BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN PROTOCOL #0604

A Multi-Center, Phase II Trial of Non-Myeloablative Conditioning (NST) and Transplantation of Umbilical Cord Blood (UCB) from Unrelated Donors in Patients with Hematologic Malignancies

Significant Changes to Version 1.0 of the 0604 Protocol:

- *§2.3 – Patient Inclusion Criterion #1*
  Changed to read (new text highlighted in *italics):* Age: Subjects 21-70 years old. Subjects ~~*<21*~~ *1 – 21* are also eligible if they are ineligible for BMT CTN #0501.

- *§2.3 – Patient Inclusion Criterion #4*
  Changed to read (new text highlighted in *italics*): Patients must have received ~~multi-agent~~ *cytotoxic* chemotherapy within 3 months of consent date (measured from the start date of chemotherapy).

- *§2.3 – Patient Inclusion Criterion #5*

  Changed to read (new text highlighted in *italics*): Acute Leukemias *(includes T lymphoblastic lymphoma) in 2nd or subsequent CR (see remission definition in Chapter 3:*

- *§2.3 – Patient Inclusion Criterion #7a*

  Changed to read (new text highlighted in *italics*): Chemotherapy-sensitive (complete or partial response; see response criteria in Chapter 3) large cell, *Mantle Cell* or Hodgkin's lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are ineligible for an autologous transplant.

Minor Changes/Clarifications to Version 1.0 of the 0604 Protocol:

- The cover page was revised to reflect the current center participants.

- *§2.5 – Graft Selection #2*
  Changed to read the following (new text in *italics): If the units are red cell-depleted,* the minimum cryopreserved nucleated cell *(TNC)* dose of each *unit* must be $\geq 1.5 \times 10^7$ /kg (actual body weight). ~~If the unit contains red cells at the time of cryopreservation~~ *If the unit was NOT red cell-depleted,* the *minimum* cryopreserved *TNC* dose of each unit must be at least 2.0×10^7 TNC/kg.

- *§2.5 – Graft Selection #5*
  Changed to read the following (new text in *italics*): Above the cell dose threshold of 1.5×10^7 TNC/kg ~~(2.0×10^7 TNC/kg for red cell containing units~~ (*or 2.0×10^7 TNC/kg for units that were not red cell-depleted*), HLA-match will take priority in unit selection. However, within the best available HLA match grade (e.g. 5/6), units with the largest TNC should be chosen.

- *§2.6.1.1 – Fludarabine*

Changed to read the following (new text in *italics*): Fludarabine 40 mg/m^2/day IV x 5 days, total dose 200 mg/m^2. *Fludarabine will be dosed according to the recipient's actual body weight, unless the actual body weight is greater than or equal to two times their ideal body weight, in which case the protocol team must be consulted for instruction.* For patients who have a creatinine clearance < 70 ml/min/1.73 m^2, or prior CNS disease, or prior brain radiation, and/or prior intrathecal chemotherapy, the Fludarabine dose should be reduced by 20%.

- *§2.6.1.2 – Cyclophosphamide*
  The following was added (new text in *italics*): *It is recommended that fludarabine should be the first chemotherapy drug administered on Day -6, followed by the administration of cyclophosphamide, to allow for fludarabine to be infused at approximately the same time each day.*

- *§2.6.3 – UCB Infusion*
  Following the administration of the preparative therapy, all subjects will undergo UCB transplantation. Under no circumstances is the cord blood to be irradiated. No in-line leukocyte filter should be used and no medications or fluids should be given piggyback through the catheter lumen that is being used for cord blood infusion. Vital signs should be monitored before beginning the infusion and periodically during administration. The two units for double UCB transplantation are infused one after the other with no need for interval between units.

  Contingency plans for UCB units that cannot be infused (due to viability, etc.) will be made according to institutional policies. These plans may include obtaining marrow from a haploidentical relative, supportive care, acquisition of another compatible UCB unit, following local institutional practices or autologous marrow back up.

  ~~The cord blood should be thawed and administered per institutional practice per validated thawing and administration procedures at the institution. Infusion should begin within 3 hours of washing. The infusion should take no longer than 1 hour. Pre-medications (if any) prior to cord blood infusion will be at the discretion of the transplant center.~~

  The cord blood should be thawed, diluted with or without wash per validated institutional or supplying cord blood bank procedures with the exception that bedside thawing and direct infusion is not allowed. Bedside thaws are not recommended because of the inability to rescue the product if there is loss of integrity of the UCB bag on thaw at the bedside and because of the instability of the cells in 10% DMSO post thaw.

  All transplant centers/cellular therapy laboratories must be familiar with thawing of cord blood units. They must have validated procedures and maintain competency in the thaw process. The cord blood unit must be thawed in a qualified laboratory by trained personnel. Generally the cryopreserved unit is removed from the protective cassette, placed in a ziplock bag and thawed rapidly in a 37° C waterbath. The ziplock bag allows for recovery of cells if the cryopreservation bag cracks or leaks during the thawing process, a rare but possible event. Once the contents of the bag reach a slushy consistency, the cells can be diluted in dextran/albumin, a hypertonic solution that buffers against the intracellular hypertonicity created by DMSO. Cell suspensions can subsequently be washed to remove DMSO, free hemoglobin and other cellular debris allowing for resuspension in a volume appropriate for the size of the patient to be transplanted.

  Benadryl, epinephrine, and hydrocortisone should be available at the bedside for emergency use if necessary. Oxygen with nasal prongs for standby use should be present in the room.

- *§4.2.1. Follow Up Schedule – CIBMTR Data Reporting*

  Changed to read the following (new text highlighted in *italics*): ~~All participating transplant centers are required to **pre-register** all transplant recipients with the Center for International Blood and Marrow Transplant Research (CIBMTR), whether or not they enroll in a BMT CTN Protocol. In addition, the transplant center must complete the CIBMTR Day 100 Report Form (including the Core, Graft and Disease Inserts) and CIBMTR Follow-up Forms (including the Core and Disease Inserts) yearly for all patients enrolled in BMT CTN protocols. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule; additionally, annual IBMTR Follow-up Forms must be submitted for at least five years post-transplant.~~ *Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment of BMT CTN #0604 must be indicated on the SCTOD pre-transplant registration form, if applicable. Additionally, CIBMTR pre- and post- transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.*

- *§4.2.1. Follow Up Schedule – Weekly GVHD Monitoring*

  Changed to read the following (new text highlighted in *italics*): GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day *56* ~~100~~ post-transplant for GVHD. After Day 56 ~~100~~ patients will be assessed at each follow-up visit (Day 180~~,~~ *and* 365 ~~and 730~~) for the presence of GVHD.

- *§4.2.3.1. Pre-transplant evaluations #12*

  Changed to read the following (new text highlighted in *italics*): *Peripheral* ~~heparanized~~ blood for pre-transplant *RFLP analysis,* ~~chimerism assay~~ *to establish a reference profile of host hematopoiesis.*

- *§4.2.3.2. Post-transplant evaluations #1*

  Changed to read the following (new text highlighted in *italics*): History and physical exam to assess GVHD and other morbidity weekly until Day *56* ~~100~~ post-transplant, then at six months, *and* one year *pos- transplant* ~~and then yearly until two years post transplant~~. GVHD evaluation and grading to be in keeping with BMT CTN MOP.

- *§4.2.3.2. Post-transplant evaluations #2*

  Changed to read the following (new text highlighted in *italics*): CBC at least three times a week from Day 0 until ANC > 500 mm^3 for 3 days after nadir reached. Thereafter CBC twice per week until Day 28, then weekly until 12 weeks, then at six months, *and* one year *post-transplant*.~~ and then yearly until two years post transplant~~

- *§4.2.3.2. Post-transplant evaluations #3*

  Changed to read the following (new text highlighted in *italics*): Creatinine, bilirubin, alkaline phosphatase, ALT, AST, *LDH*, *sodium, magnesium, potassium, chloride, and thyroid function tests* twice a week until Day 28 (or four weeks) and then weekly until 12 weeks, and then at six months, *and* one year *post transplant*. ~~and then yearly until two years post transplant~~.

- *§4.2.3.2. Post-transplant evaluations #4*

  Changed to read the following (new text highlighted in *italics*): *Peripheral* ~~heparanized~~ blood on Day ~28, ~56, ~180, and ~365 for post-transplant chimerism assay.

- *§4.2.3.2. – Post-transplant Evaluations #8*
  The following was added (new text in *italics)*: Disease status evaluation required at Days ~~60~~ *56*, 6 months and 1 year. Testing to determine disease status should follow pre-transplant evaluation process. Disease status evaluation before Day ~~60~~ *56* should follow institutional practices. *Bone marrow biopsy and aspirate to pathology is required for disease status evaluation at Days 56 and 365.*

- *§4.2.3 Summary of Patient Clinical Assessments (Table)*
  Deleted the row "Blood samples for immune reconstitution assays[5]."

- *§4.2.3 Summary of Patient Clinical Assessments (Table) – Footnote #1*
  Changed to read (new text highlighted in *italics*): CBC performed at least ~~twice~~ *three times* a week from Day 0 until ANC >500 mcL for ~~two~~ *three* days after nadir. CBC performed twice weekly until Day 28. CBC performed weekly after Day 28 until 12 weeks post-transplant.

- *§4.2.3 Summary of Patient Clinical Assessments (Table) – Footnote #4*
  Changed to read (new text highlighted in *italics*): Bone marrow biopsy and aspirates to pathology required at Day 21 *if WBC < 500*. Day 28 only to be done if slow neutrophil recovery to evaluate for graft failure. Cytogenetics and flow cytometry should be sent as clinically indicated by patient's diagnosis. *Baseline, Day 56 and Day 365 are required; Day 180 is optional. This information was also updated in the body of the table.*

- *§4.2.3 Summary of Patient Clinical Assessments (Table) – Footnote #~~6~~5*
  Changed to read (new text highlighted in *italics*): GVHD and other morbidity assessments performed weekly until Day ~~100~~ *56* post-transplant, and then at Day 180~~,~~ *and* 365 ~~and 730~~. *This information was also updated in the body of the table.*

- *§5.6.2 Probability of Ruling Out a Threshold of Size T for Various True Underlying Overall Survival Percentages (Table) – Label*
  Changed to read the following: Probability of Ruling Out Overall Survival Percentages of Size T ~~or Smaller~~

- *§APPENDIX C: LABORATORY PROCEDURES*
  Changed to read the following (new text in *italics*): Samples of peripheral blood or marrow are collected from the patient and samples from the UCB pre-transplant for chimerism studies according to institutional standards. Patient samples are also collected on Day ~28, ~60, ~180 and ~365 post-transplant. Chimerism will be measured by RFLP or microsatellite. *FISH should not be used to assess chimerism*. Donor chimerism after transplantation shall be measured on samples of whole blood or mononuclear fraction.

Minor Changes/Clarifications to Version 1.0 of the Participant Informed Consent for the 0604 Protocol:

- *§ How long will I be in this study?*
  Changed to read the following (new text highlighted in *italics*): Your treatment will last approximately 2-3 months at this center but possibly longer if there are complications. We would like to see you in clinic for follow-up at 6 months, if possible, and then ~~yearly after transplant for at least two years~~ *I*~~~~*one year post- transplant*.