PROTOCOL SYNOPSIS - BMT CTN PROTOCOL #0301

Fludarabine-based Conditioning for Allogeneic Marrow Transplantation from HLA-compatible Unrelated Donors in Severe Aplastic Anemia

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Primary Objective: The primary objective of this study is to determine the feasibility and toxicity of employing fludarabine-based conditioning to reduce transplant-related toxicity while maintaining (or ideally improving) engraftment in allogeneic donor marrow transplantation from matched (and mismatched) unrelated donors (MUD) in patients with severe aplastic anemia (SAA). The combination of reduced transplant-related toxicity and preserved engraftment should translate into improvement in long-term survival, which is the ultimate goal of the study. More specifically, the study will determine the degree of cyclophosphamide (CY) dose reduction achievable with the introduction of fludarabine in the preparative regimen, with the goal of maintaining (or improving) engraftment, reducing major transplant-related toxicity and early deaths, and thereby ultimately improving long-term survival. The primary endpoints of the dose-finding (Phase I) portion of the study are engraftment as well as major regimen-related toxicity and early deaths. The primary endpoint of the Phase II portion of the study is the two-year post-transplant survival achieved with the level of CY dose reduction selected in the dose-finding portion of the study.

Secondary Objectives: Secondary endpoints of clinical interest include secondary graft failure and acute and chronic GVHD.

Study Design: The study is a prospective Phase I/II dose optimization study. All patients are given a fixed dose of ATG (either thymoglobulin: 3 mg/kg IV daily x 3 or ATGAM 30 mg/kg IV daily x 3, on Days –4 to –2), Fludarabine (30 mg/m^2 IV daily x 4, on Days – 5 to –2), and TBI (200 cGy from a linear accelerator at ≤ 20 cGy/min on Day –1). The starting CY dose will be 150 mg/kg (50 mg/kg intravenously daily, Days –4 to –2), and will be de-escalated depending on engraftment and toxicity. The Phase I portion of the trial (maximum of 24 patients) tests each of four dose levels of CY for adequate safety and graft retention. The Phase II portion of the trial refines the dose selection and allocates patients to the optimal dose, at which two-year post-transplant survival will be assessed. The combined enrollment in Phase I and II will total 78 patients.

Dosage Levels for CY		
Days	**Dose**	**Total Dose**
3 (Day –4, –3, –2)	50 mg/kg/day	150 mg/kg
2 (Day –3, –2)	50 mg/kg/day	100 mg/kg
1 (Day –2)	50 mg/kg/day	50 mg/kg
0 (None)	None	0 mg/kg

Dose Finding Plan

Patients will be treated in groups of six, with the first patients receiving a dose of 50 mg/kg intravenously daily, on Days –4 to –2 (total dose of 150 mg/kg). The doses to be considered range from 150 mg/kg to 0 mg/kg, in 50 mg/kg decrements. At each dose level, six patients are initially evaluated.

The study design uses an adaptive Bayesian method for dose-finding in Phase I/II clinical trials based on trade-offs between the true (i.e., population) rates of engraftment and toxicity (i.e., severe clinical toxicity, early death or both)[1].

Patients will be enrolled in cohorts of six patients, with a wait period of at least 42 days for endpoint assessment between enrollment of successive cohorts. Doses for subsequent patient cohorts are based on the engraftment and toxicity experience in preceding cohorts. The total sample size of 78 patients enrolled in Phases I and II of the trial contribute to selection of the optimal dose. For a complete description of the Study Design refer to Chapter 5 of the Protocol.

Accrual Objective: A maximum of 78 patients will be enrolled and followed for 24 months post-transplant.

Accrual Period: The estimated accrual period is two to four years.

Eligibility Criteria: Patients up to 65 years of age with a diagnosis of SAA and an available unrelated donor with a 5/6 or 6/6 match for HLA-A, B and DRB1 antigen and willing to provide a marrow allograft. HLA-C typing is also required. If an HLA-C mismatch is present, no other mismatches are allowed.

Treatment Description: The preparative regimen will consist of:

- Fludarabine: 30 mg/m^2 IV daily x 4, on Days –5 to –2
- Cyclophosphamide (CY): the CY dose will be de-escalated (see Study Design above). Full details on the de-escalation scheme are provided in the Statistical Section (Chapter 5) of the protocol.
- Antithymocyte globulin (ATG; Thymoglobulin): 3 mg/kg IV daily x 3, on Days –4 to –2. A biologically equivalent dose of ATGAM (horse ATG; conversion ratio 10:1) is recommended.
- TBI: 200 cGy from a linear accelerator at ≤ 20 cGy/min on Day –1.
- Day 0 will be the day of transplantation. GVHD prophylaxis will consist of cyclosporine (to be administered for no less than nine months after transplant) in combination with methotrexate at Days 1, 3, 6 and 11. Tacrolimus may be substituted for cyclosporine intolerance.

Study Duration: Patients will be followed for 24 months post-transplant.

TREATMENT SCHEMA