There were 22 males, 18 females, ages 7 mo – 18.7 yrs, median 5.5 years. Stem cell sources for the msibs were marrow for 7 and PBSC for 11. Conditioning regimen was fTBI based in 25, busulfan based in 15–of those, 5 were reduced intensity. Graft-versus-host disease prophylaxis included cyclosporin A and either methotrexate (n = 35) or mycophenolate (n = 5). Disease status at time of HSCT was CR1 in 23, 11 were in CR2 and 6 had evidence of residual AML (~5% by morphology or [+] cytogenetics).

The median time to reach an ANC > 500/μl was 18 days (29 days for UCB vs 12 after m/PBSC). An unsupported Plt Ct > 20,000/μl was achieved in 36 pts at a median of 21 days (49 for UCB vs 13 after m/PBSC). 4 UCB pts failed to engraft with donor hematopoiesis. 14 pts developed Gr II-IV acute GVHD, 8 of the 35 pts surviving more than 100 days developed chronic GVHD (2 limited, 6 extensive). 9 UCB and 5 m/PBSC pts developed acute GVHD. 7 m/PBSC patients but only 1 UCB patient developed chronic GVHD.

Overall survival (OS) rates 3 years post HSCT were similar when comparing UCB recipients (63%) versus combined matched m/PBSC donors (78%), respectively. This result is despite the higher proportion of CR2 and PR patients in the UCB cohort (64 vs 17%). OS of patients in CR1 and CR2 at the time of HSCT are 87 % and 43 % respectively.

Table 1. HSCT for Pediatric AML-msib v UCB

	All pts, n=40	Matched sibs, n=18	UCB, n=22
Male–Female	22–18	12–6	10–12
Age (yrs, median +/− sd)	5.5 +/− 5.6	11.6 +/− 5.7	3.5 +/− 4.2
Weight (kg, median)	21	38	15
Diagnosis to HSCT (mo, median)	5.1	3.5	6.4
CR1	23	15	8
CR2 or PR	17	3	14
fTBI-VP-CY	25	8	17
Bu4-CY+/−VP	10	6	4
Flu-Bu2 +/− ATG	5	4	1
ANC engraft (days, median)	18	12	29
Platelet engraft (days, median)	21	13	49
Non-engraft	4		4
TRM	5	1	4
Relapse	8	4	4
Overall Survival (%)	69	78	63

Our experience supports continued consideration of allogeneic HSCT for pediatric AML in CR1 utilizing matched sibling donors. The results using unrelated UCB stem cell sources suggest that young AML patients lacking a msib donor should search for an UCB match and consider that option for HSCT in CR1. Methods to enhance engraftment/limit rejection of UCB could potentially further improve the results using UCB stem cells.

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HIGH DOSE CARBOPLATIN, ETOPOSIDE, MELPHALAN AND AUTOLOGOUS HEMATOPOIETIC STEM CELL RESCUE WITH FOR THE TREATMENT OF RELAPSED PEDIATRIC GERM CELL TUMORS

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High dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) is the treatment of choice for relapsed or refractory germ cell tumors (GCT) but few pediatric patients are included in most reports. Our objective is to describe the institutional experience with autologous HSCT for GCT.

Results: From November, 2001 to October, 2010, 11 patients with GCT underwent HSCT after conditioning therapy with carboplatin (425 mg/m^2/day x 4 days), etoposide (337.5 mg/m^2/day x 4 days) and melphalan (70 mg/m^2/day x 2 days) - doses for children older than 2 years of age and with normal renal function. Their median age was 12.5 years (2-19)and seven were female. One had primary central nervous system (CNS) tumor, 6 gonadal and 4 extra-gonadal tumors. Most patients had been treated according to the Brazilian GCT Protocol-99 and received TIP – paclitaxel, ifosfamide and cisplatin as second line chemotherapy. One patient was in the first remission of a testicular tumor with trophoblastic component and multiple brain and lung metastases; seven were in second remission; one was in third remission and two had refractory disease with partial response to therapy. All patients had a normal bone marrow aspirate and biopsy prior to stem cell collection. Eight patients had peripheral blood stem cell harvest, one marrow, and one both, for a target cell dose of 5 million CD34 cells/kg. All patients had febrile neutropenia (seven also had positive blood cultures), oral mucositis (all needed IV morphine) and diarrhea. One 3-year-old girl in second remission had a CNS bleeding and died two months after HSCT. Five patients had disease progression or relapse, three of them with advanced diseases. Five patients are alive in complete remission with a median follow up of 6.8 years (2-8 years). In conclusion, GCT is a rare indication of autologous HSCT in pediatrics (11/123 autologous transplants in 10 years). Despite acceptable results in adults with refractory diseases, the best timing for autologous transplantation in pediatrics seems to be second remission. Carboplatin, etoposide and melphalan, the same regimen that has been used for many years for stage 4 neuroblastoma, is associated with considerable toxicity but four of six evaluable patients with GCT in second remission remain tumor-free more than six years after transplant.

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FLUDARABINE, BUSULFAN, AND ALEMTUZUMAB AS A REDUCED TOXICITY REGIMEN FOR CHILDREN WITH MARROW STEM CELL DEFECTS AND MALIGNANCY IMPROVES ENGRAFTMENT AND GRAFT VERSUS HOST DISEASE WITHOUT DELAYING IMMUNE RECONSTITUTION

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For many children with malignancies and MSCD, allogeneic hematopoietic cell transplant (HCT) provides the best chance of cure. However, toxicity of conditioning and graft failure remain challenges. We previously reported that busulfan, fludarabine and rabbit ATG conditioning (total dose = 8mg/kg) resulted in less toxicity but no improvement in engraftment rates. Alemtuzumab has been shown to enhance engraftment and reduce rates of GVHD in myeloablative regimens. Thus, we prospectively evaluated targeted IV busulfan, fludarabine and Alemtuzumab (total dose = 1.5mg/kg) in a Phase II study of children receiving closely matched related or unrelated HCT. Thirty-five children were enrolled: 5 with malignancies and 30 with MSCD. Twelve donors were HLA matched relatives, 16 were fully HLA allele-matched unrelated donors and 7 were 9/10 HLA allele-matched unrelated donors. No patient had more than a Grade 2 reaction to Alemtuzumab. The most common toxicity (n = 15) was Grade 3 mucositis. One patient had Grade 4 mucositis. Only 1 patient developed VOD (Grade 3). 11/15 CMV seropositive patients had reactivation and 3/17 CMV seronegative patients had primary CMV infection. None developed CMV disease. Thirty-one of 34 (88%) evaluable patients achieved durable engraftment. Neutrophil recovery occurred at a median of 16 days (range 10-25). Three patients (2 mismatched at 1 antigen) with MSCD failed to engraft from unrelated donor HCT and underwent subsequent transplants. One is alive and progression free. For those successfully engrafted, the median time to CD4 > 200x10e6cells/L and PHA > 50% was 6 months with a maximum of 9 months. At 1 year post transplant, 18/19 evaluable patients had 87% or more donor chimerism in whole blood, CD14/15+ and CD19+ subsets and 71% or more donor chimerism in the CD3+ subset. One patient had only 55% whole blood donor chimerism at 1 year but ultimately achieved 82%. Six patients developed acute Graft versus Host Disease (GVHD) of Grade 2-4 with only 1 patient progressing to chronic GVHD. Seven patients had disease progression/relapse with 1 dying from disease. Four patients died of Transplant Related Mortality (11%). At a median follow up of 29 months (range 3-74), the EFS was 60+/− SE9% with an Overall Survival of 81+/

−SE6%. These results suggest that replacement of rabbit ATG with Alemtuzumab may improve engraftment and decrease GVHD rates without resulting in delays in immune reconstitution.

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CYSTATIN C IS A MORE SENSITIVE ESTIMATE OF KIDNEY FUNCTION THAN CREATININE IN PEDIATRIC AUTOLOGOUS BONE MARROW TRANSPLANTATION

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Overview: Accurate assessment of kidney function is essential in the care of bone marrow transplant (BMT) patients. Both cystatin C, a protease inhibitor produced by all nucleated cells and measured in a single blood sample, and creatinine are used to estimate kidney function (glomerular filtration rate, GFR). While creatinine is influenced by muscle mass, cystatin C is potentially modified by corticosteroids, thyroid function, and the white blood cell count (WBC). The literature is conflicting on the validity of cystatin C measurements in BMT and oncology patients, and the effect of leukopenia is understudied. We hypothesize that cystatin C is a more sensitive estimate of kidney function in BMT patients, while controlling for the WBC.

Methods: We retrospectively compared cystatin C to creatinine for predicting nuclear GFR (technetium-99m-DTPA; nucGFR) in pediatric recipients of autologous BMTs. General linear mixed models were used to calculate regression and intra-class correlation coefficients (ICC, ranging from 0-1 with higher values indicating less variation/greater reliability between the estimates). Prediction models used cystatin C GFR = [77.24*cys$^{-1.2623}$] (cysGFR), with and without WBC, and Schwartz GFR = [0.413*height (cm)/creatinine] (schGFR).

Results: 12 patients (median age 3.5 yrs, range 2-10 yrs) underwent 29 tandem BMTs (median 2 BMTs/patient, range 1-4) for medulloblastoma (n = 7), neuroblastoma (n = 4), and atypical teratoid rhabdoid tumor (n = 1). All patients except 1 had normal thyroid function. 3 patients received steroids (2 stress dosing and 1 high-dose for veno-occlusive disease of the liver). GFRs (mean±std error) in ml/min/1.73m^2 (normal > 90) were 142.0±9.0 (nuc), 136.5±6.2 (cys), and 132.1±5.1 (sch). ICCs were 0.54 for nucGFR versus cysGFR and 0.26 for nucGFR versus schGFR. Furthermore, the Pearson correlation coefficient was much higher for cysGFR (0.80, $p < 0.001$) than for schGFR (0.22, $p = 0.36$) compared to nucGFR. Regression coefficients and the 95% confidence intervals (CI) for the prediction models are shown in the table.

Conclusions: Cystatin C was a statistically significant predictor of nucGFR while creatinine was not. WBC was of borderline significance in prediction of nucGFR using cysGFR. To maximize clinical utility, future research will confirm these findings by accounting for additional confounders in a larger group of patients and a wider range of GFR.

Independent predictors in model for nucGFR	β regression coefficients [95% CI]
cysGFR*	0.96 [0.77, 1.14]
cysGFR* & WBC	1.08 [0.94, 1.23] & 0.67 [-1.02, 2.36]
schGFR	0.17 [-0.072, 0.41]

*statistically significant ($p<0.05$)

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A MULTIDISCIPLINARY APPROACH TO ADHERENCE IMPROVEMENT USING EDUCATION AND MEDICATION BOXES FOR ADOLESCENTS AND YOUNG ADULTS WHO HAVE UNDERGONE ALLOGENEIC HEMATOPOEITIC STEM CELL TRANSPLANTATION

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Achieving adherence to immunosuppressive medications in the adolescent population of post allogeneic stem cell transplant can be challenging. Literature has documented consistently a link between regimen complexity and adherence rates. Non-adherence can put patients at increase risk of uncontrolled graft versus host disease. While there is literature describing adolescent barriers to adherence and their attitudes regarding medications, no studies have evaluated the use of medication boxes in combination with a multidisciplinary patient education on adherence. A pilot study was undertaken to see if use of a medication box combined with a 15 minute discussion with a pharmacist and social worker about barriers to adherence, the importance of medication adherence, and how to use the box will improve adherence in adolescent post allogeneic stem cell transplant patients. Medication boxes were initially filled by a health care professional on the patients' clinic day. Pill counts were used to assess adherence rates. Patients completed surveys about their perception on their medications prior to, during, and after the intervention. 11 patients consented to study to date (ages 13-25); 1 patient withdrew, 1 patient died prior to start of the study, and 1 patient has yet to start. During the active medication box phase of the study, patient's adherence rates ranged from 57-100% with all but one patient having an adherence rate > 80%. When study participants where asked if they do a good job caring for themselves 7 out of 9 responded positively (somewhat to strong agreement); although, 5 out of 8 reported missed doses at least once during the study duration. Of note, 6 out of 9 participants at some point during the study duration reported agreement or neutrality to the statement 'I don't think I need my medication' and 8 out of 9 patients reported agreement or neutrality to the statement 'My doctors want me to take too many medications'. These findings are of interest because they may reflect unique characteristics of adolescent development, how their views on their health and medications may change throughout a treatment course, which may have direct effect on medication adherence. This pilot study supports the use of medication boxes for adolescents post allogeneic stem cell transplantation. Further studies need to be done to assess what patients would most benefit by having their medication box filled for them.

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ENGRAFTMENT KINETICS IN CHILDREN AFTER REDUCED INTENSITY CONDITIONING HEMATOPOIETIC STEM CELL TRANSPLANTATION (RIC-HSCT)

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The kinetics of stem cell engraftment following RIC-HSCT are different from that of myeloablative transplant; previous analyses are limited to adults. Between 2003 and 2010, we performed RIC-HSCT in 88 children with malignant (n = 40) or non-malignant (48) diseases; none had prior HSCT. Patient characteristics are shown in Table 1. Post-HSCT, total white cells donor chimerism was monitored serially by variable number tandem repeat analysis once the peripheral white blood cell count exceeded 1,000 cells/ml. The cumulative incidence of patients reaching 50% and 90% donor chimerism by +20/40/60 days post-HSCT was 67/85/86% and 41/68/72%, respectively. Eight patients (8/88 = 9%) had primary graft failure, with chimerism never reaching 20%. Sixty-six patients (75%) have peak chimerism over 90%, whereas 14 patients (16%) have peak chimerism between 20-90%. Among those engrafted (n = 82), chimerism in 57 patients (70%) was durable and did not decline with time, but in 25 patients (30%), there was a drop in chimerism of > 10% between two consecutive measurements. Median time of chimerism drop was +60 days post-HSCT (range 17-193 days). Seven patients (7/82 = 8%) experienced relapse of leukemia soon after the drop was detected, 12 patients (15%) had stabilization or improvement of chimerism after withdrawal of immunosuppression and/or donor lymphocyte infusion (DLI), and 6 patients (7%) had no recovery despite immune manipulation, resulting in secondary graft failure. There is no correlation between the magnitude of chimerism drop and the response to immune manipulation. There were differences in engraftment kinetics among patients with malignant or non-malignant diseases. In the malignant group, the cumulative incidence of 90% donor chimerism at +100 days was 87.5%, and at one year, the percentage of patients with full or mixed chimerism was 90% and 10%, respectively. By contrast, in the non-