BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 1503: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Hematopoietic Stem Cell Transplantation for Young Adults with Sickle Cell Disease

1. Why run a phase II trial comparing hematopoietic cell transplantation (HCT) to the standard of care in young adults with sickle cell disease?

HCT from an HLA-matched sibling donor is curative in children with SCD.[1,2] However, HCT is used sparingly for young adults with SCD, in part because HCT-related complications are more likely in adults compared to children. HCT-related complications add to the burden of morbidity and mortality and typically occur within the first 1-2 years after HCT.[3-5] While the burden of morbidity is also relatively high for young adults with severe SCD, death occurs later; the expected mortality rate is 4.4 per 100 person years.[6-7] Therefore in this phase II trial we are studying whether the up-front risk of morbidity and mortality associated with HCT (curative treatment) will eventually result in better survival compared to the standard of care (non curative treatment). To our knowledge there are no clinical trials directly comparing HCT with standard medical care for survival and protection from SCD-related events. Not everyone with severe SCD will have a tissue-matched donor needed for HCT. Therefore the trial will assign patients to a donor arm and a no donor arm based on whether a tissue-matched donor is available.

The primary outcome of interest is overall survival at 2-years. We designed the trial to accept no more than 15% difference in survival between those with a donor and those without a donor, i.e., donor vs. no donor arms of the trial. The 2-year survival for the donor arm is based on survival in young adults receiving HCT for severe aplastic anemia and, for the no donor arm, on SCD patients receiving standard of care.[3,7] Severe aplastic anemia like SCD affects the blood cells and HCT is curative. By allowing no longer than 15% difference in survival between the treatment groups, survival beyond 2-years will be better than with standard of care. In addition, we plan to study whether there are improvements in sickle-related organ injury and events using a system identified by Elmariah,[8] functional assessment by administering the 6 minute walk distance (6MWD) test; and Health related quality of life (HRQoL) as assessed by the PROMIS 57, which includes a pain intensity score, and a 28-day electronic pain diary to capture mean pain intensity.[9-12] The secondary endpoints will examine changes between baseline (enrollment on trial which is when the participant is assigned to the treatment arm) and 2 years between the participants on the donor and no donor arms; changes by treatment received will also be reported.

In summary, this trial will first establish that 2-years after enrollment, survival difference between the treatment arms is no more than 15%. If the difference is greater than 15% it is unlikely to result in longer-term survival advantage for those assigned to the donor arm and expected to receive HCT (curative treatment). Our second aim is to establish whether HCT will protect from sickle-related events and organ injury, quality of life and pain compared to the standard of care. The findings of this trial have the potential to change the treatment option for young adults with SCD, from a supportive care approach to one that is curative.

2. How were the interventions used in this study selected?

An R34 planning grant from the National Heart Lung and Blood Institute (NHLBI) allowed us to complete a pilot trial using the same transplant conditioning regimen and graft-versus-host disease (GVHD) prophylaxis regimen for young adults with severe SCD. The eligibility criteria for this trial (BMT CTN 1503) are similar to the eligibility criteria for the pilot trial. We enrolled 21 patients on the pilot trial. None of these patients rejected their graft. The 6-month probability of overall survival was 94%; the 6-month probability of being alive and free of SCD was also 94%. One patient died; cause of death was intra-cranial hemorrhage associated with posterior reversible encephalopathy (PRES). This suggests the regimen proposed in this phase II trial is safe and curative. None of the patients developed grade II-IV acute GVHD and 2 patients developed chronic GVHD. Thus having established a transplant-conditioning regimen with acceptable survival, the current trial is seeking to study whether HCT may offer an advantage over standard of care for young adults with severe SCD.

3. Why select a biologic assignment study design?

In this trial we sort patients into their treatment groups based on whether a suitably tissue matched donor is available (i.e., donor versus no donor treatment groups).[13] The ideal manner to study a treatment is to "flip a coin" and assign treatment otherwise known as randomization. Randomization is very challenging for a number of reasons: 1) not everyone who may benefit from HCT will have a suitable donor; only about ~30% will have a suitable donor. So such a trial would take a very long time to enroll patients during which time other treatment options could arise and/or physicians and patients might lose interest, which also lengthen the study period; 2) HCT is a very complex treatment that require patients and their families to accept that there are complications from HCT and may lead to death at the expense of cure. This often involves a complex decision making process; the possibility of complications from an intense treatment that may result in death in the first 1-2 years after HCT versus death from the disease (SCD) several years later. Therefore we designed the trial in a manner that once eligibility for the trial is confirmed, HLA typing is performed and a donor search is initiated. Those found to have a suitably matched donor are assigned to the donor arm and expected to undergo HCT and those without a donor are assigned to the no donor arm and expected to receive standard of care (i.e., continuing their current treatment plan). We plan to enroll patients over 3 years and follow them for 2 years; from enrollment through 2 years we will assess survival and compliance with treatment; at enrollment and at 2-years, we will evaluate disease severity, quality of life and pain. All analyses will be based on treatment assigned (donor versus no donor); we except most patients to remain in the treatment arm

they were assigned for 2-years. There may be few patients who may decide not to be in the trial after enrolling; we hope to minimize such loss through intensive counseling prior to enrollment so all patients and their families understand the study design and have plenty of opportunities to ask questions.

4. Why was the graft source limited to bone marrow?

In patients with severe aplastic anemia undergoing HCT, there is a higher risk of acute and chronic GVHD when peripheral blood is used as a graft compared to bone marrow. GVHD is a complication that offers no advantage for patients with SCD and if severe can lead to death. Therefore only allow bone marrow grafts from tissue matched donors are allowed. Umbilical cord blood is not allowed due to a high risk of graft rejection in SCD. Our pilot trial included HLA-matched donors who were related (i.e., brother or sister) or unrelated.

5. What was the rationale for selecting the disease status for eligibility in this trial?

The definition of disease severity for SCD used in this protocol is similar to criteria applied in other trials in adults with SCD.[6,7] Further, the inclusion criteria for this trial have been discussed extensively with both SCD and HCT physicians and there is general agreement amongst the referral and treating physicians. An objective of this trial is to determine if HCT can alleviate the severity of the disease; therefore disease assessments are conducted at enrollment and at 2-years (upon completion of the trial).

6. 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 especially following HCT.[14-16] 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. Factors contributing to PRES and other neurologic complications include the administration of calcineurin inhibitors (drugs used for GVHD prophylaxis), hypertension (high blood pressure), hypomagnesemia (low magnesium level in blood), fluid shifts (e.g., fluid loss without adequate replacement), and thrombocytopenia (low platelet counts; $<50 \times 10^9$/L).[17,18] The supportive care section of the protocol offers guidelines about reducing the risk of PRES, seizures and other neurological complications.

7. Why are calcineurin inhibitors used in this study despite the risk of PRES?

Although some investigators have used a different GVHD prophylaxis agent called sirolimus, the experience with sirolimus is very limited.[19,20] There are no advantages to GVHD in patients with severe SCD. Therefore, in our pilot trial we used a calcineurin inhibitor for GVHD prophylaxis with strict motoring of drug levels. This trial avoids the use of steroids, which is another agent associated with PRES.

8. Why does this study use a conditioning regimen with myeloablative doses of busulfan with fludarabine and thymoglobulin as opposed to a reduced intensity

regimen with alemtuzumab/fludarabine with melphalan or low dose total body irradiation (TBI)?
The rate of acute and chronic GVHD is unacceptably high after HCT in SCD patients using alemtuzumab/fludarabine with melphalan. As GVHD adds to the burden of morbidity and mortality we piloted a myelobaltive regimen with a lower dose of busulfan than the conventional dose. Alemtuzumab/fludarabine/low dose TBI regimen does not result in stable chimerism when used in the setting of unrelated donor HCT. In this trial, matched related and unrelated donors are allowed to donate bone marrow. Consequently, we chose a transplant conditioning that is acceptable when using matched related and unrelated donors.

10. Is this trial feasible?
The planning grant assembled 13 clinical sites that enrolled patients. That trial has completed its planned accrual. An additional 10-12 clinical sites expressed interest in participating in this comparison trial. The trial will also target enrollment in BMT CTN clinical sites that did not participate in the pilot investigation. Therefore, we believe we will be able to enroll 200 patients over a 3-year period. Please see separate document for accrual plan.

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