

BMT CTN 1204 FREQUENTLY ASKED QUESTIONS (FAQs)

REDUCED-INTENSITY CONDITIONING FOR CHILDREN AND ADULTS WITH HEMOPHAGOCYtic SYNDROMES OR SELECTED PRIMARY IMMUNE DEFICIENCIES (RICHI)

1. What patients are eligible for this study?

This study will enroll patients with hemophagocytic syndromes and selected primary immune deficiencies. While each disease listed below is unique, all are associated with defects in immune function. Hemophagocytic syndromes are characterized by uncontrolled inflammation due to defects in immune function and include familial hemophagocytic lymphohistiocytosis (HLH), acquired HLH, and chronic active EBV infection (CAEBV). Patients with selected immune deficiencies including chronic granulomatous disease (CGD), hyper IgM syndrome (HIGM1), IPEX syndrome and severe leukocyte adhesion deficiency (LAD-I) are also eligible to participate. Patients from 4 months of age to 45 years are eligible for this study. Although most patients are children there are some older patients who may benefit from this study.

2. What is the rationale for studying reduced intensity conditioning (RIC) hematopoietic cell transplant (HCT) in patients with hemophagocytic syndromes and selected primary immune deficiencies?

HCT is a potential cure for patients with HLH, CAEBV, CGD, HIGM1, IPEX and LAD-I through replacement of a dysfunctional immune system with the functional donor immune system. However, many patients experience complications from their underlying disease, such as chronic infections, that may increase the risks of HCT. Transplant-related complications have decreased, and survival has increased in many case series reporting outcomes of HCT with RIC compared to standard myeloablative approaches. This study will evaluate the safety and efficacy of this strategy in a prospective, multicenter trial.

3. What conditioning regimen does the recipient get before transplantation in this trial?

The conditioning regimen uses 3 drugs: Campath-1H, fludarabine, and melphalan. Campath-1H is a protein antibody that targets lymphocytes and macrophages. Fludarabine is a purine analog that decreases lymphocyte numbers and function. Melphalan is an alkylator that is cytotoxic for malignant and non-malignant hematopoietic cells. Because Campath-1H has a very long half-life, it is given about 2 weeks before the actual transplant. The other 2 drugs are given in the week before the transplant as is standard for pre-transplant conditioning.

4. How does conditioning for transplantation in this trial differ from other conditioning regimens used in transplantation for hemophagocytic syndromes and selected immune deficiencies?

Previous transplant approaches trials have used myeloablative high dose chemotherapy in the conditioning regimen to achieve donor cell engraftment. This study uses a reduced intensity conditioning regimen with doses of cytotoxic agents not expected to cause high rates of regimen-related toxicity. This means that the conditioning regimen does not use high dose chemotherapy or radiation to achieve engraftment of donor cells. Instead, it uses medications that suppress the immune system of the recipient to allow donor cells to engraft. Cases where there is partial donor engraftment (chimerism) may still be curative. In some cases, if the donor cells fail to engraft or if the donor chimerism decreases rapidly, a donor lymphocyte infusion or second HCT may be required. In one study where there were a large number of patients who required lymphocyte infusions or second HCT, survival remained significantly higher than patients transplanted with myeloablative approaches from the same institution. Preliminary results from a single institution study with the RIC strategy used in this study demonstrated very few problems with engraftment and high survival rates.

5. How were the matching criteria for selection of donor sources chosen?

Preliminary data from an earlier trial at a single institution using this approach have shown that the use of bone marrow from related and unrelated donors was associated with good engraftment and survival. Data from the Center for International Blood and Marrow Transplant Research suggest that engraftment and survival is lower after unrelated umbilical cord blood compared to bone marrow from unrelated adult donors.

6. Why are peripheral blood stem cells not permissible as a donor stem cell source?

It is not clear at present whether peripheral blood cells when used as a stem cell source have advantages or disadvantages over bone marrow cells. Generally chronic graft-versus-host disease is higher after transplantation of peripheral blood compared to bone marrow. In the absence of data supporting peripheral blood and bone marrow transplants from unrelated adult donors lead to comparable survival in children, peripheral blood will not be permissible as a stem cell source for this trial of transplantation for a non-malignant disorder that has no role for GVHD.

7. Why are cord blood stem cells not permissible as a donor stem cell source?

There is little data comparing outcomes of patients with HLH and selected immune deficiencies eligible for this study when transplanted with bone marrow versus cord blood stem cells. However, CIBMTR experience demonstrates that patients with these diseases had rejection of cord blood grafts in more than 35% of the cases using both RIC and myeloablative approaches vs. 5% for unrelated BM/PBSC grafts. This has contributed to worse survival using this stem cell source. Other approaches may be developed that result in better engraftment and survival using cord blood, but because successful approaches have yet to be developed, we are currently restricting this protocol to bone marrow donors.

8. What safety measures are in place for this trial? How is safety going to be monitored in this group of patients that don't have an immediately life-threatening disease?

Monitoring of a key safety endpoint (overall mortality) will be conducted monthly, and if rate significantly exceeds pre-set thresholds, the NHLBI will be notified in order that the Data and Safety Monitoring Board (DSMB) can be advised. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

9. Accrual estimates – How many transplants will be performed as part of this trial?

This trial is designed to enroll 35 recipients over 3 years.

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

Core Clinical Centers including PBMTTC centers as well as 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. The screening reports will summarize reasons for non-enrollment and reasons for ineligibility.

11. 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 case report 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.

12. 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)?

An investigators meeting will be conducted for this protocol at the annual Tandem BMT Meetings. Training meetings for CRAs will be regularly conducted in conjunction with the annual Tandem BMT Meetings and or the NMDP and/or CIBMTR annual meetings and by teleconference.

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 (physician) for medically related protocol queries and the medical monitor (physician) who monitors adverse events.

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 a protocol monitor, 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 and site performance,.

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.

13. 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 online training session and completing a practicum. No other certifications or workshops will be required for this study.