OMICS Group Conferences
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International Conference on
Hematology & Blood Disorders
September 23-25, 2013 DoubleTree by Hilton Hotel Raleigh-Durham Airport at RTP, NC, USA

From CD34 positive selection, to negative depletion approaches of CD3 and T-cell receptor (TcR)αβ T lymphocytes in haploidentical transplant in Thalassemia patients

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Feto-maternal microchimerism suggests immunological tolerance between mother and fetus. Thus, we performed primary hematopoietic stem-cell transplantation (HSCT) from mismatched mother to thalassemic patient without an HLA-identical donor. 42 patients with thalassemia major were conditioned with 60 mg/kg hydroxyurea and 3 mg/kg azathioprine from day -59 to -11, 30 mg/m2 fludarabine from day -17 to -11, 14 mg/kg busulfan starting on day -10 were administered orally 3 times daily over 4 days in the first 17 patients, and corresponding dose of busulfan give intravenous in the following 25 patients, and 200 mg/kg cyclophosphamide,10 mg/kg Thiotepa, and 10 mg/kg ATG (Fresenius) daily from day -5 to -2. 34 patients received CD34+ mobilized peripheral and bone marrow progenitor cells; 8 patients received marrow graft selected PBSC CD34+ and BM CD3/CD19 depleted. T-cell dose was adjusted to 2x105/kg by fresh marrow cell add back at the time of transplant. Both groups received cyclosporine for graft versus host disease prophylaxis for two months post transplant. 3 patients died, 12 patients reject their grafts, and 27 showed full chimerism with functioning grafts at a median follow-up of 56 months. The overall survival, thalassemia free survival and mortality is 90%; 59% and 11%.To analyze immunohematologic reconstitution, particularly NK cells, we evaluated 13 thalassemia patients after 20 and 60 days and 1 year post transplantation with T cell-depleted HLA-haploidentical stem cells. NKs were the first lymphocytes to repopulate the peripheral blood. A significant increase in CD4+ and CD8+ markers paralleled an increase in CD3-CD16+ NKs, especially with full engraftment. In order to increase the T-cell depletion of PBSC while maintaining the anti-infectious and the engraftment facilitating effects of the depleted grafts, we have introduced the depletion of αβ T Lymphocytes using the CliniMacs System. In addition to the CD3 depletion, αβ-depleted grafts contain large number of γδ T lymphocytes. Studies were then conducted to determine if γδ T cells were capable of preventing graft rejection in the context of haploidentical transplant. Using this new strategies in 3 haploidentical transplant in thalassemia patients we observed more rapid immunological reconstitution after 60 days post transplant, with an increase of T cells (CD4+ and CD8+), B cells (CD19+) and NK cells (especially CD3-CD16+, with cytotoxic potential) in the peripheral blood of these patients.

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