BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PROTOCOL #1904

FREQUENTLY ASKED QUESTIONS (FAQs)

1. Why is BMT CTN protocol 1904 exploring Treosulfan-based conditioning?

Patients with certain bone marrow failure diseases (BMFD) have poor hematopoietic cell transplantation (HCT) outcomes using conventional myeloablative approaches with increased risk for transplant related morbidity and mortality TRM) from complications such as sinusoidal obstructive syndrome (SOS). Therefore, less toxic conditioning regimens that are effective at establishing multi-lineage engraftment are needed.

Treosulfan is a pro-drug of an alkylating agent structurally related to busulfan but with a different mode of alkylation. Treosulfan is water soluble and bypasses hepatic enzyme activation, leading to a decreased risk for SOS, with highly predictable pharmacokinetics in adults. Treosulfan combined with fludarabine has been used by European groups for almost a decade as a high intensity, yet reduced toxicity, regimen with low TRM. In the US, there have been several prospective studies using treosulfan combined with fludarabine for the treatment of hematologic malignancies, which have also demonstrated low TRM.

Burroughs and colleagues at the Fred Hutchinson Cancer Center have been conducting a phase II prospective study using treosulfan-based conditioning in patients with non-malignant diseases including 23 patients with BMFD. Outcomes of the first 14 patients have been published.[1] Conditioning consisted of treosulfan (14 g/m^2, days -6 to -4), fludarabine (30 mg/m^2/day, days -6 to -2), +/- rabbit ATG (thymoglobulin; 1 mg/kg/day, day -4, 2.5 mg/kg days -3 and -2) followed by HLA-matched sibling (n=5) or HLA-matched unrelated donor (URD) (n=15) bone marrow (BM), peripheral blood stem cell (PBSC), or sibling BM plus sibling cord blood grafts. Three patients received a single class 1 allele (n=2) or DQB1 antigen (n=1) mismatched graft. Graft versus host disease (GVHD) prophylaxis consisted of tacrolimus and methotrexate. With a median follow-up of 2 years, the 2-year survival and event-free survival (EFS) were both 96%. The 1-year GVHD-free, EFS was 87%. The cumulative incidences of grades II-IV and III-IV acute GVHD at day 100 and NIH chronic GVHD at 1 year were 39%, 4% and 9%, respectively. None of the patients experienced graft rejection, with 22 patients having full (≥95%) and one patient having stable mixed donor myeloid engraftment. These data provide strong support for BMT CTN 1904 to evaluate the 1-year GVHD-free, EFS in patients with BMFD undergoing HCT using treosulfan-based conditioning in a multi-center prospective clinical trial.

2. Why is Thymoglobulin (rabbit ATG) part of the conditioning regimen?

The initial treosulfan-based conditioning regimen used by the FHCRC group was based on data from malignant patients and consisted of Treosulfan combined with fludarabine without ATG. However, 3 of the first 9 patients with non-malignant diseases developed grade III-IV acute GVHD. Thereafter, thymoglobulin was added to the regimen, which resulted in a marked decrease in the incidence of severe acute GVHD. In the 23 patients with BMFD, none have developed grade III-IV GVHD since the addition of ATG. Therefore, thymoglobulin is an integral

component of the conditioning regimen for patients with nonmalignant diseases including BMFD.

3. Why did we include certain bone marrow failure diseases and exclude others?

BMT CTN protocol 1904 will enroll patients with BMFD treatable by allogeneic HCT including but not limited to Shwachman Diamond syndrome, Diamond Blackfan anemia, congenital sideroblastic anemia, GATA 2 mutation with associated marrow failure, SAMD9 or SAMD9L disorders, congenital amegakaryocytic thrombocytopenia, and paroxysmal nocturnal hemoglobinuria. In addition, patients with an undefined BMFD (a patient with bone marrow failure for whom a genetic mutation has not been identified) or a BMFD with a genetic mutation not listed above but treatable by allogenic HCT will be eligible for this trial following approval by the BMT CTN 1904 Eligibility Review Committee.

Patients with idiopathic aplastic anemia will be excluded as this group of patients does not require myeloablative conditioning. In addition, patients with dyskeratosis congenita will also be excluded as this group of patients also does not require myeloablative conditioning and there is reason to avoid alkylators in this group of patients given long-term risks for malignancy and pulmonary toxicity. Lastly, patients with Fanconi anemia will also be excluded due to limited data using treosulfan in this group.

4. Why did we create the BMT CTN 1904 Protocol Eligibility Review Committee?

For some BMFD, there are not standard agreed upon criteria for when to take a patient to HCT. In addition, there are many patients with BMFD who do not have a genetic mutation identified, but who would benefit from an allogenic HCT based upon their phenotype. The BMT CTN 1904 Protocol Eligibility Review Committee (ERC) will provide a comprehensive review of the patient's diagnosis and ensure that all patients enrolled onto BMT CTN 1904 meet protocol eligibility in terms of the patient's underlying disease.

5. Why is GVHD-free, Event-Free Survival the primary endpoint?

Although, allogeneic HCT is curative for many patients with (BMFD), often patients with BMFD do not need to go to HCT immediately. For example, a patient with Diamond Blackfan anemia can continue to receive life-long red blood cell transfusions and chelation therapy versus preceding forward with HCT. Therefore, we need to set a high bar for an effective endpoint for this HCT trial. Specifically, we need to strive for excellent event-free survival (an event is defined as death, rejection, or 2nd HCT) as well as GVHD-free survival since GVHD is of no benefit for patients with non-malignant diseases.

6. Why are we including bone marrow and peripheral blood stem cell grafts and not alternative donors?

BM will be the preferred stem cell source. PBSC will be allowed if a suitable BM donor is not available, or the donor refuses to donate BM. We do not want to potentially lose a well-matched donor if they are only willing to give PBSC. We excluded alternative donor grafts (cord blood or haploidentical) as there is little data using treosulfan based conditioning regimen with these graft sources in patients with BMFD.

7. Why did we choose a sample size of 40 patients and is this accrual goal feasible?

From 2015-2017, 92 patients (roughly 30 patients per year) with BMFD underwent HCT and had their information recorded in the CIBMTR database**.** About 25-30% of patients who undergo HCT across the United States are enrolled onto BMT CTN clinical trials. Therefore, an accrual goal of 40 patients over 4 years will be feasible.

In addition to the BMT CTN consortium, the Pediatric Transplantation and Cellular Therapy Consortium, and The North American Pediatric Aplastic Anemia Consortium (NAPAAC) have agreed to participate in BMT CTN 1904. In addition, many co-investigators on this trial will raise awareness of this protocol nationally with patient and family advocacy groups.

8. Why is the study not a superiority trial or a randomized clinical trial?

Given the heterogeneity of the diseases and the incomplete historical data in the CIBMTR database, a superiority trial is also not feasible. A randomized clinical trial is not feasible because there is no accepted standard of care conditioning regimen for patients with BMFD. Additionally, there are too few patients with our accrual estimate of 40 patients over 4 years.

9. How were the stopping rules chosen?

Two stopping rules were chosen to help ensure patient safety: 1) Day 100 overall mortality >15% and 2) Day 100 graft failure/rejection >10%. These stopping rules were chosen based on preliminary data from the FHCRC in 23 patients with BMFD who received Treosulfan-based conditioning in whom both day 100 overall mortality and day 100 graft failure/rejection were <10%.

Reference:

1. Burroughs LM, Shimamura A, Talano JA, et al. Allogeneic hematopoietic cell transplantation using treosulfan-based conditioning for treatment of marrow failure disorders. *Biol Blood Marrow Transplant*. 2017;23(10):1669-1677.