BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 1301

A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus-Host Disease

1. Why run a phase III trial focused on the use of calcineurin inhibitors?

Graft-versus-host disease (GVHD) remains one of the greatest barriers to successful allogeneic transplants. Several participating BMT CTN core centers are working on ways to abrogate this complication without increasing disease relapse. The BMT CTN conducted a phase II clinical trial (BMT CTN 0303) to assess the feasibility of using graft processing with T-cell depletion by CD34-selection in a multicenter setting (1). The findings demonstrated promising results with low rates of chronic GVHD and a reproducible performance of the CliniMACS CD34 Reagent System in graft processing (2). Additional retrospective comparisons demonstrated that the rates of chronic GVHD are consistently lower than those observed after standard calcineurin inhibitor (CNI) based GVHD prophylaxis, without differences in survival, relapse or transplant-related mortality (3, 4). In parallel to this experience, the Johns Hopkins University (JHU) group developed an approach using post-transplant cyclophosphamide (PTCy) in HLA-matched donors on the same platform as haploidentical donor transplant, but without the requirement for CNI based GVHD prophylaxis (5-7). Initial data also demonstrated lower levels of chronic GVHD compared to historical controls. The rationale behind exploring alternatives to CNI-based GVHD prophylaxis is to further improve transplant outcomes. CNI-based GVHD prophylaxis has the requirement for chronic immunosuppression, requiring adherence to the treatment. It is also associated with complications such as renal and liver impairment and it does not sufficiently reduce rates of chronic GVHD. Additionally, the development of a CNI-free transplant platform would allow the introduction of different cellular therapies for the prevention of disease relapse and other post transplant complications.

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

The BMT CTN GVHD committee led a benchmark analysis to assess six different single center GVHD prophylaxis approaches compared with standard tacrolimus/methotrexate prophylaxis using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The benchmark analysis compared each of these 6 interventions directly with a control group adjusting for differences in the populations related to patient age, diseases, disease status, conditioning intensity, donor type and HLA matching. The two interventions selected for this trial were associated with the lowest rate of chronic GVHD compared to the control group.

3. Why select a composite primary endpoint?

Historically, trials that tested new GVHD prophylaxis strategies primarily evaluated the rate of acute GVHD and most recently, acute GVHD-free survival (BMT CTN 0402). As these approaches are

potentially more immunosuppressive than standard GVHD prophylaxis regimens, an increase in malignant disease relapse is a potential risk. In parallel to the assessment of promising GVHD prophylaxis approaches described above, the BMT CTN GVHD committee discussed novel endpoints to determine success that not only included GVHD and survival, but also accounted for disease relapse and combined GVHD manifestations that would have a significant impact on the health of patients. Among the endpoints discussed, the requirement for prolonged chronic immunosuppression was of interest as it represented ongoing problems with chronic GVHD and a higher risk for late mortality. Due to the absence of baseline data and a multitude of practice patterns related to tapering of immunosuppression, this endpoint was considered to not be optimal at the present time. It was however included as a secondary endpoint and expressed as immunosuppression and relapse-free survival. The composite endpoint that could be easily applied in a clinical setting was a time-to-event assessment of chronic GVHD/relapse-free survival (CRFS). This endpoint defines the events as moderate to severe chronic GVHD according to the NIH consensus guidelines of diagnosis of chronic GVHD, relapse and death. The rationale for assessing only chronic GVHD in this trial was that this was the strongest effect of these interventions in the benchmark analysis. When applying this composite endpoint to the control group in the benchmark analysis, the baseline rate was 22% within the first year of transplant among recipients of myeloablative regimens. Thus, with current transplant practice, only a fifth of the patients alive by the end of the first year from transplant are free from GVHD and relapse complications. Improvement of this outcome would advance the field of transplantation.

4. Why was the graft source in the control arm prescribed in the protocol?

The two interventions being tested have different graft sources - bone marrow (BM) for PTCy and mobilized peripheral blood stem cells (PBSC) for CD34-selection. The options for the control arm should be the standard of care. Even though the use of PBSC is the most common graft used in the U.S., the results of a recent BMT CTN study (#0201) demonstrated significantly higher rates of chronic GVHD with PBSC (8). Considering the variability that graft source has on the incidence of chronic GVHD, allowing the use of any graft source would make the control group too heterogeneous, and the interpretation of the results would be dependent on the proportion of BM and PBSC in the control arm. Thus, prescribing a particular graft source was important for interpretation and applicability of the results. Based on the BMT CTN 0201 study, bone marrow is the graft source associated with lower rates of chronic GVHD, and a winner arm would have to be better than this standard of care in order to be considered a success.

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

There is a potential concern related to the association between graft manipulation with T-cell depletion and disease relapse. Early studies demonstrated that T-cell depletion was associated with greater relapse risk in patients with chronic myelogenous leukemia but not in acute myeloid leukemia. Recent experience using the CliniMACS CD34 Reagent System in a better selected patient population demonstrated equivalent relapse rates compared to CNI-based GVHD prophylaxis approaches. Thus, most of the recent experience is in patients with early disease or in patients in complete remission (3, 4).

6. What are the safeguards and modifications in this trial to safeguard the participation of children?

Chronic GVHD is also a serious complication in pediatric hematopoietic cell transplantation (HCT). The experience of CD34 selection at Memorial Sloan-Kettering Cancer Center (MSKCC) includes pediatric populations, and demonstrates similar outcomes to those seen in adults. Children with an available HLA-matched related donor are only eligible if the donor is greater than 25kg of body weight in the case of randomization to the CD34 selection arm. All children who enroll will be eligible to participate in the ancillary study related to immune recovery, and blood collection will be based on the recipient's weight to determine the amount of blood that can be safely collected.

7. Are donors considered research subjects?

The FDA specifies that in trials under Investigation Device Exemption (IDE) category, that donors whose cells are being manipulated through an investigational device should be consider research subjects. In complying to this rule, only donors whose recipients are randomized to the CD34+ selection arm will required to be consented prior to donation. Donors will be consented after the recipient is randomized. The transplant center will be responsible for consenting related donors. For unrelated donors, the National Marrow Donor Program will oversee the consent procedures. Donors of patients randomized to the PostCy or control arms are not considered research subjects in this trial, and thus will not be required to sign a donor research informed consent.

During the donor screening process for patients being evaluated for this trial, donors will be requested to donate either BM or PBSC depending on the randomization. These two graft sources are routinely requested for standard of care HCT. Donors in this clinical trial are not undergoing any specific interventions and are not being followed for any trial-specific outcomes. In cases where a donor can only donate one type of graft, the transplant center will have the option to proceed with transplantation "off study" or request another donor. This clinical decision will be based on institutional guidelines and clinician preference.

For unrelated donor, once the results of confirmatory typing are available, in some cases the donor center will provide information related to specific preference or contraindication to a specific graft type. If this information is available at time of enrollment, another donor should be selected or the patient would not be eligible. Conversely, if there is no specific language or information from the donor center in this respect, it is assumed that the donor would be available to donate either graft source. Then, the transplant center may proceed with enrollment and randomization. Depending on the randomization results the work up request should include the specific graft type and cell dose required.

8. Why is ATG allowed in the CD34-selected arm?

The CD34-selected arm is based on the MSKCC experience. ATG is given early in the conditioning regimen with the intent of promoting engraftment and not for GVHD control. There is some experience in not using ATG with total body irradiation (TBI)-based regimens (9), however non-TBI regimens always included ATG. ATG was included in used in BMT CTN 0303. The protocol team decided that ATG is

part of the CD34-selected treatment package and exclusion without robust data would not be an optimal approach.

9. Why are there different choices of conditioning regimens on each arm?

In current HCT practice there is a variety of commonly used myeloablative intensity conditioning regimens. In order to make this trial as broadly applicable as possible, the most commonly used regimens were included in the control arm. In the PTCy arm, several of the most common regimens have also been studied and thus are allowed as options in this arm. The only modification to standard regimens in this arm has been to decrease the dose of cyclophosphamide in the conditioning regimen to ensure that the total dose, including post-transplant cyclophosphamide, is capped. In the CD34-selected arm there is a TBI-based regimen and a non-TBI-based regimen. The experience here is limited to these two regimens and, similarly to question #8, the use of the CD34-selected approach is based entirely on the experience from MSKCC. The TBI regimen is identical to the one used in BMT CTN 0303.

10. Is this trial feasible?

Feasibility is a concern for this trial. The protocol team distributed two separate surveys to BMT CTN sites and received positive feedback from 30 centers that had an interest in participating in this trial. The eligibility criteria is broad and includes the most common indications of transplant with myeloablative conditioning. There are no currently open competing trials within the BMT CTN.

The fact that the protocol prescribes BM is also a major concern related to feasibility. Currently in the U.S., 10% of all HLA-matched sibling donor transplants and 22% of all unrelated donor transplants use BM as the graft source. In some ways, the selection of BM as the best control for this trial will increase the use of BM as a graft source. Regardless, strong promotional materials will be developed and distributed to encourage participation in this study and boost accrual. The protocol team developed a name and logo for this trial: PROGRESS is the acronym for Prevention and Reduction of GVHD, Relapse and Enhancing Survival after Stem cell transplant.

Figure 1: Trial name and logo for accrual promotion

11. Why was a stopping rule for futility included in the design?

An analysis of this new composite endpoint in a population similar to that planned for this trial demonstrated that most of the events occur within the first 6 to 12 months from transplant. Comparison

with the control as an interim analysis could inform the likelihood of a particular arm being superior to the control. This stopping rule for futility could allow the DSMB to close one or both arms if it is unlikely to show benefit compared to control by the end of the trial.

12. Explain the methodology to evaluate overall survival as a secondary endpoint.

Since the primary endpoint of this trial is novel, we also included a provision to evaluate overall survival formally using a gatekeeper approach if there is a difference in the CRFS endpoint. Using this approach will result in a 79% power to detect a 20% difference and a 49% power to detect a 15% difference in OS. The gatekeeper approach in the analysis can test for a survival effect with formal control of the type I error in case there is an unexpected effect on overall survival, without penalizing the primary comparison of CRFS. Overall survival will only be formally compared in the intention to treat population at the Bonferroni adjusted significance level of 0.05/3 if the corresponding pairwise comparison of CRFS is significant. All other secondary endpoints will be considered exploratory.

13. What is the definition of relapse used for this trial?

Disease relapse is a component of the CRFS endpoint and thus, definition of what constitutes a relapse is important. According to the study eligibility, patients who are in morphologic complete response are allowed to enter the trial. Relapse is defined as reappearance of morphologic disease post transplant or a therapy instituted in response to relapse. This includes multi-agent chemotherapy, donor lymphocyte infusions or other disease specific therapy. Post-transplant therapy for prevention of relapse in patients who are in remission is not allowed under this trial. One exception is the use of tyrosine kinase inhibitors (TKI) in patients with acute lymphocytic leukemia with t(9;22) for prevention of morphologic relapse in patients with or without minimal residual disease.

14. How are infectious complications being captured in this clinical trial?

Graft manipulation with T-cell depletion is associated with post-transplant viral infections, most concerning are EBV and CMV infections. All infections will be collected in calendar-driven forms on all patients. EBV monitoring through weekly assessment through nucleic acid amplification test (NAAT) is standard for the recipients of CD34 selected grafts, but not for the other arms in this trial. The trial requires EBV monitoring only for patients randomized to the CD34 selected arm. This creates an imbalance and ascertainment bias when comparing the rate of EBV reactivations across treatment arms. Thus, rates of EBV activation, disease and treatment will be described for the CD34 selected arm, but will not compared across arms. Conversely, CMV monitoring is standard practice for all transplant recipients and reactivation rates will be compared across arms. Overall infection rates in each arm will be summarized and compared across arms.
Toxoplasmosis reactivation is also a risk for recipient of CD-34 selected grafts. Patients and donors are checked for toxoplasmosis serology and for those who are positive, the risk of reactivation is higher. Patients with high risk of reactivation will require prophylaxis until normalization of CD4+ cell count in the peripheral blood. Additionally, if available, it is recommended that patients with high risk of toxoplasmosis reactivation to be monitor weekly with Toxoplasmosis NAAT.

15. Accrual Estimates: ***please see separate document***

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