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Outcomes after addition of rabbit-ATG to the standard Bu+CY preparative regimen for allogeneic matched sibling donor (MSD) hematopoietic stem cell transplantation (HSCT) for hemoglobinopathies in children: A single center experience

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Abstract

Introduction: Allogeneic HSCT for hemoglobinopathies following myeloablative conditioning in a matched sibling donor (MSD) setting has resulted in excellent outcomes in children (90–95% EFS). Though the outcomes are encouraging, there is still a 7%–10% incidence of rejection, 15–20% incidence of acute GVHD, and 12%–15% incidence of chronic GVHD. Also, there is a high incidence (15–30%) of non-compliance and lack of adherence with oral medications in this population due to multiple factors. The addition of anti-thymocyte globulin (ATG) leads to in-vivo T-cell depletion improving engraftment. We proposed the hypotheses that using a medium dose of r-ATG (10 mg/kg; Thymoglobulin, Genzyme, Cambridge, USA; equivalent to ~100 mg/kg of Fresenius r-ATG) during the peritransplant period will eliminate the risk of rejection and GVHD, especially in this psychosocially-challenged patient population where non-compliance with GVHD prophylactic medications is very high.

Methods: Patients of severe sickle cell disease (SCD) with sequelae and transfusion dependent beta thalassemi—who had appropriately matched sibling donors—have been enrolled in an IRB approved study since January 2003. All patients have received IV busulfan (16 mg/kg over 4 days with targeted AUC 900–1350 μM/mt, based on first-dose pharmacokinetics), cyclophosphamide (50 mg/kg for 4 days), and r-ATG (Thymoglobulin, 2.5 mg/kg/day from days -6 to -3). GVHD prophylaxis was with cyclosporine (dose adjusted to maintain a nadir serum level of 200–300 ng/ml for 6 months) and a standard short course of methotrexate (15 mg/kg followed by 10 mg/kg IV) given on days +1, +3, and +6. All patients have received levetiracetam for seizure prophylaxis.

Results: Ten patients (8 severe SCD and 2 beta thalassemia) have received the MSD HSCT using the described preparative regimen. Median age of patients' was 4 years (18 months–18 years) and there were 6 females and 4 males. The regimen was very well tolerated. All patients developed mucositis grade II–III. One patient developed mild VOD that responded to supportive care. Most of the patients developed hypertension secondary to cyclosporine use and required aggressive anti-hypertensive management. There was no incidence of seizures or reversible posterior leukoencephalopathy syndrome. One patient developed CMV reactivation on day +17 and responded to IV foscarnet. No other viral (CMV, EBV, HHV-6, etc.) or fungal infections were detected.

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All patients have received BM grafts from MSD with the median cell dose of 3.5 x 10^8 TNC /kg (1.8–10.1 x 10^8/kg). One hundred percent have engrafted with ANC >500 by a median of day +15 (range: 10–23 days). Serial peripheral blood donor chimerism analysis post-HSCT has revealed stable engraftment in all patients ranging from 51–100%. None of the patients have developed acute GVHD. One patient developed limited chronic GVHD of the skin requiring only topical treatment. All patients assessed >1 year post-HSCT have reconstituted their immune system. All SCD patients have shown complete resolution of disease related symptoms. All thalassemia patients are transfusion free and end organ function is stable in all patients >1 year post-HSCT.

Conclusions: Addition of r-ATG to the standard Bu+CY myeloablative regimen has further reduced the incidence of rejection and acute/chronic GVHD without increasing the toxicity or incidence of viral infections in HSCT for hemoglobinopathies.

Keywords: HSCT, hemoglobinopathies, sickle cell disease, sibling donor, rabbit ATG