iron overload pre-HSCT who required aggressive iron management post-HSCT. Liver iron concentration (LIC), a surrogate of total body iron burden, was assessed by liver biopsy and/or magnetic reasonance imaging (T2* or R2 MRI). Abnormal LIC was defined as >1.5 mg iron/g dry liver tissue. **Results:** Patient characteristics are presented in Table 1. 7 out of the 11 patients identified were not previously known to have iron overload. The majority of these patients presented with elevations in liver transaminases as the primary sign of excess iron. Liver biopsy and/or MRI were used to diagnose iron overload, and in all cases MRI was the method used to assess the change in iron burden while patients were receiving therapy. Most patients were managed with phlebotomy (range: 4–10 cc/kg of blood removed every 2–4 weeks). Phlebotomy was effective in reducing iron burden as evidenced by normalization of transaminases and decrease in LIC and ferritin. One patient, managed with an oral iron chelator, did not have a reduction of overall iron burden. **Conclusions:** . Iron overload should be considered in HSCT patients presenting with abnormal transaminases and/or hyperferritinemia after transplant. MRI is a useful diagnostic tool and may obviate the need for invasive liver biopsy. Phlebotomy appears to be effective in reducing iron burden, however the safety and efficacy of chelators is not yet established. There is a need for prospective studies to define the prevalence of iron overload, establish guidelines for screening, and develop safe and effective therapies. As a result, we have initiated a prospective study using R2 MRI to determine the incidence and morbidity associated with iron overload in this patient population.

Characteristics of Patients With Iron Overload

Number	Diagnosis, Age	Type of HSCT	Condition Leading to Iron Overload Diagnosis	Managment of Iron Overload	LIC pre/post treatment (mg iron/g liver)	ALT max/min (u/L)	Ferritin max/min (ng/mL)
1	Relapsed ALL, 1 yo	MURD	Abnormal LFT's	Phlebotomy	7.3/4.0	254/38	2,896/449
2	PNH, 18 yo	MURD	Abnormal LFT's	Desferasirox	10.7/13.6	910/56	5,127/2,527
3	Relapsed ALL, 6 yo	MURD	Abnormal LFT's	Phlebotomy	5.1/1.9	404/57	4,071/796
4	Relapsed ALL, 10 yo	MURD	Abnormal LFT's	Phlebotomy	16.0/–	314/53	5,586/2,350
5	Sickle Cell Anemia, 9 yo	MRD	Abnormal LFT's	Phlebotomy planned	4.9/–	313/–	1,810/–
6	AML, 4 yo	MRD	Hyperferritinemia	Phlebotomy planned	5.1/–	70/–	1,938/–
7	ALL, 12 yo	4/6 Cord	Abnormal LFT's	Phlebotomy planned	13.0/–	209/–	3,645/–
8	Diamond-Blackfan Anemia, 9 yo	MRD	Chronic transfusion history	Phlebotomy	17.5/0.9	13/4	1,029/119
9	Aplastic Anemia, 6 yo	MRD	Chronic transfusion history	Phlebotomy	22.5/–	35/20	4,574/2,824
10	Beta-thalassemia, 8 yo	MRD	Chronic transfusion history	Phlebotomy	7.0/–	38/31	3,900/658
11	Beta-thalassemia, 7 yo	MRD	Chronic transfusion history	Phlebotomy planned	8.6/–	94/41	1,888/–

Abbreviations: PNH = Paroxysmal Nocturnal Hemoglobinuria, ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia, MURD = Matched Unrelated Donor, MRD = Matched Related Donor, ALT = Alanine Aminotransferase.

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CHALLENGES IN THE USE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY

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Genetic mutations affecting regulatory proteins of NF-κB result in heritable diseases of development and immunity. Hypomorphic, X-linked mutations in the *IKBKG* gene (NEMO protein), and hypermorphic, autosomal dominant mutations in the *IKBA* gene (IκBα protein), are associated with a phenotype of ectodermal dysplasia with immune deficiency (ED-ID). ED-ID predisposes patients to bacterial and mycobacterial infections, and is typically fatal. Allogeneic HSCT may correct the immune deficiency associated with NEMO or IkBα mutations, but there are few reports. We report 3 patients with ED-ID who underwent HSCT. All patients experienced engraftment difficulties. Patient 1 presented with fevers, diarrhea, diffuse erythema and desquamation. Hypogammaglobulinemia with normal B- and T- cell numbers and subsets were noted, and genetic analysis revealed a hypomorphic NEMO mutation. He received matched sibling donor peripheral blood stem cells (PBSC) at 6 months following reduced-intensity conditioning with fludarabine, busulfan and ALG. Neutrophil engraftment was achieved at day +17, and maximal donor T-cell chimerism of 53% at day +77, which then declined. A second PBSCT from the same donor was undertaken after conditioning with alemtuzumab, fludarabine and melphalan, with stable donor chimerism through day +310. Patient 2 developed diarrhea, failure to thrive and recurrent infections including MAI. Inadequate antibody responses, but normal B- and T- cell numbers and subsets were noted. Genetic analysis demonstrated a hypomorphic NEMO mutation. A MUD BMT was performed at 3 years of age following myeloablative conditioning with busulfan, cyclophosphamide and ALG. Poor engraftment was noted, with persistent neutropenia despite chimerism of 95% donor at day +38. The patient was re-conditioned with fludarabine, and a CD34-selected PBSC boost from the same donor. Although complete chimerism was achieved, the patient remained pancytopenic and died at day +314 of gram-negative infection. Patient 3 presented with recurrent bacterial infections, p.carinii, and chronic diarrhea. Genetic analysis confirmed an IκBα mutation. The patient underwent a MUD cord blood transplant following myeloablative conditioning with busulfan and cyclophosphamide, but expired from sepsis prior to engraftment. These cases suggest that patients with immune deficiencies caused by NEMO or IκBα mutations may have intrinsic barriers to successful engraftment, which require further investigation.

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LOWER LEUKEMIA RELAPSE IN PATIENTS WITH PULMONARY CYTOLYTIC THROMBI AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT

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Pulmonary cytolytic thrombi (PCT) is an uncommon post-transplant complication, which is more commonly reported in children than adults. PCT typically presents with low grade fever, cough, shortness of breath and/or hypoxia. Lung CT findings range from small, peripheral nodules to large diffuse infiltrates. The diagnosis is established by lung biopsy, which reveals areas of the pulmonary vasculature which are occluded with cellular debris. Bronchoscopy and lung biopsy are negative for infectious organisms by both immuno-stains and culture. While the pathogenesis of PCT is not currently known, it has been previously shown that patients with PCT frequently have concurrent aGVHD and that PCT responds to systemic corticosteroid treatment. Considering that such treatment may impair graft vs. leukemia (GVL) reactions, we investigated the outcome of patients who developed PCT after transplantation for hematological malignancy. From 1993–2006, we identified 14 pediatric patients with biopsy proven PCT and a hematological malignancy (9 ALL, 3 AML and 2 CML). PCT was diagnosed at an average of 90+/-38 days (range 38–342) after transplant. We compared outcomes to a cohort of pediatric leukemia patients that not develop PCT, but were transplanted during the same time interval (n = 323). There were no significant differences

between the two groups with respect to age, gender, disease type, or CMV status. Likewise, there were no significant differences between the PCT and control groups with respect to donor source (related vs. unrelated), progenitor cell source (BM vs. UCB) or HLA disparity. In this cohort, PCT patients were more likely to have grade II-IV aGVHD (86 vs. 35%, p = 0.01) and grade III-IV aGVHD (35 vs. 15%, p = 0.03). Similarly, PCT patients were more likely to have cGVHD (36% vs. 13%, p = 0.01). The cumulative incidence of non-relapse mortality and overall survival at 5 yrs, however, was similar in both groups (p = 0.29 and p = 0.12, respectively). In univariate analysis, a significantly lower risk of relapse at 3 years was noted in patients with PCT (0% vs. 30% [25–36%], p = 0.02). In Cox regression, aGVHD (p = 0.05), cGVHD (p = 0.01) and development of PCT (p < 0.01) were associated with protection form relapse. Of the 6 deaths in the PCT group, 5 patients had pulmonary complications at the time of death. Collectively these data suggest that patients with PCT are at high risk for cGVHD and pulmonary associated toxicity, but lower risk of relapse.

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HYPERCALCEMIA AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR OSTEOPETROSIS

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Osteopetrosis (OP) is a clinical syndrome characterized by insufficient osteoclastic activity resulting in defective bone resorption and marked increase in bone density. The recessive form of osteopetrosis ("malignant osteopetrosis") has been successfully treated with allogeneic hematopoietic cell transplantation (HCT), secondary to engraftment of donor-derived functioning osteoclasts resulting in bony remodeling and establishment of normal hematopoiesis. While hypocalcemia is a common presenting feature of recessive osteopetrosis, hypercalcemia may be observed following HCT due to rapid engraftment of osteoclasts differentiated from the hematopoietic precursors. To investigate the incidence of hypercalcemia after HCT, we have evaluated nine patients with osteopetrosis (a median age of 2 years, range 0.5 – 28 yrs) treated at the University of Minnesota during a 7 year period (2000–2007). Eight patients were receiving their initial transplant, and one patient received a second HCT, following graft failure. The conditioning regimen consisted of busulfan, fludarabine, equine ATG and total lymphoid irradiation. Donor grafts consisted of URD BM (2), URD UCB (3), REL PBSC (2), and URD PBSC (2). All patients that received a BM or PBSC graft engrafted with donor grafts, while recipients of UCB had a transient partial engraftment followed by autologous recovery. The median day of myeloid recovery (defined as an absolute neutrophil count of 500 or above for 3 consecutive days) was day 20 (range 14–42 days). Elevated calcium levels were found in three of the nine patients. The elevation of calcium levels was observed at a median day 12 (range 10–15) which correlated with initial count recovery. The median day of highest calcium levels in these three patients was day 21 with a mean calcium level of 12.9 mg/dL (SD 1.18). Clinically, hypercalcemia was managed with intravenous fluids, furosemide diuresis and calcitonin. The median age of the group of patients with hypercalcemia was 24 years. In contrast the median age of the patients that didn't experience hypercalcemia was 1 year of age. No correlation was found between hypercalcemia and type of donor graft, HLA match, or $CD34^+$ cell dose. The implications of the current study are that hypercalcemia occurs after HCT in approximately one third of the OP patients and that it may be more common in older patients, perhaps due to age dependent increase in bone mass.

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TOLERABILITY OF DAPSONE IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT

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Dapsone is a commonly used drug for pneumocystis carinii pneumonia (PCP) prophylaxis in pediatric Hematopoietic Stem Cell Transplant (HSCT) patients. However, its use is frequently limited by toxicities such as hemolysis and methemoglobinemia. We performed a retrospective medical record review of all pediatric HSCT patients at our institution between January 1, 2001 and June 8, 2007. We identified all patients that received dapsone as PCP prophylaxis and documented course limiting adverse effects. 402 patients received 447 transplants during the study period. Dapsone was prescribed as PCP prophylaxis in 111 instances (24.8%). In 27.9% of these instances patients completed the recommended course without incident. 72.1% of the time patients were changed to an alternative prophylactic agent due to dapsone-associated adverse events. Hemolysis was the most common reason for discontinuation of dapsone and it occurred in 41(36.9%) cases. Methemoglobinemia was the second most common adverse effect and it occurred in 27 (24.3%) instances. The mean methemoglobin level for this group was 4.4% with a range of 2.2–16% (upper limit of normal at our institution is 1.5%). Dapsone was discontinued in the remaining patients because of rash (7), increased liver function tests (1), and tachycardia and vertigo (1). Three patients were lost to follow-up. In patients who received dapsone there were no documented cases of PCP. Dapsone was an effective, yet poorly tolerated agent in this group of pediatric stem cell transplant patients. Providers should maintain a high level of awareness for toxicities when utilizing dapsone in pediatric stem cell transplant patients.

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PRELIMINARY RESULTS OF NON-ABLATIVE CONDITIONING (NAC) WITH BUSULFAN (Bu), FLUDARABINE (Flu) AND ALEMTUZUMAB FOLLOWED BY ALLOGENEIC STEM CELL TRANSPLANTATION (AlloSCT) TO INDUCE MIXED DONOR CHIMERISM IN PATIENTS WITH SICKLE CELL DISEASE (SCD)

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SCD is associated with a decrease in lifespan and quality of life in children. The only known cure is AlloSCT from a matched family donor with only 15% of patients having an unaffected, HLA-matched identical sibling. Patients undergoing myeloablative AlloSCT are at risk for numerous complications post SCT including death, graft versus host disease (GVHD), and infections. Full donor chimerism is not necessary to correct the underlying genetic defect and eliminate symptoms in patients with SCD. In this study, we report the preliminary results of NAC and AlloSCT from related matched family and unrelated umbilical cord blood (UCB) donors in 7 patients (7M:0F) with high risk SCD (HbSS = 4, HbSC = 2, HbSßThal = 1). Conditioning was Bu (4 mg/kg × 4 d ≤ 4 yrs and 12.8 mg/kg × 4 d > 4 yrs), Flu (30 mg/m^2 × 6 d), and Alemtuzumab (2 mg/m^2 × 1 d, 6 mg/m^2 × 2 d, and 25 mg/m^2 × 2 d). UCB recipients also received rabbit antithymocyte globulin (2 mg/kg × 4 d). Mean age was 5.8 years +/-4.03 (1.4–13.75 years). Donor sources were: 2 6/6 HLA-matched sibling bone marrow (BM), 2 6/6 HLA-matched UCB, and 3 4/6 unrelated UCB. Mean cell dose was 12.02+/-13.0 × 10^7 TNC/kg and 1.03+/-1.66 × 10^6 CD34/kg. Patients received tacrolimus and mycophenolate mofetil as GVHD prophylaxis and phenytoin as seizure prophylaxis for 180 days post SCT. Of 5 patients evaluable for myeloid recovery (1 did not nadir, 1 too early), mean neutrophil and platelet recovery was on day +30 ± 7(n = 5) and day +60 ± 18(n = 5), respectively. One patient had primary graft failure at day +60 post SCT (Bu steady state concentration (Css) 552 ng/ml). Busulfan pharmakokinetics were then changed to maintain Css between 600–900 ng/ml. Mean whole blood donor chimerism on days +30, +60, and +100 was 49% ± 33(n = 6), 61% ± 32(n = 5), and 82% ± 13(n = 4), respectively. More recently, erythroid engraftment (CD71) is being determined. Mean CD71 chimerism on days +30 and +60 was 55.3% ± 41(n = 3) and 61.1% ± 17.5(n = 3), respectively. Hb electrophoresis was done on all patients with mean %HbS levels of 1.80 ± 1.02(n = 5) and 7.46 ± 9.88(n = 5) on days +30 and +100, respectively. Grades II-IV acute GVHD was seen in 3/7 patients(42%). Chronic extensive GVHD was seen in 1/5(20%) patients. All patients are alive with the longest follow up being 1120