chimerism or failure to achieve neutrophil recovery by day 42. Median patient age and weight was 22 years (r: 0–69) and 61 kg (r: 4–149 kg), respectively, with 66 having had a prior autologous transplant. Time from diagnosis to transplant was 13.3 months (1.26–250 months), 57 patients were CMV+, 186 received a sex-matched graft, 132 ABO-matched, 168 minor ABO-MM, and 229 major ABO-MM. Median graft cell doses were 3.8×10^7 nucleated cells (NC)/kg (r: 0.7–48.9) and 4.6×10^5 CD34/kg (r:0.4–275.3). Fifty-seven received 6/6 HLA-matched units, 196 received at least one 5/6 matched unit and 286 received at least one 4/6 matched unit. GF was observed in 43/338 (12.7%) after MA and 36/201 (17.9%) after RI UCBT. Risk factors associated with GF in logistic regression were transplantation of HLA mismatched units (5/6 match, OR 9.13, 95%CI, 1.19–70.38; 4/6 match, OR 11.66, 95%CI 1.53–89.00; $p < .01$), treatment of non-malignant disease (OR 2.55, 95%CI, 1.35–4.81, $p < .01$), low CD34 cell dose (top low quartile OR 2.33, 95%CI, 1.07–5.05; bottom low quartile, OR 3.11, 95%CI, 1.44–6.70; $p < .01$), and use of a RIC (OR 2.40, 95%CI 1.35–4.26; $p < .01$). Patients who received a prior autologous transplant had lower odds of GF (OR 0.12, 95%CI, 0.03–0.52, $p < .01$). Factors not impacting risk of GF were recipient age, sex-match, ABO-match, CMV serostatus, performance status, diagnosis, disease risk, interval from diagnosis to transplant, NC dose, and CD3 cell dose. In addition to CD34 cell dose and HLA match, patients with non malignant disease and recipients of a RIC are at higher risk of GF. These results support the need for greater investment in banking UCB with larger cell doses and HLA diversity and development of improved strategies for overcoming GF in high risk patient populations.

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COSTIMULATORY BLOCKADE (CSB) DURING MIXED LYMPHOCYTE REACTION (MLR) PREVENTS IL27 UPREGULATION AND SIGNALLING

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Numerous methods for selectively depleting or manipulating alloantigen (alloAg) specific CD4 T cells (CD4 T) are being studied for their potential in improving transplant outcomes by limiting GVHD or graft rejection. However, their effects on off-target CD4 T cellular pathways and functions and on other PBMC are not well described. We used global gene expression profiling (GEP) to elucidate the molecular impacts on bystander PBMC after inducing alloAg specific CD4 T anergy by CD28:B7 costimulatory signal blockade (CSB) via humanized anti B7.1/B7.2 MoAbs. Mimicking our ex vivo clinical anergization protocol, PBMC were isolated from fully-HLA mismatched healthy donors (n = 12) to perform ex vivo primary MLR+/-anti B7.1/B7.2 MoAbs. CSB inhibited mean proliferation by 73% after 72 h of MLR. GEP was performed using Affymetrix hu133 plus2 chips on monocytes (Mo), CD4 and CD8 T, B and NK cells purified from these MLR. Despite low published frequencies (1–10%) of alloAg-specific CD4 T, we detected global gene expression variance ($P < 0.05$) between CD4 T isolated from MLR+/-CSB suggesting effects on non-alloAg specific CD4 T. Analysing these differentially expressed genes by cellular pathway highlighted those active in cell proliferation and differentiation. Particularly, differences in IL27 signaling molecules in Mo and CD4 T were prominent. IL27, a heterodimer of p28 and EBV-Induced gene 3 (EBI3) and IL12 family member produced by APC, signals through its receptor, IL27R, on CD4 T. IL27 regulates adaptive immunity by controlling T cell proliferation, Th1 differentiation and IFNg synthesis. Both p28 and EBI3 gene and protein expression levels were decreased in Mo from MLR+CSB. After CSB, CD4 T showed decreased IL27R and STAT3 expression and inactivation of pSTAT1 and NFkB. Intracytoplasmic cytokine (ICC) analysis showed decreased IL2 and IFNg expression in CD4 T, decreased IL15 and increased IL10 in Mo from MLR+CSB supporting the negative effect of IL27 on Th1 differentiation. These data suggest that CD28:B7 signaling during MLR is required for Mo production of IL27. Decreased expression of IL27R, pSTAT1 and NFkB after CSB may contribute to CD4 T alloAg anergy induction by suppressing effector cytokines and Th1 differentiation. CD28:B7 modulation of IL27 and IL27R emphasizes that targeted therapies used in the complex environment of human PBMC may have effects unpredicted by in vitro clonal systems, which may be important in the functional outcome of the intervention.

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RISK FACTOR ANALYSIS FOR THE DEVELOPMENT OF RESTRICTIVE AND OBSTRUCTIVE PULMONARY FUNCTION CHANGES AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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Pulmonary complications after allogeneic stem cell transplantation (allo-SCT) significantly contribute to morbidity and mortality. We analyzed 207 patients receiving allo-SCT at our institution between 1998 and 2005 for the development of restrictive (PRC) and obstructive (POC) pulmonary function changes. Pulmonary function tests (PFT) were performed before and routinely every 3 to 6 months after allo-SCT. After follow-up >2 years, PFTs were obtained yearly. 142 patients were included according to the availability of PFTs; 65 patients were excluded due to early mortality and/or the lack of PFT data. PRC were defined as a forced vital capacity (FVC) at least once ≤90% of pre-transplant values, POC as a forced expiratory volume (FEV1) at least once ≤80% of baseline. Median time of follow-up was 1071 days (107–2924). For PRC, median time of first onset was at 180 days (30–1482) and for POC at 270 days (60–1800) after allo-SCT. The cumulative incidence for PRC was 70.7% and for POC 34.2%. Risk factor analysis included patient/donor age and gender, type of transplant, stem cell source, conditioning regimen intensity, TBI, T cell depletion, pretransplant-CMV serology of donor and recipient, acute (aGVHD) and chronic GVHD (cGVHD) and previous thoracic irradiation.

In univariate analysis, positive patient CMV serology was associated with the development of both PRC ($p = 0.05$) and POC ($p = 0.005$), whereas CMV immunity of the donor affected only the risk of POC ($p = 0.002$). In addition, the cumulative incidence of POC rose to 57.3% when both donor and recipient had positive pretransplant anti-CMV immunity ($p = 0.0002$) and to 51.4% in patients with proven CMV reactivation ($p = 0.1$). cGVHD increased the risk of POC ($p = 0.0045$) but not of PRC ($p = 0.127$). Risk factors for PRC but not POC were bone marrow derived stem cells ($p = 0.045$) and female patient gender ($p = 0.057$). In multivariate analysis, cGVHD ($p = 0.037$; HR 2.3 [1.1–5.0]), anti-CMV IgG positivity of the donor only ($p = 0.026$; HR 2.3 [1.1–5.29]) and of both donor and recipient combined ($p = 0.004$; HR 3.7 [1.5–9.3] were independent risk factors for POC, the latter also being the only independent risk factor identified for PRC. Therefore, our data confirm the previously described association between cGVHD and the development of pulmonary obstructive changes. In addition, this analysis strengthens the concept, that anti-CMV immunity and CMV reactivation contribute to pulmonary function impairment after allo-SCT.

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UNRELATED CORD BLOOD TRANSPLANTATION (UCBT) FOR TRANSFUSION-DEPENDENT THALASSEMIA – A CIBMTR AUDITED RETROSPECTIVE ANALYSIS OF 51 CONSECUTIVE PATIENTS

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UCBT offers a cure for thalassemia and has advantages as a stem cell source for minorities where thalassemia is prevalent, but cell