**UNIVERSITY OF MINNESOTA BLOOD AND MARROW TRANSPLANT PROGRAM**

# TRANSPLANTATION OF UNRELATED DONOR UMBILICAL CORD BLOOD IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN

**MT2005-02**
**CPRC #2005LS036**


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## Revision History

| Version Date | Details of changes | Consent change? |
|---|---|---|
| 11/08/2013 | • Section 5.2.1 - Add pediatric dosing for sirolimus<br>• Section 6 – add testing for anti-HLA antibodies<br>• Appendix I – replace eligibility checklist with the current checklist in use reflecting changes from 02/2013 (protocol document not previously updated) and correct wording in arm 6 | No |
| 02/22/2013 | • Reduce fludarabine dose from 40 mg/m2 to 30 mg/m2 to match current practice (creating 2 new treatment arms for statistical analysis – arm 5 and arm 6) in patients other than those co-enrolled in MT2006-01(arm 4) and those with aplasia (arm 3).<br>• Delete year 3 follow-up visits as all transplant patients are transferred to the long-term follow-up by the database after 2 years<br>• For clarification and simplification - remove reference to treatment arms for statistical analysis from all sections except registration and statistical considerations<br>• General editing for clarity throughout | No |
| 09/11/2012 | • Replace cyclosporine with sirolimus sections 5.2.1 and 8.9 | Yes |
| 05/07/2012 | • Update eligibility for acute lymphoblastic leukemia/lymphoma (section 3.2.1.ii) to allow MRD and include other gene arrangements (hypodiploidy and IKZFI); modify eligibility for CLL/SLL, marginal zone B-cell lymphoma and follicular lymphoma (section 3.2.7) to include patients who progress within 12 months of previous CR or PR;<br>• delete research related bloods, remove lists of procedures as in table format already;<br>• general updating and reformatting throughout<br>• add eligibility checklist appendix I, renumber remaining appendices | Yes |
| 10/22/10 | Revised to remove Appendix VIII: cord blood selection algorithm (U of MN Institutional Guidelines will now be a separate document). | |
| 6/29/10 | •Modified graft selection for patient co-enrolled in 2006-01 Treg study | |
| 4/23/2010 | Added research bone marrow sample to section 7.0, required observations | No |
| 02/16/2010 | Section 4.1.1 and synopsis - changed eligibility criteria to include patients aged >70 but ≤75 with a co-morbidity score ≤ 2; add co-morbidity scoring as appendix XII<br>Update sections 5 ( patient registration); 9.4 (DSMP) 9.5 (SAE reporting), and delete appendix VII (same information as in section 9.5); Removed Marcie Tomblyn from protocol team | No |
| 11/5/2008 | • Clarified immune reconstitution testing table (deleted day +28, +60, and +100 cytokine levels and PCR)<br>• Clarified that only subjects on Arm A will have immune reconstitution tests<br>• Deleted appendix which had FHCRC local guidelines. | Yes |
| 7/17/2008 | • Clarified immune reconstitution testing table | Yes |
| 4/8/2008 | • Added immune reconstitution testing: Section 7.1.2 | Yes |
| 10/4/2007 | • Section 9.5 clarified definition of serious adverse events | No |
| 7/20/2007 | • Eligibility section 4.2, added NK cell malignancies and Burkitt's lymphoma in remission<br>• Section 7.2.5 clarified to define who needs to have 24 hour creatinine clearance; removed transferring and albumin testing<br>• Section 7.1 and 7.3 have been made consistent in regards to chimerism studies<br>• Section 9.5 Reporting requirement modified to include only grades 3-5 | No |
| 11/15/2006 | • Modified sections 7.4.11 and 7.5.11 to include the wording " For patients who received ATG as part of the conditioning regimen" to clarify that the EBV viral load will not be | No |

| Version Date | Details of changes | Consent change? |
|---|---|---|
| | required of all subjects. | |
| 11/1/2006 | • Fred Hutchinson Cancer Research Center will no longer be an affiliate in this study. All references to FHCRC removed. | Yes |
| 6/19/2006 | • Corrected typographical errors<br>• Added table of contents<br>• Added Appendix XI with clarification of ideal body weight formulas for U of MN and FHCRC<br>• Section 6.0 reworded to clarify dose-adjustment instructions | No |
| 4/6/2006 | • Section 4.0 reworded to clarify eligibility based on tumor size, prior autologous transplant, and the utilization of the PET scan for staging<br>• Section 4.3.8, 4.3.9, and 4.3.10 added to clarify eligibility criteria<br>• Section 4.4 added to exclude subjects with active CNS malignancy<br>• Section 6.0 adjusted formula to adjust cyclophosphamide based on weight, and fludarabine based on renal function and prior CNS malignancy/radiotherapy<br>• Section 6.1.1 added CSA dose adjustment criteria<br>• Section 9.5.1.1 added contact numbers for reporting SAEs | |
| 12/21/2005 | • In section 6.0 wording referring to Appendix II has been modified<br>• In section 6.1.2 clarification of pediatric dose of MMF to be administered every 8 hours<br>• In sections 7.3.7, 7.4.8 and 7.5.6 we have removed the required peripheral blood chimerism studies; and table 7.1 has been similarly modified<br>• Sections 7.2.11 and 7.2.12 pediatric pretransplant evaluation modified for children unable to cooperate for MUGA/echocardiography and/or pulmonary function tests<br>• Section 7.3.4 wording of CMV surveillance modified.<br>• Title of Appendix III modified to “recommended” radiation therapy.<br>• Appendix III modified to allow for local radiation guidelines<br>• Title of Appendix IV modified to “recommended” supportive care.<br>• Wording of Appendix V modified to allow for local guidelines<br>• Appendix IX modified to reflect current protocol number<br>• Appendix XI and XII deleted | |
| 10/28/2005 | Modified MMF section 6.1.2 to read: Mycophenolate mofetil (MMF) 3 gram/day for patients who are ≥ 40 kg divided in 2 or 3 doses. Pediatric patient (<40 kilograms) will receive MMF at the dose of 15 mg/kg. | |
| 9/7/05 | Added Myeloproliferative syndromes to eligibility; Added appendix X and XI | |

# TABLE OF CONTENTS

# Protocol Synopsis – MT 2005-02

## Transplantation of Umbilical Cord Blood from Unrelated Donors in Patients With Hematological Diseases Using a Non-Myeloablative Preparative Regimen

**Study Design:** This is a non-randomized phase II trial using a non-myeloablative cyclophosphamide/fludarabine/TBI prep with modifications based on factors including diagnosis, disease status, and prior treatment. One or two cords will make up the graft.

**Primary Objective:** Estimate probability of one and two year survival

**Secondary Objectives:**

- Six month non-relapse mortality
- Chimerism at days 21,60,100,180 and 365
- Incidence of neutrophil engraftment by day 42
- Incidence of platelet engraftment by six months
- Incidence of day 100 grade II-IV and III-IV acute GVHD
- Incidence of one year chronic GVHD
- Probability of one and two year progression-free survival for each diagnosis cohort
- Probability of one and two year survival for each diagnosis cohort
- Incidence of one and two year relapse or disease progression for each diagnosis cohort.

**Eligible Diseases:** **Hematological malignancies/diseases:** acute leukemias in complete remission (high risk CR1 or subsequent CR); chronic myelogenous leukemia (except refractory blast crisis); myelodysplastic syndrome with severe pancytopenia or complex cytogenetics, large-cell lymphoma, Hodgkin lymphoma and multiple myeloma, chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone b-cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, mantle-cell lymphoma, prolymphocytic leukemia may be eligible after initial therapy

**Aplasia after induction:** refractory leukemia or MDS in aplasia after chemotherapy or radiolabeled antibody; bone marrow failure syndromes, except for Fanconi Anemia

**Eligibility Criteria:**

- must be <70 years old with no matched 5/6 or 6/6 sibling donor - patients ≥ 70 but ≤ 75 are eligible if the co-morbidity scores is ≤ 2 (refer to appendix VI)
- Karnofsky score ≥ 60% (adults) or Lansky score ≥ 50 (pediatrics)
- > 3 months after prior myeloablative transplant (if applicable)
- UCB units will be selected according to current University of Minnesota umbilical cord blood graft selection algorithm. One or 2 UCB units may be used to achieve the required cell dose.

**Organ Function:**

- Cardiac: Absence of decompensated congestive heart failure, or uncontrolled

arrhythmia and left ventricular ejection fraction ≥ 35%
- Pulmonary: DLCO > 30% predicted, and absence of $O_2$ requirements
- Liver: Transaminases < 5 x upper limit of normal and bilirubin < 3 x upper limit of normal
- Renal: Creatinine ≤ 2.0 mg/dl (adults) and creatinine clearance > 40 ml/min (pediatrics). All adults with a creatinine > 1.2 or a history of renal dysfunction must have estimated creatinine clearance > 40 ml/min

**Exclusion Criteria:**
- pregnant or breastfeeding
- evidence of HIV infection or known HIV positive serology
- current active serious infection
- acute leukemia in relapse/persistent disease CML in refractory blast crisis
- large cell lymphoma, mantle cell lymphoma and Hodgkin lymphoma that is progressive on salvage therapy - stable disease is acceptable to move forward provided it is non-bulky

**Accrual Objective:** The accrual goal is set at 320 patients – estimated disease distribution may be found in section 8.4

# Treatment Plan

| Disease/Prior Treatment Status | Preparative Regimen |
|---|---|
| **CY/FLU/TBI, no ATG** hematological diseases with prior autologous transplant, ≥ 2 cycles of multi-agent chemotherapy or severely immunosuppressive therapy in the last 3 months | • cyclophosphamide 50 mg/kg day -6<br>• fludarabine 30 mg/m$^2$ days -6 to -2*<br>• TBI 200cGy day -1<br><br>* if co-enrolled through MT2006-01(T-reg) give fludarabine 40 mg/m$^2$ days -6 to -2 |
| **CY/FLU/TBI, ATG** hematological diseases with prior autologous transplant > 12 months or ≤ 1 cycle of multi-agent chemotherapy or no immunosuppressive chemotherapy in the last 3 months | • cyclophosphamide 50 mg/kg day -6<br>• fludarabine 30 mg/m$^2$ days -6 to -2<br>• TBI 200cGy day -1<br>• equine ATG 15 mg/kg twice daily days -6 to -4 |
| **CY/FLU/TBI for aplasia after induction** refractory leukemia and lymphoma in aplasia after induction chemotherapy or radioimmunoconjugated monoclonal Ab therapy | • cyclophosphamide 50 mg/kg day -6<br>• fludarabine 40 mg/m$^2$ days -6 to -2<br>• TBI 200cGy day -1 |

# 1 Objectives

## 1.1 Primary Objective

Estimate probability of one and two year survival

## 1.2 Secondary Objectives

- Six month non-relapse mortality
- Chimerism at days 21, 60, 100, 180 and 365
- Incidence of neutrophil engraftment by day 42
- Incidence of platelet engraftment by six months
- Incidence of day 100 grade II-IV and III-IV acute GVHD
- Incidence of one year chronic GVHD
- Probability of one and two year progression free survival for each diagnosis cohort
- Probability of one and two year survival for each diagnosis cohort
- Incidence of one and two year relapse or disease progression for each diagnosis cohort

# 2 Background and Significance

Conventional allogeneic hematopoietic stem cell (HSC) transplantation is limited by lack of rapidly available, human leukocyte antigen (HLA)-matched donors and excess transplant-related mortality (TRM). Umbilical cord blood (UCB) is an alternative HSC source with the advantages of relative tolerance of HLA-disparity [1-5] and rapid availability[6]. UCB transplantation (UCBT), a standard therapy for pediatric leukemia[2-5], is now being investigated in adults [7-10]. However, many older patients, or those with extensive prior therapy or serious co morbidities, are unable to tolerate conventional conditioning. Therefore, reduced intensity or non-myeloablative (NMA) regimens are being investigated using either related or unrelated volunteer donors[11-19]. However, given many patients will not have a suitable donor, to further extend access to allogeneic transplant we have investigated the combined use of unrelated donor UCB as HSC source with NMA conditioning in adults with advanced or high-risk hematologic malignancy who are ineligible for conventional conditioning. Augmentation of graft cell dose was achieved by the combined use of 2 partially matched units in a double unit graft for those patients without access to a satisfactory single unit [20]. Our hypothesis was that alloreactive T cells in a UCB graft consisting of either single or double units are sufficient to effect donor engraftment after NMA conditioning.

The current experience at the University of Minnesota after NMA conditioning (MT-2000-15) in 59 high-risk adults with advanced or high-risk hematologic malignancy were analyzing factors influencing engraftment and TRM is summarized below. Eligible patients received a non-myeloablative (NMA) preparative regimen with single dose of cyclophosphamide 50 mg/kg on day –6, fludarabine 40 mg/m$^2$ daily x 5 days (days –6 to –2), and a single dose of 200 cGy of total body irradiation (day –1) (Cy50/Flu200/TBI200). During the conduct of the study equine anti-thymocyte globulin (ATG, ATGAM, Pharmacia) 15 mg/kg every 12 hours for 6 doses on days –3 to –1 was added to the preparative regimen for patients (n = 12) without combination chemotherapy in the preceding 4 months or with only a single induction regimen for acute myelogenous leukemia (AML) prior to transplant. All patients received cyclosporine-A (CSA) from day –3 for at least 3 months (aiming for a

trough blood level of > 200 μg/l). In addition, patients received mycophenolate mofetil (MMF) 1 gram twice daily either orally or intravenously from days –3 to 30.

In the 58 evaluable patients neutrophil recovery occurred at a median of 8 days (range 5-32) after UCB infusion. Four patients had primary and 2 had secondary graft failure for a cumulative incidence of sustained donor derived engraftment of 89% (95%CI: 81-97). The cumulative incidence of sustained donor engraftment in single unit recipients was 100% as compared to 86% (95%CI: 76-96) in double unit recipients ($p = 0.17$). The cumulative incidence of platelet engraftment to > 50 x $10^9$/l by day 180 was 68% (95%CI: 53-83) overall, and 64% (95%CI: 36-92) in single unit and 69% (95%CI: 52-86) in double unit recipients ($p = 0.76$).

Among engrafting patients, there was no significant difference in total donor chimerism between single and double unit recipients. Six patients had primary or secondary graft failure. One died of infection on day 34 whereas 5 were re-transplanted with a second UCB graft. Two of these 5 patients engrafted with the second UCB graft whereas 3 had autologous hematopoietic recovery. Only patient's prior therapy had a significant association with sustained engraftment. For patients with a Prior autograft or chemotherapy within 3 months preceding UCBT, the cumulative incidence of sustained donor engraftment was 98% (95%CI: 94-100), compared to a 64% (95%CI: 39-89) incidence in patients who had never had chemotherapy or whose most recent chemotherapy was at least 4 months prior to UCBT ($p = 0.03$). Thirteen of the 40 (32.5%) patients who were transplanted with 2 UCB units and had primary donor engraftment had evidence of both donors in their BM at day 21. However, one unit ultimately predominated in all patients. There was no predicting factor for winning unit.

The cumulative incidences of grade II-IV and III-IV acute GVHD were 63% (95%CI: 49-77) and 25% (95%CI: 14-36) at day 100, with no significant differences between single and double unit recipients. Of the 15 patients with grade III-IV acute GVHD, 13 had grade III and 2 had grade IV disease with patients exhibiting involvement of the skin (n = 13), upper gut (n = 10), rectum (n = 11) and liver (n = 8). All patients with grade III-IV acute GVHD responded to therapy. The cumulative incidence of chronic GVHD was 28% (95%CI: 16-40) at 1 year. There were no statistically significant differences in the incidence of acute or chronic GVHD between recipients engrafted with 4/6 and 5-6/6 matched units.

For the entire group, TRM was 19% (95%CI: 9-29) at day 180. Day 180 TRM in the older patients was relatively low at 14% (95%CI: 4-24), and in patients with extensive prior therapy was 24% (95%CI: 8-40), and was not significantly different to the younger or less extensively pre-treated patients, respectively. However, patients with poor fitness at transplant work-up had a significantly increased risk of Day 180 TRM of 44% (95%CI: 20-68) as compared to an incidence of 7% (95%CI: 0-15) in patients with satisfactory fitness ($p < 0.01$). Further, of these 3 factors, Cox regression analysis demonstrated that only poor fitness had a significant impact on TRM [relative risk 8.0 (95%CI: 2.0-32) ($p < 0.01$)]. Cell dose (total NC and CD34+ dose) had no impact on day 180 TRM (data not shown). Patients engrafting with a 5-6/6 HLA-matched unit had a day 180 TRM of 12% (95%CI: 0-24%) as compared to 21% (95%CI: 7-35%) in patients engrafting with a 4/6 unit ($p = 0.46$).
The incidence of relapse or disease progression was 33% (95%CI: 20-46) at both 1 and 2 years. Regression of relapsed or persistent disease post-transplant has been seen in patients with MDS (n = 2), CML (n = 1), intermediate and low grade NHL/CLL (n = 11), Hodgkin's lymphoma (n = 1) and

myeloma (n = 1). This occurred either spontaneously or with the reduction in immunosuppression, with 4 of the NHL/CLL patients also receiving additional post-transplant rituximab.
With a median follow-up of 16 months (range 4-30), the probability of overall and progression-free survival is 52% (95%CI: 39-65) and 41% (95%CI: 28-54) at 1 year, and 44% (95%CI: 30-58) and 35% (95%CI: 21-49) at 2 years, respectively, with no difference between single and double unit recipients. Cell dose (total NC and CD34+ dose) had no demonstrable impact on survival (data not shown). Patients engrafting with a 5-6/6 HLA-matched unit had a 1 year progression-free survival of 52% (95%CI: 32-72%) as compared to 30% (95%CI: 13-47%) in patients engrafting with a 4/6 unit (p = 0.13).

## 2.1 Overall Summary of Rationale for Study

These results demonstrate that UCB may be successfully used as the HSC source in this setting, extending the experience of our group[20] and others[21-24]. Notably, the Cy50/Flu200/TBI200 preparative regimen is both NMA and effective in inducing sustained donor engraftment in the majority of patients with an incidence comparable to that of NMA in the setting of unrelated donor HSC transplantation[16-18]. Despite the high-risk nature of this patient population, the incidence of TRM in this study was relatively low and comparable to reports of NMA unrelated donor HSC transplantation[16, 17, 19]. Of the patient factors dictating NMA conditioning (older age, extensive prior therapy and poor fitness), only poor fitness was independently associated with increased TRM in the setting of a NMA regimen. This demonstrates that UCBT after NMA conditioning is generally well tolerated and may be safely extended to older adults who are otherwise fit. Also, while transplantation prior to multiple treatment regimens is ideal, NMA UCBT may offer a treatment approach for some patients who have failed multiple prior regimens or autologous transplantation.

The aim of this study is to better assess efficacy as measured by probability of 1 year survival.

For the purpose of analysis, patients will be stratified by diagnosis into one of 5 disease groups:

1. AML/secondary AML
   MDS
   CML CP1
   CML CP2 after myeloid BC
2. ALL/Lymphoblastic lymphoma
   Burkitt's lymphoma
   CML CP2 after lymphoid BC
3. large-cell B and T-cell lymphomas
   mantle cell lymphoma
4. CLL/SLL
   prolymphocytic leukemia
   lymphoplasmacytic lymphoma
   marginal zone B-cell lymphoma
   follicular lymphoma
5. Hodgkin lymphoma
   multiple myeloma

In addition, analysis will by treatment arm as assigned at the time of study entry. Treatment arms will be added as needed to accommodate changes in the preparative regimen. A list of treatment arms for statistical purposes is found in section 4 (Patient Registration) and section 8 (Experiment Design, Endpoints, and Statistics).

# 3 Patient Selection

## 3.1 Age, Graft Cell Dose and Graft HLA Criteria

**3.1.1** Must be <70 years old with no matched 5/6 or 6/6 sibling donor - patients ≥ 70 and ≤ 75 years of age may be eligible if they have a Co-Morbidity score ≤ 2 (Appendix VI)

**3.1.2** UCB units will be selected according to current University of Minnesota umbilical cord blood graft selection algorithm. One or 2 UCB units may be used to achieve the required cell dose.

**3.1.3** The UCB graft is matched at 4-6 HLA-A, B, DRB1 antigens with the recipient. This may include 0-2 antigen mismatches at the A or B or DRB1 loci. If 2 UCB units are required to reach the target cell dose, each unit must be a 4-6 HLA-A, B, DRB1 antigen match to each other, as well as a 4-6 antigen match to the recipient.

**3.1.4** Patients co-enrolled in MT-2006-01 Phase I Study of Infusion of Umbilical Cord Blood Derived CD25+CD4+ T-Regulatory (Treg) Cells after Non-Myeloablative Cord\Blood Transplantation will receive grafts composed of 2 UCB units.

**3.2 Disease Criteria:** All diseases listed below are advanced hematologic malignancies not curable by conventional chemotherapy. Responses to conventional treatment range from zero to 30% but are typically short lived [25].

**3.2.1 Acute Leukemias:** Must be in remission by morphology (<5% blasts). Note cytogenetic relapse or persistent disease *without* morphologic relapse is acceptable. Also a small percentage of blasts that is equivocal between marrow regeneration vs. early relapse are acceptable provided there are no associated cytogenetic markers consistent with relapse. (refer to exclusion criteria section 3.5 for more detailed definition).

i. Acute myeloid leukemia: high risk CR1 (as evidenced by preceding MDS, high risk cytogenetics such as those associated with MDS or complex karyotype, > 2 cycles to obtain CR or erythroblastic and megakaryocytic); second or greater CR.
ii. Acute lymphoblastic leukemia/lymphoma: high risk CR1 as evidenced by high risk cytogenetics (e.g. t(9;22), t(1;19),t(4;11), other MLL rearrangements, hypodiploidy or IKZF1), > 1 cycle to obtain CR or evidence of minimal residual disease (MRD). Patients in second or greater CR are also eligible.

**3.2.2 Burkitt's lymphoma in CR2 or subsequent CR**

**3.2.3 Natural Killer cell malignancies**

**3.2.4 Chronic myelogenous leukemia:** all types except refractory blast crisis. Chronic phase patients must have failed or been intolerant to Gleevec

**3.2.5 Myelodysplastic syndrome:** any subtype including refractory anemia (RA) if severe pancytopenia or complex cytogenetics. Blasts must be less than 5%. If 5% or more requires induction therapy pre-transplant to reduce blast count to ≤5%.

**3.2.6 Large-cell lymphoma, Hodgkin lymphoma and multiple myeloma** with chemotherapy sensitive disease that has failed or patients who are ineligible for an autologous transplant.

**3.2.7 Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma, follicular lymphoma,** which have progressed within 12 months of achieving a partial or complete remission. Patients who had remissions lasting > 12 months, are eligible after at least two prior therapies. Patients with bulky disease should be considered for debulking chemotherapy before transplant. Patients with refractory disease are eligible, unless has bulky disease and an estimated tumor doubling time of less than one month.

**3.2.8 Lymphoplasmacytic lymphoma, mantle-cell lymphoma, prolymphocytic leukemia** are eligible after initial therapy if chemotherapy sensitive.

**3.2.9 Refractory leukemia or MDS.** These patients may be taken to transplant in aplasia after induction or re-induction chemotherapy or radiolabeled antibody. These high risk patients will be analyzed separately (Arm 3).

**3.2.10 Bone marrow failure syndromes**, except for Fanconi Anemia

**3.2.11 Myeloproliferative syndromes**

Patients who have undergone an autologous transplant >12 months prior to allogeneic transplantation and who have not received multi-agent or immunosuppressive chemotherapy within the preceding 3 months must receive ATG as part of the preparative regimen.

### 3.3 Organ Function and Performance Status Criteria (all patients)

Adequate organ function is defined as:

**3.3.1** **Cardiac:** Absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction ≥ 35%. For children that are not able to cooperate with MUGA and echocardiography, such should be clearly stated in the physician's note

**3.3.2** **Pulmonary:** DLCO > 30% predicted, and absence of $O_2$ requirements. For children that are not able to cooperate with PFTs, a pulse oximetry with exercise should be attempted. If nether test can be obtained it should be clearly stated in the physician's note.

**3.3.3** **Liver:** Transaminases < 5 x upper limit of normal and bilirubin < 3 x upper limit of normal

**3.3.4** **Renal:** Creatinine ≤ 2.0 mg/dl (adults) and creatinine clearance > 40 ml/min (pediatrics). Adults with a creatinine > 1.2 or a history of renal dysfunction must have estimated creatinine clearance > 40 ml/min.

**3.3.5** Adequate **performance status** is defined as Karnofsky score ≥ 60% (> 16 years of age) or Lansky score ≥ 50 (pediatrics) (Appendix II)

### 3.4 Other Inclusion Criteria (all patients)

**3.4.1** If recent mold infection e.g. *Aspergillus* - must have minimum of 30 days of appropriate treatment before BMT and infection controlled and be cleared by Infectious Disease.

**3.4.2** Second BMT: Must be ≥ 3 months after prior myeloablative transplant.

**3.4.3** Patients must be ineligible for autologous transplantation due to prior autologous transplant, an inadequate autologous stem cell harvest, inability to withstand a myeloablative preparative regimen, or clinically aggressive/high risk disease.

**3.4.4** Patients are eligible for transplantation if there is no evidence of progressive disease by imaging modalities or biopsy. Persistent PET activity, though possibly related to lymphoma, is not an exclusion criterion in the absence of CT changes indicating progression.

**3.4.5** Patients with stable disease are eligible for transplantation if the largest residual nodal mass is < 5 cm (approximately). For patients who have responded to preceding therapy, the largest residual mass must represent a 50% reduction and be < 7.5 cm (approximately).

### 3.5 Exclusion Criteria

**3.5.1** < 70 years with an available 5-6/6 HLA-A, B, DRB1 matched sibling donor

**3.5.2** Pregnancy or breastfeeding

**3.5.3** Evidence of HIV infection or known HIV positive serology

**3.5.4** Current active serious infection

**3.5.5** Unless in post-chemotherapy and radioimmunoconjugated antibody induced aplasia, when he/she would be eligible, patients with acute leukemia in morphologic relapse/ persistent disease defined as > 5% blasts in normocellular bone marrow OR any % blasts if blasts have unique morphologic markers (e.g. Auer rods) or associated cytogenetic markers that allows morphologic relapse to be distinguished are not eligible.

**3.5.6** CML in refractory blast crisis

**3.5.7** Large cell lymphoma, mantle cell lymphoma and Hodgkin disease that is progressive on salvage therapy. Stable disease is acceptable to move forward provided it is non-bulky.

**3.5.8** Active central nervous system malignancy

## 4 Patient Registration

Patient consent must be signed prior to the performance of any study related procedures or assessments.

To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record.

### 4.1 Registration with the University of Minnesota Clinical Trials Office (CTO)

Upon completion of the screening evaluation, eligibility checklist and obtaining consent, the study coordinator or designee will enroll the patient into OnCore.

At the time of registration in OnCore, the treatment arm related to statistical analysis will be recorded using the following definitions:

**Arm 1 –** hematologic malignancy patients who have received a previous autologous transplant or ≥ 2 cycle of multi-agent chemotherapy within the 3 months previous to UCBT; fludarabine dose of 40 mg/m$^2$/day x 5 (suspended with February 2013 revision, except Arm 4 will continue to mirror this treatment plan)

**Arm 2 -** hematologic malignancy patients who have not been treated with prior autologous transplant or ≤ 1 cycle of chemotherapy in the 3 months previous to UCBT,

and who should receive ATG as part of their conditioning regimen; fludarabine dose of 40 mg/m$^2$/day x 5 (suspended with February 2013 revision)

**Arm 3 -** patients with refractory leukemia or lymphoma who have been rendered aplastic either by induction chemotherapy or radioimmunoconjugated monoclonal antibody therapy

**Arm 4** – patients co-enrolling through MT2006-01, treat per Arm 1 (fludarabine dose of 40 mg/m$^2$/day x 5)

**New with the February 2013 protocol amendment using a lower fludarabine dose as in current practice:**

**Arm 5 -** hematologic malignancy patients who have received a previous autologous transplant or ≥ 2 cycle of multi-agent chemotherapy within the 3 months previous to UCBT; fludarabine dose of 30 mg/m$^2$/day x 5

**Arm 6 -** hematologic malignancy patients who have not been treated with prior autologous transplant or ≤ 1 cycle of chemotherapy in the 3 months previous to UCBT, and who should receive ATG as part of their conditioning regimen; fludarabine dose of 30 mg/m$^2$/day x 5

### 4.2 Patients Who Are Registered and Do Not Begin Study Treatment

If a patient is registered to the study, and is later found not able to begin the planned study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. Study data will be collected until the time the patient is off study. The reason for removal from study will be clearly indicated in OnCore.

## 5 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, G-CSF, antimicrobials, etc.).

For chemotherapy drug information see Appendix III. For information regarding recommended total body irradiation (TBI) see Appendix V.

### 5.1 Preparative Regimen

The administration of the preparative regimen will follow institutional drug and supportive care guidelines. Dose and/or schedule adjustments consistent with the standard of care may be made on an individual patient basis as needed for safety.

| Day | Treatment |
|---|---|
| Day -7 | Begin allopurinol (Day –7 to Day 0) |
| Day –6 | Fludarabine 30* mg/m$^2$ IV over 1 hour<br>Cyclophosphamide 50 mg/kg IV over 2 hours |
| Day –5 | Fludarabine 30* mg/m$^2$ IV over 1 hour |
| Day -4 | Fludarabine 30* mg/m$^2$ IV over 1 hour |
| Day –3 | Fludarabine 30* mg/m$^2$ IV over 1 hour |
| Day –2 | Fludarabine 30* mg/m$^2$ IV over 1 hour |
| Day –1 | TBI 200 cGy |
| Day 0 | UCB transplant |

***Administer fludarabine at 40 mg/m$^2$ IV for patients co-enrolled on MT2006-01 or refractory leukemia or lymphoma who have been rendered aplastic either by induction chemotherapy or radioimmunoconjugated monoclonal antibody therapy**

**Fludarabine** will be administered as a 1 hour infusion per institutional guidelines on day -6 through day -2. Dose adjustments will be made for adult patients with renal impairment defined as CrCL < 70mL/minute. Fludarabine dose MAY also be reduced to this dose if there is prior malignancy involvement of the central nervous system with intrathecal chemotherapy and/or cranio-spinal irradiation

**Cyclophosphamide** will be administered as a 2 hour intravenous infusion with a high volume fluid flush and mesna per institutional guidelines on day -6.

**TBI** will be administered as a single treatment on day -1 per guidelines in appendix V.

**ATG -** Patients who have had exposure ≤1 cycle of combination or high dose chemotherapy in the three months preceding transplant will also receive ATG in the preparative regimen. Also any patient who has had only a single induction cycle for the treatment of acute leukemia or MDS or CML blast crisis will also receive ATG during conditioning.

Patients with a prior autologous transplant in the year prior to second transplant DO NOT require ATG.

**Equine ATG (ATGAM)** 15 mg/kg IV will be administered every 12 hours for 6 doses beginning on day -6 per institutional guidelines. Methylprednisone 1 mg/kg IV will be administered prior to each dose of ATG per institutional guidelines. Additional steroids and/or other medications may be used as needed per the discretion of the treating physician.

## 5.2 Immunosuppressive Therapies

All patients will receive prophylaxis for GVHD with 2 drugs both beginning at day -3 as follows:

### 5.2.1 Sirolimus

Adult Dosing: Sirolimus will be administered starting at day -3 with 8mg-12mg mg oral loading dose followed by single dose 4 mg/day with a target serum concentration of

3 to 12 mg/mL by high-performance liquid chromatography (HPLC) and will be monitored per institutional guidelines. In the absence of acute GVHD sirolimus may be tapered starting at day +100 and eliminated by day +180 post-transplantation.

Pediatric Dosing: Sirolimus will be administered starting on day -3 with an oral loading dose of 5 mg/m2/day (Maximum daily dose of 8 mg for 1 day followed by maintenance dosing of 2.5 mg/m2/day (Maximum total daily dose of 4mg) as per institutional guidelines. Target serum concentration goals are 3 to 12 mg/mL by high-performance liquid chromatography (HPLC) and will be monitored per institutional guidelines.

Due to the long and variable half life in pediatric patients, it is recommended that sirolimus dosing changes must not be made until 3 days after a dose change or using best clinical judgment. In the absence of acute GVHD sirolimus may be tapered starting at day +100.

Sirolimus is available as 0.5 mg tablet, 1 mg tablet, 2 mg tablet and 1mg/ml oral suspension. The oral tablets and oral suspension are not bio-equivalent. No IV formulation is available.

### 5.2.2 Mycophenolate mofetil (MMF)

Mycophenolate mofetil (MMF) 3 gram/day IV/PO for patients who are ≥ 40 kg divided in 2 or 3 doses. Pediatric patient (<40 kilograms) will receive MMF at the dose of 15 mg/kg/dose every 8 hours beginning day -3. MMF dosing will be monitored and altered as clinically appropriate based on institutional guidelines. Patients will be eligible for MMF dosing and pharmacokinetics studies.

Stop MMF at day +30 *or* 7 days after engraftment, whichever day is later, if no acute GVHD. (Definition of engraftment is 1$^{st}$ day of 3 consecutive days of absolute neutrophil count [ANC) $\geq$ 0.5 x $10^9$ /L]). If no donor engraftment, do not stop MMF.

If the patient has acute GVHD requiring systemic therapy, MMF may be stopped 7 days after initiation of systemic therapy for acute GVHD (e.g. resolution of skin rash, vomiting, and diarrhea).

## 5.3 UCB Thaw and Infusion

Cord blood products are thawed and filtered (170-micron) in the Molecular and Cellular Therapeutics (MCT) Lab using the method of Rubinstein et al.

Infusion will be per current institutional policies. The infusion of the first UCB unit should begin within 15 minutes, and no later than 30 minutes after arrival on the Unit. If 2 units are used, both cords will be infused within 30-60 minutes of each other as deemed clinically safe by the BMT attending or designee.

Vital signs will be checked before and after the infusion, and one hour post infusion per University Of Minnesota transplant guidelines. More frequent vital signs may be

required depending on reactions to the product infusion. Notify the resident physician immediately if patient exhibits signs or symptoms of a reaction.

### 5.4 Expected Toxicities and Complications

Refer to Appendix IV

### 5.5 Management of Slow Engraftments or Graft Failure

Patients with ANC < 1000 any time after cord infusion will be started on G-CSF support at 5 mcg/kg (IV/SQ)(round to vial size) daily until ANC > 2500/μL for 2 consecutive days. Once a patient has met these criteria, the ANC will be monitored and G-CSF restarted if ANC falls to < 1000.

If no evidence of donor engraftment on the day +21 bone marrow biopsy, notify URD search coordinator to pursue back-up UCB and arrange day +28 bone marrow biopsy per current institutional slow engraftment guidelines.

### 5.6 Supportive Care

Supportive care will be provided per University Of Minnesota institutional guidelines for transplant patients including any supportive care research protocols.

All patients will receive standard supportive transfusion care according to transfusion committee guidelines or as modified based on clinical parameters.

Antimicrobial prophylaxis directed towards bacteria, fungi and viruses will be per University Of Minnesota current institutional guidelines for transplant patients.

# 6 Required Observations

Scheduled evaluations for days 21, 28 may be performed (+/-3 days) from the targeted date; assessments to be performed on day 60 and 100 may be done on (+/-) 7 days of the targeted date; assessments on day 180, 1 and 2 years may be performed (+/- 30) days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

| ACTIVITY | PRE-BMT WORK-UP | DAY 1 TO ENGRAFTMENT* | FOLLOW-UP DAYS 31-100 | FOLLOW-UP ( >DAY 100) |
|---|---|---|---|---|
| Consent | X | | | |
| Medical History | X | X(1) | X(2) | X(day 180, 360, 720) |
| Physical Exam | X | X(1) | X(2) | X(day 180, 360, 720) |
| Karnofsky/Lansky | X | | day 100 | X(day 180, 360, 720) |
| PFT/DLOC | X | (As clinically indicated) | (As clinically indicated) | (As clinically indicated) |
| MUGA or Echo | X | | | |
| Creatinine, Na, K HC03 | | X(1) | X(2) | X(day 180, 360) |
| CBC/diff/plt | X | X(1) | X(2) | X(day 180, 360) |
| PT/PTT | X | | | |
| Viral Screen | X | | | |
| Serum Chemistry | X | | | |
| testing for anti-HLA antibodies | X# | | | |
| Urinalysis | X | | | |
| Cr Cl for adults with creat > 1.2 or hx or renal dysfunction | X | | | |
| Pregnancy test for FOCBP | X | | | |
| BM Biopsy chimerism | X (on BM or blood) | BM (day 21) | BM (day 100) | BM (day 180, 360, 720) |
| Blood chimerism | Patient and UCB | PB (day 21, 28) | PB (day 60) | |
| GVHD Assessment | | X(1) | X(2), day 100 | X (day 180, 360) |
| EBV Assessment (ATG patients only) | | | X(3) | X(3) until day 180 |
| Chest CT | X** | | | |
| Disease Evaluation | X | X(day 28) | X(day 100) | X (day 180, 360, 720) |

# obtain as soon as possible once the patient is determined to be a candidate for UCB transplantation in order to guide unit selection

* engraftment defined as absolute neutrophil count (ANC) $\geq 5 \times 10^8$/L for 3 consecutive measurements

**Patients with a history of MDS or a history of 2 or more consecutive inductions/re-inductions to treat acute leukemia or CML blast crisis or prolonged neutropenia of at least 2 months immediately preceding transplant should have a chest CT without contrast to exclude occult fungal infection prior to transplant.

x(1)=perform test daily or as clinically indicated

x(2)=perform test weekly or as clinically indicated

x(3)=perform test every 2 weeks or as clinically indicated

NOTE: In certain clinical circumstances (e.g. relapse or patients terminally ill) study tests may be omitted at the physician's discretion).

# 7 Event Monitoring and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 3.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page http://www.eortc.be/services/doc/ctc/ctcaev3.pdf

## 7.1 Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

**Adverse Event:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

**Suspected Adverse Reaction:** Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

**Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction:** An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

**Serious Adverse Event Or Serious Suspected Adverse Reaction**: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**Unanticipated (unexpected) problems/events** as defined by the University Of Minnesota IRB are those that are *not* already described as potential risks in the consent form, *not* listed in the Investigator's Brochure or *not* part of an underlying disease.

**UPIRTSO:** Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that researchers promptly report "any unanticipated problems involving risk to subjects or others" (UPIRTSOs). The University of Minnesota IRB defines a UPIRTSO as any problem or event which in the opinion of the local

researcher was *unanticipated, reflects new or increased risk to the subjects and at least possibly related* to the research procedures.

In addition, the IRB has defined the following problems/events as reportable within 10 working days using the UPRITSO form found on the IRB website:

- Any accidental or unintentional change to the IRB-approved protocol that increases risk or has the potential to recur
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research
- Any breach in confidentiality that may involve risk to the subject or others
- Any complaint of a subject that cannot be resolved by the research staff
- Any other possibly related event which in the opinion of the investigator constitutes an unanticipated risk

**Expedited (Rapid) Reporting:** Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB) as detailed in section 7.2. For the IRB this is 10 working days.

## 7.2 Adverse Event Monitoring

All subjects will be monitored from the initiation of any study treatment through day 100 as it is expected that most serious adverse events will occur during this period.

After day 100, monitoring for serious adverse events will become less frequent based on the schedule in section 6.0. However, the investigator is obligated, upon knowledge of, to report any adverse event according to the schedule in section 7.3.

## 7.3 Required Reporting

The reporting period for this study is from the first dose of fludarabine through day +100; however after day +100, the investigator must report upon knowledge any event meeting the expedited reporting criteria below.

| Agency | Criteria for reporting | Timeframe | Form to Use | Submission address/ fax numbers | Copy AE to: |
|---|---|---|---|---|---|
| **U of MN IRB** | **UPIRTSO**: any event which is unanticipated, involved new or increased risk to subjects, and was at least possibly related to study procedures | 10 Working Days | UMCC SAE | University Of Minnesota IRB MMC 820 | Masonic Cancer Center SAE Coordinator mcc-saes@umn.edu |
| | **Other Problems or Events** meeting the definition of UPIRTSO in section 7.1 | | UPIRTSO form | | |
| **MCC SAE Coordinator** | Any event meeting an early study stopping rule per section 8.9 | at time of reporting | Early Study Stopping Rule Form | SAE Coordinator mcc-saes@umn.edu | Not applicable |

The SAE Coordinator will provide the Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

**FOR UNLICENSED UCB UNITS ONLY: Selected expected adverse reactions** determined to be caused by or at least possibly caused by the UCB unit based on objective evidence will be reported in an expedited manner to the FDA under University of Minnesota IND BB-14797 (C. Brunstein, MD, PhD – sponsor/investigator).

# 8 Experimental Design, Endpoints and Statistics

## 8.1 Primary clinical endpoint: Probability of one year survival

The principal objective of this study is to determine an estimate of one year survival among the hematologic malignancy patients. Whereas the previous study was meant to ensure safety this study will be used to establish more precise estimates of survival both for the group as a whole and for patients within certain disease groups. The group of patients with refractory acute leukemia in chemotherapy induced aplasia has not yet been tested with this regimen. The primary objective for this third group will simply be to ensure safety through the assessment of non-relapse mortality.

## 8.2 Secondary Endpoints

**8.2.1** Probability of two year survival

**8.2.2** One year and two year survival within

- Acute myelogenous leukemia, myelodysplastic syndrome, chronic myelogenous leukemia (CML) in first (CP1) and second chronic phase (CP2) after myeloid blast crisis
- Acute lymphoblastic leukemia, CML CP2 post lymphoid blast crisis, lymphobalstic lymphoma, Burkitt's and Burkitt's like lymphoma
- Large cell B and T cell lymphomas, mantle cell lymphoma
- Chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone B-cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, mantle-cell lymphoma, prolymphocytic leukemia
- Hodgkin lymphoma and multiple myeloma

**8.2.3** Incidence of six month non-relapse mortality

**8.2.4** Chimerism values at days 21, 60, 100, 180 and 365

**8.2.5** Incidence of day 42 Neutrophil Engraftment

**8.2.6** Incidence of six month Platelet Engraftment

**8.2.7** Incidence of day 100 Acute GvHD and one year extensive Chronic GvHD

**8.2.8** Probability of one and two year Progression-Free survival

**8.2.9** Incidence of one and two year relapse

### 8.3 Statistical Analyses

This study will be separated into treatment arms for the purposes of analysis, with arms added as needed to accommodate changes in the preparative regimen:

Arm1 – Hematologic malignancy patients that do not receive ATG as part of their conditioning regimen (fludarabine dose of 40 mg/$m^2$/day x 5).

Arm2 – Hematologic malignancy patients who do receive ATG as part of their conditioning regimen (fludarabine dose of 40 mg/$m^2$/day x 5).

Arm3 – Aplastic leukemia patients who are considered high risk

Arm4 – co-enrolled with MT2006-01 – treat according to Arm1 (fludarabine dose of 40 mg/$m^2$/day x 5).

Added with the February 2013 revision:

Arm5 – Hematologic malignancy patients that do not receive ATG as part of their conditioning regimen (fludarabine dose of 30 mg/$m^2$/day x 5).

Arm6 – Hematologic malignancy patients who do receive ATG as part of their conditioning regimen (fludarabine dose of 30 mg/$m^2$/day x 5).

Survival and progression-free survival will be estimated by the Kaplan-Meier method. Non-relapse mortality, relapse, neutrophil and platelet engraftment, acute and chronic GVHD will be estimated by cumulative incidence using competing risk methods. 95% confidence intervals will be used to make inferences on survival both overall as well as in the disease specific categories. Comparisons of endpoints by various factors will be completed by the Log-rank test.

### 8.4 Rationale for Sample Size

In order to achieve a precise estimate of the probability of survival at one year post transplant we would like to have an estimate of survival with a 95% confidence interval that has a band width of less than 0.15. We expect to enroll approximately 290 patients on arms 1, 2, 5 and 6 of the study. Assuming that the proportion surviving at one year is 50%, the 95% confidence interval should have a band width of approximately 0.12. This is assuming that there are no patients lost to follow-up and that all patients have been followed for at least one year post transplant at the time of analysis. Twenty and ten patients are expected to be enrolled on arms 4 and 3 respectively of the study. The total enrollment will therefore be approximately 320 patients.

For all arms of the study, the disease distribution is estimated as follows:

- Fifty percent of patients with acute myelogenous leukemia, myelodysplastic syndrome, chronic myelogenous leukemia (CML) in first (CP1) and second chronic phase (CP2) after myeloid blast crisis

- Eight percent of patients with Acute lymphoblastic leukemia, CML CP2 post lymphoid blast crisis, lymphoblastic lymphoma, Burkitt's and Burkitt's like lymphoma
- Seventeen percent of patients with large cell B and T cell lymphomas, mantle cell lymphoma
- Seventeen percent of patients with Chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone B-cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, mantle-cell lymphoma, prolymphocytic leukemia
- Eight percent of patients with Hodgkin's lymphoma and multiple myeloma

Given these sample sizes, we can expect to get estimates of one year survival in the disease specific groups with 95% confidence bands of widths 0.39, 0.28 and 0.16 for the group sizes of 25, 50 and 150, respectively.

### 8.5 Engraftment and Chimerism Evaluation

Hematopoietic recovery and engraftment will be evaluated with peripheral blood counts AND chimerism studies in peripheral blood and bone marrow.

1) Engraftment/hematopoietic recovery
   - Time to 1st 3 consecutive days with ANC > 5 x $10^8$/L and percentage of patients with neutrophil recovery by day 42 (Cumulative incidence)
   - Time to platelets > 20,000 (first of 3 consecutive days) with no platelet transfusions for seven days and percentage of patients with platelet engraftment >50,000 by day 100.
   - Time to RBC independence (Hb > 9gms and no transfusions for 30 days)
2) Chimerism
   - Chimerism studies will be performed on the blood and bone marrow. BM chimerism days 21 and 100, at 6 months and 1 year (see table) to determine the relative contribution of donor and recipient hematopoiesis. If the patient's peripheral blood counts are slow to recover, ANC $\leq$5 x $10^8$/L by day 28, or the peripheral blood counts drop below $\leq$1.0 x $10^8$/L after an initial recovery, the peripheral blood and bone marrow will be evaluated at that time unless a cause has been determined (e.g., use of Gamciclovir for treatment of CMV).
   - Patients diagnosed with failure of count recovery by day 42 should be reported to the University of Minnesota Clinical Trials Office and BMT Database.

### 8.6 GVHD Evaluation

Patients will be staged weekly between days 0 and 100 after transplantation using standard criteria. Patients will be assigned an overall GVHD score based on extent of skin rash, volume of diarrhea and maximum bilirubin level. Incidence of grades II-IV and grades III-IV GVHD by day 100 will be monitored. Patients will be rescored on day 180 and at 1 year with additional scores as events occur.

### 8.7 Relapse of Disease

This will be documented at days 30, 100, 180, 360 and 720 and as clinically indicated. Patients with leukemia and lymphoma involving the BM and multiple myeloma will have this done by BM biopsy and additional special studies such as cytogenetics or flow cytometry as

appropriate. Patients with lymphoma and myeloma will have radiology studies such as plain X-rays or CT scans and/or other studies such as blood tumor markers to document presence or absence of disease as clinically indicated.

## 8.8 Death Post Transplant

As the stopping rule for Arm 3 is based on non-relapse mortality up to Day 100, a death not due to relapse prior to Day 100 must be reported to the BMT data base and the Biostatistics Team for the appropriate review and reporting.

## 8.9 Monitoring Boundaries

### 8.9.1. Monitoring Boundaries Arm 2 with Sirolimus/MMF as GVHD prophylaxis

Monitoring guidelines for grade III-IV acute gvhd in the gvhd prophylaxis arm (Sirolimus/MMF) were developed using the sequential probability ratio test with the level of significance and power preset at 5% and 80% respectively.

Day 100 grade III-IV AGvHD for arm 2 (Sirolimus/MMF): Given a hypothesized gvhd rate of 20%, a maximum tolerated level of 40%, and a maximum monitoring size of 100 patients, the trial will be halted and reviewed if 4 events occur within the first 4 patients, 5 in the first 7, 6 in the first 10, 7 in the first 14, 8 in the first 17, 9 in the first 21, 10 in the first 24, 11 in the first 27 or 12/31, 13/34, 14/38, 15/41, 16/44, 17/48, 18/51, 19/55, 20/58, 21/61, 22/65, 23/68, 24/72, 25/75, 26/79, 27/82, 28/85, 29/89, 30/92, 31/96 or 32/99.

### 8.9.2 Arm 3 Monitoring Guidelines for Non-Relapse Mortality

Monitoring guidelines for non-relapse mortality in arm 3 were developed using the sequential probability ratio test with the level of significance and power preset at 5% and 80% respectively.

**Day 100 non-relapse mortality for arm 3**

Given a hypothesized non-relapse mortality rate of 30%, a maximum tolerated level of 50%, and a sample size of 20 patients, the trial will be halted and reviewed if 5 deaths occur within the first 5 patients, 6 in the first 7, 7 in the first 9, 8 in the first 11, 9 in the first 14, 10 in the first 16 or 11 in the first 19.

Because arms 1 and 2 have already been evaluated in a safety study, safety parameters such non-relapse mortality and graft failure for these two arms will be evaluated in a summary format on an annual basis by the study statistician and principal investigator.

### 8.9.3 Monitoring Guidelines For Primary Graft Failure At Day 42 Arms 5 And 6

Guidelines were developed separately using the sequential probability ratio test with the level of significance and power preset at 5% and 80% respectively.

**Day 42 primary graft failure**

Given a hypothesized non-relapse mortality rate of 8%, a maximum tolerated level of 15%, and a maximum sample size of 100 patients, the trial will be halted and reviewed if in either arm

there are 5 graft failures in the first 9 patients, 6/18, 7/27, 8/36, 9/45, 10/54, 11/63, 12/72, 13/81, 14/90 or 15/99.

Because arms 1 and 2 have already been evaluated in a safety study, safety parameters such non-relapse mortality and graft failure for these two arms will be evaluated in a summary format on an annual basis by the study statistician and principal investigator.

### 8.10 Data Management

The University of Minnesota database collection staff will perform basic data management functions associated with the study. Patient, transplant characteristics, adverse events and disease endpoints will be verified and dual entered into the BMT Clinical Database. Computer edit checks will be used to ensure that the data are logical and consistent. Data will be analyzed and reported by SAS™ software.

### 8.11 Data Collection

Standard pre- and post-transplant data will be recorded on the BMT research database, including the occurrence of toxicity and chimerism evaluations at day 100. Patients will be followed for relapse and death according to standard procedures. All patients will be followed beyond the conclusion of the study per standard procedure at the University of Minnesota.

### 8.12 Record Retention

The investigator will retain study records in a secure facility, including source data, and all study correspondence for at least 6 years after the study file is closed with the IRB. In addition, the Clinical Trials Office may keep a master log of all reported and registered patients participating in the study which may provide sufficient information to allow retrieval of the medical records.

## 9 Ethical and Regulatory Considerations

### 9.1 Ethical Considerations

Patients are referred to the University of Minnesota Medical Center, Fairview for consideration of hematopoietic cell transplantation. While there will be every effort to seek out and include women and minority patients, the patient population is dependent upon the referral pattern and the ability to identify suitable UCB donors. Women and minority patients are eligible for all aspects of the study and their participation will be actively encouraged.

### 9.2 Patient Consent

The principles of informed consent described in FDA Regulations (21 CFR Part 50) will be followed to comply with Food and Drug Administration regulations. A patient will give written consent prior to study participation. The original consent will be retained by the investigator as part of the study records. A copy of the consent form will be given to the patient.

Once a potentially eligible patient and donor graft have been identified, the patient will be fully evaluated by a physician who subsequently outlines the course of therapy. Assuming the patient meets the medical requirements for undergoing the transplant procedure, the patient will then be admitted to the inpatient unit where the course of therapy will again be reviewed. The risks of the procedures to the patient will be discussed in detail. The purpose and plan of the study, including the potential risks and benefits, will be presented as objectively as possible.

### 9.3 Institutional Board Review (IRB)

Before the initiation of this study, this protocol will have been reviewed and approved by the University of Minnesota Human Subjects Committee, as defined by FDA regulations (21 CFR Part 56).

IRB approval of any future modifications of the protocol or consent form for this study will be given in writing.

### 9.4 Data Safety Monitoring

This study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan, which can be accessed at http://www.cancer.umn.edu/exfiles/research/dandsmplan.pdf

For the purposes of data and safety monitoring, this study is classified as moderate risk (phase II). Therefore the following requirements will be fulfilled:

- The PI will complete and submit a twice yearly Trial Progress Report to the Masonic Cancer Center Data and Safety Monitoring Council (DSMC) with the understanding more frequent reporting may be required by the Cancer Protocol Review Committee.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the reporting of all adverse events meeting the definition of reportable in section 7.3 to the University Of Minnesota IRB and the Masonic Cancer Center SAE Coordinator.

In addition, at the time of the continuing review with the University Of Minnesota IRB, a copy of the report will be submitted to the Cancer Protocol Review Committee (CPRC).

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# Appendix I: Eligibility Checklist

**MT2005-02 TRANSPLANTATION OF UNRELATED DONOR UMBILICAL CORD BLOOD IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN**



Patient initials ☐☐☐☐ Patient ID☐☐☐

1st 2 initials of first name + 1st 2 initials of last name OnCore Sequence #

**INCLUSION CRITERIA (answers must be yes):**

<table>
<tr><th></th><th></th><th>Yes</th><th>No</th></tr>
<tr><td>1.</td><td>Subjects must be <70 years old. (Subjects ages ≥ 70 and ≤ 75 may be eligible if they have a HCT-CI score ≤ 2) Age ☐☐ HCT-CI score, if applicable ☐</td><td>☐</td><td>☐</td></tr>
<tr><td>2.</td><td>Adequately matched UCB unit(s) selected according to the current U of MN cord blood selection algorithm to achieve the required cell dose. Patients co-enrolled in MT-2006-01 will receive grafts composed of 2 UCB units</td><td>☐</td><td>☐</td></tr>
<tr><td>3.</td><td>One of the following advanced hematologic malignancies not curable by conventional chemotherapy (refer to section 3.2 of the protocol for disease specific eligibility requirements)<br>☐ acute leukemias<br>☐ Burkitt's lymphoma in CR2 or subsequent CR<br>☐ Natural Killer cell malignancies<br>☐ Chronic myelogenous leukemia<br>☐ Myelodysplastic syndrome<br>☐ Large-cell lymphoma, Hodgkin lymphoma and multiple myeloma<br>☐ Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma, follicular lymphoma<br>☐ Lymphoplasmacytic lymphoma, mantle-cell lymphoma, prolymphocytic leukemia<br>☐ Patients who have undergone an autologous transplant >12 months prior to allogeneic transplantation<br>☐ Refractory leukemia or MDS<br>☐ Bone marrow failure syndromes (except FA)<br>☐ Myeloproliferative syndromes</td><td>☐</td><td>☐</td></tr>
<tr><td>4.</td><td>Adequate organ function is defined as:
<table>
<tr><th>Organ system</th><th>requirement</th><th>value</th><th>date</th></tr>
<tr><td>cardiac</td><td>Absence of decompensated congestive heart failure, or uncontrolled arrhythmia an left ventricular ejection fraction ≥ 35% - if uncooperative child, document eligibility</td><td>☐☐%</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>pulmonary</td><td>DLCO > 30% predicted and absence of O2 requirements. For children not able to cooperate with PFTs, a pulse oximetry with exercise should be attempted</td><td>☐☐%</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>hepatic</td><td>Transaminases < 5 x upper limit of normal and bilirubin < 3 x upper limit of normal</td><td>☐☐☐☐<br>☐☐☐☐<br>☐☐.☐</td><td>☐☐/☐☐/☐☐</td></tr>
<tr><td>renal</td><td>Creatinine ≤ 2.0 mg/dl (adults) and creatinine clearance > 40 ml/min (pediatrics) Adults with a creat > 1.2 or a history of renal dysfunction must have estimated crcl > 40 ml/min</td><td>☐.☐ mg/dl<br>or<br>☐☐.☐<br>ml/mn</td><td>☐☐/☐☐/☐☐</td></tr>
</table></td><td>☐</td><td>☐</td></tr>
</table>

**MT2005-02 TRANSPLANTATION OF UNRELATED DONOR UMBILICAL CORD BLOOD IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN**

**Eligibility Checklist –** Page 30 of 39

Patient initials ☐☐☐☐

**INCLUSION CRITERIA (answers must be yes):**

| | | Yes | No |
|---|---|---|---|
| **5.** | Karnofsky score ≥ 60 or Lansky score ≥ 50% (pediatrics) PS - ☐☐☐ | ☐ | ☐ |
| **6.** | If recent mold infection e.g. *Aspergillus* - must have minimum of 30 days of appropriate treatment before BMT and infection controlled and be cleared by ID ☐ - n/a, check yes | ☐ | ☐ |
| **7.** | Second BMT: Must be ≥ 3 months after prior myeloablative transplant ☐ - n/a, check yes | ☐ | ☐ |
| **8.** | Ineligible for autologous transplantation (due to prior autologous transplant, an inadequate autologous stem cell harvest, inability to withstand a myeloablative preparative regimen, or clinically aggressive/high risk disease). | ☐ | ☐ |
| **9.** | Patients with Lymphoma : have<br>*must have no evidence of progressive disease by imaging modalities or biopsy.<br>***Or** persistent PET activity, in the absence of CT changes indicating progression<br>*-patients with stable disease if the largest residual nodal mass is < 5 cm.<br>* Responsive disease with the largest residual mass having 50% reduction and be < 7.5 cm | | |

**EXCLUSION CRITERIA**
**(answers must be NO):**

| | | Yes | No |
|---|---|---|---|
| **10.** | Have an available 5-6/6 HLA-A, B, DRB1 matched sibling donor | ☐ | ☐ |
| **11.** | Pregnancy or breastfeeding | ☐ | ☐ |
| **12.** | Evidence of HIV infection or known HIV positive serology | ☐ | ☐ |
| **13.** | Active serious infection | ☐ | ☐ |
| **14.** | Acute leukemia in morphologic relapse/ persistent disease defined as > 5% blasts in normocellular bone marrow OR any % blasts if blasts have unique morphologic markers (e.g. Auer rods) or associated cytogenetic markers that allows morphologic relapse to be distinguished ( Unless on Arm 3) | ☐ | ☐ |
| **15.** | CML in refractory blast crisis | | |
| **16.** | Active central nervous system malignancy | | |

**MT2005-02 TRANSPLANTATION OF UNRELATED DONOR UMBILICAL CORD BLOOD IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN**

**Eligibility Checklist –** Page 31 of 39

Patient initials ☐☐☐☐

| Please indicate which treatment ARM patient will be placed on. | |
|---|---|
| **Arm 3:** For patients with refractory leukemia or lymphoma who have been rendered aplastic either by induction chemotherapy or radioimmunoconjugated monoclonal antibody therapy.<br>Cy 50mg/kg, FLU **40** mg/m$^{2,}$ TBI 200 | ☐ |
| **Arm 4: TReg only**<br>Cy 50mg/kg, FLU **40** mg/m$^{2,}$ TBI 200 | ☐ |
| **Arm 5**: **NO ATG** For patients with hematologic malignancy patients who have received a previous autologous transplant or ≥ 2 cycle of multi-agent chemotherapy within the 3 months previous to UCBT<br>Cy 50mg/kg, FLU **30** mg/m$^{2,}$ TBI 200 | ☐ |
| **Arm 6**: **ATG** For patients who have NOT been treated with prior autologous transplant or ≤ 1 cycle of chemotherapy in the 3 months previous to UCBT.<br>Cy 50mg/kg, FLU **30** mg/m$^{2,}$ TBI 200 | ☐ |

Date consent form signed: _____

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is:

☐ Eligible ☐ Ineligible

Date registered _____

_____ _____

Signature of person verifying eligibility Date

# Appendix II: Karnofsky and Lansky Performance Status Scale

**Karnofsky Performance Status Scale**

| Percentage | |
|---|---|
| 100 | Normal, no complaints, no evidence of disease |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 80 | Normal activity with effort; some signs or symptoms of disease |
| 70 | Cares for self; unable to carry on normal activity or do active work |
| 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| 50 | Requires considerable assistance and frequent medical care |
| 40 | Disabled; requires special care and assistance |
| 30 | Severely disabled, hospitalization indicated. Death not imminent |
| 20 | Very sick, hospitalization necessary, active supportive treatment necessary |
| 10 | Moribund, fatal processes, progressing rapidly |
| 0 | Dead |

REFERENCE
Karnofsky DA: Meaningful clinical classification of therapeutic responses to anti-cancer drugs. Editorial: Clin Pharmacol Ther 2:709-712, 1961.

**LANSKY PLAY PERFORMANCE STATUS SCALE**

| Percentage | |
|---|---|
| 100 | Fully active, normal |
| 90 | Minor restrictions in physically strenuous activity |
| 80 | Active, but tires more quickly |
| 70 | Both greater restriction of, and less time spent in, play activities |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities |
| 50 | Gets dressed but lies around much of the day, no active play; able to participate in all quiet play and activities |
| 40 | Mostly in bed; participates in quiet activities |
| 30 | In bed; needs assistance even for quiet play |
| 20 | Often sleeping; play entirely limited to very passive activities |
| 10 | Unresponsive |
| 0 | Dead |

# Appendix III: Chemotherapy Drug Information

*Fludarabine* (Fludara- Berlex) (F-Ara-A, fludarabine phosphate)
Formulation: Vials (lyophilized solid cake): 50 mg (25 mg/ml after reconstitution)
Storage: Between 2 and 8° centigrade (36 and 46 F)
Mixing: Adding 2 mL of sterile water for injection to the 50 mg vial, producing a solution containing 25 mg/mL (the solid cake should fully dissolve within 15 seconds). Solutions may be further diluted in 100 or 125ml of 5% dextrose injection or 0.9% sodium chloride injections for administration by intravenous infusion.
Stability: Once diluted, solutions should be promptly administered or stored in the refrigerator for no more than 8 hours prior to administration.
Administration: Fludarabine is administered over a 1-hour period.

*Cyclophosphamide*. Cyclophosphamide is a nitrogen mustard-derivative, polyfunctional alkylating agent. Cyclophosphamide for injection is commercially available as a sterile solution in sodium chloride or as a powder that is reconstituted in sterile or bacteriostatic water. Institutional guidelines for handling, reconstitution and administration should be followed. Cyclophosphamide can cause temporary hair loss, nausea, vomiting, diarrhea, and lowering of the blood cell counts. Anti-emetics should minimize nausea and vomiting.
Formulation: parenteral 100 mg and 500 mg vials. Commercially available.
Storage: room temperature.
Mixing: i.v. drug should be mixed with sterile water for i.v. Use. Dissolves very slowly with cold water. It helps to warm the water or to warm the vial after adding water.
Stability: i.v. Solution should be used within 12 hours of mixing.
Administration: cyclophosphamide is added to D5w and administered i.v.

*Mycophenolate mofetil* (cellcept®)
formulation: vials - 500 mg powder for iv injection, capsule - 250 mg blue-brown, two-piece hard gelatin capsule.
Mixing: each vial of lyophilized mycophenolate mofetil powder should be reconstituted by adding 14 ml of 5% dextrose for injection. Once powder is dissolved, a vial should be further diluted to a final concentration of 6 mg/ml. Available in 500 mg vials.
Stability: once diluted, iv solutions should be promptly administered and stored at 25ºc for no more than 4 hours after reconstitution.
Administration: iv mycophenolate is administered over a 2-hour period at a constant rate.

Equine ATG (atgam®) thymoglobulin (genzyme) is a purified pasteurized, gamma immune
Globulin obtained by immunization of rabbits with human thymocytes. This immunosuppressive product contains cytoxic antibodies directed against antigens expressed on human t-lymphocytes. Institutional guidelines for handling, reconstitution and administration should be followed.
Formulation: intravenous lyophilized powder

Storage: store in refrigerator between +2 degrees c to +8 degrees c, protect from light, do not freeze.
Mixing: 5-ml sterile water for injection as diluent.
Stability: should be used within 4 hours of reconstitution if kept at room temperature.
Administration: infusion - deliver dose over a minimum of six hours for the first dose, and over at least 4 hours for subsequent doses.

# Appendix IV: Expected Treatment Related Toxicity

## Cyclophosphamide

| **Common**<br>Occurs in 21-100 people out of every 100 | **Less Frequent**<br>Occurs in 5-20 people out of every100 | **Uncommon**<br>Occurs in <5 people out of every 100 |
|---|---|---|
| nausea/vomiting<br>mucositis<br>sterility<br>severe suppression of blood counts<br>diarrhea<br>fluid weight gain/edema<br>alopecia | hemorrhagic cystitis | cardiomyopathy<br>skin rash<br>SIADH (Syndrome of Inappropriate Anti-diuretic Hormone) |

## Fludarabine

| **Common**<br>Occurs in 21-100 people out of every 100 | **Less Frequent**<br>Occurs in 5-20 people out of every100 | **Uncommon**<br>Occurs in <5 people out of every 100 |
|---|---|---|
| severe suppression of blood counts<br>diarrhea<br>anorexia<br>mucositis<br>nausea/vomiting<br>stomatitis<br>osteoporosis<br>dysuria | chills<br>fever<br>GI bleeding<br>peripheral edema | neurotoxicity<br>agitation and confusion<br>blurred vision<br>peripheral neuropathy<br>hearing loss<br>headache<br>cerebellar syndrome<br>blindness<br>coma<br>weakness<br>depression<br>insomnia<br>hemorrhagic cystitis (except in FA)<br>abnormal renal function test<br>autoimmune hemolytic anemia<br>deep venous thrombosis<br>aneurysms<br>pruritic skin rash<br>abnormal liver function/liver failure<br>constipation<br>transient ischemic attack<br>dysphagia<br>myalgia<br>arthralgia<br>renal failure |

**Total Body Irradiation (TBI) (arms 1 and 3)**

| **Common**<br>Occurs in 21-100 people out of every 100 | **Less Frequent**<br>Occurs in 5-20 people out of every100 | **Uncommon**<br>Occurs in <5 people out of every 100 |
|---|---|---|
| nausea and vomiting<br>diarrhea<br>cataracts<br>sterility<br>endocrinopathies<br>growth failure<br>intestinal cramps<br>mucositis | parotitis<br>interstitial pneumonitis<br>generalized mild erythema<br>veno-occlusive disease | dysphagia<br>vertebral deformities<br>nephropathy<br>risk of 2nd malignancy years later (when given along with chemotherapy) |

**Anti-Thymocyte globulin (ATG) (arm 2 only)**

| **Common**<br>Occurs in 21-100 people out of 100 | **Less Frequent**<br>Occurs in 5-20 people out of every 100 | **Uncommon**<br>Occurs in <5 people out of every 100 |
|---|---|---|
| fever<br>chills<br>leukopenia<br>pain<br>headache<br>abdominal pain<br>diarrhea<br>hypertension<br>nausea<br>thrombocytopenia<br>peripheral edema<br>dyspnea<br>asthenia<br>hyperkalemia<br>tachycardia | malaise<br>dizziness | severe allergic reaction (anaphylaxis) |

**Toxicities potentially associated with the UCB graft:**
Potential toxicities associated with the infusion include DMSO toxicity and side effects from red cells. DMSO toxicity and side effect of red cells may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, headache, allergic reaction, presence of DMSO taste and odor, hemoglobinuria, and acute renal failure. Due to the washing and processing steps, these toxicities are unlikely.

## Risks of the Immunosuppressive Therapies:

**Mycophenolate mofetil (MMF)** can cause nausea and vomiting, diarrhea or constipation, a lowering of blood counts, leg cramps, skin rash, difficulty sleeping, chemical imbalances including high blood sugar, headaches, dizziness and high blood pressure.

## Sirolimus adverse reactions

Most side-effects of sirolimus occur with prolonged use, especially when used in combination with CNIs like tacrolimus and cyclosporine. Sirolimus alone is not associated with neurotoxicity or nephrotoxicity because of its inability to inhibit calcineurin. Adverse reactions that resulted in rates of sirolimus discontinuation > 5% were increased creatinine, hypertriglyceridemia and thrombotic thrombocytopenic purpura.

| Sirolimus Adverse Events | | | |
|---|---|---|---|
| | **Common**<br>>20% | **Occasional**<br>5-20% | **Rare**<br><5% |
| **Immediate**<br>Within 1-2 days of receiving drug | Headache (L), hypertension (L), nausea, diarrhea, immuno-suppression (L), fever, constipation | Chest pain, insomnia, dyspepsia, vomiting, ***dyspnea*** | Hypotension, asthma, increased cough, flu like syndrome, tachycardia, anorexia, ***hypersensitivity reactions*** (exfoliative dermatitis, angioedema) |
| **Prompt**<br>Within 2-3 weeks, prior to the next course | Tremor (L), renal dysfunction, elevated creatinine/BUN, anemia, pain (abdominal, back, pain), ***hyperlipidemia***, hypercholesteremia, hypertrigylceridemia, hyperglycemia, ***peripheral edema***, weight gain, arthralgia | Elevated LFTs (with elevated sirolimus levels), stomatitis, urinary tract infections, URIs, mild ***thrombocytopenia***, ***leukopenia***, hyper/hypokalemia (L), hypophosphatemia, rash, hives, pruritis, ***delayed wound healing or dehiscence (L)***, hypomagnesaemia (L), ***proteinuria*** | Opportunistic infections, pleural and pericardial effusions, ***non-infectious pneumonitis or bronchiolitis-obliterans organizing pneumonia*** and pulmonary fibrosis, thrombosis, myalgias, ***increased risk of CNI-induced HUS/TTP/TMA (L)*** |
| **Delayed**<br>Any time later during therapy, excluding the above conditions | Acne | | Chronic renal dysfunction, renal tubular necrosis, CHF, ascites, arthrosis, bone necrosis, osteoporosis |
| **Late**<br>Any time after completion of treatment | | | Lymphoproliferative disorders, skin malignancies |
| **Unknown Frequency and Timing** | Sirolimus was embryo/fetotoxic in rats at dosages of approximately 0.2 to 0.5; clinical doses were adjusted for body surface area. It is not known whether sirolimus is excreted in human milk. | | |

# Appendix V: Radiation Therapy Guidelines

All patients who have had previous radiation therapy or TBI will be seen by Radiation Oncology prior to entrance on the protocol for approval for additional 200 cGy of TBI. TBI may be delivered by local guidelines provided the effective dose is equivalent to what is recommended in the TBI Guidelines.

Patients ineligible for this protocol include those who have had previous irradiation to areas of the body such that the Radiation Oncologist feels that even a relatively small dose of total body irradiation (TBI) cannot safely be given.

If the patient has previously had total body irradiation (TBI), the radiation oncologist will have the option of deciding whether the patient is still eligible to receive additional TBI. Based on the recommendation of the treating Radiation Oncologist, the patient may be eligible for this protocol with modifications to the beam such that the lungs and or kidneys are partially shielded from the radiation beam. No other organs may be shielded.

Patients who have not had previous TBI

The dose of TBI will be 200 cGy given in a single fraction on day -1.

The dose rate will be between 10-19 cGy/minute prescribed to the midplane of the patient at the level of the umbilicus.

The TBI will be delivered with right and left lateral fields with the patient semi-recumbent in a semi-fetal position with their arms at their sides.
Based on measurement of transverse thickness, aluminum compensators will be used to ensure that the dose homogeneity across the fields is within 10% of the prescribed dose. Usually head/ neck, leg and lung compensators are used (although based on calculated mid-mediastinal doses, lung compensators are often not needed if the thickness of the arms, which partially shield the lung, are taken into the thickness consideration).

TBI will be delivered with a linear accelerator using 6, 18 or 25 MV photons. The energy used will be based on the calculated dose to midline at points along the patient's torso. The lowest energy that give 90-100% of the prescriptions point dose will be used.

A beam "spoiler" will be used to ensure a full skin dose.
Half value layer lung and kidney blocks will not be utilized for patients who have not previously received total body irradiation.

Patients who have received previous TBI

The dose of TBI will be 200 cGy given in a single fraction on day -1.

The dose rate will be between 10-19 cGy/minute prescribed to the midplane of the pelvis,

The TBI will be delivered with AP and PA fields with the patient standing.
If the patient is less than 40 inches in height and requires anesthesia, he/she will be treated supine and prone on a couch on the floor.

One half value layer lung blocks will be used to decrease the photon contribution to the lung dose to approximately half that of the prescription point.

The chest wall areas blocked by the 1 HVL lung blocks will be boosted with electrons of the appropriate energy (determined by CT scanning) such that the electrons D90 is at the chest wall-lung interface. The dose to the chest wall will be 200 cGy prescribed to Dmax.

One half value layer POSTERIOR kidney blocks will be used to decrease the photon contribution to the kidneys to approximately 75% that of the prescription point.

TBI will be delivered with a linear accelerator using 6 MV photons.

A beam "spoiler" will be used to ensure a full skin dose.

# Appendix VI: Co-Morbidity Scoring

**PATIENT NAME:**_____ **W/U DATE:** _____

**Patient ID** ___ ___ ___ ___ ___ ___ ___ ___ **TxDate** ____/ _____/_____ **- For database only**

**CIBMTR Pre-Transplant Essential Data**
**COMORBID CONDITIONS**

Is there a history of mechanical ventilation? 1☐ Yes 2☐ No

Is there a history of proven invasive fungal infection? 1☐ Yes 2☐ No

Were there ***clinically significant*** co-existing disease or organ impairment at time of patient assessment prior to preparative regimen?

1☐ Yes – Complete the following questions:

2☐ No – **DO NOT NEED TO COMPLETE FOLLOWING QUESTIONS**

| Yes | No | Not Done | Comorbidity Definitions |
|---|---|---|---|
| 1☐ | 2 | 3 | Arrhythmia Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias |
| 1☐ | 2 | 3 | Cardiac Coronary artery disease §, congestive heart failure,myocardial infarction, or EF ≤ 50% |
| 1☐ | 2 | 3 | Cerebrovascular disease Transient ischemic attack or cerebrovascular accident |
| 1☐ | 2 | 3 | Diabetes requiring treatment with insulin or oral hypoglycemics but not diet alone |
| 1☐ | 2 | 3 | Heart valve disease Except mitral valve prolapse |
| 1☐ | 2 | 3 | Hepatic, mild Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN |
| 1☐ | 2 | 3 | Hepatic, moderate/severe Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN |
| 1☐ | 2 | 3 | Infection Requiring continuation of antimicrobial treatment after day 0 |
| 1☐ | 2 | 3 | Inflammatory bowel disease Crohn's disease or ulcerative colitis |
| 1☐ | 2 | 3 | Obesity Patients with a body mass index > 35 kg/m2 |
| 1☐ | 2 | 3 | Peptic ulcer requiring treatment |
| 1☐ | 2 | 3 | Psychiatric disturbance Depression or anxiety requiring psychiatric consult or treatment |
| 1☐ | 2 | 3 | Pulmonary, moderate DLco and/or FEV1 66-80% or dyspnea on slight activity |
| 1☐ | 2 | 3 | Pulmonary, severe DLco and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen |
| 1☐ | 2 | 3 | Renal, moderate/severe Serum creatinine > 2 mg/dL or >177 μmol/L, on dialysis, or prior renal transplantation |
| 1☐ | 2 | 3 | Rheumatologic SLE, RA, polymyositis, mixed CTD, or polymyalgia Rheumatica |
| 1☐ | 2 | 3 | Solid tumor, prior Treated at any time point in the patient's past history, excluding non melanoma skin cancer |
| 1☐ | 2 | 3 | Other Specify:_____ |

One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft. EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.
*Source: Blood, 2005 Oct 15;106(8):2912-2919*

PHYSICIAN'S SIGNATURE _____ DATE _____ **Revised 2/21/08**