OUTCOME FOLLOWING UNRELATED CORD BLOOD TRANSPLANT IN 136 PATIENTS WITH MALIGNANT AND NON-MALIGNANT DISEASES: A REPORT FROM THE AUSTRALIAN AND NEW ZEALAND CHILDREN’S HAEMATOLOGY AND ONCOLOGY GROUP (ANZCHOG)

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Unrelated cord blood (UCB) is an alternate stem cell source for patients lacking matched family donors. Speed of availability, tolerance of HLA disparity, reduced acute GVHD and reduced risk of viral disease transmission are advantages of UCB over unrelated bone marrow. We report the results of all unrelated UCB transplants performed in Australasian paediatric HSCT centres over the last 10 years. Between April 1995 and July 2005, 136 patients were transplanted for malignant (n = 101; 74%) and non-malignant (n = 33) diseases. Log-rank tests and Cox regression analysis were used to determine the effects of demographic, graft-related and treatment factors on engraftment, GVHD, TRM and survival. Median follow-up for surviving patients is 19 months (range, 1-108). The median age and weight of recipients is 5.1 years (range, 0.2 to 18) and 19 kg (range, 7 to 101), respectively. Median infused total nucleated cell (TNC) dose was 4.6 x 10^8/kg (range, 0.7-49.9) and median infused CD34 cell dose was 1.9 x 10^7/kg (range, 0.1-33). 16% of patients received a 6/6 HLA-matched unit, 44% a 5/6, 39% a 4/6 and 1 patient received a 3/6 HLA-matched unit. The incidence of neutrophil recovery by day 42 was 0.82 (95% CI, 0.75-0.89) with a median time of 23 days to achieve a platelet count of 20 x 10^9/L. The incidence of platelet recovery by day 60 was 0.46 (CI, 0.37-0.55) with a median time of 47 days to achieve a platelet count of 20 x 10^9/L. Incidences of grades II-IV and III-IV acute GVHD were 0.41 (CI, 0.32-0.5) and 0.18 (95% CI, 0.10-0.26), respectively. TRM and survival at 1-year post transplant was 0.31 (CI, 0.23-0.39) and 0.62 (CI, 0.54-0.70), respectively. Leukaemic relapse at 2 years was 0.23 (CI, 0.12-0.34). In Cox regression analysis, time to engraftment was consistently the only factor identified to be of significance. Time to engraftment was significantly faster when the infused CD34 dose was >1.7 x 10^7/kg (P = .001) (median 18 days (CI 16-20) vs. 26 days (CI 22-29). A TNC dose of 3.0 x 10^8/kg was associated with higher overall engraftment rates but had no significant impact on speed of engraftment (P = .08). This large paediatric series confirms that unrelated UCB is a viable stem cell source and that higher CD34 cell doses results in a significantly faster time to engraftment.

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A SELECTABLE BICISTRONIC RETROVIRAL VECTOR CORRECTS THE MOLECULAR DEFECT IN A CELL LINE DERIVED FROM A PATIENT WITH LEUKOCYTE ADHESION DEFICIENCY

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Leukocyte adhesion deficiency (LAD) is an immunodeficiency disease resulting from defects in the integrin CD18. Children with LAD suffer severe, recurrent bacterial infections due to failure of leukocytes to adhere to endothelium and migrate to sites of infection. Approximately 75% of severe LAD patients die by two years of age. Allogeneic hematopoietic stem cell transplant after myeloablation can cure LAD, however regimen-related toxicity and graft-vs.-host disease (GVHD) limit the use of this approach. Genetic correction of autologous CD34+ cells represents an optimal therapy for LAD since no donor is required, nor is GVHD a risk. In this study we developed a retroviral vector that confers a selectable growth advantage for pre-clinical testing of gene therapy in the canine model of LAD (CLAD). This retroviral vector allows for correction of the CD18 defect in CLAD and selection of the corrected cells. The vector, MSCV(5A18IRES-MGMT+1P44K, harbors the canine CD18 cDNA followed by an internal ribosome entry site (IRES) for expression of mutated canine methylguanine methyltransferase (MGMT). Mutant MGMT confers resistance to the combination of carmustine (BCNU) and O6-benzylguanine (BG). A high-titer producer line was identified using the PG13 packaging line, and supernatant from this producer line was used to transduce an EBV-transformed B cell line derived from a CD18- LAD patient. Transduced and mock-transduced cells were grown in 25 μM BG and increasing concentrations of BCNU. In one experiment, 5 μM BCNU + 25 μM BG allowed selection of CD18+ cells to >99% purity, however a distinct CD18- population remained. In a second experiment, cells selected in 10 μM BCNU + 25 μM BG were ~99.9% CD18+ with no distinct CD18- population. These studies demonstrate that a bicistronic retroviral vector leads to selection of a population of molecularly corrected LAD cells. Selection was achieved despite placement of MGMT after the IRES, where expression of the selectable gene product is expected to be decreased. Experiments with CD34+ cells from CLAD dogs will allow this approach to be tested in vivo. These studies
SOLID TUMORS

EUROPEAN EXPERIENCE OF ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR METASTATIC RENAL CARCINOMA: ON BEHALF OF THE FRENCH ITAC GROUP AND THE EBMT SOLID TUMOUR WORKING PARTY

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The immunological graft-versus-tumor (GVT) effect has been reported in various solid cancers after allogeneic hematopoietic stem cell transplantation (HSCT). We evaluated the experience of allogeneic HSCT for renal cell carcinoma (RCC) in Europe. Methods and Patients: We report the data on 124 patients with clear cell RCC, median age 52 years (range 18-68) transplanted in 21 European centers. Various reduced intensity conditioning (RIC) based on fludarabine were used. All patients received allogeneic peripheral blood cells: 106 from an HLA-identical sibling, 5 from mismatched related donor and 13 from matched unrelated donor (MUD). GVHD prophylaxis consisted of cyclosporine A (CyA) alone, or combined with methotrexate or mycophenolate mofetil. All patients with mismatch or MUD received anti-T-lymphocyte immunoglobulin. Donor lymphocyte infusions (DLI) were given to 42 patients. The median follow-up was 15 months (range 3-41). Results: All but 3 patients engrafted. The cumulative incidence of grades II-IV acute graft-versus-host disease (GVHD) was 40% and for chronic GVHD it was 33%. Transplant-related mortality was 16% at one year. Complete (n = 6) or partial (n = 24) responses, median 130 (range 42-600) days posttransplant, were associated with time from diagnosis to HSCT, mismatched donor and acute GVHD II-IV. Factors associated with survival included chronic GVHD (hazards ratio, HR 4.12, P < .001), 3 metastatic sites (HR 2.61, P < .03), Karnofsky score < 70 (HR 2.33, P = .03). Patients with chronic GVHD and given DLI (n = 17) had a 2-year survival of 70%. Conclusions: Our data demonstrate that i) RCC patients with less than 3 metastatic locations and a Karnofsky score > 70% may be considered for HSCT, ii) RIC and allogeneic HSCT is feasible in RCC patients with a low non-progression-mortality (16%), iii) a clinically meaningful GVT effect can be generated in these patients, often associated to DLI and chronic GVHD.