



**A Phase II Multicenter Trial of Myeloablative Double Unit  
Umbilical Cord Blood Transplantation (UCBT) in Adults with  
Hematologic Malignancy**

**CIBMTR PROTOCOL 05-DCB  
Version 1.0**

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**PROTOCOL SYNOPSIS – CIBMTR PROTOCOL 05-DCB****A Phase II Multicenter Trial of Myeloablative Double Unit Umbilical Cord Blood Transplantation (UCBT) in Adults with Hematologic Malignancy**

**Study Chairperson:** Juliet Barker, MBBS, (Hons).

**Study Design:**

This study is a Phase II, open-label, multicenter, prospective study of double unit UCBT in adult patients with hematologic malignancies.

**Primary Objective:**

The primary aim of this study is to establish the one year overall survival after myeloablative double unit UCBT in a multi-institution setting.

**Secondary Objectives:**

- 1) Incidence of donor-derived neutrophil and platelet recovery
- 2) Contribution of each unit to initial (day +21 BM, +28 PB) and sustained engraftment (day +100 BM; PB at +60, +100, +180, +1 and 2 years)
- 3) Incidence and severity of acute graft-versus-host disease (GVHD) at 100 days
- 4) Incidence and severity of chronic GVHD at one year
- 5) Incidence of day 100 and 180 transplant-related mortality (TRM)
- 6) Incidence of malignant relapse at one and two years after UCBT
- 7) Incidence of serious infectious complications in the first year after transplant
- 8) Incidence of immune reconstitution (serial T, B and NK measurements by flow and Ig levels)
- 9) Probability of overall survival at one and two years
- 10) Probabilities of disease-free survival at one and two years after UCBT.

**Eligibility Criteria:**

- 1) Age 22 - 50 years.
- 2) Patients will have one of the following hematological malignancies:
  - Acute myelogenous leukemia (AML):
    - Complete first remission (CR1) at high risk for relapse as defined by:
      - Known prior diagnosis of myelodysplasia (MDS); or
      - Therapy related AML; or
      - White cell count at presentation > 100,000; or
      - Presence of extramedullary leukemia at diagnosis; or
      - Unfavorable FAB type (M0, M5-7); or
      - High-risk cytogenetics (those associated with MDS, abnormalities of 5, 7, 8, 11q23 translocations, Philadelphia chromosome, complex karyotype); or
    - Complete second remission (CR2)
  - Acute lymphoblastic leukemia (ALL):
    - Complete first remission (CR1) at high risk for relapse as defined by:
      - White cell count at presentation > 50,000; or

- Presence of high-risk cytogenetic abnormality such as t(9;22), t(1;19), t(4;11) or other MLL rearrangements (11q23), t(8;14); or
  - Failure to achieve complete morphologic remission after four weeks of induction therapy.
- Complete second remission (CR2)

Acute undifferentiated leukemia (AUL) or biphenotypic leukemia in CR1 or CR2

Myelodysplastic Syndrome (MDS) with one of the following:

- Low and Intermediate-1 International Prognostic Scoring System (IPSS) score with
    - Life-threatening neutropenia or thrombocytopenia; or
    - Platelet transfusion dependence
  - Intermediate-2 or High IPSS score
- 3) Patients with adequate organ function and performance status criteria measured by:
- Karnofsky score  $\geq 70$  %
  - Renal: Calculated creatinine clearance  $\geq 60$  mL/min OR if creatinine  $\geq 1.5$  or a history of renal dysfunction must have a *measured* creatinine clearance (using 24 hour urine collection)  $\geq 60$  mL/min
  - Hepatic: Total bilirubin  $< 2.5$  mg/dL unless benign congenital hyperbilirubinemia (Gilbert's syndrome) and ALT/AST  $< 3$  x upper limit of normal
  - Albumin  $\geq 2.5$  g/dl
  - Pulmonary: Pulmonary function (spirometry and corrected DLCO)  $\geq 60\%$  normal
  - Cardiac: Left ventricular ejection fraction  $\geq 50\%$
- 4) Double Unit Umbilical Cord Blood Grafts:
- Patient must undergo a UCB search at both NMDP banks (Domestic and Co-op) and NYBC at a minimum
  - Each unit must have a cryopreserved dose of at least  $1.5 \times 10^7$  TNC/kg (actual body weight). If the unit contains red cells at time of cryopreservation, the cryopreserved dose must be at least  $2.0 \times 10^7$  TNC/kg. See Appendix B for unit selection details.
  - Each unit must be at least 4/6 HLA-A, B, DRB1 antigen and allele matched with the recipient
  - Each unit must be at least 3/6 HLA-A, B DRB1 antigen matched to each other
  - Above the cell dose threshold of  $1.5 \times 10^7$  TNC/kg ( $2.0 \times 10^7$  TNC/kg for red cell containing units), 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.

**Exclusion Criteria:**

- 1) Patient with suitable related donor
- 2) AML, ALL, AUL, biphenotypic leukemia beyond CR2
- 3) AML evolved from myelofibrosis
- 4) Any acute leukemia with:

- Morphologic relapse or persistent disease in the BM (cytogenetic relapse without morphologic evidence of relapse, or cytogenetic persistent disease in the BM is acceptable); or
  - Active extra-medullary leukemia including active CNS leukemia; or
  - Requiring greater than two cycles of chemotherapy to obtain present remission status
- 5) Bone marrow aplasia (defined as BM cellularity < 5% at transplant work-up)
  - 6) MDS with 10% or greater bone marrow blasts at pre-transplant workup
  - 7) Prior autologous or allogeneic HSC transplant at any time
  - 8) Prior radiation therapy rendering patient ineligible for TBI
  - 9) Any uncontrolled infection at time of study enrollment
  - 10) Seropositive or NAT positive for HIV or HTLV1
  - 11) Females who are pregnant or breast feeding
  - 12) Patient unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up, and research tests

**Treatment Description:**

Cyclophosphamide 60 mg/kg/day IV days –7 and –6 (total dose 120 mg/kg)

Fludarabine 25 mg/m<sup>2</sup>/day IV days –8 to –6 (total dose 75 mg/m<sup>2</sup>)

Hyperfractionated TBI 1320 cGy in 8 165 cGy fractions days –4 to –1

GVHD prophylaxis: cyclosporine A (CSA) day –3 to maintain level 200 - 400 µg/L (ng/mL) until day 100 then taper if no GVHD; mycophenolate mofetil (MMF) 1 gram BID (or 15 mg/kg BID if < 50 kg) day –3 to +45 (must be IV while inpatient and IV at least until day +21).

G-CSF 5 mcg/kg/day IV/SQ (maximum 480 mcg; dose rounded to vial size) from day +1 until ANC ≥ 2500/uL x 2 days.

**Accrual Objective:** The target sample size is 55 patients.

**Accrual Period:** The estimated accrual period is three years.

**Study Duration:** Patients will be followed for 24 months post transplant.