BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 1101

1. Why conduct a transplant trial studying reduced intensity bone marrow transplantation (BMT) from family members who are haploidentical ("half-matched") or unrelated cord blood (UCB) in patients with myeloid and lymphoid malignancies?

Donor availability is a significant obstacle for patients who need a bone marrow transplant but lack a suitably matched relative. The lack of an available donor is a particular problem for members of ethnic minorities, especially African Americans, because their likelihood of finding a suitable donor from the national bone marrow registry is low. If a mismatched family member (Haplo-BM) or unrelated umbilical cord blood (UCB) could be used, nearly all patients would have a readily available donor. This is because in case of considering a Haplo-BM, half of the patient's siblings and any child or parent would be a potential donor. Alternatively, if considering unrelated umbilical cord blood, the less stringent HLA-matching requirement allows finding a suitable UCB graft for most patients. In addition, patients who are older and/or have serious coexisting illnesses are at a higher risk of serious complications, including death, from the transplant procedure itself. Clinical trials carried out by the Blood and Marrow Transplant Clinical Trials Network have shown that both procedures with a reduced intensity conditioning (RIC) regimen are safe and effective in getting the graft to take in most patients.

In BMT CTN protocol 0603 that used Haplo-BM following RIC, the 1-year cumulative incidence of TRM was 7% (95% CI, 0-15%) and of relapse/progression was 45% (95% CI, 30-61 The 1-year probability of progression-free survival (PFS)was 48% (95% CI, 32-62%) and overall survival (OS) was 62% (95% CI, 44-76%).

In BMT CTN protocol 0604 that used unrelated double UCB grafts following RIC, the 1-year cumulative incidence of TRM was 24% (95% CI, 11-36%) and of relapse/progression was 31% (95% CI, 17-44%). The 1-year probability of PFS was 46% (95% CI, 31-60%) and OS was 54% (95% CI, 38-67%).

These results of the RIC followed by Haplo-BM (0603) or double UCB (0604) transplantation in multicenter Phase II trials were quite encouraging. Importantly, in this multicenter group setting (17 different centers entered patients on the haploidentical trial and 16 on the UCB trial), both of these alternative donor approaches produced early results similar to that reported with unrelated

donor, and even HLA-matched sibling, BMT. These data demonstrate not only the efficacy of both of these approaches, but also that both can be safely exported from the single center setting. However, the numbers of patients in the two BMT CTN trials were relatively small and assignment was not randomized. Accordingly, this protocol is a multi-center, randomized Phase III trial of double UCB versus related haplo-BM transplantation after RIC in patients with hematologic malignancies. Confirming the safety and efficacy of double UCB and/or Haplo-BM would allow access to transplant for essentially all patients in need. The central hypothesis of this trial is that PFS at two years after RIC haplo-BM transplantation is similar to the PFS after RIC dUCB transplantation.

2. What is the current "standard of care" for patients requiring transplantation but do not have a HLA matched sibling donor?

An unrelated volunteer adult donor who is suitably matched is considered the "standard of care". Disadvantages of such donors include cost and time of searching which can prevent transplantation for advanced disease to occur in a timely manner and the relative lack of suitable donors for patients who are members of ethnic minority groups. In studies of Haplo-BM and double UCB transplantation carried out by the BMT CTN showed that these donor types are safe and effective sources of hematopoietic grafts with outcomes similar to those of conventional donors as described in FAQ #1.

3. Why were theses preparative regimens chosen for transplantation of haplo-BM and double UCB?

The conditioning regimen in both arms were developed to overcome the complications seen with myeloablative transplantation in older and less fit patients and at the same time promote engraftment, and reduce the risks of severe GvHD and transplant-related mortality. The basic platform was the reduced intensity regimen for conventional transplants pioneered by Storb and co-workers at the Fred Hutchinson Cancer Research Center. Early phase I trials, determined that additional immunosuppression with cyclophosphamide and fludarabine chemotherapy pre-transplant was required to facilitate engraftment in both transplant settings. In the haplo-BM arm, an important element of the regimen is the high-dose cyclophosphamide (Cy) administered 3 and 4 days after transplant. When given this way, Cy is able to selectively eliminate the highly alloreactive T-cell clones which become activated in the first 3 days after transplant and would be responsible for the unwanted complication of severe GvHD (hematopoietic stem cells are insensitive to cyclophosphamide). Otherwise, additional pharmacologic immunosuppression is given in both study arms to further modulate alloreactivity.

4. What are the potential risks of using haploidentical or UCB donors?

The main risks of using haplo-BM or double UCB donors are graft rejection and severe graft-versus-host disease. Since the chemotherapy and radiation therapy that are given do not destroy the patient's own blood stem cells, patients with graft rejection are likely to recover their own ability to make blood cells. Moreover, the rate of serious GVHD is no greater than is seen after BMT from matched sibling donors.

5. Who is responsible for the costs of the transplant procedure?

As these are both clinically established transplantation techniques, the patient and/or the patient's insurance carrier are responsible for the cost of treatment. While most third party payers have routinely approved these types of transplants, we recommend that patients only be enrolled if they have been approved or are very likely to be approved for the cost of the treatment.

6. Is there need for the transplant center to hold an IND in order to able to use UCB as a graft source?

Beginning October 20, 2011, the FDA will require that unlicensed UCB units be used only under an IRB-approved clinical protocol, with the corresponding signed consent form, as part of an active IND. Your center can hold its own IND or can participate in the NMDP IND. If your center is planning to participate in the NDMP IND, it should be going through your IRB now. Please note that the NMDP IND covers the use of unlicensed cord blood units for specific indications outlined in the FDA guidance.

In order for your Center to continue to receive unrelated donor cord blood units under an after October 20, 2011, you must document one of the following:

1. Contractual agreement with the NMDP to access unlicensed UCB units under their IND and documentation that the protocol associated with this IND has been approved by your IRB;
2. FDA approval of an institution-specific IND for access to unlicensed UCB units This is optional for the FDA designated indications but required for other indications (e.g. Sickle Cell Disease, other inborn errors of metabolism).
3. Use of licensed UCB units only**

** Currently there are no licensed cord blood units available.

7. Accrual estimates – See separate summary of Accrual Estimates.

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

Core Clinical Centers and Affiliate Centers will participate. Transplant centers will follow their local institutional practices for recruiting patients on research studies.

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.

9. 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.

10. What is the monitoring and overall coordination of protocol management (e.g. 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 visit schedule will be provided to the transplant centers for every enrolled patient. This schedule will detail the dates of all expected visits and list of forms and/or samples required at each visit.

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 and safety 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.

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

CRAs will be certified for data submission by the DCC after participating in an in-person meeting or in a training session conference call with the protocol coordinator. No other certifications or workshops will be required for this study.