

Total Body Irradiation Dose De-escalation Study in FA Patients Undergoing Alternate Donor Hematopoietic Stem Cell Transplantation

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Over the last decade, major advances have been made to improve survival of Fanconi anemia (FA) patients undergoing alternate donor hematopoietic stem cell transplantation (HSCT). Currently we are investigating thymic shielding (TS) as a strategy to improve immune reconstitution and reduce the risk of opportunistic infections. One of the remaining major obstacles to long-term survival is the development of late malignancies. We hypothesize that FA patients undergoing alternate donor HSCT can achieve neutrophil engraftment with the use of fludarabine (FLU), cytoxan (CY) and ATG, without the use irradiation. It is anticipated that rates of regimen related toxicity (RRT) and graft-versus host (GVHD) will be lower with this non-irradiation based approach, resulting in improved survival. We also anticipate that risk for late malignancies will be reduced.

Objective: This is a single center, single arm, total body irradiation (TBI) dose de-escalation study designed to determine the lowest dose of TBI required to achieve neutrophil engraftment after alternate donor HSCT in FA patients.

Methods: All patients receive CY 10 mg/kg x 4 days, FLU 35 mg/m² x 4 days and ATG 30 mg/kg x 5 days. Single fractionated TBI (with TS) is given in a dose de-escalation manner in the following cohorts: cohort 1: TBI 300 cGy; cohort 2: TBI 150 cGy; cohort 3: no TBI. GVHD prophylaxis consists of CSA and methylprednisolone. The decision to proceed with each stepwise decrease in TBI is based upon achieving adequate neutrophil engraftment in the current cohort of patients.

Results: Between July 2006-April 2007, 9 FA patients were enrolled in cohort I. They received HLA matched bone marrow (BM, n=5), 5/6 HLA matched BM (n=2) or 5/6 matched umbilical cord blood (n=2). All patients achieved primary engraftment at a median of 11 days after HSCT. One patient developed secondary graft failure at day 178 and died at day 253 from septic shock. Two patients developed grade II acute GVHD and none developed chronic GVHD. 8 of 9 patients are alive and well. A tenth patient is about to undergo HSCT in cohort 1. If primary engraftment is achieved, enrollment will commence in cohort 2 using TBI 150 cGy.

Conclusions: The preliminary results of this ongoing study suggest neutrophil engraftment can be achieved after alternate donor HSCT in FA patients using lower doses of TBI than the standard TBI 450 cGy. These results also suggest that reduced RRT, GVHD and improved immune recovery lower the morbidity and mortality of HSCT. Further enrollment and follow-up are necessary to determine the lowest TBI dose necessary for successful HSCT, and whether a decrease in TBI results in a reduction of late malignancies.

Translational Applicability: The results of this study may provide further understanding of the pathophysiology of late malignancies in FA patients.