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NON-MYELOABLATIVE ALLOGENIC STEM CELL TRANSPLANT (NASCT) WITH UNRELATED CORD BLOOD AND MATCHED FAMILY DONORS IN CHILDREN AND ADOLESCENTS

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NASCTs are successful in establishing durable grafts from both matched family and unrelated adult donors while substantially reducing regimen related toxicity (Slavin et al, Blood: 99:1071, 2002; Chakravarty et al, Blood: 99:1071, 2002). There is little information about NASCT from UCB donor sources, which have a log less nuc/kg and CD34/kg. We report preliminary data in 11 recipients (<21 yrs) of NASCT. HLA typing was performed by scrology class I (A&B) and high resolution DNA typing class II (DRBI). Chimerism was performed by VNTR (D1580, D1757, D1511, APO B) (Luhm et al, Mol Diag 5; 129, 2000). Donor sources: 7 UCB (5 4/6, 2 5/6), 1 Allo BM (6/6) and 3 Allo PBSC (2 6/6, 1 5/6). NA conditioning: Flu 150 mg/m^2, IV Bu 8 mg/kg and ATG 8 mg/kg (N=6); Flu 180 mg/m^2, Bu 8-16 mg/kg, alemtuzumab 54 mg/m^2 (N=2); Flu 150 mg/m^2, Cy 120 mg/kg, ATG 8 mg/kg (N=1); Flu 150 mg/m^2, Cy 600 mg/m^2, ATG 8 mg/kg (N=1); Flu 150 mg/m^2, Mel 140 mg/m^2, ATG (H) 90 mg/kg (N=1). GVHD prophylaxis: IV Tacrolimus 0.03 mg/kg/day and mycophenolate mofetil 15 mg/kg q 12 hr. Demographics: median age 13 (0.5-21) yrs; 4F, 7M; 2 CR2 HD, 1 PR2 HD, 1 PD HD, 1 PR NHL, 1PD neuroblastoma, 1 PD Wilms', 2 B-Thal, 1 WAS, 1 CP CML. UCB median nuc/kg and CD34/kg 5.1 x 10^7/kg (1.6-9.5) and 2.1 x 10^5/kg (1.1-4.8), respectively. Allo BM/PBSC CD34/kg was 5.6 x 10^6/kg (5.0-6.3). Median time to ANC ≥500/mm^3 x 2 D was 15 (3-29) days and platelet >20 k/mm^3 UNTX x 7 D was 22 (6-170) days. Maximal donor chimerism following UCBT was 100% x 4 pts, 95% x 1 pt, 95% (2nd graft) x 1 pt, and 55% x 1 pt (died of PD day +79); AlloPBSC 100% x 3 pts and AlloBM 55% x 1 pt (day +60). Grade IV Tox: 1 hepatic (LFTs, resolved), 1 encephalopathy (death), and 1 grade III-IV AGVHD (death). Infectious complications: 6 bacterial sepsis (resolved), 1 systemic candidiasis (resolved), GI adenovirus (persistent) and 1 pulmonary adenovirus (death). Incidence of grade II-IV and III-IV AGVHD was 54.4% and 27.3%, respectively, and CGVHD was 9.1%. Graft failure occurred in 1/11 (B-Thal) (UCBT) that was successfully regrafted following full ablation. Probabilty of 1-yr overall survival is 60%. In summary, these results suggest that NASCT especially from UCB HLA disparate donors in children and adolescent is feasible and tolerable (<10% GF) and results in 100% of patients having >50% mixed donor chimerism.

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HLA-IDENTICAL ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN HOMOZYGOUS β THALASSEMIA AND SEVERE β THALASSEMIA/HEMOGLOBIN E DISEASE PATIENTS

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Background: Thalassemia is the most common genetic disease in Thailand. Curative treatment with allogeneic bone marrow and cord blood transplantation has been reported. However, peripheral blood stem cell transplantation (PBSCT) data in this disease is limited. Objective: To determine the outcome of β thalassemia major patients who underwent HLA-identical allogeneic PBSCT. Methods: We conducted a cohort study of allogeneic PBSCT in homozygous β (β/β) thalassemia and severe β thalassemia /Hemoglobin E (β/E) disease patients who had HLA-matched sibling donors. All patients received conditioning regimen including busulfan and cyclophosphamide (BU/CTX) except one received BU/CTX and antithymocyte globulin. Acute GVHD prophylaxis consisted of cyclosporin A (CSA) and methotrexate for 8 patients and CSA and mycophenolate motifil for 1 patient. Donors received G-CSF for 4 days before leukapheresis collection. Results: Five β/β and four severe β/E diseases patients were studied. The median age was 10 years (1.5 to 11 years). The median CD 34+ cells was 8.48 x 106 cells/kg recipient body weight. All patients achieved myeloid and platelet engraftment with a median time of 15 days and 21 days respectively. Acute GVHD grade II-IV appeared in four patients (grade II = 3, grade IV = 1). Three patients developed chronic GVHD (limited = 1, extensive = 2). All patients were alive with a median follow up time of 18 months (2-47 months). Neither graft failure nor graft rejection was observed in this study. Conclusion: Allogeneic PBSCT is feasible for children with β thalassemia major although GVHD was apparently high compared to BMT studies in Thais.

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ALLOGENEIC BONE MARROW TRANSPLANTATION FOR CHILDREN WITH HEMATOLOGIC MALIGNANCIES

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Allogeneic BMT is potentially curative for patients with high risk or recurrent hematologic malignancy. In this series, we report 249 children with ALL, AML, CML, or MDS who underwent allogeneic BMT at St. Jude Children's Research Hospital between 1992-2000. The median age at BMT was 11.2 years; 22 had received a prior autograft. 86 patients received unrelated donor (MUD) grafts matched at 6 HLA loci, 48 MUD grafts matched at 5 HLA loci, 84 matched sibling (MSD) grafts and 31 mismatched family member (MMFM) grafts. The conditioning regimen included cytarabine, cyclophophamide, total body irradiation. ATG was provided to enhance the immunosuppression for recipients of MUD and MMFM grafts. MUD and MMFM grafts were depleted of T-lymphocytes using antibodies against CD6 and CD8 with rabbit complement. Grafts from MSD were unmanipulated. Cyclosporine GVHD prophylaxis was given to all patients, and pentoxifylline or short-course methotrexate was provided to MSD graft recipients. The cumulative incidence of grade 2-4 acute GVHD was 23%; the cumulative chronic GVHD was 17%. The two year probability of disease-free (DFS) and overall survival (OS) were 44% and 47%, respectively. The cumulative incidence of relapse was 25%; the cumulative incidence of regimen-related mortality was 35%. Favorable prognostic factors for OS included a diagnosis of CML, not having a secondary malignancy, receiving a graft matched at HLA class I, younger patient age, and lower T-cell graft content. Favorable prognostic factors for DFS included not having a second malignancy, receiving a graft matched at HLA class I, and lower T-cell graft content. Probabilities of DFS by donor status were as follows: MSD 46.8%, MUD matched at 6 HLA loci 46.2%, MUD matched at 5 HLA loci 31.2%, and MMFM 25.4% (p=0.026). Recipients of MSD and MUD grafts matched at 6 HLA loci had similar outcomes; recipients of MMFM grafts and MUD grafts matched at 5 HLA loci had similar outcomes. These results suggest that MMFM donors may be preferred over MUD grafts matched at 5 HLA loci for patients lacking a MSD or MUD matched at 6 HLA loci.

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A LIMITED SAMPLING STRATEGY (LSS) TO TARGET SYSTEMIC EXPOSURE (SE) OF BUSULFEX (BUSULFAN) INJECTION (IVBU) IN PEDIATRIC PATIENTS (PEDS)

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PURPOSE: A clinical trial of IVBU (BuCy4) in 24 peds used initial IVBU doses of 1.0 or 0.8mg/kg for ages < 4y or >4y, respectively Q.6 hrs x 4 days. Full pharmacokinetic (PK) profiling and a single dose adjustment (when necessary) were used to target SE to 900 - 1350 mM.min. This full-sampling approach allowed ~90% patients to achieve target SE at steady state. The purpose was to further analyze these data to refine the dosing strategy and to develop a LSS to achieve the target IVBU SE. METHODS: PK modeling yielded a 2-dose level mg/kg regimen: <= 12 kg dosed at 1.1 mg/kg, >12 kg dosed at 0.8 mg/kg. Modeled area-under-the-curve data (AUC) for Doses 1 and 9 were compared to AUC estimated from a LSS. The LSS used 3 time-points for Dose 1 (2hr -