relative or Matched Related Donor (MRD). From 1990 to 2007, a total of 15 pediatric or young adult patients with MDS received bone marrow or cord blood transplant from an HLA matched sibling at our institution. M:F ratio of the study group was 0.9; Two patients belonged to ethnic minorities (13%); the median age at transplant was 13.4 years (range 1.1-20.6) and median weight was 54.9 kg (range 10.8-80.2). Three patients had therapy-related MDS (2 ALL, 1 NHL). MDS stage was RA/RC in 2 pts, RARS in 1 pt, RAEB in 6 pts, RAEB-T in 2 pts, and AML in 4 pts. Monosomy 7 was present in 4 (27%) pts. Median time from diagnosis to transplant was 3 months (range 1.3-25.8). Preparative regimen was non-TBI based in 13 (87%) pts. TBI was used for 2 of the patients with AML. Fourteen (93%) patients received melphalan. Cyclosporine was used for GVHD prophylaxis with methotrexate in 12 pts and Solu-medrol in 2 pts. The grafts (14 BM, 1 UCB) contained a median of 2 × 10e8 (range 0.7-8.4) nucleated cells/kg infused. All patients achieved neutrophil engraftment. Median time to neutrophil recovery (ANC > 500) was 17 days (range 10-33), and that to platelet recovery (>50 K untransfused) was 43 days (range 21-150). Acute GVHD, grade II-IV, was seen in 6 (40%) patients; none of the patients had grade III-IV acute GVHD. Chronic GVHD was seen in 4 (27%) patients, 2 limited (skin), and 2 extensive (skin, gut). The only patient with RARS died from lactic acidosis secondary to MELAS syndrome diagnosed post mortem. One patient, who had undergone a prior transplant for ALL, acquired monosomy 7 clone 40 months later. She underwent BMT from the same donor, relapsed again after 22 months, underwent a third successful transplant from the same donor with non-myeloablative conditioning and peripheral blood stem cells. She is disease free 8 years from the last transplant. Thus, 14 (93.3%) of the 15 patients are surviving long term and disease free with a median follow-up of 8.5 years (range 2.3-19). Bone marrow or cord blood transplant from matched related donor with non-TBI based, melphalan containing regimen is very effective in curing MDS affecting children and young adults.

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HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR DNA-DSB REPAIR DEFECTS USING A MODIFIED FANCONI ANAEMIA CONDITIONING REGIMEN

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Lymphocyte receptor generation requires proteins in the DNA-double strand break (DNA-dsb) repair and non-homologous end-joining pathway. Nibrin senses DNA-dsb, DNA ligase IV (LIG4) and Cernunnos-XRCC4-like factor (C-XLF) ligate DNA-dsb to form lymphocyte receptors, as well as general DNA-dsb repair. Deficiency of these enzymes confers radiosensitivity (RS) and primary immunodeficiency (PID). Patients with PID due to deficiencies in these genes are increasingly offered HSCT. Many conditioning regimens (CR) damage DNA and RS patients die from CR toxicity; less toxic CR are required to successfully treat these patients. We report 3 microcephalic RS patients treated using a modified Fanconi anaemia CR of C-1H 0.2 mg/Kg D-9 – D-5, fludarabine 30 mg/m^2 D-9 – D-5, cyclophosphamide 5 mg/kg D-5-D-2.

Patient 1 presented with prolonged RSV excretion. She had panlymphopenia with marked CD8 lymphopenia, reduced PHA response and pan-hypogammaglobulinaemia with poor vaccine antigen antibody responses. A homozygous 1089C > A mutation in *NBS1* confirmed Nijmegen breakage syndrome. She underwent HLA-identical sibling HSCT age 2 years. At 5 years post-HSCT she has stable mixed donor chimerism in all cell lineages, with normal lymphocyte numbers and antibody responses to vaccine antigens.

Patient 2 presented with failure to thrive, persistent diarrhoea, recurrent respiratory infection and severe lymphopenia with hypogammaglobulinaemia. She had a homozygous c.833 G > A *LIG4* mutation. She underwent a 9/10 (Amm) HLA mis-matched parental HSCT aged 4.5 years. CSA and MMF were used as GvHD prophylaxis. Initial donor chimerism was 12%, but by 1 year post-HSCT was 100% with full immunoreconstitution.

Patient 3 presented with developmental delay, severe lymphopenia and hypogammaglobulinaemia, recurrent respiratory infection and cytomegaloviremia (CMV). He had a homozygous c.169C > T mutation in *NHEJ1*, confirming C-XLF deficient PID. He underwent 9/10 (Amm) HLA-mis-matched URD HSCT aged 3.5 years. CSA and MMF were used as GvHD prophylaxis. Initial donor chimerism was 25%, but by 2 months post HSCT was 100%. There was no conditioning-related toxicity and immunoreconstitution at 4 months was 100% donor. Subsequent complications included CMV reactivation and skin and liver GvHD, from which he died at 358 days post-HSCT. These, and a survey of other cases, demonstrate safety and efficacy of this conditioning protocol. Further studies will be required to assess the long term outcome.

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PEDIATRIC AUTOLOGOUS PERIPHERAL BLOOD STEM CELL HARVEST FACTORS AFFECTING TIME TO ENGRAFTMENT AND TRANSPLANT TOXICITY

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Intensive chemotherapy dependent on autologous stem cell transplants (ASCT) is used in many protocols for solid tumors, including brain tumors, and leukemias. ASCT allow the use of more intensive chemotherapy and faster neutrophil and platelet recovery. Previous studies have shown that the time to engraftment ranges from 9-28 days for neutrophils (ANC > 500/microliter). ASCT may also be followed by engraftment toxicity, including fever, sepsis, shock, and in rare instances, death. Between January 2001 and June 2009, 92 brain tumor, neuroblastoma, and primitive neuro-ectodermal tumor patients (age 6 months to 27 years at transplant) underwent 186 peripheral blood ASCT at Children's National Medical Center. Multivariate analysis was used to determine variables affecting patient outcome measures (time to engraftment, transplant toxicity, and time to pre-harvest absolute CD34+ peak). Transplant toxicity was scored on an ordinal scale based on the severity of transplant-related complications. Independent variables analyzed included variables that were patient specific (age, weight, tumor type, chemotherapy administered, and primary vs relapsed disease) and those related to the harvest or transplant (WBC and CD34+ counts prior to transplant and quantity of total nucleated cells and CD34+ cells infused during transplant). All cell counts were normalized to patient weight.

Results: The time to engraftment post transplant was positively correlated with absolute CD34+ cells transfused ($p = 0.01$) and had a less significant correlation with total WBC and CD34% transfused ($p = 0.09$). No significant correlation was found between platelet recovery and quantity of WBC or CD34+ cells transfused. Transplant toxicity was significantly less with increasing with CD34+ and CD34%, and was significantly greater in neuroblastoma patients. The toxicity was significantly greater in younger patients. The time to CD34+ recovery pre-harvest was significantly affected by patient diagnosis, chemotherapy regimen, and primary versus recurrent disease.

Conclusions: Infusion of larger numbers of CD34+ cells decreased time to engraftment and transplant toxicity. In this pediatric population, neuroblastoma patients and younger patients had more transplant toxicity.

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A STUDY OF THE BARRIERS PREVENTING ACCESS OF U.S. PEDIATRIC SICKLE CELL DISEASE PATIENTS TO TECHNOLOGIES THAT FACILITATE COMPATIBLE SIBLING HEMATOPOIETIC CELL TRANSPLANTATION

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Children who receive hematopoietic cell transplantation (HCT) for sickle cell disease (SCD) from an HLA-matched, SCD-free sibling show disease-free survival of at least 85%, yet the majority of children with SCD do not undergo HCT.