BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 1102

1. Why conduct a transplant vs. non-HCT trial for MDS?

The incidence and prevalence of MDS has increased significantly over the past 20 years as a result of increasing longevity of the population and increasing physician awareness. New therapeutic options, such as hypomethylating agents, immunomodulatory drugs, and differentiation induction agents, improve hematologic parameters and reduce transfusion requirements, but allogeneic hematopoietic stem cell transplantation (HCT) is the only known curative therapy for MDS. While advances in reduced intensity conditioning (RIC) have resulted in significant increases in the number of older patients who undergo transplantation for a number of diseases, the efficacy of this strategy in older MDS patients is not well-established.

In the United States, one of the obstacles to HCT for older patients with MDS has been lack of consistent third party reimbursement. The Centers for Medicare and Medicaid Services (CMS) recently released a Decision Memo stating that HCT for MDS is covered by Medicare only for beneficiaries with MDS participating in an approved clinical study which address at least one of the following three questions:

- Prospectively, compared to Medicare beneficiaries with MDS who do not receive HCT, do Medicare beneficiaries with MDS who receive HCT have improved outcomes?
- Prospectively, in Medicare beneficiaries with MDS who receive HCT, how do IPSS score, patient age, cytopenias and comorbidities predict outcomes?
- Prospectively, in Medicare beneficiaries with MDS who receive HCT, what treatment facility characteristics predict meaningful clinical improvement in outcomes?

The proposed trial is developed to address the first of these questions – the relative benefit of HCT versus non-HCT therapy for MDS.

2. Why choose 3-year OS as the primary endpoint?

OS is selected since it is the most important endpoint to demonstrate benefits of HCT in MDS patients who are >50 years of age. While other endpoints such as disease-free survival (DFS), progression-free survival (PFS), and leukemia-free survival (LFS) are also important, OS is the most relevant outcome for patients and for the question raised by CMS.

The 3-year endpoint was selected because HCT is associated with higher early mortality rates but a subsequent higher chance of cure than non-HCT therapy such that the expected survival benefit would become apparent only after 2-3 years of observation.

3. What is the importance of the secondary endpoints of the trial?

In this trial of HCT vs. non-HCT therapy in MDS, clinical endpoints only relevant to HCT (i.e. GVHD, transplant-related mortality) or non-HCT therapy (i.e. disease response, hematologic improvement) are not appropriate. Since MDS patients without a donor will be followed by their primary hematologists, not all endpoints can be assessed similarly in the two arms. DFS or RFS is difficult to assess since most MDS patients will be enrolled with existing disease without being in complete remission and complete remission is not necessarily a goal of non-HCT therapy. LFS was chosen as a secondary endpoint, since avoidance of transformation to leukemia is a goal of both HCT and non-HCT therapy and is clinically meaningful, as it is correlated with generally more aggressive clinical course and poorer survival/quality of life (QOL). Additionally, progression to AML from MDS is generally well documented even in a community setting by bone marrow biopsies and peripheral blood differential counts, and, consequently, ascertainment bias may be limited.

QOL is increasingly recognized as an important clinical endpoint in MDS therapy and HCT. Although potentially lifesaving, HCT carries an attendant risk of significant acute complications and late effects including chronic GVHD, organ toxicity, osteoporosis, infections, cataracts, secondary cancers, and infertility, all of which can result in decrements in QOL. At the same time, MDS patients receiving non-HCT therapy generally require continued treatment and supportive care including transfusion, which are known to be associated with decreased QOL. Therefore, it is critically important to assess QOL in both arms (HCT and non-HCT) in addition to survival outcomes in this trial.

4. Is our accrual goal feasible?

Yes. The length of time required to accrue the targeted sample size for this study depends on the proportion of enrolled patients with a matched related or matched unrelated donor which is believed to be 60% - 70%. Accrual will remain open until 135 patients are assigned to the non-transplant arm if the proportion of patients with a matched donor is 60% and until 120 patients are assigned to the non-HCT therapy arm if the proportion with a matched donor is 70%. Based on historical CIBMTR data, it is estimated that 420 patients receive HCT from a matched sibling or unrelated donor for MDS per year in the US. Further assuming that 50% of these patients have had Intermediate-2 or high risk IPSS, approximately 210 patients will be eligible to enroll in the HCT arm. Assuming an accrual rate of 40%, we expect annual enrollment of 84 patients to the RIC HCT arm. Table 1 provides estimated annual accruals for various proportions of donor availability. Based on these assumptions, it is estimated that 2.5 - 3.5 years of accrual will be necessary to enroll the targeted sample size.

TABLE 1: ESTIMATED ANNUAL ACCRUAL

	Donor Availability	
	60%	**70%**
Donor	84	84
No Donor	56	36
Total	**140**	**120**

5. Why not allow alternate donor (mismatch URD/haplo-identical) HCT or cord blood transplants? Why not include therapy-related MDS?

Alternate donor transplantation will be excluded in an attempt to keep the study population as homogeneous as possible. In addition, according to the most recent analysis of the CIBMTR data, 7/8 match URD HCT is associated with a significantly inferior survival compared with MRD or 8/8 match URD HCT, and therefore might not be an appropriate treatment strategy for older patients. Our power calculation is based on better established survival data using MRDs and 8/8 URDs.

In general, the benefit of HCT for therapy-related MDS has been well established as the prognosis of therapy-related MDS is extremely poor with non-HCT therapy. Thus, we exclude this disease entity from our trial.

6. Why not allow patients whose donor search has been initiated? Also why allow patients whose sibling donors have been typed?

The major challenge in designing a study comparing HCT and non-HCT in MDS, conducted by the CTN, is to establish a comparable cohort of MDS patients who are "transplant candidates" yet not undergoing HCT. If a patient comes to a CTN transplant center with already identified unrelated donor for a transplant evaluation, the patient will be assigned to the HCT arm (donor arm) right away. In this case, the only comparable cases would be the ones who failed to find a donor (at least 3 months of search) and then come to a transplant center for a transplant evaluation. These patients may be referred to the CTN centers for cord blood or mismatch donor HCT, but these transplants are excluded from our trial. Therefore it is essentially impossible to enroll such failed-to-find-donor patients in this study through the CTN network.

On the other hand, we plan to allow patients who have a sibling donor identified prior to the enrollment. This will improve the accrual of MDS patients whose referring physicians (community hematologists or academic leukemia program physicians) might have started HLA typing of the patients/their siblings while arranging the referral. This rule assumes that all (or almost all) MDS patients who were considered eligible for HCT will proceed with an unrelated donor search if there is no sibling available.

7. How will the trial determine donor (HCT arm) versus no-donor assignment?

If at any time within the 90 days, a suitable transplant donor is identified, the subject will be assigned to the transplantation arm; otherwise, the subject will be assigned to the non-transplantation arm.

Example 1. Subject is consented and enrolled. A transplant donor is identified 30 days from consent. The subject undergoes transplantation 70 days from consent.

Analysis: Transplantation Arm

Example 2. Subject is consented and enrolled. A transplant donor is identified 30 days from consent. The subject receives 4 cycles of hypomethylating therapy and undergoes transplantation 200 days from consent.

Analysis: Transplantation Arm

Example 3. Subject is consented and enrolled. A transplant donor is identified 30 days from consent. The subject receives 4 cycles of hypomethylating therapy and expires related to an infection prior to transplantation.

Analysis: Transplantation Arm

Example 4. Subject is consented and enrolled. The patient has an identified sibling donor on the date of consent. The patient eventually declines transplantation.

Analysis: Transplantation Arm

Example 5. Subject is consented and enrolled. A donor search is begun, and the subject begins hypomethylating therapy. The subject expires 80 days after consent without a donor being identified.

Analysis: Non-Transplantation Arm

Example 6. Subject is consented and enrolled. A donor search is begun, and the subject begins hypomethylating therapy. No donor is identified after a 90 day search. The subject continues on hypomethylating therapy.

Analysis: Non-Transplantation Arm

Example 7. Subject is consented and enrolled. A donor search is begun, and the subject begins hypomethylating therapy. No donor is identified after a 90 day search. The subject progresses and undergoes alternative donor transplantation 150 days from consent.

Analysis: Non-Transplantation Arm

8. When do observations for survival start? What if patients die within 3 months from enrollment, either before or after finding a donor?

The primary outcome analysis will use the date of consent and registration for survival analyses because that is the time in which the patient was determined as potential HCT candidate. There will be inherent time lag between the enrollment (time 0) to the biologic assignment (up to 3 months). The biologic assignment will occur at anytime between enrollment (time 0) and 90 days from enrollment, at which all patients will be assigned to the

non-HCT arm. Up until the time of donor identification, all patients will be in the non-HCT cohort.

9. What are the recruitment strategies if applicable, and proposed plans for monitoring study accrual?

Core Clinical Centers and non-Core Centers will participate. Transplant centers will follow their local institutional practices for recruiting patients on research studies. Due to Medicare coverage issues, it is expected that a majority of MDS patients ≥65 years of age will be identified as potential study candidates at their first consultation visit to Core Clinical Centers and non-Core Centers. In addition, MDS patients who are enrolled onto the SWOG/Intergroup MDS trial will be encouraged to participate in this CTN trial.

Patient information and educational materials explaining this study will be prepared by the NMDP Office of Patient Advocacy and made available to centers in paper form and on the Web.

Monthly accrual reports will be provided to the NIH. Additionally, recruitment reports based on the CIBMTR database will be provided every six months. The screening reports will summarize reasons for non-enrollment and reasons for ineligibility.

10. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used for all BMT CTN supplemental forms. Data are transmitted encrypted using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference and training of clinical research associates (CRAs).

Data collected on CIBMTR Initial and Follow-up Report Forms will be transferred electronically from the CIBMTR to EMMES on a regular basis. Any data relevant to real-time monitoring of safety or efficacy endpoints will be collected on BMT CTN supplemental forms, e.g. deaths.

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in each protocol.

11. What is the monitoring and overall coordination of protocol management (eg. brief summary of plans to run the study – initiation, coordination, data collection, and monitoring)?

A protocol coordinator is assigned to each BMT CTN protocol. The protocol coordinator is responsible for the daily operational needs of the study and of the participating transplant centers. The protocol coordinator oversees enrollment and data collection issues and is in regular communication with CRAs at participating transplant centers. The protocol coordinator also works closely with the protocol officer with respect to adverse event reporting and to medically related protocol questions.

A form submission schedule is developed for each BMT CTN protocol and is included in these materials. A follow up schedule will be provided to the transplant centers for every enrolled patient. This schedule will detail the dates of all follow-up time points and list of forms required at these time points.

Initiation site visits will be conducted for all participating centers. These visits will either be in-person visits to the centers or be held via conference call with all transplant center personnel involved with this protocol.

DCC staff, including at a minimum the protocol coordinator, will conduct periodic monitoring visits to the participating clinical centers and laboratories. The primary purpose of these visits is to conduct data audits. Other activities include those required to enhance data quality, ensure study integrity, satisfy regulatory requirements, and evaluate site performance. Site visits will occur at variable frequency throughout the course of the studies, depending primarily upon the stage of the study, site performance, and sponsoring agency requirements.

Unexpected serious adverse experiences will be reported according to BMT CTN guidelines. The protocol officer will review all unexpected serious adverse experiences. Expected transplant-related toxicities will be collected on each patient using the calendar-driven reporting system that has been previously reviewed and approved by the DSMB. There is an interim statistical monitoring plan for efficacy endpoints. The protocol statistician or other DCC statistical staff will ensure that programs are in place to conduct the interim monitoring in accordance with the statistical analysis plans in each protocol.

12. Are there any specific study training plans necessary to accomplish the research goals (eg. workshops, study certification)?

There is no specific training plan in this study.