BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED

FAQs for BMT CTN PROTOCOL 0901

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

1. Why conduct a phase III clinical trial comparing conditioning intensity in hematopoietic cell transplantation?

Conditioning regimen has the main objective to allow engraftment of donor cells, which is achieved by administration of chemotherapy and or irradiation prior to hematopoietic cell infusion. The conditioning regimen intensity is determined by the dose of chemotherapy or irradiation and the combination of different agents used (1). High-dose regimens, also defined as myeloablative (MAC), destroy the recipients' hematopoietic function and also have higher cytotoxic effect against the malignancy. However, these myeloablative regimens are associated with other non-hematopoietic toxicity resulting in more transplant morbidity and mortality. Attenuating the conditioning regimen intensity allows donor engraftment by utilizing immunossupressive regimens without irreversible bone marrow damage. This approach, also defined as minimally ablative or nonmyeloablative conditioning regimens indeed decreased transplant related toxicity and mortality (2, 3). This benefit is offset by increased rate of malignant disease relapse (3). Newer regimens with intermediate intensity, or reduced intensity conditioning (RIC), are currently been used in patients who are deemed not fit to undergo a myeloablative conditioning. The objective of this approach is to minimize regimen related toxicity regimens without excess disease relapse. Retrospective comparisons between different conditioning regimen intensities demonstrate an increase risk of disease relapse with less intensive regimens and higher transplant related mortality with MAC regimens (4, 5). The available data are confounded by patient-selection bias, as older, more infirmed patients are often chosen for RIC approaches. There is a need for phase III clinical trial comparing conditioning regimen intensity in the same patient population. The concept of such a trial was deemed as high priority during the 2007 BMT CTN State of Science Symposium (6). Results from this clinical trial will be important to the transplant community, and are likely to change current practice patterns.

2. Why does the transplant indication for this clinical trial limited to AML and MDS?

The BMT CTN 0901 is a clinical trial for adult patients presenting for an allogenic hematopoietic cell transplantation (HCT). The most common indications for an allogeneic transplant in the US are AML and MDS (CIBMTR data). Additionally, conditioning regimens used in these diseases are more homogenous than expanding the eligibility to lymphoproliferative disorders. The conditioning intensity question does not apply to non-malignant transplant indications, which usually the objective is mainly to restore hematopoiesis and not to eliminate a malignant clone.

3. Why two intensity levels are being tested in this trial?

Nonmyeloablative regimens have the least cytotoxic potential thereby minimizing post-transplant cytopenias and regimen-related organ toxicity. There is a concern that relapse rates with nonmyeloablative intensity level would be higher than the other two intensity levels (3). Feasibility assessments of including nonmyeloablative intensity in this trial were done through transplant center surveys during the initial phases of trial development. There was a lack of enthusiasm from transplant physicians to participate in a trial with nonmyeloablative conditioning for AML and MDS because of the concerns of disease relapse. According to a CIBMTR study on conditioning regimen intensity, the rate of relapse among recipients of nonmyeloablative conditioning regimens for AML and MDS was higher compared to recipients of myeloablative regimens (7). We looked at the patient population in this study and applied the BMT CTN 0901 eligibility criteria. Recipients of nonmyeloablative regimens experienced worse outcomes than other groups. The concept of three way comparison among all intensity levels was also entertained. However, the sample size required for such study would be impractical for a timely completion. Considering all these points the Protocol Team decided to exclude the nonmyeloablative intensity level and focus on a comparison between RIC and MAC regimens.

4. Why not compare a single reduced intensity regimen to a single myeloablative regimen?

Current practice of allogeneic HCT in the US varies, and many transplant centers have preferred conditioning regimens. The Protocol Team surveyed all BMT CTN transplant centers regarding the use of one regimen for each arm. Results from the survey indicated a choice of conditioning regimens was necessary in order for this study to succeed. The most commonly used MAC regimens include: busulfan/cyclophosphamide, cyclophosphamide/total body irradiation and busulfan/fludarabine (Bu >9mg/kg); and RIC regimens include: melphalan/fludarabine and busulfan/fludarabine (Bu<9mg/kg). These are the regimen options for the BMT CTN 0901. All these regimens have been previously studied and outcomes have been reported in the literature (8-14). They have garnered widespread acceptance in the transplant community such that they are considered “standard of care” at the transplant center.

5. Given that there are multiple choices for conditioning regimens, how will selection bias be avoided in this trial?

This is a randomized clinical trial that will assign eligible patients with AML or MDS to a MAC or RIC prior to HCT. The transplant center will be asked to declare the MAC and RIC regimen option at time of registration and prior to randomization. This will avoid changing regimens after treatment assignment.

6. Why is the choice of GVHD prophylaxis left to institutional guidelines?

Similar to the situation with conditioning regimen choices, there is great variability in practice regarding the choice of GVHD prophylaxis regimens. Utilization of GVHD prophylaxis varies according to transplant center and mandating a particular GVHD prophylaxis regimen would impact on transplant center participation and patient accrual. Furthermore, the notion of treatment packages, i.e. use of a particular GVHD prophylaxis paired with a conditioning regimen, is no longer the standard practice with the same GVHD prophylaxis regimens being used regardless of the conditioning intensity.

The GVHD prophylaxis techniques of ex-vivo T-cell depletion and post-transplant cyclophosphamide were excluded from this trial as it was felt that these practices remains investigational in this patient population and transplant setting.

7. Why choose 18-month overall survival as the primary endpoint?

Overall survival was selected because it was best suited to determine superiority of a specific conditioning regimen intensity. Improvements in transplant related mortality or relapse free survival, although important will not have the same impact on transplant practices as changes in overall survival. The 18 month endpoint was selected using the same CIBMTR analysis mentioned above. We determined that the majority of events after transplantation, i.e. relapse and mortality, occurred within the first 18 months following transplantation. This end point will provide enough time to assess the difference in outcomes while minimizing resource utilization that would be required for a longer study.

8. Is this study feasible?

AML is the most common indication for allogeneic HCT in the US. Approximately 1,800 patients with AML in remission and MDS are treated with an allogeneic HCT in the US annually according to CIBMTR data. Despite this large number of patients, accrual to this trial still might be difficult due to competing trials and lack of equipoise regarding the conditioning regimen intensity choice. Competing trials with overlapping eligibility will likely affect accrual at large transplant centers, thus we estimate that the majority of patients will be enrolled from BMT CTN Affiliate centers. The initial survey to transplant centers also confirmed a larger annual accrual estimates from Affiliate centers. The lack of equipoise regarding conditioning regimen intensity will likely affect mostly younger patients, since there is a firm belief that younger patients benefit from higher intensity regimens, despite the lack of solid phase III data.

The targeted sample size for this clinical trial is 356 patients and based on these potential challenges we will require a minimum of four years to complete accrual.

9. Why are children excluded from the study?

The utilization of reduced intensity conditioning in the pediatric population remains largely investigational. Also, there are a number of multicenter transplant clinical trials that will directly compete with the BMT CTN 0901 in the pediatric population. Participation of children in this trial is likely to be very small and thus it was decided to limit this to the adult population only.

10. Why not conduct a non-inferiority study?

While it is true that the limited available data suggest similar outcomes between RIC and MAC (4, 5), we believe that this is a consequence of patient selection bias. We are testing the hypothesis whether RIC is indeed superior to MAC prior to transplantation on the premise that reductions of TRM will result in improved survival. The selection of patients with early disease (AML and MDS with <5% bone marrow blasts) and utilization of RIC as oppose to nonmyeloablative regimens will mitigate relapse rates that could otherwise offset the benefits of reducing TRM. A non-inferiority protocol design was considered, however it was determined that the sample size required for this design would jeopardize the feasibility of the trial.

11. Accrual estimates – See separate Summary of Anticipated Accrual Report

References

1. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the Intensity of Conditioning Regimens: Working Definitions. Biology of Blood and Marrow Transplantation. 2009;15(12):1628-33.
2. Sorror ML, Maris MB, Storer B, Sandmaier BM, Diaconescu R, Flowers C, et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. Blood. 2004 Aug 15;104(4):961-8.
3. de Lima M, Anagnostopoulos A, Munsell M, Shahjahan M, Ueno N, Ippoliti C, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. Blood. 2004 Aug 1;104(3):865-72.
4. Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006 Aug 1;108(3):836-46.
5. Valcarcel D, Martino R, Caballero D, Martin J, Ferra C, Nieto JB, et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. J Clin Oncol. 2008 Feb 1;26(4):577-84.
6. Weisdorf D, Carter S, Confer D, Ferrara J, Horowitz M. Blood and marrow transplant clinical trials network (BMT CTN): addressing unanswered questions. Biol Blood Marrow Transplant. 2007 Mar;13(3):257-62; discussion 5-6.
7. Luger S, Ringden O, Perez WS, Zhang M-J, DiPersio JF, Sierra J, et al. Similar Outcomes Using Myeloablative Versus Reduced Intensity and Non-Myeloablative Allogeneic Transplant Preparative Regimens for AML or MDS: From the Center for International Blood and Marrow Transplant Research. ASH Annual Meeting Abstracts. 2008 November 16, 2008;112(11):348-.
8. Alyea EP, Kim HT, Ho V, Cutler C, Gribben J, DeAngelo DJ, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. Blood. 2005 Feb 15;105(4):1810-4.
9. Giralt S, Aleman A, Anagnostopoulos A, Weber D, Khouri I, Anderlini P, et al. Fludarabine/melphalan conditioning for allogeneic transplantation in patients with multiple myeloma. Bone Marrow Transplant. 2002 Sep;30(6):367-73.
10. Giralt S, Thall PF, Khouri I, Wang X, Braunschweig I, Ippolitti C, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood. 2001 Feb 1;97(3):631-7.
11. Andersson B, Kashyap A, Gian V, al. e. Conditioning therapy with intravenous busulfan and cyclophosphamide (IV BuCy2) for hematologic malignancies prior to allogeneic stem cell transplantation: a phase II study. Biol Blood Marrow Transplant. 2002;8(3):145-54.
12. Bornhäuser M, Storer B, Slattery J, al e. Conditioning with fludarabine and targeted busulfan for transplantation of allogeneic hematopoietic stem cells. Blood. 2003;102(3):820-6.

13. Deeg H, Storer B, Slattery J, al e. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. Blood. 2002;100(4):1201-7.
14. Kroger N, Schetelig J, Zabelina T, al. e. A fludarabine-based dose-reduced conditioning regimen followed by allogeneic stem cell transplantation from related or unrelated donors in patients with myelodysplastic syndrome. Bone Marrow Transplant. 2001;28(7):643-7.