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

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Myelodysplastic syndromes (MDS) in children are associated with significant risk of leukemic transformation. Allogeneic stem cell transplantation is the only cure. Many patients do not have a suitable donor. Between 1995 and 2004, we transplanted 30 children lacking matched living stem cell donors with unrelated umbilical cord blood (UCB). The M:F ratio of the patients was 1. Nine patients belonged to ethnic minorities (30%), median age was 9.06 years (range, 1.36–16.83 years), and median weight was 28.4 kg (range, 8.3–62.6 kg). Eight patients had secondary MDS (3 Kostmann's, 1 Shwachman-Diamond, 3 post-ALL, and 1 post-neuroblastoma therapy). Ten patients had bone marrow blasts > 20% pretransplantation (8 of 22 with primary MDS and 2 of 8 with secondary MDS). The preparative regimen was TBI-based in 19 patients and chemotherapy-based in 11 patients. Cyclosporine and solumedrol were used for GVHD prophylaxis. Grafts were matched at HLA class I (A,B) at the serologic level and at class II (DRB1) at the allelic level. Grafts matched at 5/6 HLA loci in 8 patients, 4/6 HLA loci in 21 patients, and 3/6 HLA loci in 1 patient. Grafts delivered a median of 4.12×10^7 (range, 1.68–29.16) nucleated cells/kg precryopreservation. Median CD34+ cell dose infused postthaw was 1.48×10^5/kg (range, 0.17–28.46). Twenty-four of 30 patients (80%) engrafted with donor cells. Of the engrafting patients, median time to ANC > 500/μL was 24 days (range, 6–48 days), and median time to platelet recovery (platelets > 50K untransfused) of evaluable patients was 72 days (range, 41–137 days). Acute GVHD grade III-IV occured in 5 patients, all of whom had gut involvement. Limited chronic GVHD was seen in 4 patients. Fifteen patients died, 5 of infections (1 of pseudomonas, 1 of toxoplasmosis, 1 of aspergillosis, 2 of EBV), 3 of graft failure, 2 of GVHD, 2 of relapse, 1 of pulmonary hemorrhage, 1 of CNS hemorrhage, and 1 of MSOF. Fifteen patients (50%) are surviving in remission from 3.4 to 107 months (median, 50 months) posttransplantation. Thirteen of 20 patients (65%) with &le: 20% blasts pretransplantation are alive disease-free, whereas only 1 of 10 (10%) patients with > 20% blasts is alive. Six of 8 children with secondary MDS (75%) are alive, compared with 13 of 22 (40%) with primary MDS, possibly due to the greater number of patients with > 20% blasts in the latter group. These results, especially in patients with < 20% blasts pretransplantation, are equivalent to matched allogeneic bone marrow transplantation data. We conclude that unrelated UCB donors should be actively considered for pediatric patients with MDS who lack a living related or unrelated stem cell donor to enable transplantation when the blast counts are low.

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RISK FACTORS FOR LIVER DYSFUNCTION IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) RECIPIENTS

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Background: Liver dysfunction (LD), inlcuding veno-occlusive disease (VOD), is common following HSCT. Though there are a number of studies in adults on LD following HSCT, data from children are limited. The aim of this study was to characterize LD in pediatric HSCT recipients during the initial 100 days follwing HSCT. **Methods:** A retrospective analysis of patients under age 21 years who had undergone HSCT over a 4-year period (July 1999-June 2003) was conducted. LD was defined as the presence of clinical jaundice and/or elevated ALT/GGT(1.5 times normal). **Results:** A total of 58 patients underwent HSCT (25 allogeneic) during the study period (34 males; mean age, 7.3 ± 6.1 years). The underlying conditions included acute lymphocytic leukemia (9 cases), acute myelocytic leukemia (16 cases), lymphoma (7 cases), and solid tumors (26 cases). LD was seen in 47 (81%) patients. LD was caused by VOD[VOD] in 12.8%, graft- versus-host disease in 14.9%, sepsis in 2.8%, viral hepatitis in 2.1%, drugs in 8.9%, underlying disease in 3.3%, biliary disease in 3.3%, and indeterminate cause in 9.6%, and was multifactorial in 42.3%. Patients with LD had mean peak ALT values of 243 ± 287 U/L), mean peak GGT values of 389 ± 576 U/L, and mean peak bilirubin values of 5.1 ± 8.5 mg/dL. There was no significant difference in LD between autologous and allogeneic HSCT recipients, or between those with HLA mismatch and perfect match ($P > .2$). There was no difference in conditioning regimen GVHD prophylaxis between patients with LD and without LD ($P > .2$). Patients who developed LD received parenteral nutrition for significantly longer periods (39 days vs 22 days; $P < .02$) and had a higher pretransplantation ALT (52 vs 23; $P < .009$) and GGT (69 vs 26; $P < .02$) compared to those without LD. Patients who received amphotericin B during the posttransplantation period had a higher chance of developing LD ($P < .05$). Twleve patients died in the initial 100 days; 3 had VOD. Total bilirubin was significantly elevated in those who died compared to survivors (median, 2.7 mg/dL [range, 0.6–34] vs median, 1 mg/dL [range, 0.3–10]; $P < .02$). **Conclusion:** LD was a frequent occurrence in patients in this study. The majority of LD was multifactorial in etiology. Development of LD was not related to stem cell source or to conditioning regimen. LD was more likely to occur in those with elevated pretransplantation ALT and/or GGT. The risk of developing LD was greater in those who received amphotericin B and those who received prolonged parenteral nutrition. LD contributes significantly to the morbidity and mortality in post-HSCT recipients.

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NONMYELOABLATIVE CONDITIONING WITH 200 CGY TOTAL BODY IRRADIATION (TBI) PRIOR TO MATCHED LITTERMATE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN DOGS WITH CANINE LEUKOCYTE ADHESION DEFICIENCY RESULTS IN HIGHER LEVELS OF ENGRAFTMENT AND DONOR CHIMERISM COMPARED TO BUSULFAN ALONE

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Leukocyte adhesion deficiency (LAD) is due to defects in the integrin CD18 and results in a syndrome of severe, recurrent bacterial infections as a result of the failure of leukocytes to adhere to endothelium and migrate to sites of infection. Approximately 75% of children with severe deficiency LAD die by age 2 years. Allogeneic HSCT after myeloablative conditioning has been shown to cure LAD; however, regimen-related toxicity (RRT) and graft-versus-host disease (GvHD) have restricted the use of this approach. We used dogs with canine leukocyte adhesion deficiency (CLAD), which closely resembles severe deficiency LAD, to test nonmyeloablative transplantation approaches before their use in human LAD.

CLAD pups, identified by the absence of CD18 on their leukocytes, were DLA-typed using microsatellite repeats closely linked to the DLA class I and II loci. Six pups were given 200 cGy TBI, followed by 8.4 ± 1.2 (mean ± SEM) CD34+ cells/kg from matched littermates. Three pups were given 10 mg/kg busulfan intravenously, followed 2 days later by $12.0 \pm 2.5 \times 10^6$ CD34+ cells/kg. Posttransplantation immunosuppression with cyclosporine A and mycophenolate mofetil was used in both groups. Dogs were observed for evidence of infection, regimen-related toxicity (RRT), GvHD, and overall health. Chimerism was assessed by flow cytometry for CD18. Three dogs lacking a matched littermate died from infection before 6 months of age.

All of the TBI-treated animals and 2 of the 3 busulfan-treated dogs engrafted. In the TBI cohort, donor chimerism at 1 year averaged 34% ± 8.6% and continues to rise. In the busulfan cohort, donor chimerism at 6 months averaged 16% ± 7.6%, with chimerism peaking at 4 months posttransplantation. There was no RRT or GvHD in either group.

Because TBI in children is associated with growth suppression, sterility, and increased cancer risk, a non-TBI regimen before HSCT has important advantages. The busulfan regimen used here allowed for sufficient chimerism to reverse the CLAD phenotype in 2 of 3 dogs. More intensive conditioning and/or immunosuppression, or