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Table 1. Baseline patient characterisitcs

Patient Characteristics	TCD group (n=95)	Non-TCD group (n=55)
Sex: n (%)		
Men	60 (63)	34 (62)
Women	35 (37)	21 (38)
Age: median (range)	50 (17-69)	48 (20-63)
Diagnosis: n (%)		
Acute Leukemia/MDS	53 (56)	35 (64)
Non-Hodgkin Lymphoma	23 (24)	4 (7)
Chronic Leukemia	9 (9)	14 (25)
Others	10(11)	2 (4)
Conditioning regimen: n (%)		
Myeloablative	69 (72.6)	45 (81.8)
Reduced intensity / non-myeloablative	26 (27.4)	10 (18.2)
Risk group: n (%)		
Standard risk	13 (14)	21 (38)
High risk	82 (86)	34 (62)
Donor type: n (%)		
Sibling	36 (37.9)	39 (70.9)
Unrelated	59 (62.1)	16 (29.1)
HLA mismatch: n (%)	13 (13.7%)	4 (7.3%)
CD 34+ dose: median (range) x 10*6/Kg body wt.	6.2 (1.9-16)	5.4 (1.2-12.9)

(28.9% v 50%; p = 0.06), URD (48.3% v 64.7%; p = 0.23) and HLA mismatched AHCT (p = 0.59), were not significantly different. The incidence of chronic GVHD in the TCD and non-TCD groups was 41.1% (n = 39) and 45.5% (n = 25) respectively (p0.86). On subgroup analysis of patients undergoing matched sibling, URD and HLA-mismatched AHCT, no significant difference in rates of cGVHD between the two groups was seen (p > 0.05). Relapse rates in the TCD and non-TCD groups were 32.6% and 40% (p = 0.22) respectively. The overall survival at 3years was 39.2% in the TCD group and 39.3% in the non-TCD group; p = 0.93. The 3year progression free survival in similar order were 34.8% and 27.2% respectively (p = 0.85). Non relapse mortality at day 100 respectively were 12.8% and 16% and at 3years were 40% and 41% (p > 0.05).

Our limited, single institution experience in a cohort of 150 consecutive patients suggest no significant benefit with routine use of *in vivo* TCD with AHCT. These results highlight the need to develop novel strategies for preventing GVHD and for improving transplantation outcomes.

430

OUTCOMES FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION FOR WISKOTT ALDRICH SYNDROME

Shin, C.R.[1], Kim, M.[2], Li, D.[2], Jordan, M.B.[3], Bleesing, J.J.[3], Jodele, S.[3], Mehta, P.[3], Marsh, R.[3], Filipovich, A.H.[3] [1] Lucile Packard Children's Hospital, Palo Alto, CA; [2] Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3] Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Human leukocyte antigen (HLA) identical sibling donor transplantation remains the treatment of choice for Wiskott Aldrich Syndrome (WAS), however, utilization of alternative donor sources has significantly increased since 1990. We report the hematopoietic cell transplantation (HCT) outcomes of 47 patients with WAS treated at a single center since 1990 with significant improvement in outcomes after 2000 despite the increased use of alternative donors. 5 year overall survival (OS) improved from 62.5% (95% CI: 34.9% to 81.1%) to 90.8% (95% CI: 67.7% to 97.6%) for patients transplanted during 1990-2000 and 2001-2009, respectively. When adjusted for age at HCT, OS was significantly higher in the 2001-2009 era (p = 0.04, Cox proportional hazard analysis). No early transplant related mortality (within the first 100 days) occurred among patients transplanted during 2001-2009 compared to 3/16 during 1990-2000, (p = 0.03, Fisher's exact test). The extent of HLA mismatch did not significantly affect the incidence of acute GVHD, chronic GVHD, or survival. Post-HCT autoimmune cytopenias were frequently diagnosed after 2001: 17/31 (55%) patients. Their occurrence was not associated with transplant donor type (p = 0.53), or occurrence of acute GVHD (p = 0.74), chronic GVHD (p = 0.12), or mixed chimerism (p = 0.50).

431

ALLOGENEIC STEM CELL TRANSPLANTATION FOR CHRONIC ACTIVE EBV INFECTION (CAEBV)

Craddock, J.A.[1], Bollard, C.M.[1], Krance, R.A.[1], Cowan, M.J.[2], Cairo, M.S.[3], Heslop, H.E.[1], Gottschalk, S.[1] [1] Baylor College of Medicine, Houston, TX; [2] UCSF Children's Hospital, San Francisco, CA; [3] Columbia University, New York, NY

Chronic active Epstein Barr virus infection (CAEBV) encompasses a variety of EBV-associated lymphoproliferative diseases (LPD) in the non-immunocompromised host. In CAEBV either B, T, and/or NK cells are primarily infected with EBV and patients present with a variety of clinical signs and symptoms including fever, hepatosplenomegaly, and lymphadenopathy. While rare in the Western hemisphere, T and NK cell CAEBV is most commonly seen in Japan. In Japan, current treatment protocols rely on chemotherapy and hematopoietic stem cell transplantation (HSCT).

To evaluate the clinical outcome of HSCT in CAEBV patients in the United States, we reviewed our experience with 6 CAEBV patients (4 T-cell, 1 NK-cell, 1 B-cell), who underwent allogeneic HSCT for their disease. Median age at transplant was 11 yrs (range 6 – 25 yrs) and the median time to transplant from diagnosis was 3.7 years (range 4.3 yrs – 8.5 yrs). Four of 6 patients had persistent or refractory disease at the time of HSCT. Four patients received myeloablative conditioning while 2 patients received reduced intensity conditioning (RIC). Median time to neutrophil engraftment was 16 days (range days 11 – 21 days) with no long-term engraftment failure. Five patients received infusions of donor derived EBV-specific cytotoxic T cells (CTLs) at a median of 6 months (range 2.5 months – 12 months) post HSCT. Five patients are alive and in complete remission with a median survival of 2.5 yrs (range 7 months – 10 yrs). One patient developed recurrent T-cell CAEBV immediately post transplant and died of an aggressive T-cell lymphoma 3.7 years post transplant.

Our results support published data from Japan showing good outcomes for CAEBV patients after allogeneic HSCT. Factors that may influence outcome and warrant further study include the timing of transplantation after diagnosis and the use of EBV-directed T-cell therapies.

432

HAPLOIDENTICAL STEM CELL TRANSPLANTS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN FIRST OR SECOND REMISSION

Kennedy-Nasser, A.A., Leung, K.S., Martinez, C.A., Bollard, C.M., Gottschalk, S., Craddock, J.A., Ahmed, N., Heslop, H.E., Brenner, M.K., Krance, R.A. Baylor College of Medicine, Texas Children's Hospital, Houston, TX

Allogeneic hematopoietic stem cell transplant (SCT) offers curative therapy to children with high-risk or relapsed acute lymphoblastic leukemia (ALL). Here, we report encouraging results using haploidentical related donor CD34+ selected (T-cell depleted) peripheral blood stem cell transplants in children with ALL in first or second remission (CR1 or CR2). From May 2002 to September 2009, we transplanted 17 children (13 male, 4 female) in CR1 (n = 6) and CR2 (n = 11) using primarily a fully myeloablative conditioning regimen consisting of cyclophosphamide 45mg/kg x 2 doses, cytarabine arabinoside 3gm/m^2 x 6 doses and total body irradiation (TBI) 1400cGy (n = 12). Five patients received either a reduced-intensity regimen or busulfan-based regimen for clinical purposes (such as to avoid TBI exposure). All patients received alemtuzumab (3, 5 or 10mg/dose depending on body weight) during conditioning for *in vivo* T-cell depletion to promote engraftment and provide additional GvHD protection. If the infused T-cell dose was less than

$5x10^4$ CD3 cells/kg, no additional GvHD prophylaxis was administered. The median age at transplant was 9.9 years (range, 2.9 to 21.6) and median follow-up 44 months post SCT (range, 13 to 102). Median CD34+ cell dose infused was $1.14x10^7$/kg (range, 0.49-$6.83x10^7$/kg) and median CD3+ T-cell dose was $3.08x10^4$/kg (range, $1.8x10^4$-$1.6x10^5$/kg). The rate of donor engraftment was 82.4% – 3 patients failed to achieve initial donor engraftment but did so after receiving subsequent haploidentical SCT. Eleven of 17 (65%) patients received additional T-cell therapies post SCT (donor lymphocytes for mixed chimerism, cytotoxic T-lymphocyte therapy or planned T-cell addback strategies to re-establish T-cell immune reconstitution) and 2 received additional CD34+ cells for poor graft function. Two-year disease-free survival for these children is 60.5%. Of the 5 children who died, 2 died of relapse and 3 of treatment-related causes, primarily infection. One patient with p53 mutation developed secondary MDS 2 years post SCT and is alive with disease. In conclusion, while this data is preliminary, haploidentical transplants using *in vivo* T-cell depletion with alemtuzumab and *ex vivo* T-cell depletion with CD34+ selection offers promising clinical results in children with ALL in CR1 or CR2. With the addition of new clinical immunotherapy trials post SCT, we hope to achieve even higher survival with decreased relapse and deaths related to viral infection.

433

LEUKEMIA RELAPSE: DETECTED BY BONE MARROW CHIMERISM ANALYSIS BUT MISSED BY PERIPHERAL BLOOD ENGRAFTMENT MONITORING ALONE

Chen, J.[1], Chang, C.-C.[1,2], Land, G.[1,2] [1]The Methodist Hospital, Houston, TX; [2]Weill Cornell Medical College, Houston, TX

Chimerism analysis is frequently used for the surveillance of engraftment especially post allogenic stem cell transplantation for malignant hematopoietic diseases (HSCT). The most common method, PCR-based short tandem repeats (STR) analysis, offers high sensitivity and specificity in monitoring graft chimerism after HSCT. Multiple panels of STRs have been developed for use on bone marrow aspirate (BMA) and peripheral blood (PB). In accordance with 2001 workshop (tandem meeting ASBMT) recommendations, PB has been widely used to serially characterize the hematologic course of engraftment and/or occurrence. In the present study, we evaluated the value of STR assay for surveillance of acute leukemia relapse in patients with established HSCT engraftments. A total of 87 HSCT recipients with clinically stable and established engraftment were retrospectively analyzed. All cases had been monitored by serial STR analysis using both BMA and PB samples with a commercially available panel of ten markers (D3S1358-vWA-FGA-AMEL-D8S1179-D21S11-D18S51-D5S818-D13S317-D7S820). Additionally, patients' bone marrow biopsies were also reviewed at the time of BMA STR analysis. Among these 87 patients, 70 patients sustained complete remission and their PB and BMA showed 100% donor origin in the STR assays. There were 17 patients who had relapse ranging from 81 days to 442 days after transplantation, as documented by BM biopsy and/or clinical presentation. All of these 17 patients showed a mixed chimerism on BMA STR assay at the same time BM biopsy showed relapse. In these relapse patients, the percentage of donor origin were lower in granulocytes than in mononuclear cells (52.4±8% *vs* 84.5±4%; $p < 0.05$) while 3 patients showed mixed chimerism in the mononuclear cells only. In contrast, there were 4 out of the 17 patients with negative PB STR assays in the immediate time period around which the BMA STR analysis became positive. Interestingly, in one patient when BM STR assay showed mixed chimerism, the BM biopsy obtained at the same time was inconclusive for relapse. Our findings indicated that caution should be taken when using PB STR solely to monitor leukemia relapse because it may miss early recurrence. This may delay a change in treatment. Second, BM STR assay is a very sensitive method in HSCT surveillance even in patients with a negative or inconclusive BM biopsy. At last, mononuclear cells are more sensitive in detecting mixed chimerism than granulocytes.

434

FACILE DOUBLE CORD TRANSPLANT SCREENING AND MONITORING

Bost, D.A., McLaughlin, I.J., Beckert, S. Celera, Alameda, CA

STR-PCR is limited in its utility for screening and monitoring of donors and recipients in double cord transplants, given its inherent lack of sensitivity and the presence of stutter artifacts which obscure potentially informative alleles. If markers are identified for each individual in a double cord transplant, the manual execution of the algorithm for quantification of individuals is quite time-consuming. To simplify these analyses, we designed a multiplexed system of RUO assays and software enabling instantaneous marker identification and quantification post-PCR.

We employ a panel of 34 quantitative PCR research assays to biallelic indels in which the probability of finding at least one informative marker is > 99.9% in unrelated individuals (Caucasian, African, Japanese, Amerindian populations). The probability of finding at least one informative marker in siblings is > 99%, 98%, 98% and 97% for European Caucasian, Japanese, Amerindian and African populations, respectively.

Results: Each research assay was tested using simulated DNA mixtures at 0.05%, 0.1%, 0.2% and 0.4% minor component for 250 ng of input genomic DNA. Each assay detected the 0.05% minor component mixture. The limitation at this low sensitivity is input copy number. In addition, each of the assays in the panel was able to detect, with statistical significance ($p < 0.05$), the 2-fold change between the 0.1% and 0.2% minor component mixtures. Multiple assays tested on the same mixtures gave highly reproducible results. We also developed research use software allowing for facile analysis of marker screening and post-transplant monitoring quantification. Results are generated with one click of a mouse button.

Conclusions: Use of this research qPCR system for screening and engraftment monitoring of double cord transplants would enable rapid identification of informative markers and several logs increase in sensitivity over the current standard practices. The ability to detect early changes in increasing mixed chimerism, with greater accuracy and precision, allows for more effective research into the potential benefits of earlier detection of clinically significant events, such as relapse or rejection.

435

ATTEMPTS TO OPTIMIZING THE OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN OLDER PATIENTS (≥60 YEARS) WITH ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME

Hu, J.[1], Sykes, J.[2], Panzarella, T.[2], Sharma, A.[1], Kuruvilla, J.[1], Lipton, J.H.[1], Wright, J.[1], Messner, H.[1], Gupta, V.[1] [1]Princess Margaret Hospital, Toronto, ON, Canada; [2]Princess Margaret Hospital, Toronto, ON, Canada

Using a non-myeloablative (NMA) regimen [Fludarabine 125 mg/m^2 and total body irradiation (TBI) 200cGY], we previously reported the feasibility of allogeneic hematopoietic cell transplantation (HCT) in older patients (n = 24) with AML/MDS using matched sibling donors (MSD) (Gupta et al, 2005, BBMT). GvHD prophylaxis was with Cyclosporine (CsA) (42 days) and Mycophenolate (MMF) for (30 days); CsA was tapered at 42 days in the absence of GvHD. While survival was reasonable; 2 main issues were identified: early relapse and severe chronic GvHD in some patients. To address these issues, we added IV Busulphan (3.2 mg/KBW IV daily x 2 days) to Flu/TBI regimen, and increased the duration of GvHD prophylaxis with CsA from 42 days to 100 days. We compare the outcomes of these 2 sequential strategies: Cohort 1 (n = 24, treated 2000-2004), less intense NMA regimen and shorter GvHD prophylaxis; Cohort 2 (n = 31, treated 2005-2009), more intense NMA regimen and longer GvHD prophylaxis. The median age of all study patients (n = 55) was 63 years (range 60-71); 47 (86%) had AML in CR1 (n = 33) or CR2 (n = 14), and 8 (14%) had MDS; 22% had severe comorbidities; and 29% had adverse risk cytogenetics. Baseline characteristics were well-matched in the two cohorts, except cohort 2 had 6 (19%) patients with unrelated donors HCT. Median follow-up of survivors in cohort 1 and 2 was 72 months (13-102) and 31 months (16-49), respectively. A significantly higher proportion of patients had grade ≥ 2 stomatitis (Bearman Criteria) in the later cohort