DYNAMICS OF RECOVERY IN DOUBLE UMBILICAL CORD BLOOD TRANSPLANTATION WITH AN EX-VIVO MESENCHYMAL CELL EXPANDED UNIT: FASTER RECOVERY WITH ENGRAFTMENT OF THE EXPANDED UNIT
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Double cord blood transplantation (CBT) with ex-vivo expansion aims at overcoming the delayed engraftment frequently observed after CBT. Thirty-one patients received myeloablative therapy with melphalan, fludarabine, thiotepa and ATG followed by double CBT for treatment of hematologic malignancies. One of the 2 units was expanded (exp) ex-vivo in a co-culture with either third party haploidentical family member marrow derived mesenchymal stem cells (N = 8) or off-the-shelf mesenchymal progenitor cells from Angioblast (N = 23). Both CB units were matched in at least 4/6 HLA antigens with the patient, and contained a minimum of 1x10^7 TNC/Kg per unit. The majority of patients (pts) received CBT for treatment of acute leukemia including AML / MDS (64%) and ALL (19%), and 42% were in remission at CBT. Median age was 36 years (range 2.8-62). The non-exp unit was matched with the pt in 6/6 HLA antigens in 3%, 5/6 in 26% and 4/6 in 71% of cases; the corresponding distribution for the exp unit was 6%, 29%, 64%. Engraftment was documented in 29 evaluable pts at a median of 15 (range 9 to 42) days for neutrophils and 40 (range 18 to 62) days for platelets. Day 30 chimerism showed evidence of engraftment of the non-exp unit only in 15 (52%) pts, and of both units in 13 (45%) pts, including 9 and 4 in whom the non-exp and the exp unit dominated, respectively. Chimerism was undetermined in 1 pt. Comparison of the rate of recovery in pts who had (N = 13) and those who did not have (N = 15) evidence of engraftment of the exp unit showed that neutrophils and platelet recovery was faster when the exp unit engrafted (median of 15 vs. 19 days for neutrophils; and 38 vs. 40 days for platelet). This difference did not reach statistical significance however. The median numbers of TNC and CD34+ cells/kg were significantly higher in the exp group than in the non-engrafted exp unit (p < 0.05). Sixteen pts were diagnosed with grade II-IV aGVHD including 12 within 100 days post CBT. GVHD was severe (grade III-IV) in 5 pts. On univariate analysis, there was a trend for a higher 6 month rate of grade II-IV aGVHD when the exp unit engrafted (cumulative incidence (CI) 65% vs 49%, P = 0.2); when the non-exp unit was only 6/6 HLA matched with the pt (CI 65% vs 25%), p = 0.2; and when CMV serostatus was reactive in both the recipient and in the non-exp unit (CI 77% vs 35%, p = 0.1). The investigation of CB expansion is warranted in a larger study population and accrual to our study continues.

L-LEUCYL-L-LEUCINE METHYL ESTER (LLME) TREATED NON-MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR PATIENTS WITH HEMATOLOGICAL MALIGNANCIES
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GVHD remains an obstacle for allogeneic HSCT. While T cell depletion of donor grafts results in much lower incidences of GVHD, rejection and poor immune recovery are often associated with this approach. To address these issues, we developed a transplant approach using LLME to test the hypothesis that the selected depletion of T cells containing cytotoxic effector granules would result in less significant GVHD while at the same time preserving GVT effects and infectious immunity. LLME preferentially kills cytotoxic effector granule bearing lymphocytes including most NK and CD8 T cells with relative sparing of CD4 T cells. Patients were conditioned with fludarabine/TBI 200cGy conditioning with cyclosporine (CSA) and mycophenolate mofetil (MMF) graft versus host disease (GvHD) prophylaxis. Prior to the infusion of the donor inoculum, we performed CD34 selection using the Isolux® system to separate the graft into CD34+ and CD34- fractions. The CD34+ fraction was then treated with LLME to selectively deplete the cytotoxic effector granule containing subset, thus avoiding stem cell exposure to LLME. Patients received the CD34 selected stem cell product (median CD34 dose 4.13 x 10^6/kg). This HSC product contained 5 x 10^6 untreated CD3 cells/kg in the initial 6 patients treated, but due to significant GVHD, the final 8 patients received 2.5 x 10^6 untreated CD3 cells/kg. One day later, the LLME treated CD34+ fraction (median CD3 dose 8.74 x 10^6/kg) was infused. One patient died shortly after the stem cell infusion from infectious complications. All 13 evaluable patients engrafted WBC by day 14. Two patients experienced late rejection. One of these patients is still alive 3 years later with evidence of recurrent disease and the other patient eventually died of relapsed disease. Of the remaining 11 patients, 3 patients developed grade III-IV GVHD and 1 patient developed cGVHD. All 4 of these patients died of GVHD related causes. Three patients died of complications from relapsed disease and 1 additional patient died of infectious complications. Four patients are alive at a minimum of 3 years post transplant. Two of these patients have relapsed disease, 1 patient is disease free with 100% donor chimerism and one patient is disease free with a persistence of 5% host cells. This study shows that LLME can be used to treat lymphocytes without affecting initial engraftment, but relapse and GVHD remain significant barriers in this high risk population.