CLINICAL CELLULAR THERAPY

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In Vitro Expanded Umbilical Cord Blood T Cells Used for Donor Lymphocyte Infusions after Umbilical Cord Blood Transplantation

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Umbilical cord blood (UCB) is an alternative graft source for hematopoietic stem cell transplantation and has been shown to yield results comparable to transplantation with other stem cell sources. Donor lymphocyte infusion (DLI) is an effective treatment for relapsed hematological malignancies after hematopoietic stem cell transplantation. However, DLI is not available after UCB transplantation.

In this study, in vitro cultured T-cells from the UCB graft were explored as an alternative to conventional DLI. The main aim was to study the safety of treatment with the cultured UCB T-cells, as cell products prepared in this particular manner has not been used before. We also wanted to study potential benefits of the treatment.

The cultured UCB T cells (UCB DLI) were given to four patients with mixed chimerism (n = 2), minimal residual disease (n = 1) and graft failure (n = 1). No adverse reactions were seen at transfusion. Graft-versus-host disease (GVHD) is a known risk in conventional DLI treatment. We thus carefully assessed the included patients for signs of GVHD. Three of the patients did not show any signs of GVHD after treatment with UCB DLI. However, GVHD could not be wholly excluded in the last patient. The symptoms were, however, not consistently in temporal association with the treatment, and the patient also had a severe adenovirus infection that could explain the symptoms. In the patient with minimal residual disease, the malignant cell clone was detectable shortly before infusion but undetectable at treatment and for 3 months after infusion. In one patient with mixed chimerism, the percentage of recipient cells decreased in temporal association with UCB DLI treatment.

In summary, we saw no certain adverse effects of treatment with UCB DLI. Events that could indicate possible benefits were seen but with no certain causal association with the treatment.

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Immunological Effects of Decidual Stromal Cell Treatment in Patients with Severe Chronic Graft-Versus-Host Disease

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Introduction: Decidual stromal cells (DSCs) isolated from fetal membranes of term placentas are easily expanded and highly immunosuppressive *in vitro*. DSCs have a high expression of integrins that are of importance for homing to damaged tissue. In the present study, we introduce DSCs as a cellular therapy for chronic Graft-versus-Host Disease (cGvHD).

Patients and Methods: Three patients (1 (ALL), 2 (AML), and 3 (CML)) with severe extensive cGvHD were treated with DSCs (1-2.8 x 10^6 cells/kg). Patients 1 and 2 received two infusions and patient 3 received one dose. One third of DSCs administered to patient 1 and 2 were labelled with ^{111}Indium and the *in vivo*-distribution was tracked for 48h. Blood samples were obtained before and up to 4-10 weeks after the first infusion. Samples were analyzed by flow cytometry and luminex.

Results: All patients had cGVHD of skin, liver and obstructive bronchiolitis. Patients 1 and 2 are regarded as partial responders (PR) and patient 3 as a non-responder (NR). Response was evaluated according to the NIH guidelines for diagnosing cGvHD.

Patients receiving ^{111}In-DSCs showed the same distribution pattern of the isotope over time. The isotope was initially located in the lungs, followed by dissemination to liver and spleen.

The flow cytometry and luminex data are presented as the median frequency of data from all time points for each patient. Patient 3 had high frequencies of HLA-DR$^+$ cells within the CD3$^+$CD4$^+$ cell population (Th) (median 72.9%, range 72.7-73.3%). The corresponding proportions in patients 1 and 2 were 21.5% (17.6-21.9) and 36.5% (25.8-50-8), respectively. Among CD3$^+$CD8$^+$cells (Tc), the frequency of HLA-DR-expression was 33.6% (30.9-37.5), 60.5% (56.7-68.1) and 80.6% (70.8-83.8) for patient 1, 2, and 3, respectively.

The percentage of Th-cells with a naïve (CD45RA$^+$CCR7$^+$) phenotype was 4.8% (3.6-6.3) in patient 3, but 24.4% (4.3-24.4) and 25.1% (11.2-26.3) in patient 1 and 2, respectively. The proportion of terminally differentiated (CD45RA$^-$CCR7$^+$) Th-cells was 2.3% (2.1-2.6), 7.4% (2.4-8.7) and 12.7% (10.9-23.2) in patients 1, 2, and 3, respectively.

The frequency of Tregs (CD4$^+$CD25^{high}CD127$^{low/-}$) was 11.5% (8.63-15.9) for patient 3, whereas they were 6.4% (4.8-6.5) and 3.3% (2.5-4.8) for patient 1 and 2, respectively. Patient 3 had the highest proportion Th-cells with a Th17 (CD45RA$^-$CXCR3$^-$CCR4$^+$CCR6$^+$), Th1/Th17 (CD45RA$^-$CXCR3$^+$CCR4$^-$CCR6$^+$) and Th2 phenotype (CD45RA$^-$CCR4$^+$CXCR3$^-$CCR6$^-$). Patient 3 also had the highest median plasma concentrations of IL-17, IL-4 and IFN-γ.

Discussion: DSCs are safe to infuse with no adverse effects. We determined how stromal cells are distributed *in vivo* following infusion in a GvHD setting. The data also support that the non-responder had a more activated/exhausted immune system than the partial responders. This study may provide a basis for further controlled investigations into use of DSCs as a treatment for severe cGvHD.

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Increased Collection Efficiency of Spectra OPTIA Reduces the Blood Volume Processed to Acquire Targeted CD34+ Dose

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Peripheral blood progenitor cell collection (PBPC) is a routine procedure in auto-HCT recipient and allo-HCT donors. Spectra Optia is a next generation apheresis platform following Cobe Spectra. Increasing the efficiency of PBPC