASTIC SYNDROME

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Between 1995 and 2007, 24 pediatric patients were transplanted with unrelated donor umbilical cord blood (UCB). M:F ratio was 1.4; the median age was 10.5 years (range 1.11–19.73). Median time from diagnosis to transplant was 6.43 months (range 2.00–61.37). Patients were followed for a median time of 5.68 years (range 0.45–11.57). Eighty percent had primary disease. MDS stage was RA/RC 12 pts, RAEB 8 pts and RAEB-T 4 pts. Monosomy-7 was present in 18 (75%) patients. Patients with frank AML were excluded. Preparative regimen was TBI based in 19 (79%) patients while Melphalan was used in 14 (58%) patients. GVHD prophylaxis consisted of CSA/steroids (19 pts) and CSA/mycophenolate (5 pts). Grafts were selected for matching at HLA Class I (A and B) at low resolution and HLA Class II (DRB1) at the allelic level resulting in 17 (71%) 4/6 and 7 (29%) 5/6 matched transplants. The grafts contained a median of 4.22 × 10^7 (range 1.68–12.58) total nucleated cells (TNC)/kg pre-cryopreservation; 3.58 × 10^7 (range 1.01–12.00) TNC/kg and 1.71 × 10^5/kg (range 0.17–28.46) CD34+ cells were infused. Cumulative incidence of neutrophil engraftment (ANC > 500/μL) at Day 42 and Day 100 was 70.8% (95% CI 51.8%-89.8%) and 92.7% (95% CI 75.5%-100.0%), respectively, and that of platelet engraftment (50K) at 180 days was 66.7% (46.9%-86.5%). Three pts had graft failure while 4 pts (16%)

engrafted slowly, after Day 42, perhaps related to some underlying marrow dysfunction caused by MDS. Four patients developed acute GvHD grades II-IV with a cumulative incidence at 100 Days of 16.7% (95% CI 1.4%-32.0%). Four patients relapsed with a CI of relapse at 3 years of 15.0% (95% CI 0.0%-31.5%). Cumulative incidence of non-relapse mortality at 1 year was 26.1% (95% CI 7.7%-44.5%). Nine pts died: 4 of infections (2 EBV, 1 adenovirus, 1 toxoplasmosis), 2 of graft failure, 2 of relapse, and 1 of MSOF. Overall survival probability at 1 and 3 years were 70.4% (95% CI 51.9%-88.8%) and 59.5% (95% CI 38.7%-80.4%) respectively. Event-free survival (EFS) probabilities at 1 and 3 years were 70.8% (95% CI 52.6%-89.0%) and 59.9% (39.2%-80.7%), respectively. Factors associated with better EFS were age $\leq$ 10 years ($p = 0.03$) and weight $\leq$ 38 kg ($p = 0.02$). These results, especially in younger patients with Monosomy 7 and MDS, are equivalent to matched allogeneic bone marrow transplant data. UCB should be actively considered for pediatric MDS patients lacking matched related or unrelated adult donors.

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THE ADDITION OF ETOPOSIDE TO Bu_{16}/Cy_{200} IN THE CONDITIONING OF CHILDREN WITH ACUTE MYELOID LEUKEMIA (AML) UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) IS ASSOCIATED WITH IMPROVED SURVIVAL

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Relapse remains the major concern for children with AML undergoing SCT, and we have previously shown that intensifying the conditioning by adding etoposide at 60 mg/kg and consequently reducing the busulfan (Bu) dose to 12 mg/kg and the cytoxan (Cy) to 90 mg/kg did not result in any significant improvement of the survival; we suggested then that the reduction of Bu/Cy doses necessitated by addition of the high dose of etoposide could have affected the outcome and we hypothesized that adding a lower dose of etoposide and keeping the Bu/Cy at the conventional doses may offer better survival to AML patients undergoing allogeneic SCT. We present here our results using such a protocol.

Patients and Methods: From March 2003 until December 2006, 33 patients with AML (24 in CR1, 8 in CR 2) underwent allogeneic SCT and were conditioned with Bu 16 mg/kg po, Cy 200 mg/kg iv plus etoposide 900 mg/m^2 iv, median age was 9.6 years. This cohort of patients (group B) was compared with 18 AML patients (17 in CR 1, 1 in CR 2) who underwent SCT from July 93 thru February 96, median age at SCT was 7.25 years, patients were conditioned with only Bu 16 mg/kg po and Cy 200 mg/kg iv (group A). **Results:** Median days to ANC $\geq 500 \times 10^6$/l was 21 days and 15 days in groups A and B respectively, median days to platelet count $\geq 20 \times 10^9$/l was 22 days and 26 days in groups A and B respectively (P= NS). The incidence of complications was similar, acute GVHD grade 2 or higher developed in 5% and 9% in groups A and B respectively (P= NS), hemorrhagic cystitis developed in 11% and 15% in groups A and B respectively, no VOD developed in either group. The 4 year overall survival for groups A and B respectively was 50% and 68.2% ($P = 0.3$) and the 4 year event-free survival for groups A and B respectively was 33% and 68.2% ($P = 0.1$). **Conclusions:** The addition of etoposide to Bu_{16}/Cy_{200} was not associated with increased toxicity, and although it did not reach statistical significance, it does appear to be associated with a better overall and event-free survival. Larger scale studies are advised to further corroborate our findings.

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SINGLE DAILY DOSE (SDD) BUSULFAN (BU) IN CHILDREN: COMPARISON OF PHARMACOKINETICS (PK) AND ENGRAFTMENT BETWEEN ACUTE LEUKAEMIA (AL) AND NON MALIGNANT DISEASE (NM)

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Methods: We studied BU PK, engraftment and survival in children who underwent allogenic BMT for NM (n = 33) or AL (n = 41) after BU-based conditioning. The dose of oral BU was 4 mg/kg (n = 16) or 150 mg/m^2 (n = 32) and intravenous (IV) 3.2 mg/kg (n = 3), 120 mg/m^2 (n = 3) or 130 mg/m^2 (n = 20). In 62 cases, blood was collected after the first dose, BU levels were measured and BU area-under-the-concentration-versus-time curve (AUC) was determined using the Kinetica software (Innaphase, USA), then normalized to 130 mg/m^2 for IV BU and 150 mg/m^2 for oral BU. PK-guided dose adjustments were made in 7 patients with NM. Total exposure to BU was determined by dividing first dose AUC by first dose (mg) and then multiplying by the total dose (mg) administered. **Results:** In the NM group, 26(79%) are still alive. 5 (of 7) deaths occurred early (<118 d post BMT) due to transplant-related causes: VOD (1), VOD and GVHD (2), GVHD (1) and sepsis (1). Full engraftment was achieved in all but 5 patients (85%): 2 had stable mixed chimerism (MC) >95% donor, 3 had inadequate engraftment; 4 of these were part of a group of 12 who had T cell depletion. Total Bu exposure ranged from 57 to 146 mg/L.h (median 90 mg/L.h). In the AL group, 29 (71%) are still alive, with 4 early transplant-related deaths from GVHD (2), relapse (1) and sepsis (1). Full engraftment was achieved in all but 3 patients (93%): 2 children had MC and one of these subsequently lost the graft, another was fully donor but died prior to obtaining full haematological recovery. Total Bu exposure ranged from 40 to 345 mg/L.h (median 99 mg/L.h). Results of the normalised AUC (nAUC) in mg/L.h are shown in the table. nAUC was significantly higher in the oral BU group (n = 36) than in the IV BU group (n = 26): 27 $\pm$ 6 mg/L.h versus 23 $\pm$ 8 mg/L.h, $p < 0.01$. **Conclusions:** Single daily dose BU is generally safe and effective for use in children with AL and NM. A dose of 130 mg/m^2 IV gives less exposure than 150 mg/m^2 oral. Wide variability in BU pharmacokinetics indicates a need for measurement and perhaps targeting in some patients, especially those with immune deficiencies or those more likely to reject.

normalised AUC (nAUC) mg/L.h

Diagnosis:	Genetic	SCID	non-SCID	AL
IV Bu				
nAUC (range)	**20–44**	**14–50**	**18–31**	**14–30**
median	**23**	**16**	**21**	**18**
fold variation	**2.2**	**3.6**	**1.9**	**2.2**
n	**6**	**3**	**7**	**10**
Oral Bu				
nAUC (range)	**15–38**	**18–25**	**27–36**	**15–43**
median	**25**	**25**	**30**	**28**
fold variation	**2.5**	**1.4**	**1.3**	**2.9**
n	**9**	**3**	**4**	**20**

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FUNGAL INFECTIONS: A SURVEY OF PEDIATRIC SURVEY OF PEDIATRIC BLOOD & MARROW TRANSPLANT CONSORTIUM INSTITUTIONS

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This survey was designed to identify the fungal infection management used for the pediatric BMT patient and to develop a standard of care for fungal infection management by institutions within the Pediatric Blood & Marrow Transplant Consortium (PBMTC).

Twenty five percent of the surveys were returned. 100% of the institutions performed allogeneic and autologous transplants. Nonmyeloablative transplants were performed by 89% of the institutions.

All institutions used some type of fungal prophylaxis during transplant, 77% used fungal prophylaxis on all their transplant patients. 50% of the centers differed on the prophylaxis used in the BMT sub-groups, with 85% of the centers using Fluconazole, and 15% of the institutions using no prophylaxis in autologous patients. 100% of centers administered prophylaxis to the allogeneic transplant group. The break down of agents utilized in the allo-graft group was Fluconazole (47%), Voriconazole (23%) and low dose