**Poster Session III**

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**DELAYED INFUSION OF ALLOENERGIZED DONOR PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC) AUGMENTS PATHOGEN-SPECIFIC IMMUNE RECONSTITUTION AFTER T CELL DEPLETED (TCD) HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR HIGH-RISK ACUTE LEUKEMIA/MDS**


**Dana-Farber Cancer Institute, Boston, MA; 2 Massachusetts General Hospital, Boston, MA; 3 Children’s Hospital Los Angeles, Los Angeles, CA; 4 M.D. Anderson Cancer Center, Houston, TX; 5 Children’s Cancer Hospital, M.D. Anderson Cancer Center, Houston, TX**

Adoptive transfer of alloenergized donor T cells is a simple approach to augment immune reconstitution while limiting GVHD after TCD haploidentical (haplo) HSCT. However, the optimal dose and impact on antigen-specific immune reconstitution remain unknown. On a new study, 7 adults and 4 children received fractionated TBI (12 Gy, n = 5) or melphalan (140 mg/m², n = 6), fludarabine, thiotepa and ATG followed by CD34-selected peripheral blood stem cells (median 9.4 CD34+ and 0.02 CD3+ × 10⁶ cells/kg) from haplo donors without further GVHD prophylaxis. All engrafted rapidly with full donor chimerism. Using an adaptive trial design, 10 pts received alloenergized donor PBMC (generated by co-culture with irradiated stimulator PBMC and humanized anti-B7.1 and -B7.2 antibodies resulting in a median 6-fold reduction in alloresponses) in escalating dose (Ds) cohorts: Ds1, 10⁶ CD3+ cells/kg (n = 4), Ds2 10⁶/kg (n = 3) and Ds3 10⁷/kg (n = 3). 3 pts developed Gr 2–4 acute GVHD. CD3+ (1 Ds 2, 2 Ds3), all responsive. 0.25/1.0/2.0 eval pts developed chronic GVHD. 7/11 pts are alive (median f/u 8 months). 3 pts died from regimen related toxicity before D+100 and 1 from post-operative bleeding (D+738). 2 pts relapsed. CD4 T cell recovery was faster and functional pathogen-specific CD4 and CD8 T cells became detectable earlier in pts receiving higher doses of alloenergized PBMC. Median time to CD4 cr >10⁹/ml was 9, 3 and 2 months and CMV or VZV-specific IFN-γ. CD8 T cells became detectable earlier in pts receiving higher doses of alloenergized PBMC and CD4+ (up to 10%) before D+100, coinciding with clearance of CMV viremia. One Ds3 pt had adenoviremia despite high dose defoivir, resolving with expansion of infused donor T cells. 2 Ds1 pts developed late viral infections: 1 reactivated EBV, and 1 developed disseminated VZV resolving after VZV-specific T cells became detectable. No late viral infections occurred in assessable Ds2/3 pts. These early data support a contribution of alloenergized donor PBMC to quantitative and qualitative immune reconstitution after TCD haploHSCT. Further recruitment will determine the optimal dose that can be safely administered in this setting.

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**RAPID LYMPHOCYTE RECOVERY AND INTRAVENOUS IMMUNOGLOBULIN INDEPENDENCE IN CHILDREN WITH SEVERE COMBINED IMMUNODEFICIENCY (SCID) UNDERGOING ALLOGENIC STEM CELL TRANSPLANTATION WITH REDUCED INTENSITY CONDITIONING (RIC)**

**Guarino, J.A., Ketzel, M., Schneiderman, J., Jacobsohn, D., Chadbury, S., Duester, R., Tse, W. Children’s Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL**

Allogeneic SCT is curative for patients with SCID. We evaluated a RIC SCT approach in these patients for engraftment, toxicity and immune reconstitution. Between 2000 and 2008, RIC transplant was performed in 14 SCID patients (8 males and 6 females; median age 3 months (range 1.1–98.3)). Median time from diagnosis to transplant was 1.8 months (range 1.0–96.3). Donor sources included: HLA-matched related donor peripheral blood stem cells (PBSC) (n = 1), unrelated donor PBSC (7), related cord blood (CB) (1) and unrelated CB (6). The median cell dose was 10.3 × 10⁶ TNC/kg and 9.2 × 10⁶ CD34+ cells/kg, respectively. The effector memory phenotype of recovering T cells was consistent with peripheral expansion of infused alloanergized donor T cells. The effector memory phenotype of recovering T cells was consistent with peripheral expansion of infused alloanergized donor T cells. Using an adaptive trial design, 10 pts received alloenergized donor PBMC (generated by co-culture with irradiated stimulator PBMC and humanized anti-B7.1 and -B7.2 antibodies resulting in a median 6-fold reduction in alloresponses) in escalating dose (Ds) cohorts: Ds1, 10⁶ CD3+ cells/kg (n = 4), Ds2 10⁶/kg (n = 3) and Ds3 10⁷/kg (n = 3). 3 pts developed Gr 2–4 acute GVHD. CD3+ (1 Ds 2, 2 Ds3), all responsive. 0.25/1.0/2.0 eval pts developed chronic GVHD. 7/11 pts are alive (median f/u 8 months). 3 pts died from regimen related toxicity before D+100 and 1 from post-operative bleeding (D+738). 2 pts relapsed. CD4 T cell recovery was faster and functional pathogen-specific CD4 and CD8 T cells became detectable earlier in pts receiving higher doses of alloenergized PBMC. Median time to CD4 cr >10⁹/ml was 9, 3 and 2 months and CMV or VZV-specific IFN-γ. CD8 T cells became detectable at 7.5, 3 and 2.5 months at Ds 1,2 and 3 respectively. The effector memory phenotype of recovering T cells was consistent with peripheral expansion of infused alloenergized donor T cells. 5 pts reactivated CMV before alloenergized PBMC infusion, but no new episodes of CMV reactivation or CMV disease occurred after infusion. 2 pts had large expansions of CMV-specific CD4 and CD8 T cells (up to 10%) before D+100, coinciding with clearance of CMV viremia. One Ds3 pt had adenoviremia despite high dose defoivir, resolving with expansion of infused donor T cells. 2 Ds1 pts developed late viral infections: 1 reactivated EBV, and 1 developed disseminated VZV resolving after VZV-specific T cells became detectable. No late viral infections occurred in assessable Ds2/3 pts. These early data support a contribution of alloenergized donor PBMC to quantitative and qualitative immune reconstitution after TCD haploHSCT. Further recruitment will determine the optimal dose that can be safely administered in this setting.

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**NK CELL RECONSTITUTION AFTER ALLOGENEIC TRANSPLANTATION FROM UNRELATED DONORS USING CD3/CD19 DEPLETED GRAFT**

**Diaz, M.A., Gonzalez Vicent, M., Perez, A., Sevilla, J., Abad, I., Ramires, M. Hospital Niño Jesús, Madrid, Spain**

We analyzed immune recovery after allogeneic PBSC transplantation from unrelated donors using CD3/CD19 depleted graft. Between June 2005 and June 2008, thirteen pediatric patients (9 males and 4 females) aged between 1 and 16 years (median 5 years) diagnosed of leukemia were included. Ten patients were in 1st CR and three in 2nd CR. A fludarabine-RIC was used. Grafts were manipulated by CD3/CD19 depletion using CliniMACS® Cell Separation System. Graft composition was as follows: CD3+; 11.0 × 10⁶/kg (range 5.66–62.77), CD3+; 0.5 × 10⁶/kg (range 0.1–2.07) and CD56+; 44.45 × 10⁶/kg (range 17.0–149.82). Results were compared to a group of pediatric patients (n = 13) with leukemia conditioned with the same RIC and grafted with a CD3+ selected PBSC from unrelated donors. There were not differences in T and B lymphocyte recovery between groups. However, a significantly difference was observed in the NK cell reconstitution. NK cells were observed to AUC 4000–5000 microMol/min/day, days -5 and -4, and anti-thymocyte globulin 2mg/kg/day, days -4 through 3. GVHD prophylaxis included cyclosporine A and mycophenolate mofetil. Engraftment occurred in 8/8 (100%) PBSC recipients and 4/6 (67%) CB recipients. Absolute neutrophil count (ANC) >1000/µl was achieved at a median of 17 days (range 4+2) and platelets >50K was achieved at a median of 23 days (12–90). The ANC never dropped <500 for 8/14 (57%), and platelets never dropped <20K for 8/14 (57%) patients. Full donor chimerism (VNTR > 95%) was achieved by a median of 26 days in 11/14 patients (79%; 8 received PBSC, 3 received CB). Stable mixed donor chimerism (VNTR ≥ 50%) was achieved by 74 days for 1 patient who received CB. Two patients who received CB doses of 1.19×10⁶/kg TNC/kg, and 0.60/0.55 × 10⁶ CD34+ cells/kg, respectively, experienced graft failure and died from complications. The other patients tolerated the transplant with mild toxicities. No VOD or grade III/IV acute or chronic GVHD was seen. Infections seen post-transplant (bacterial (n = 9), candidemia (1), and viral (8)) responded to antimicrobial therapy except in 1 graft failure patient. Immune reconstitution studies performed post-transplant showed rapid recovery of various lymphocyte subsets (table). Normal endogenous IgG levels were achieved by day +180 and patients no longer required IV immunoglobulin. The 100-day transplant mortality was 14.3%. The Kaplan-Meier estimate of overall survival at 2 years was 80% (95% CI 47.5–90%). This RIC protocol is a novel, non-toxic approach that allows for adequate donor engraftment with early immune reconstitution and correction of the underlying immunodeficiency in children with SCID.