THE TREATMENT OF HEMATOLOGIC MALIGNANCIES WITH SINGLE OR DOUBLE UMBILICAL CORD BLOOD TRANSPLANTATION

A STANDARD TREATMENT PROTOCOL OF THE STEM CELL TRANSPLANT PROGRAM VANDERBILT UNIVERSITY MEDICAL CENTER VETERAN AFFAIRS TENNESSEE VALLEY HEALTHCARE SYSTEM
SCHEMA A  
FULLY ABLATIVE TRANSPLANT  
(For Patients Equal to or Greater than 18 but Equal to or Less than 50)

<table>
<thead>
<tr>
<th>DAY</th>
<th>DRUG</th>
<th>DOSE</th>
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<tbody>
<tr>
<td>-6</td>
<td>Fludarabine</td>
<td>25 mg/m² IV</td>
</tr>
<tr>
<td>-5</td>
<td>Fludarabine</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>60 mg/kg IV with Mesna prophylaxis</td>
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<tr>
<td>-4</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<tr>
<td>-3</td>
<td>TBI</td>
<td>200 cGy BID</td>
</tr>
<tr>
<td>-2</td>
<td>TBI</td>
<td>200 cGy BID</td>
</tr>
<tr>
<td>-1</td>
<td>TBI</td>
<td>200 cGy BID</td>
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<tr>
<td>0</td>
<td>Cord Blood infusion</td>
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<tr>
<td>+1</td>
<td>G-CSF</td>
<td>5 mcg/kg/day IV or SC</td>
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<tr>
<td></td>
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The order of TBI and chemotherapy can be reversed at the discretion of the OTU Attending physician.

Cyclophosphamide will be dosed on the actual body weight or the adjusted ideal body weight at the discretion of the treating attending physician. Patients will receive standard mesna prophylaxis to prevent hemorrhagic cystitis.

ANTIEMETICS:

Ondansetron 8mg IV prechemo/TBI then every 8 hours day -6 thru -1  
Emend 150mg IV x 1 dose on day -5 only  
Dexamethasone 12mg PO prechemo/TBI on days -6 and -5  
Dexamethasone 8mg PO prechemo/TBI day -4 only  
Dexamethasone 8mg PO twice daily on days -3 and -2
### SCHEMA B

**REDUCED INTENSITY CONDITIONING**

For Patients With Age Greater than 50 Years but Less than 55 Years  
Or Patients Age 18-49 Who are Deemed Ineligible for  
Myeloablative Conditioning Regimen

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<td>40 mg/m² IV</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
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</tr>
<tr>
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1.0 PURPOSE
The purpose of this protocol is to define the standard treatment protocol of umbilical cord blood transplantation for adults with hematologic malignancies

2.0 INCLUSION/EXCLUSION CRITERIA

2.1 Inclusion Criteria
A. All patients undergoing HCT must be able to give a signed informed consent (see Clinical SOPCL0001.xx for process of informed consent)
B. All patients undergoing HCT should have a KPS ≥ 70%
C. All patients undergoing HCT must have no evidence of active uncontrolled infection
D. Patients must be HIV non-reactive
E. All cases must be discussed and approved in transplant meeting
F. All patients must undergo detailed pre-transplant evaluation (see Clinical SOPCL0002.xx-allogeneic HCT)

2.2 Exclusion Criteria
A. Patients who have angina and/or congestive heart failure requiring treatment, or who have had a myocardial infarction within the past year. All patients with known cardiac problems (CAD, CABG) will need evaluation by a cardiologist prior to being considered for HCT as a protocol deviation.
B. Patients who have had any complication that makes the risk of death during transplantation from non-malignant causes greater than the risk of relapse.
C. Patients who have uncontrolled diabetes mellitus will be considered on a case-by-case basis.
D. Uncontrolled psychiatric illness requiring psychiatric counseling or medical intervention other than antidepressant medications may make an individual ineligible.
E. Psychosocial assessment by the bone marrow transplant team may identify individuals for whom this form of therapy may be contraindicated. These decisions will be based upon estimated adequacy of patient support systems and prediction of patient’s compliance with medications, required diagnostic procedures and/or follow up care.
F. Patient with evidence of cirrhosis of the liver based on imaging and/or liver biopsy are not considered suitable candidates for HCT. All patients with cirrhosis will need evaluation by a hepatologist prior to being considered for HCT as a protocol deviation.
G. Patients with uncontrolled CNS disease
H. Patients who are pregnant or at risk of pregnancy and unwilling to use acceptable birth control methods.

I. Patients who are actively abusing alcohol, recreational drugs or tobacco as evidenced by a positive screening just prior to the initiation of the preparative regimen.

J. Patients with other malignancies will be excluded except for the following:
   1) Diagnosis of skin cancer (squamous cell or basal cell carcinoma)
   2) Diagnosis of cervical dysplasia (CIN I-III)
   3) Any other malignancy which is currently in remission and was treated with curative intent more than 5 years preceding study entry.
   4) Secondary AML or Secondary MDS - the previous neoplastic disease is in remission but can be within 5 years of study entry.

   Any deviation must be discussed in transplant meeting and must be approved as a protocol deviation

K. Patients with active uncontrolled bacterial, fungal, viral or parasitic infection

2.3 Age 18-50 years for adult myeloablative conditioning.
   Age greater than 50 years but less than 55 years for adult reduced intensity conditioning. If patients are 18-49 years and have organ dysfunction (as outlined below) they can be considered for Reduced Intensity Conditioning. These cases need to be discussed on a case by case basis in the transplant meeting.

2.4 Organ Function Inclusion and Exclusion Criteria

   A. Inclusion Criteria. Patients must have a pre-transplant multi-organ assessment within 60 days prior to starting conditioning regimen or as clinically indicated (see clinical SOPCL0002.xx-allo-HCT)
      1) An ejection fraction of 50% or greater demonstrated by echocardiogram or MUGA.
      2) A FEV1, and an adjusted diffusion capacity of 60% or greater
      3) An estimated creatinine clearance of 60 ml/min or greater
      4) A total bilirubin and SGOT of equal or less than 1.5 times the upper limit of normal

   B. Exclusion Criteria. Patients not fulfilling above inclusion criteria are not eligible for ablative allogeneic HCT unless specified in disease specific protocol.

   All patients undergoing HCT who do not fulfill above criteria will be considered as protocol deviation and cases will be discussed and approved on a case-by-case basis

2.5 Indications For Allogeneic Hematopoietic Cell Transplantation

   A. Inclusion Criteria
      1) Acute lymphoblastic leukemia in high risk CR1 as defined by at least one of the following
a) Adverse cytogenetics such as t(9;22); t(1;9); t(4;11), MLL rearrangements
b) WBC > 30,000 wbc/mcL
c) Patients > 30 years of age
d) Time to complete remission > 4 weeks

2) Myelofibrosis: Patients with significant splenomegaly who will undergo non-ablative transplant should have splenectomy done prior to transplant.

3) Acute myelogenous leukemia in high risk CR1 as defined by at least one of the following
   a) Greater than 1 cycle of induction therapy required to achieve remission
   b) Preceding MDS
   c) Presence of FLT-3 abnormalities
   d) FAB M6 or M7 AML
   e) Non-favorable cytogenetics for overall survival such as
      i) Those associated with MDS
      ii) Complex karyotype (≥ 3 abnormalities)
      iii) Any of the following: inv (3) or t(3;3); t (6;9); t(6;11), +8 [alone or with other abnormalities except for t(8;21); t(9;11); inv (161) or t (6;16)]; t (11;19)(q23;p13.1)

4) Acute leukemias in 2nd or subsequent CR

5) Biphenotypic/undifferentiated leukemias is 1st or subsequent CR; secondary acute leukemias in 1st or subsequent CR

6) Burkitt’s lymphoma in second or subsequent CR

7) Lymphoma
   a) Chemotherapy-sensitive (CR/PR) B cell, T cell, Hodgkin’s lymphomas that have failed at least one prior regimen and are ineligible or unable to collect adequate autologous stem cells
   b) Marginal zone B-cell NHL or FCC NHL that has progressed after at least 2 prior therapies but are chemosensitive (CR/PR) at time of allo-HCT

8) Myeloma
   a) Chemotherapy sensitive (at least PR) that have failed at least one prior regimen including an autologous transplant.
   b) Only patients unable to collect stem cells for an autologous transplant can proceed directly to allo-HCT provided they are chemotherapy sensitive (at least PR)

9) MDS
   a) ≥ Int-1 and high risk MDS by IPSS
   b) Low risk MDS but with a high transfusion burden and clinically significant infections (due to neutropenia) and bleeding (due to thrombocytopenia)
   c) MDS with complex karyotype or adverse cytogenetics that predict for poor overall survival (-7, -5)
   d) MDS-RCMD, RAEB-1, RAEB-2
   e) Secondary MDS
2.6 Donor Selection Criteria For Umbilical Cord Blood Unit

A. Inclusion Criteria: Donor Issues
   1) No available HLA identical or 1 antigen/allele mismatched (Class I-A, B or Class II DR locus) related donor
   2) **Low likelihood** of finding a 10/10 or 9/10 allele matched unrelated donor in a **timely** manner.

B. Inclusion Criteria: Umbilical Cord Blood Unit-HLA Typing
   1) At least a HLA 4/6 match (Class I-A, B by low resolution, Class II-DR by high resolution) to recipient
   2) For double UCB SCT each unit should be at least a 4/6 match (Class I-A,B by low resolution, Class II-DR by high resolution) to recipient, and should be at least a 4/6 match (Class I-A,B by low resolution, Class II-DR by high resolution) to each other

3.0 DRUG ADMINISTRATION

3.1 Schema A: Fludarabine, Cyclophosphamide, and TBI

   A. Fludarabine 25 mg/m²/day IV (actual BW) over 30 minutes for a total of 3 doses on Day -6 through Day -4. NS at 250ml/hr should be infused 1 hour prior to the start of fludarabine and for 1 hour after.

   B. Cyclophosphamide 60mg/kg IV over 2 hours for a total of 2 doses on Day -5 and -4.
      1) Begin NS at 125ml/m²/hr 4 hours prior to start of cyclophosphamide and continue for 24 hours after last dose. If outpatient, begin NS at 300cc/hr 4 hours prior to starting cyclophosphamide and continue while in clinic.
      2) Once cyclophosphamide administration begins patient’s output must be at least 100 ml/hr over a 4 hour period.
      3) Check urine output for heme every 2 hours during cyclophosphamide. If greater than trace positive x 2, increase IV hydration by 50 cc/hr and give furosemide in 2 hours **(Do not exceed the baseline hydration rate by 100 cc/hr)**.

   C. Mesna 20 mg/kg/dose IV prior to Cyclophosphamide, 3 hr and 6 hr after.

   D. Furosemide 20mg IV after each dose of cyclophosphamide then as needed.

   E. Total Body Irradiation
      The TBI dose will be a total of 12 Gy delivered with six 2 Gy fractions on days -3, -2, and -1 prior to UCB SCT. Each fraction should be **separated by at least 6 hours**. The patient should receive NS 1000ml over 2 hours prior to each fraction of TBI.

3.2 Schema B: Fludarabine, Cyclophosphamide, and TBI

   A. Fludarabine 40 mg/m²/day IV (Actual BW) over 30 minutes for a total of 5 doses on Day-6 through Day-2.

   B. Cyclophosphamide 50mg/kg IV over 2 hours on Day -6 only.
1) Begin NS at 125ml/m2/hr 4 hours prior to start of cyclophosphamide and continue for 24 hours after the last dose. If outpatient, begin NS at 300cc/hr 4 hours prior to starting cyclophosphamide and continue while in clinic.

2) Once cyclophosphamide administration begins patient’s output must be at least 100 ml/hr over a 4 hour period.

3) Check urine output for heme every 2 hours during cyclophosphamide. If greater than trace positive x 2, increase IV hydration by 50 cc/hr and give furosemide in 2 hours (Do not exceed the baseline hydration rate by 100 cc/hr).

C. Mesna 20 mg/kg/dose IV prior to Cyclophosphamide, 3 hr and 6 hr after.

D. Furosemide 20mg IV after each dose of cyclophosphamide then as needed.

E. Total Body Irradiation
   The TBI dose will be a total of 2 Gy delivered with one fraction on day -1 only prior to UCB SCT. The patient should receive NS1000 ml over 2 hours prior to TBI.

4.0 STEM CELL SOURCE/DOSE

Cord blood (CB) unit selection criteria, thawing and infusion (single or double CBT)

4.1 CB Selection:

A. CB units will be selected according to current umbilical cord blood graft selection summarized below. One or 2 CB units may be used to achieve the required cell dose.

B. The CB graft is matched at 4-6 HLA-A, B (antigen), DRB1 (allelic) with the recipient. This may include 0-2 antigen mismatches at the A or B or DRB1 loci.

C. Unit selection is based on the cryopreserved total nucleated cell (TNC) dose and matching at HLA-A, B antigen level and DRB1 allele level typing. While HLA-C antigen/allele level typing is not considered in the matching criteria, if available, may be used to optimize unit selection.

D. Selection of two CB units is allowed to provide sufficient cell dose (actual weight). When multiple units are selected, the following rules apply:
   1) The CB unit with the least HLA disparity (with the patient) will be selected first (i.e., selection priority is 6/6 match >5/6 match>4/6 match).
   2) Each CB unit MUST contain at least 0.5 x 10^7 TNC per kilogram recipient weight.
   3) The total cell dose of the combined units must be at least 2.5 x 10^7 TNC per kilogram recipient weight.
      a) CD34+ cell dose will not be used for unit selection unless 2 units of equal HLA-match are available from the same cord blood bank. Then the unit with the larger CD34+ dose (if data available) should be selected.
      b) A CB unit that is 5/6 mismatched but homozygous at the locus of mismatch should be chosen over a 5/6 unit with bidirectional mismatch even if the latter unit is larger (has more cells). This also applies to 4/6 units. This is only applicable to choosing units within a given match grade.
      c) Within an HLA match grade, the unit containing the greatest number of cells will be chosen. If there are two units of equivalent cell dose (± 0.5 x
Within a match level, choose the unit with match by higher resolution molecular typing, if known.

d) Within an HLA match grade, matching at DR takes preference. The youngest unit would also be preferred.

E. For Single CB SCT: the unit will have \( \geq 3.5 \times 10^7 \) NC/kg of recipient body weight. Recipient body weight will be determined as per standard guidelines.

F. For Double CB SCT: (done only if no single CB unit \( \geq 3.5 \times 10^7 \) NC/kg of recipient body weight is available)

4.2 Cord blood unit exclusions:

A. Any cord blood units with \(<0.5 \times 10^7\) total nucleated cells per kilogram recipient weight.

B. Any cord blood units without full maternal testing and negative results for hepatitis A, B, C, HIV, and HTLV-1 viruses.

4.3 Thawing and washing procedure

CB units will be thawed and washed prior to infusion.

There are two types of CB products that are currently banked: red cell and plasma depleted or plasma depleted only. The later products have a larger amount of lysed red blood cells in the product and thus there is a greater risk of hemolytic reaction during infusion. Since the majority of red cells in the product are lysed during thaw, the presence or absence of ABO incompatibility is not significant. It is important that the our cellular therapy laboratory and clinical team review the type of unit(s) that are being used and the thaw plans prior to the day of transplant.

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 CB bag on thaw at the bedside and because of the instability of the cells in 10% DMSO post thaw.

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.

4.4 Cord blood infusion

Blood sample from patient and cord blood (donor) will be obtained pre-transplant and sent to VU molecular lab for DNA extraction for later determination of chimeric engraftment post-transplant.

Following the administration of the preparative therapy, patient will undergo CB infusion on day 0. CB will not be irradiated under any circumstances. No in-line leukocyte filter should be used and no medications or fluid should be given piggyback through the catheter lumen that is being used for CB infusion. Vital signs should be monitored before
beginning the infusion and periodically during administration. Infusion should begin as soon as possible after washing. The HPC, Cord Blood product will expire 6 hours after thawing begins. Depending on the total volume of cord blood and the number of bags the cord is frozen in, thawing, washing, and distribution of one cord should take no longer than 3 hours. If there is more than one cord and there is only one tech available to thaw and wash them, then the tech should be advised to thaw, wash, and distribute one cord, return to the Processing Lab and do the same with the other cord in order to minimize time between thawing and infusion. The infusion should take no longer than 1 hour. Pre-medications and hydration prior to cord blood infusion will be administered. Diphenhydramine, epinephrine, and hydrocortisone should be available at the bedside for emergency use if infusion reactions occur. Oxygen with nasal prongs for standby use should be present in the room. The two units for double UCB transplantation are infused one after the other.

4.5 Post Transplant White Cell Growth Factor
For all patients granulocyte colony-stimulating factor (G-CSF, Filgrastim) will be administered beginning on Day +1 after stem cell infusion at the dose of 5 microgram/kg/day actual body weight IV or SC (IV administration will be preferred due to prolonged thrombocytopenia). G-CSF will be continued in all patients until the absolute neutrophil count (ANC) is greater than 2.5 x 10^9/L for 2 days. G-CSF will then be tapered per the transplant attending.

5.0 Prophylaxis for Graft-Versus-Host Disease (GVHD)
All patients will receive identical GVHD prophylaxis. This will consist of tacrolimus (FK 506) or cyclosporine (CSA) and mycophenolate mofetil (MMF, CellCept).

5.1 Tacrolimus (FK): will be given orally at 0.12 mg/kg/day in 2, divided doses (or intravenously at 0.03 mg/kg/day by continuous infusion if the patient is unable to tolerate PO medication) starting from day -2 through day +180. When switching from an IV to an oral route, the oral dose should be started 8-12 hours after stopping the infusion. Patients who are unable to tolerate FK will be switched to Cyclosporine.

5.2 Cyclosporine (CSA): Patients will receive cyclosporine (CSA) therapy beginning Day -3 maintaining a level of > 200 ng/mL. For adults the initial dose will be 2.5 mg/kg IV over 4 hours every 12 hours. Dose adjustments will be made on the basis of toxicity and CSA levels with a targeted trough level of 200-400 ng/mL. Once the patient can tolerate oral medications and has a normal gastro-intestinal transit time, CSA will be converted to an oral form. CSA dosing will be monitored and altered as clinically appropriate. Initial cyclosporine doses are calculated using actual body weight unless patient with greater than 100% ideal body weight in which case calculation of dose using adjusted body weight is recommended. Patients will receive CSA until Day +100. If there is no GVHD (and patient is not on daily steroid for h/o GVHD), the dose will be tapered 10% per week beginning Day 101, to discontinue no sooner than 6 months post transplant.

5.3 Mycophenolate Mofetil (MMF): All patients will begin IV/PO mycophenolate mofetil (MMF) on Day -3. Patients ≥ 40 kilograms will receive MMF at the dose of 1 gram every 8 (MST) -12 (RIC) hours. Stop MMF at Day +30 to +45 or 7 days after engraftment, whichever Day is later if there is no acute GVHD. (Definition of engraftment is 1st Day of 3 consecutive days of absolute neutrophil count (ANC > 0.5x10^9/L). If GVHD has been diagnosed, continued treatment and eligibility for acute GVHD protocols is at the attending physician’s discretion. If there is no donor engraftment, do not stop MMF and discuss case by case in multidisciplinary meeting.
5.4 At day +180 if there is no evidence of GVHD, the tacrolimus will be tapered at approximately 10% every 5-7 days until finishing or development of GVHD. Tacrolimus will be given according to the patient’s IDEAL body weight. This usually corresponds to a drug level of about 10-20 ng/mL (whole-blood enzyme-linked immunosorbent assay). The goal (ideal) drug concentration will be about 10ng/ml. There is no standard frequency at which levels need to be monitored. Levels will be monitored at least once a week until day +100 post transplant.

6.0 SIDE EFFECTS

6.1 Cyclophosphamide (Cytoxan)
The following side effects of cyclophosphamide are common (occurring in greater than 30%) for patients taking cyclophosphamide:
- Pancytopenia
- Alopecia
- Nausea and vomiting
- Poor appetite
- Infertility
- Discoloration of the skin or nails

These are less common side effects:
- Diarrhea
- Mouth sores
- Hemorrhagic cystitis

6.2 Fludarabine
The following side effects of fludarabine are common:
- Bone marrow suppression
- Peripheral neuropathy

The following side effects of fludarabine are less common:
- Tumor lysis syndrome
- Pulmonary hypersensitivity reactions
- Nausea
- Hemolytic anemia

6.3 Total Body Irradiation (TBI)
The following side effects of TBI are common:
- Nausea
- Vomiting
- Diarrhea
- Fatigue

The following side effects of TBI are less common:
- Lung toxicity
- Liver damage
- Sterility
- Hormonal dysfunction
- Prolonged low blood counts
6.4 **Tacrolimus**

The following side effects are **common**:
- Headache
- Uncontrollable shaking
- Diarrhea or constipation
- Nausea and vomiting
- Heartburn
- Loss of appetite
- Difficulty sleeping
- Dizziness
- Weakness
- Back or joint pain
- Burning, numbness, pain or tingling in hands or feet
- Rash, itching

The following side effects are **less common**:
- Decreased urination or pain or burning during urination
- Swelling of extremities
- Weight gain
- Unusual bleeding or bruising
- Seizures
- Loss of consciousness

6.5 **Cyclosporine**

The following side effects are **common**:
- Growth of excessive body hair
- Reddened gums
- Increased blood pressure
- Low blood counts
- Kidney damage

The following side effect is **uncommon**:
- Liver damage

6.6 **Mycophenolate mofetil (MMF)**

The following side effects are **common**:
- Loose stools
- Infections
- Low blood counts
- Vomiting

7.0 **SUPPORTIVE CARE**

In the first 100 days after transplant patients will be followed by the transplant team as per standard practice guidelines. Patients are typically seen 2-3 times per week, and then once a week as clinical condition mandates.

8.0 **REFERENCES**


