BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN PROTOCOL #1507

Reduced Intensity Conditioning for Haploidentical Bone Marrow Transplantation in Patients with Symptomatic Sickle Cell Disease (SCD)

FREQUENTLY ASKED QUESTIONS (FAQs)

1. Why conduct a phase II trial to evaluate haplo BMT in severe SCD inclusive of both the adult and pediatric populations?

The proposed phase II trial is designed to evaluate the safety and efficacy of haploidentical bone marrow transplantation in both children and adults with severe SCD. SCD is a congenital hemoglobinopathy. The progression of SCD over an individual's lifespan begins as an asymptomatic organ disease in infants, and may manifest with the onset of end-organ disease in children, adolescents and adults (Medicine (Baltimore) 2005; 84:363-76)[1]. This includes cerebral micro infarctions, chronic pulmonary disease with pulmonary hypertension, retinopathy, end-stage renal disease and glomerulosclerosis. Current standard of care therapies have failed to significantly prolong the lifespan of adults with severe SCD. Therefore, successful hematopoietic stem cell transplant (HSCT) in adults with severe SCD may be a successful alternative to medical management.

In children, a change in the natural progression of SCD has occurred over the past two decades, with SCD transitioning from an early, life-threatening disease to a more chronic illness during that time. Stroke (CVA), whether overt or silent, is the most common debilitating complication among children, with an estimated 35% suffering overt strokes and an estimated 2-3% percent suffering silent strokes. While regular blood transfusion therapy reduces the risk of infarct recurrence, it does not eliminate the possibility. Among children with a history of silent stroke receiving regular transfusion therapy, 45% are expected to develop infarct recurrence within 5.5 years (Blood. 2011 Jan 20; 117(3):772-9.)[2]. Among children with a history of silent stroke receiving regular blood transfusion therapy, 10% will develop infarct recurrence. Therefore, successful HSCT in children with severe SCD characterized by a history of neurologic complication (CVA/TIA) is a potential alternative to lifelong blood transfusion therapy.

The protocol's primary objective seeks to establish the efficacy of HSCT by transplanting bone marrow from a haplo-identical relative (haplo BMT). The primary objective is to establish the likelihood of being alive and engrafted 2-years after HSCT. The secondary objectives will

evaluate complications of HSCT (e.g. GVHD, infection, CNS events), overall survival and the quality of life (QoL) domains of pain and fatigue.

2. What is the rationale for the disease status criteria used eligibility requirements?

In accordance with the study design, patients are divided into 2 strata by age.

Participants enrolling on the adult stratum (ages 15.00 to 45.99 years) must have a history of ≥1 of the following characteristics of severe SCD: history of clinically significant neurological event (stroke); ≥2 episodes of ACS in the 2 years prior to enrollment despite the institution of supportive care measures (i.e. asthma therapy and/or hydroxyurea); administration of regular RBC transfusion therapy, defined as receiving ≥8 packed red blood cell transfusions per year for ≥ 1 year in the 12 months before enrollment; ≥3 vaso-occlusive pain episodes per year in the 2-year period preceding enrollment despite the institution of supportive care measures (i.e. a pain management plan and/or treatment with hydroxyurea); and/or an echocardiographic finding of tricuspid valve regurgitant jet velocity (TRJV) of ≥2.7 m/sec. These characteristics of SCD severity are similar to criteria applied in other trials in adults with SCD.[3, 4]

The criteria for enrollment to the pediatric stratum (ages 5 to 14.99 years) is a history of overt stroke. Children with progressive silent infarct despite preventive therapy will not be eligible to enroll until the DSMB has reviewed the 100-day graft failure rate in the first 12 evaluable patients in the stratum using the conditioning regimen that will be used for the remaining accruals. If the DSMB recommends continuing accrual under the current conditioning regimen in the stratum for children aged 5.00-14.99 years, then eligibility in this stratum will open to children with progressive silent infarct.

3. What are the safeguards and modifications in this trial to prevent transplant related risks unique to patients with SCD?

Individuals with severe SCD are at unique risk for posterior reversible encephalopathy (PRES), seizures and other neurological complications, particularly following HCT.[6,7] This might be related to impaired dynamic cerebrovascular autoregulation (decreased ability to buffer the transfer of blood pressure surges to the brain) and reduced cerebrovascular reserve capacity or vasodilatory capacity. One of the primary factors contributing to PRES and other neurologic complications is the administration of calcineurin inhibitors (drugs used for GVHD prophylaxis). As a result, we have replaced tacrolimus with sirolimus. Additional PRES risk factors include hypertension (high blood pressure), hypomagnesemia (low magnesium level in blood), fluid shifts (e.g., fluid loss without adequate replacement), and thrombocytopenia (low platelet counts; <50 x 109/L).[8,9] The supportive care section and Appendix H of the protocol offer guidelines about reducing the risk and/or clinical management of PRES, seizures and other neurological complications.

4. Is this trial feasible?

We are confident the proposed trial is feasible for the following reasons:

- Each of the two, age specific strata will enroll 40 participants over a 4-year accrual period. Preliminary response from BMT CTN centers as well as European and other interested centers indicate substantial interest and institutional investigator support of the study concept. This support has been reinforced by strong turn out and subsequent site/investigator engagement following recent investigator interest meetings at well-established academic conferences drawing both hematologic and transplant experts, including ASH (December 2015) and the BMT CTN Tandem (February 2016).
- Institutions interested in participating in this protocol are required to complete a feasibility survey from which we derived each site's annual accrual estimates per stratum as well as data about their patient population.

5. Accrual estimates – See separate summary of Accrual Estimates.

References:

1. Medicine (Baltimore) 2005; 84:363-76)
2. Blood. 2011 Jan 20; 117(3):772-9.
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4. Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR, Ashley-Koch AE, Telen MJ. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 89(5): 530 – 535, 2014. PMCID: PMC3988218.
5. Walters MC, Sullivan KM, Bernaudin F, et al. Neurologic complications after allogeneic marrow transplantation for sickle cell anemia. *Blood*. 1995;85(4):879-884.
6. Khademian Z, Speller-Brown B, Nouraie SM, Minniti CP. Reversible posterior leuko-encephalopathy in children with sickle cell disease. *Pediatr Blood Cancer*. 2009;52(3):373-375.
7. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 330 (23): 1639 – 1644, 1994.
8. Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR, Ashley-Koch AE, Telen MJ. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 89(5): 530 – 535, 2014. PMCID: PMC3988218.