success using HLA-matched related donors; however, use of alternative donors has been associated with increased graft failure, graft versus host disease (GVHD), and transplant-related mortality (TRM). HSCT using alternative donors with post-transplantation cyclophosphamide (PT/Cy) has been performed for hematologic malignancies with engraftment, GVHD, and TRM comparable to that seen with HLA-matched related donors. There are limited reports of HSCT in non-malignant disorders using alternative donors and PT/Cy.

Design: We transplanted 9 patients with non-malignant conditions (CGD=3, DKC=2, DBA=1, HyperIgM=1, XIAP=1, IPEX=1) using an alemtuzamab/fludarabine based reduced intensity conditioning (RIC). All patients received GVHD prophylaxis with PT/Cy, with the addition of mycophenolate mofetil and tacrolimus for HSCT with haploidentical donors and for alkylator-sensitive diagnoses (DKC). Six patients had 10/10 HLA-matched unrelated donors, and 3 had HLA-haploidentical related donors.

Results: All 9 patients successfully engrafted by day 30. Ultimately, all patients have had sustained donor engraftment sufficient to eliminate manifestations of their underlying diseases. 6 of 9 patients are full donor chimeras off immunosuppression, 1 patient is a stable mixed donor chimera (76% $CD3^+$ T cells) off immunosuppression, 1 patient is a stable mixed donor chimera on a calcineurin inhibitor (CNI), and 1 patient had secondary graft failure but was ultimately retransplanted with myeloablative conditioning using the same donor, resulting in full donor chimerism and elimination of disease. One patient developed Grade 1 and one patient Grade 2 acute GVHD, both treated successfully with steroids and a CNI. Mild skin chronic GVHD developed in 1 patient, treated successfully with phototherapy. No serious infections occurred and there was no TRM. 1 patient developed veno-occlusive disease, treated successfully with defibrotide. Disease-free survival is 89% with a median follow-up of 14 months (6-30 months). The patient with secondary graft failure is now disease-free after myeloablative transplant, for an overall disease-free survival of 100% at a median of 14 months follow-up (6-60 months). Overall survival is 100%.

Conclusion: We have observed successful engraftment sufficient to eliminate manifestations of disease, limited GVHD, and no TRM in 9 patients with nonmalignant disorders using alternative donors, RIC, and PT/Cy. RIC HSCT with PT/Cy shows promise for curing nonmalignant pediatric disorders, and potentially eliminates the need for CNI use after MUD BMT. Development of prospective clinical trials to confirm these observations is warranted.

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Autologous Transplant/Gene Therapy for Adenosine Deaminase-Deficient Severe Combined Immune Deficiency

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Autologous hematopoietic stem cell transplantation (HSCT) of gene-modified cells (gene therapy) has shown clinical benefit for ADA-SCID when combined with non-myeloablative conditioning and enzyme replacement therapy (ERT) cessation. In a Phase II study (2009-2012) closed to enrollment (NCT00794508), patients received autologous CD34+ cells modified with the MND-ADA g-retroviral vector after conditioning with busulfan (4 mg/kg) and ERT cessation (n=10). Patients were treated between 3 months and 15 years of age (median=11.5 months) and follow-up ranges from 22-64 months. With the exception of the oldest patient (at 15y), all others remain off ERT with normalized PBMC ADA activity. All nine remaining off ERT show normal proliferative responses to mitogens and three of nine were able to discontinue IVIg. MND-ADA is detected in PBMC (0.1-2.6 VCN) and in granulocytes (0.01-0.3 VCN) at most recent visit. A new Phase I/II trial was opened in May 2013 (NCT01852071) in which subjects have received autologous CD34+ cells modified with a self-inactivating lentiviral vector (EFS-ADA) after conditioning with busulfan (4 mg/kg) with ERT cessation at 30 days post-transplant (n=6). Eight subjects have been enrolled at 4-42 months old and the six who are past 30 days remain off ERT. The patients with the longest follow-up have normal or higher PBMC ADA activity and good immune reconstitution. Monitoring for insertional oncogenesis is on-going in both studies and has not detected any monoclonal proliferative events. These results demonstrate the efficacy and safety of autologous transplant/gene therapy for ADA SCID.

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Studying the Optimal Intravenous Busulfan Exposure in Pediatric Allogeneic Hematopoietic Cell Transplantation (alloHCT) to Improve Clinical Outcomes: A Multicenter Study

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Background: In children, the therapeutic drug monitoring (TDM) of intravenous (IV) busulfan (BU) in alloHCT can