pts engrafted at a md of 22 (11-41) days. 6 pts lost complete chimerism during follow up with proven relapse at a md of 401 days in four. At a md follow up of 23 (4-79) months probability of overall (OS) vs eventfree survival (EFS) was 74% vs 50% for the whole cohort. A trend towards better survival was seen in recipients of related compared to unrelated transplants (100 vs 64 %, p=0.06) and in those with less advanced disease (90 vs 68 % in Dupriez 0 vs 1+2, p=0.26). However the only significant predictor for OS by log rank test was the pretransplant CCI: 85 vs 34 % in pts with CCI 0 to 2 vs 3 to 6 (p=0.01). Probability of EFS at day 480 was significantly less in pts with abnormal karyoptype compared to those with no detectable anomalies (17 vs 61%, p=0.01). Five pts with decreasing chimerism received immunotherapy (3 DLI, 2 PBSC) with return to complete chimerism in three and postDLI aplasia in one.- **Conclusions:** Our results support the use of related and unrelated alloHCT as a curative treatment option in MMM. Outcome is better in pts without disease associated and disease independent comorbidity. For pts with abnormal karyotype there is a considerable risk of relapse/reversal post transplant. Especially in risk pts chimerism therefore should be monitored closely as disease recurrence may respond to immunotherapy.

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UMBILICAL CORD BLOOD TRANSPLANTATION – REPORT OF 106 CASES FROM A SINGLE BRAZILIAN INSTITUTION

Setubal, D.C.[1], Medeiros, C.P.[1], Bitencourt, M.A.[1], Bonfim, C.M.[1], Funke, V.A.[1], Zanis, J.[1], Cesario, E.[1], Carvalho, D.[1], Nunes, E.[1], Oliveira, M.M.[1], Pasquini, R.[1] [1]BMT Center, Hospital de Clinicas da Universidade Federal do Parana, Curitiba, Parana, Brazil.

Umbilical cord blood (UCB) has been used as a viable source of hematopoietic stem cell for patients that need transplantation but don't have a suitable related donor. Between 1983 and December 2005, we performed 106 cord blood transplantations (CBT) in our institution. Patients (pts) were treated for malignancies (n=46), Fanconi's Anemia (FA) (n=33) and other nonmalignant disorders (n=27). Median age was 6 (<1-55) years. CB units were related in 14 and unrelated in 92 pts and HLA mismatch was 5/6 in 42 and 4/6 in 38 pts. Transplantation conditioning varied according to the disease. Most pts received Cyclophosphamide with total body irradiation or Bussulfan; 54 pts received antithymocyte globulin (ATG) prior the transplantation. Graft versus host disease (GvHD) prophylaxis consisted of Cyclosporine A (CsA) + methyprednisolone in 68 pts and CsA + Methotrexate in 25 pts. Median nucleated and CD 34 cells were 6.85×10^7/Kg and 1.3×10^5/Kg respectively. Engraftment was reached in 57% of pts. Acute GvHD grade II-IV developed in 46% and extensive chronic GvHD in 18% of pts. The overall survival was 49% after median follow-up of 2.1 years. Engraftment failure (28,3%) was the main cause of death. In the Cox regression analysis ATG in the conditioning regime (p=0.002), HLA compatibility (p=0.03) and infused nucleated cell dose $\geq 3 \times 10$ 7/Kg (p=0.01) were independent predictors of neutrophil engraftment. Age $\leq$ 3 years (p=0.01), bleeding after transplantation (p<0.001) and infection with identified agent (p=0.002) were significantly associated with overall survival. CD 34 cell count and viability, clonogenic capacity, original UCB bank, cryopreservation time, malignant disease status and donor type (related vs unrelated) were not associated with engraftment or overall survival. These results confirm that HLA compatibility and the number of nucleated cells are significantly associated with neutrophil engraftment. We concluded that, despite a high engraftment failure observed, UCB is a feasible source for transplantation.

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DEMONSTRATION OF A SINGLE MIHA SPECIFICITY RECOGNIZED BY MEMORY CD8 T CELLS WHICH INDUCES RESISTANCE TO MHC-MATCHED HEMATOPOIETIC ALLOGRAFTS

Shatry, A.M.[1], Levy, R.B.[1] [1]University of Miami, Miami, FL.

T cells that recognize transplantation antigens arise in sensitized individuals following multiple blood transfusions or marrow transplants as well as in multiparous females. Resistance to allogeneic hematopoietic cell transplantation (HCT) in such sensitized individuals is consistent with the presence of a host memory T cell (TM) population specific for donor cell antigens. We hypothesized that a single donor minor histocompatibility (MiHA) epitope could elicit antigen-specific CD8 TM capable of resisting MHC-matched allogeneic hematopoietic cell engraftment. To address this question, B6 mice were sensitized 2X to the H60 immunodominant MiHA epitope utilizing marrow-derived dendritic cells pulsed with the H60 (LTFNYRNL) peptide. Three weeks following booster sensitization, circulating CD8 TM ($CD44^{hi}$, Ly $6C^+$) were detected by tetramer staining. B6 ($H2^b$) mice containing $CD8^+$ $H60^+$ T cells were subsequently conditioned with 9.0 Gy TBI and transplanted with 5×10^6 BALB.B ($H2^b$) BM-TCD. One week post-transplant, naive recipients of BALB.B ($H60^+$) or B6-H60 congenic TCD-BM contained >10-fold higher levels of circulating donor cells than the B6 dendritic cell/peptide sensitized recipients. Donor progenitor cells were also significantly reduced in sensitized recipients of allogeneic TCD-BM at this time. In contrast, two weeks post-HCT, recipients of syngeneic marrow exhibited >10-fold greater frequency of circulating donor cells compared to recipients of MHC-matched allogeneic marrow (< 5% donor chimerism was detected). These findings demonstrate that host T cells against a single donor MiHA determinant are sufficient to induce resistance to MHC-matched allogeneic marrow engraftment. These effector responses during HVG stand in contrast to those by donor T cell responses post-HCT in which single MiHA differences fail to induce GVHD. Finally, heterologous immunity to virus generates allo-reactive TM cells. Since such TM repertoires could include specificity for MiHA immunodominant epitopes, the presence of TM populations that can mediate resistance in 'naïve' recipients may be more prevalent than previously considered.

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SAFETY AND EFFICACY OF HIGH-DOSE BUSULFAN BY 90-HOUR CONTINUOUS INFUSION IN HEMATOLOGIC MALIGNANCY PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTS

Shea, T.[1], Walko, C.[1], Serody, J.[1], Gabriel, D.[1], Comeau, T.[1], Rao, K.[1], Ivanova, A.[1], Sharf, A.[1], Krasnov, C.[1], Coghill, A.[1], Whitley, J.[1], Lindley, C.[1] [1]University of North Carolina at Chapel Hill, Chapel Hill, NC.

Busulfan is used in allotransplantation for patients with hematologic malignancies. IV busulfan has recently become available and is widely used qd or qid x 4 with fludarabine in both ablative and reduced-intensity regimens. We have previously demonstrated the benefit of using a test-dose of IV busulfan to predict the systemic exposure of this drug (Walko, ASCO, 2005) and report here on this approach in pts receiving a 90 hr continuous infusion of full-dose busulfan. **Methods:** All pts received a 0.8 mg/kg test dose administered over 2 hours and PK sampling at times 0, 2.5, 4, 5, and 6 hours. Pts began treatment with 30 mg/m2 fludarabine qd x 5 and either 0.8 mg/kg ABW IV busulfan (18 pts) or targeted busulfan to achieve an AUC of 4800 (6 pts) or 5700 (5 pts) umole/min/hr/day on days –7 to –3. PK sampling was done at hours 0, 12, 16, 18, 48, 60, 72, and 89.5. All pts received tacrolimus and 0 (9 pts), 1 (10 pts), 2 (8 pts) or 3 (2 pts) doses of 30 mg of IV alemtuzamab based on disease and donor type for prevention of GVHD prior to initiation of chemotherapy. The initial 18 pts were studied without dose adjustments, followed by dose escalation with targeted systemic exposure of the busulfan and dose adjustments as needed in the last 11 pts treated. **Results:** 29 pts (15 MRD, 14 MUD) ages 18-55 (median 40) with high-risk AML (15), ALL (5), CML (2), IMF (2), MDS (2), or other diseases (3) were enrolled. All pts engrafted with a median of 14 days to an ANC > 500 and 7 days to a platelet count > 20K. No regimen-related deaths were observed in the first 100 days post-transplant. Two patients had transient grade 3 hepatitis and two had grade 3 mucositis. There have been no cases of VOD, pulmonary fibrosis, alveolar hemorrhage or CNS toxicity. One death at day 190 from pneumonia and one at day 191 from hemorrhagic cystitis and enterococcal sepsis occurred for a non-relapse mortality rate of 7%. 14 pts have developed grade 2, one grade 3 and one grade 4 aGVHD. 6 have extensive and 2 have limited