We report the experience of 41 patients (21 males, 20 females; mean age, 8.1 years; range, 0.2–22.6 years) treated with RIC and allogeneic HSCT. Diagnoses consisted of malignancies in 24 (20 hematologic and 4 refractory neuroblastoma) and nonmalignant disorders in 17: immunodeficiencies in 6, metabolic disorders in 5, hemoglobinopathies in 4, and aplastic anemia in 2. Twelve patients had prior HSCT (7 autologous and 5 allogeneic). Recipient's racial origins included 22 Caucasian, 10 Hispanic, 7 African American, and 2 Asian. A standardized RIC regimen comprised of fludarabine, 30 mg/m^2 for 6 days (days −10 to −5), followed by intravenous busulfan, 0.8–1 mg/kg for 8 doses or targeted busulfan at AUC 4000 mmol/min for 2 doses (days −5 and −4) and equine ATG, 40 mg/kg or rabbit ATG, 2 mg/kg for 4 days (days −4 through −1) was administered. Graft-versus-host disease (GVHD) prophylaxis was cyclosporin A (CsA) alone in 19 patients and CsA and mycophenolate mofetil in 22 patients. Growth factor support was not used. Stem cell sources included 27 unrelated donors and 14 related donors; 34 of 41 sources were peripheral blood stem cells. We also assessed engraftment by determining the number of days required to achieve ≥ 50% and ≥ 95% donor chimerism (Do-chim) by VNTR in total leukocyte and T-lymphocyte (CD3) populations.

The median cell doses infused were 5.8×10^8 MNC/kg and 2×10^6 CD34+ cells/kg. Seven of 41 patients failed to engraft, and 3 patients were not evaluable due to early deaths from toxicity (in 2) or relapse (in 1). Four of 16 evaluable patients with nonmalignant disorders failed to engraft versus 3 of 22 with malignancies. Patients failing to engraft were younger (median age, 6.3 vs 8.8 years) and weighed less (median weight, 18 vs 27 kg), but received lower cell infusion doses (3.9 vs 5.9×10^8 MNC/kg; $P = .05$). The median time to a postnadir ANC of 500/μL was 16.5 days, and unsupported platelet count > 20,000/μL was 19 days. Data shown in the table indicate trends for more rapid achievement of Do-chim in patients treated for malignancy. Also, within the 14 malignancy patients, those with clinically significant acute (II-IV) and/or extensive chronic GVHD demonstrated faster Do-chim.

These measures of engraftment may provide a reproducible comparison of engraftment in the setting of RIC and resulting mixed chimeric states. These parameters may provide insight to promote engraftment or to balance a desired graft-versus-tumor effect in patients with malignancies versus limitation of GVHD for patients with no benefit from an excessive alloimmune response.

Table 1. *Median Number of Days to Achieve Donor-Chimerism*

	Leukocyte Do-chim 50	Leukocyte Do-chim 95	Lymphocyte Do-chim 50	Lymphocyte Do-chim 95
Evaluable Pts (n = 26)	18	26	25	33
Non-malignant Disorders (n = 11)	19	53	26	82.5
Malignancy Pts (n = 15)	13	25	21	27
Malignancy & GVHD (n = 7)	13	17	20	19
Malignancy without GVHD (n = 8)	16	32.5	26.5	39

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CHANGE OF RISK FACTORS FOR TREATMENT-RELATED MORTALITY IN CHILDREN UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MALIGNANT AND NONMALIGNANT DISEASES

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Allogeneic hematopoietic stem cell transplantation (HSCT) offers a high chance for cure in patients with nonmalignant disorders. However, acute and late complications as consequence of the conditioning regimen and severe immunosuppression are still a matter of concern. Only few studies specifically focused on the risk for treatment-related mortality (TRM) in children. To evaluate factors influencing the outcome after HSCT we retrospectively analyzed 342 children given allogeneic SCT. The median age was 8.7 years; 230 patients suffered from hematologic malignancies, 112 from nonmalignant disorders (SAA, immunodeficiency syndromes, metabolic disorders, thalassemia, sickle cell disease, hemophagocytic syndromes). The 360-day TRM (in nonmalignant diseases, 0.17) was influenced by donor type (HLA-identical sibling donors vs phenotypically matched family or unrelated donors vs mismatched donors), time of SCT (before and after 1997), stage of disease (early vs advanced), conditioning regimen (myeloablative vs reduced), graft manipulation (T-cell depletion vs no TCD) and history of severe organ dysfunction and/or infections. Most frequent causes of death were organ toxicity, acute GvHD, and infections. The following factors were independent risk factors for TRM: graft failure, resistant disease, CMV IgG-negative donors for CMV IgG-positive patients, HLA mismatch > 2 alleles, TCD graft, and history of severe toxicity and/or infection. The pattern of severe adverse events changed over time. In the first years, GvHD was the most frequent life-threatening complication, followed by toxicity and infections. More recently, viral infections are the major reason for TRM, particularly in patients transplanted from HLA-mismatched donors given T-cell–depleted grafts. The cumulative incidence of TRM in patients transplanted after 1997 was 0.06 from matched sibling donors, 0.14 from unrelated donors, and 0.27 and from HLA-mismatched donors. Factors associated with improved survival incuded the quality of HLA typing (high-resolution techniques in HLA class I and II), reduced intensity conditioning, monitoring and preemptive treatment (pharmacologic and virus-specific cell support) of viral infections, and experience (center size > 10 allogeneic SCTs vs < 10 per year). We conclude that today, the risk for TRM especially in children with nonmalignant diseases undergoing HSCT could be reduced by multidisciplinary approaches focusing the enhancement of immunologic reconstitution.

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TREATMENT OF PEDIATRIC PATIENTS WITH SANFILIPPO SYNDROME (MPS IIIA AND IIIB) WITH UNRELATED UMBILICAL CORD BLOOD TRANSPLANTATION

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Umbilical cord blood transplantation (UCBT) favorably alters the natural history of young pediatric patients with Hurler syndrome (MPS I). We asked whether it would also be effective for patients with Sanfilippo syndrome (MPS III). Patients with Sanfilippo syndrome have less somatic and more CNS disease than patients with other MPS syndromes. They are typically diagnosed between 3 and 5 years of age. Without treatment, they develop severe neurologic dysfunction, deafness, inability to speak or ambulate, and severely autistic behaviors. Death occurs between 10 and 13 years of age. Currently, allogeneic stem cell transplantation (SCT) is the only way to deliver healthy enzyme to the brain. We hypothesized that children with Sanfilippo syndrome would benefit from UCBT, particularly if it was performed early in the course of the disease. Between February 2001 and April 2004, 12 children (age 10–59 months, 75% male, 100% Caucasian) underwent UCBT. All were prepared for transplantation with myeloablative chemotherapy (busulfan/cyclophosphamide/ATG), and all received prophylaxis against GvHD with cyclosporine and steroids. They were transplanted with unrelated donor UCB grafts matching at 6/6 (n = 1), 5/6 (n = 7), and 4/6 (n = 4) HLA loci, containing a median of 6.5×10^7 nucleated cells/kg and 1.42×10^5 CD34 cells/kg. Donor cell engraftment (ANC 500/μL) occurred in 9 of 12 children in a median of 24 days. Platelet engraftment (platelet count 50K/μL untransfused) occurred in 7 of 12 children