Masonic Cancer Center, University of Minnesota
Blood and Marrow Transplantation Program

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

MT2015-17
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Revision History

Revision Number	Version Date	Revision Summary	Consent Change?
	10/27/2015	original to CPRC	
	1/27/2016	In response to CPRC stips, original to IRB	n/a
	12/29/2016	Updated disease eligibility and general study inclusion/exclusion criteria to match institutional standard language Updated link to Cancer Center DSMP	Yes
	2/22/2018	Section 2: Updated to clarify standard of care procedures	
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Study Synopsis

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

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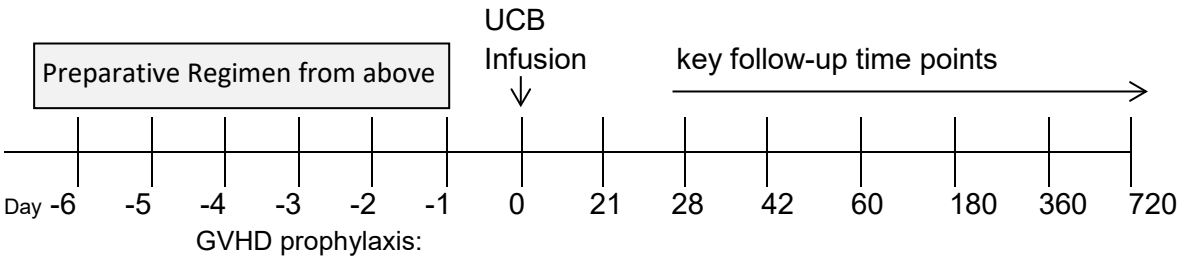
Study Design:	This is a phase II trial using a non-myeloablative cyclophosphamide/ fludarabine/total body irradiation (TBI) preparative regimen with modifications based on factors including diagnosis, disease status, and prior treatment. Single or double unit selected according to current University of Minnesota umbilical cord blood graft selection algorithm. This study uses a Minimax two-stage phase II design. Stage 1 will enroll 110 patients. If 54 or fewer develop GVHD, 45 additional patients will be enrolled. After stage 2, if 71 or fewer out of 155 enrolled develop GVHD, CSA/Sirolimus will be considered worthy of further consideration.
Primary Objective:	Estimate probability of grade II-IV acute GVHD at Day 100
Secondary Objectives:	• Incidence of Day 100 grade III-IV acute GVHD • Transplant related mortality (TRM) at 6 months • Chimerism at Day 21, 100,180 and 365 • Incidence of neutrophil engraftment by Day 42
Transplant Related Objectives:	• Incidence of platelet engraftment by six months • Incidence of one year chronic GVHD • Probability of one and two year overall survival • Probability of one and two year progression free survival (PFS) • Incidence of one and two year relapse or disease progression
Eligible Diseases:	All diseases listed below are advanced hematologic malignancies not curable by conventional chemotherapy. Refer to section 4.1.2 for specific criteria. • Acute Leukemias • Acute myeloid leukemia • Acute lymphoblastic leukemia/lymphoma • Biphenotypic/Undifferentiated/Prolymphocytic Leukemias • MRD positive leukemia • Leukemia or MDS in aplasia • Burkitt's lymphoma • Relapsed T-Cell Lymphoma • Natural killer cell malignancies • Chronic myelogenous leukemia in chronic or accelerated phase, or CML blast crisis in morphological remission (<5% blasts) • Myelodysplastic syndrome • Large-cell lymphoma, Hodgkin lymphoma and multiple myeloma • Relapsed Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma, follicular lymphoma • Lymphoplasmacytic lymphoma, mantle-cell lymphoma, prolymphocytic leukemia • Relapsed Multiple Myeloma • Plasma Cell Leukemia • Bone marrow failure syndromes, except for Fanconi anemia • Myeloproliferative Neoplasms/Myelofibrosis

Age. PS, and UCB Graft Requirements:	• Other Leukemia Subtypes - with the approval of two members of the study committee • <70 years old with no matched 5/6 or 6/6 sibling donor - patients ≥ 70 but ≤ 75 are eligible if the co-morbidity score is ≤ 2 (http://www.qxmd.com/calculate-online/hematology/hct-ci) • Karnofsky score ≥ 70% (≥ 16 years) or Lansky score ≥ 50 (< 16 years) • UCB graft to be selected according to current University of Minnesota umbilical cord blood graft selection algorithm
Other Inclusion Criteria:	• adequate liver and renal function per section 4.1.4 • absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction ≥ 40% • DLCO, FEV_1, FVC > 40% predicted, and absence of O_2 requirements
Exclusion Criteria:	• pregnant or breastfeeding • untreated active infection • Active HIV infection or known HIV positive serology • Less than 3 months since prior myeloablative transplant • 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. • CML in blast crisis • large cell lymphoma, mantle cell lymphoma and Hodgkin lymphoma that is progressive on salvage therapy • Active central nervous system malignancy
Enrollment:	15-25 patients per year over 6-10 years for a total of 163 patients

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 • fludarabine 30 mg/m^2 Days -6 to -2 • TBI 200cGy Day -1
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 • fludarabine 30 mg/m^2 Days -6 to -2 • TBI 200cGy Day -1 • equine ATG 15 mg/kg bid Days -6 to -4



GVHD prophylaxis:

MMF through Day +30 *or* 7 days after engraftment (whichever is earlier)

Sirolimus through Day +100, taper until Day +180

1 Study Objectives

1.1 Primary Objective

The primary objective is to estimate the probability of grade II-IV acute GVHD at Day 100 after unrelated donor umbilical cord blood transplantation using a non-myeloablative preparative regimen along with Sirolimus/MMF for GVHD prophylaxis in persons with hematologic malignancies.

1.2 Secondary Objectives

Secondary objectives are:

- Incidence of grade III-IV acute GVHD at 100 days
- Transplant related mortality (TRM) at 6 months
- Chimerism at Day 21, 100,180 and 365
- Incidence of neutrophil engraftment by Day 42

1.3 Transplant Related Objectives

- Incidence of platelet engraftment by six months
- Incidence of one year chronic GVHD
- Probability of one and two year overall survival (OS)
- Probability of one and two year progression free survival (PFS)
- Incidence of one and two year relapse or disease progression

2 Background and Rationale

Umbilical cord blood (UCB) is now an established alternative donor type for allogeneic transplantation. The advantages of UCB transplantation included, but not limited to, rapid availability, less restrictive HLA-selection criteria, no risk for the donor, and relative low risk of graft-versus-host disease (GVHD). The main limitations of UCB are limited stem cell content, delayed engraftment potentially increasing the risk of infections and morbidity.

Our institution has led several critical advances in the UCB transplant field. Our approach and clinical outcomes have now been reproduced worldwide as evidenced by reports from Center for International Blood and Marrow Transplant and Research (CIBMTR)(1) the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) (2) and by the Societé Française de Greffe de Moelle Osseuse et Therapie Cellulaire and Eurocord (3-5). In one of these reports, the outcomes after UCB transplantation were shown to be similar to other donor types (1).

The University of Minnesota platform consists of cyclophosphamide 50 mg/m^2, fludarabine 200 mg/m^2 divided in 5 days and total body irradiation (TBI) 200 cGy with cyclosporine A (CsA) and mycophenolate mofetil (MMF) immune suppression. This treatment platform has been shown to support single and double UCB transplantation resulting in sustained donor engraftment > 90%, transplant related mortality (TRM) between 20-30%, and long term disease free survival (DFS) in 25-50% depending on disease stage and the presence of co-morbid condition prior to transplantation.(6) Building upon this platform our groups has focused our research efforts on methods that will ultimately result in improved immune reconstitution (7-9). Our hypothesis is that reducing the risk of GVHD after UCB transplantation would facilitate the reconstitution of lymphocyte subsets and result in lower risk of infections and relapse, potentially improving survival. Recent reports by our group demonstrated the critical influence of therapeutic cyclosporine A level in the first month post-transplantation (7), the superior effectiveness in suppressing acute GVHD of MMF 3g/day(8), and the promising early results of the adoptive transfer of UCB-derived natural regulatory T cells (nTreg) (9). More recently we studied the safety and efficacy of the combination of sirolimus and MMF as immune suppressive regimen in a subset of patients.

The mTor inhibitor sirolimus has potential anti-leukemia (10) and anti-viral activity (11). As compared to calcineurin inhibitors, sirolimus has a different toxicity profile with low risk of kidney dysfunction, hypertension and seizures but it may cause hypertriglyceridemia, skin rash and, at least in lung transplant cases, interstitial pneumonia.

In matched related donors and in UCB transplantation the combination of sirolimus with tacrolimus and rabbit ATG resulted on a risk of GVHD of < 20% (12, 13). In unrelated donor transplantation the combination of sirolimus with tacrolimus and MMF resulted in a risk of acute GVHD of 47% (14). In haplo-identical transplantation, sirolimus with MMF and rabbit ATG results in 35% risk of acute GVHD and showed rapid reconstitution of nTreg cells (15). In contrast, studies combining sirolimus with CsA (16) or sirolimus with MMF (17) in adult donors were terminated due to excessive acute GVHD. The combination of sirolimus with tacrolimus has a high risk of thrombotic microangiopathy (12) and, when used in combination with busulfan based conditioning regimen, with excessive risk of veno-occlusive disease of the liver (12, 18). Taken together, these data suggest that sirolimus/MMF with or without ATG may be a suitable immune suppression regimen in specific subsets.

In pilot in the setting of UCB transplantation, recipients of ex vivo expanded UCB derived-nTreg were treated with sirolimus/MMF immune suppression that favors the survival of this important T-cell subset (19). As the combination of sirolimus/MMF has potential advantages over calcineurin inhibitor-based regimens, we modified our local protocol to incorporate this immune suppression regimen and monitored patients for increased risk of severe GVHD. As per our institutional practice we allowed for the co-administration of equine ATG in a subset of patients who were considered high risk for graft rejection. Our preliminary data comparing sirolimus/MMF ± ATG vs CsA/MMF ± ATG is summarized in the table below. Overall this immune suppression regimen resulted in similar incidence of engraftment, acute GVHD and non-relapse mortality. However, before we can definitively adopt this immune suppression regimen as our new standard of care, we need better define its safety and efficacy profile in larger numbers of patients.

Group	**N**	**Grade II-IV AGVHD (95% CI)**	**ANC (95% CI)**	**NRM (95% CI)**
Cy/Flu(40mg)/TBI±ATG + CsA/MMF	157	42% (34-50%)	95% (92-98%)	24% (17-31%)
Cy/Flu(40mg)/TBI±ATG + Siro/MMF	11	27% (2-52%)	82% (59-100%)	27% (2-52%)
Cy/Flu(30mg)/TBI±ATG + Siro/MMF	37	35% (19-54%)	81% (69-93%)	35% (17-53%)

Experimental Component

Our non-myeloablative UCB transplant platform is well established. Despite outcomes similar to other donor types there is ample room for improvement. Our preliminary data on the sirolimus/MMF ± ATG are promising. The rationale for the development of this immune suppression is that in contrast to CsA-based regimens, sirolimus is supportive of nTreg cells survival potentially reducing risk of acute and chronic GVHD and ultimately promoting immune reconstitution. Consistent with our approach of progressive changes to our platform we will further characterize the safety and efficacy of sirolimus/MMF immune suppression in the setting of non-myeloablative UCB transplantation.

Standard of Care

All pre-and post-transplant testing, graft source, chemotherapy and supportive measures listed in this protocol are standard of care but are part of the data

elements necessary to determine the long-term outcomes of the sirolimus/MMF immune suppression regimen.

3 Study Design

This is a single institution phase II study of minimally manipulated umbilical cord blood transplantation after a non-myeloablative chemo/radiation preparative regimen in persons with one of several hematologic malignancies.

This study uses a Minimax two-stage phase II design. Stage 1 will enroll 110 patients. If 54 or fewer develop GVHD, 45 additional patients will be enrolled. After stage 2, if 71 or fewer out of 155 enrolled develop GVHD, CSA/Sirolimus will be considered worthy of further consideration.

The primary objective of this study is to estimate the probability of grade II-IV acute GVHD at Day 100 and provide support that use of Sirolimus/MMF is not worse at preventing GVHD than CsA/MMF after unrelated donor umbilical cord blood transplantation. Secondary objectives include incidence of neutrophil engraftment by Day 42, incidence of grade III-IV acute GVHD, incidence of transplant-related mortality and chimerism at Day 21 and 3, 6 and 12 months post-transplant.

4 Patient Selection

Study entry is open to persons less than 70 years of age (refer to for additional eligibility ≥ 70 years, but ≤75 years of age), regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of similar studies at the University of Minnesota.

4.1 Inclusion Criteria

4.1.1 Age, Performance Status, and Graft Criteria

- <70 years of age 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 - (http://www.qxmd.com/calculate-online/hematology/hct-ci)
- Karnofsky score ≥ 70% (≥ 16 years) or Lansky score ≥ 50 (< 16 years) - refer to appendix II
- UCB graft selected according to current University of Minnesota umbilical cord blood graft selection algorithm

4.1.2 Eligible Diseases

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].

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.

Acute Myeloid Leukemia (AML) and related precursor neoplasms: 2nd or greater complete remission (CR); first complete remission (CR1) in patients > 60 years old; CR1 in ≤ 60 years old that is NOT considered as favorable-risk.

Favorable risk AML is defined as having one of the following:

- t(8,21) without cKIT mutation
- inv(16) or t(16;16) without cKIT mutation
- Normal karyotype with mutated NPM1 and wild type FLT-ITD
- Normal karyotype with double mutated CEBPA
- Acute prolymphocytic leukemia (APL) in first molecular remission at the end of consolidation

Acute lymphoblastic leukemia (ALL)/lymphoma: second or greater CR; CR1 unable to tolerate consolidation chemotherapy due to chemotherapy-related toxicities; CR1 high-risk ALL.

High risk ALL is defined as having one of the following:

- Evidence of high risk cytogenetics, e.g. t(9;22), t(1;19), t(4;11), other MLL rearrangements, IKZF1
- 30 years of age or older at diagnosis
- White blood cell counts of greater than 30,000/mcL (B-ALL) or greater than 100,000/mcL (T-ALL) at diagnosis
- CNS leukemia involvement during the course of disease
- Slow cytologic response (>10% lymphoblasts in bone marrow on Day 14 of induction therapy)
- Evidence of persistent immonophenotypic or molecular minimal residual disease (MRD) at the end of induction and consolidation therapy

Biphenotypic/Undifferentiated/Prolymphocytic Leukemias in first or subsequent CR.

Chronic myelogenous leukemia in chronic or accelerated phase, or CML blast crisis in morphological remission (<5% blasts): Chronic phase patients must have failed at least two tyrosine kinase inhibitors been intolerant to all available TKIs or have *T315I* mutation.

Myelodysplastic syndrome: IPSS INT-2 or High Risk; R-IPSS High or Very High; WHO classification: RAEB-1, RAEB-2; Severe Cytopenias: ANC < 0.8, Anemia or thrombocytopenia requiring transfusion; Poor or very poor risk cytogenetics based on IPSS or R-IPSS definitions; therapy-related MDS. Blasts must be < 5% by bone marrow aspirate morphology. If ≥5% blasts, patient requires chemotherapy for cytoreduction to <5% blasts prior to transplantation.

MRD positive leukemia (AML, ALL or accelerated/blast phase CML). Selected patients in morphologic CR, but with positive immunophenotypic (flow cytometry) or molecular evidence of MRD may be eligible if recent chemotherapy has not resulted in MRD negative status.

Leukemia or MDS in aplasia. These patients may be taken to transplant if after induction therapy they remain with aplastic bone marrow and no morphological or flow-cytometry evidence of disease ≥ 28 days post-therapy. These high risk patients will be analyzed separately.

Burkitt's lymphoma in CR2 or subsequent CR

Relapsed T-Cell Lymphoma that is chemotherapy sensitive in CR/PR that has failed or ineligible for an autologous transplant.

Natural killer cell malignancies

Large-cell lymphoma, Hodgkin lymphoma and multiple myeloma with chemotherapy sensitive disease who are ineligible for an autologous transplant.

Relapsed 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 bulky disease and an estimated tumor doubling time of less than one month.

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

Relapsed Multiple Myeloma that is chemotherapy sensitive and has failed or ineligible for an autologous transplant.

Plasma Cell Leukemia after initial therapy if achieved at least in partial remission; or relapsed and achieved subsequent remission (CR/PR)

Acquired Bone marrow failure syndromes, except for Fanconi anemia

Myeloproliferative Neoplasms/Myelofibrosis.

Other Leukemia Subtypes: A major effort in the field of hematology is to identify patients who are of high risk for treatment failure so that patients can be appropriately stratified to either more (or less) intensive therapy. This effort is continually ongoing and retrospective studies identify new disease features or characteristics that are associated with treatment outcomes. Therefore, if new features are identified after the writing of this protocol, patients can be enrolled with the approval of two members of the study committee.

4.1.3 Additional Criteria for Bulky Disease (lymphomas)

if stable disease is best response, the largest residual nodal mass must < 5 cm (approximately)

If response to previous therapy, the largest residual mass must represent a 50% reduction and be < 7.5 cm (approximately)

4.1.4 Organ Function Criteria

Adequate organ function is defined as:

Cardiac: Absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction ≥ 40%. For children that are not able to cooperate with MUGA and echocardiography, such should be clearly stated in the physician's note

Pulmonary: DLCO, FEV_1, FVC ≥ 40% 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 neither test can be obtained it should be clearly stated in the physician's note.

Liver: Transaminases ≤ 5 x upper limit of normal (ULN) and total bilirubin ≤ 2.5 mg/dL except for patients with Gilbert's syndrome or hemolysis

Renal: Creatinine ≤ 2.0 mg/dl (adults) and creatinine clearance ≥ 40 mL/min (pediatrics). Adults with a creatinine > 1.2 mg/dl or a history of renal dysfunction must have estimated creatinine clearance ≥ 40 ml/min/1.73m^2.

Adequate performance status is defined as Karnofsky score ≥ 70% (≥ 16 years of age) or Lansky score ≥ 50 (pediatrics)

4.1.5 Sexually active females of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control during study treatment.

4.1.6 Voluntary written consent (adult or parent/guardian with presentation of the minor information sheet, if appropriate)

4.2 Exclusion Criteria

4.2.1 Pregnant or breast feeding. The agents used in this study include Pregnancy Category D: known to cause harm to a fetus. Females of childbearing potential must have a negative pregnancy test prior to starting therapy.

4.2.2 Untreated active infection

4.2.3 Active HIV infection or known HIV positive serology

4.2.4 Less than 3 months since prior myeloablative transplant

4.2.5 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.

4.2.6 CML in blast crisis

4.2.7 Large cell lymphoma, mantle cell lymphoma and Hodgkin disease that is progressing on salvage therapy.

4.2.8 Active central nervous system malignancy

5 Patient Registration In OnCore

Registration will occur after the patient/parent/guardian has signed the subject consent and eligibility is confirmed. 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. A copy of the eligibility checklist is under attachments within the study in OnCore.

Patients will be registered in OnCore by the Masonic Cancer Center's Clinical Data Associates (CDA's).

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

Arm 1 (no ATG) - hematologic malignancy patients who have received a previous autologous transplant or ≥ 2 cycles of multi-agent chemotherapy within the 3 months previous to UCBT

Arm 2 (ATG) - hematologic malignancy patients who have not been treated with prior autologous transplant or ≤ 1 cycle of chemotherapy in the 3 months previous to UCBT, should receive ATG as part of their conditioning regimen

If one or both of the cord blood units used for the graft is unlicensed, the participant will co-enroll on University of Minnesota protocol MT2011-13R "Infusion of Cell Populations from Unlicensed Umbilical Cord Blood Units" as the units used for the transplant will be minimally manipulated.

6 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, antimicrobials, etc.).

All patients will receive allopurinol 300 mg/day (for peds -150 mg/m^2/day) PO, unless known allergy ending one day after the last dose of chemotherapy or TBI (may continue longer if clinically indicted).

All drugs used in this study are commercially available by prescription.

6.1 Preparative Regimen (Arm 1 - no ATG)

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.

Treatment Day	Treatment
Day -7	Begin allopurinol (Day -7 to Day 0)
Day -6	Fludarabine 30 mg/m^2 IV over 1 hour Cyclophosphamide 50 mg/kg IV over 2 hours Antiemetics and fluid flush per institutional guidelines
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 Begin MMF and Sirolimus per section 6.3
Day -2	Fludarabine 30 mg/m^2 IV over 1 hour
Day -1	TBI 200 cGy
Day 0	UCB cell infusion (transplant)

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.

Dosing is based on Actual Body Weight (ABW) unless ABW > 150% above Ideal Body Weight (IBW), in which case the dose should be computed using adjusted body weight.

Steroids and/or other medications may be used as needed per the discretion of the treating physician.

TBI will be administered as a single treatment on Day -1. Refer to appendix III.

6.2 Preparative Regimen with ATG

Patients who have had a prior autologous transplant or who have had ≤ 1 cycle of chemotherapy in the previous 3 months should receive ATG as part of their conditioning regimen.

Treatment Day	Treatment
Day -7	Begin allopurinol (day -7 to day 0)
Day -6	Fludarabine 30 mg/m^2 IV over 1 hour Cyclophosphamide 50 mg/kg IV over 2 hours ATG 15 mg/kg IV every 12 hours Antiemetics and fluid flush per institutional guidelines
Day -5	Fludarabine 30 mg/m^2 IV over 1 hour ATG 15 mg/kg IV every 12 hours
Day -4	Fludarabine 30 mg/m^2 IV over 1 hour ATG 15 mg/kg IV every 12 hours
Day -3	Fludarabine 30 mg/m^2 IV over 1 hour Begin MMF and Sirolimus per section 6.3
Day -2	Fludarabine 30 mg/m^2 IV over 1 hour
Day -1	TBI 200 cGy
Day 0	UCB cell infusion (transplant)

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.

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.

Dosing is based on Actual Body Weight (ABW) unless ABW > 150% above Ideal Body Weight (IBW), in which case the dose should be computed using adjusted body weight.

Steroids and/or other medications may be used as needed per the discretion of the treating physician.

Equine ATG (ATGAM) 15 mg/kg IV will be administered every 12 hours beginning on Day -6 and continuing on Day -5 and Day -4 (for a total of 6 doses) 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.

TBI will be administered as a single treatment on Day -1. Refer to appendix III.

6.3 GVHD Prophylaxis (begin Day -3)

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

6.3.1 Sirolimus

Adult Dosing: Sirolimus will be administered starting at Day -3 with 8-12 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 10 mg followed by maintenance dosing of 2.5 mg/m^2/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.

6.3.2 Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) 3 gram/day IV/PO for patients who are ≥ 40 kg divided in 2 or 3 doses. In obese patients (>125% IBW) 15 mg/kg every 12 hours may be considered. 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 1st day of 3 consecutive days of absolute neutrophil count [ANC) ≥ 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).

6.4 Umbilical Cord Blood Thaw and Infusion (Day 0)

Cord blood products are thawed and filtered (170-micron) in the Molecular and Cellular Therapeutics (MCT) Lab using the method of Rubinstein et al.[20]

There will be no processing of the UCB.

Note: Unlicensed UCB units will be covered by University of Minnesota IND BB 14797 (J. Wagner MD – sponsor/investigator) and therefore will be in compliance with mandatory reporting to the FDA for minimally manipulated UCB units.

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

Pre-medications and UCB infusion will be per current institutional policies/guidelines. 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.

6.5 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.

Acute and chronic GVHD will be staged and treated using current University of Minnesota BMT program GVHD protocols

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

6.6 Management of Slow Engraftment 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 +21/28 bone marrow biopsy, notify the unrelated donor (URD) search coordinator to pursue back-up graft and arrange a follow-up bone marrow biopsy per current institutional slow engraftment guidelines.

6.7 Follow-up

Patients will be followed for 2 years post-transplant per the standard of care schedule in section 8.

Follow-up after 2 years will be per the University of Minnesota standard hematopoietic stem cell transplantation protocol for long-term follow-up.

7 Expected Toxicities of the Treatment Plan

7.1 Preparative Regimen

Cyclophosphamide		
Common	**Less Common**	**Rare**
nausea/vomiting mucositis sterility severe suppression of blood counts diarrhea	hemorrhagic cystitis	cardiomyopathy skin rash SIADH (Syndrome of Inappropriate Anti-diuretic Hormone)

Cyclophosphamide		
Common	**Less Common**	**Rare**
fluid weight gain/edema alopecia		

Fludarabine		
Common	**Less Common**	**Rare**
• severe suppression of • blood counts • diarrhea • anorexia • mucositis • nausea/vomiting • stomatitis • osteoporosis • dysuria	• chills • fever • GI bleeding • peripheral edema	• neurotoxicity – agitation and confusion – blurred vision – peripheral neuropathy – hearing loss – headache – cerebellar syndrome – blindness – coma – weakness • depression • insomnia • hemorrhagic cystitis (except in FA) • abnormal renal function test • autoimmune hemolytic anemia • deep venous thrombosis • aneurysms • pruritic skin rash • abnormal liver function/liver failure • constipation • transient ischemic attack • dysphagia • myalgia • arthralgia • renal failure

Total Body Irradiation		
Common	**Less Common**	**Rare**
• nausea and vomiting • diarrhea • cataracts • sterility (inability to have children) • endocrinopathies (hormone imbalance due to damage to the endocrine gland) • stunted growth in children	• parotitis (swelling and inflammation of the parotid gland) • interstitial pneumonitis (explained below in the damage to vital organs section) • generalized mild reddening of the skin	• dysphagia (difficulty swallowing) • deformities of the backbone (vertebrae) • nephropathy (numbness or tingling in hands and/or feet) • risk of 2nd malignancy years later (when given along with chemotherapy)

Total Body Irradiation		
Common	**Less Common**	**Rare**
• intestinal cramps • mucositis (mouth sores)	• veno-occlusive disease (VOD - explained below in the damage to vital organs section)	

Anti-Thymocyte Globulin (ATG) – ARM 2 ONLY		
Common	**Less Common**	**Rare**
• fever • chills • leukopenia • pain • headache • abdominal pain • diarrhea • hypertension • nausea • thrombocytopenia • peripheral edema • dyspnea • asthenia • hyperkalemia • tachycardia	• malaise • dizziness	• severe allergic reaction (anaphylaxis)

7.2 GVHD Prophylaxis

Mycophenolate Mofetil (MMF)	Sirolimus
• pancytopenia • headache • insomnia • electrolyte imbalances • leg cramps/bone pain • hypertension • dizziness • hyperglycemia • rash • nausea/diarrhea	• fast heart rate • pain when breathing, feeling short of breath • chest pain, feeling weak or tired • coughing up blood or mucus • feeling like you might pass out • pale skin, easy bruising or bleeding, weakness • fever, chills, body aches, flu symptoms • night sweats, weight loss • swelling of face, stomach, hands or feet • rapid weight gain • pain or burning when urinating • slow healing of a wound • joint pain • nausea, vomiting, diarrhea, constipation, stomach pain • headache • acne or skin rash • high triglycerides and cholesterol

7.3 UCB Cell Infusion

With the cell infusion

- nausea and vomiting
- possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)

General transplant related risks

- slow recovery of blood counts
- graft failure
- Graft-Versus-Host Disease (GVHD)
- other complications including:
  - damage to the vital organs
  - serious infections
  - relapse of disease or a new blood cancer
  - risk to the unborn

Risks related to using a UCB stem cell source

- **Bacterial/Endotoxin Contamination** of cellular therapy products may occur, but rarely cause acute, severe or life threatening effects. However, the onset of high fever (>2ºC or >3.5ºF rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after infusion should suggest the possibility of bacterial contamination and/or the presence of endotoxin in the product.
- **Transmission of Infectious Disease** may occur because cellular therapy products are collected from human body and/or tissues. The donor selection criteria do not totally eliminate the risk of transmitting the agents currently tested such as HIV, HTLV, HBV, HCV, CMV, T. pallidum (Syphilis), West Nile Virus, and Trypanosome (Chagas). For some other infectious disease there are no routine tests to prevent disease transmission including Parvovirus spp., Plasmodium spp. (Malaria), the coronavirus associated with severe acute respiratory syndrome (SARS), and the agents of human transmissible spongiform encephalopathies (TSEs).

8 Clinical Care Activities

Scheduled evaluations after screening and until engraftment may be performed +/- 3 days from the targeted date; assessments performed after engraftment and through Day 100 may be done +/-7 days of the targeted date. After Day 100 assessments may be done +/- 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[1]	Follow-Up Days 42-100	Follow-Up (>Day 100 through Day 720)
Consent	X			
Medical History	X	daily	weekly	X (day 180, 360, 720)
Physical Exam	X	daily	weekly	X (day 180, 360, 720)
RT consultation	X			
Karnofsky/Lansky	X		day 100	X (day 180, 360, 720)
GVHD Assessment		weekly start day 7	weekly, day 100	X (day 180, 360)
CBC/diff/plt	X	daily	weekly	X (day 180, 360, 720)
PT/INR	X			
Viral Screen	X			
Basic metabolic panel		daily		
Comprehensive metabolic panel	X	2x/wk	weekly	X (day 180, 360, 720)
Testing for anti-HLA antibodies[3]	X			
Urinalysis	X			
eGFR for adults with creat > 1.2 or hx or renal dysfunction	X			
Pregnancy test for FOCBP	X			
BM Biopsy chimerism		BM (day 21/28)	BM (day 100)	BM (day 360, 720)
Blood chimerism	Patient and UCB	PB (day 21, 28)	PB (day 60)	
Quantitative Immunoglobulins[4]	X		X (day 100)	X (day 360)
PFT/DLCO	X			
MUGA or Echo	X			
Chest CT	X[2]			
Disease Evaluation	X	X(day 21 to 28)	X (day 100)	X (day 360, 720)

1 engraftment defined as absolute neutrophil count (ANC) ≥ 5 X 10^8/L for 3 consecutive measurements

2 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.

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

4 May be omitted at the physician's discretion

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

9 Adverse Event Monitoring, Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page http://evs.nci.nih.gov/ftp1/CTCAE/About.html

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

9.1 Event Documentation

Transplant related outcomes and events will be recorded in the Blood and Marrow Transplantation (BMT) database. Events requiring prompt reporting to the University of Minnesota Institutional Review Board (IRB), early stopping rule events, and protocol deviations will be documented in OnCore.

9.2 Adverse Event Reporting

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers	Copy to:
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xral0-sh	Within 5 business days of event discovery	Report Form	irb@umn.edu	SAE Coordinator mcc-saes@umn.edu
Masonic Cancer Center SAE Coordinator	Events that impact the early study stopping rules.	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu	n/a

The SAE Coordinator will provide the Masonic 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).

10 Study Data Collection and Monitoring

10.1 Data Collection

This study will track SAE's, stopping rule events, and clinical deviations using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms.

All transplant related outcomes and complications will be recorded in the Blood and Marrow Transplantation (BMT) database.

10.2 Data and Safety Monitoring

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at https://z.umn.edu/dsmp.

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

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the trial's progress twice yearly
- 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 submission of all reportable adverse events per the definition of reportable in section 9.2 to the Masonic Cancer Center's SAE Coordinator and the University of Minnesota IRB.

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

10.3 Study Related Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

10.4 Record Retention

The investigator will retain study records for at 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

11 Statistical Considerations

We have extensive experience with the use of Cy/Flu/TBI as a non-myeloablative conditioning regimen in conjunction with the use of transplantation of umbilical cord blood from unrelated donors in patients with hematological disease. We also have extensive experience using CsA/MMF as a GVHD prophylaxis. However, we have limited experience with the use of Sirolimus/MMF, showing safety and potential efficacy. Our principal objective in this study is to estimate the rate of grade II-IV AGVHD using Sirolimus/MMF as a GVHD prophylaxis. Sirolimus/MMF is preferable to CsA/MMF due to its ability to support nTreg cells which can potentially reduce GVHD and promote immune reconstitution.

11.1 Primary, Secondary and Transplant-Related Endpoints and Study Design

Our primary endpoint is the probability of grade II-IV acute GVHD by Day 100. Secondary endpoints include transplant related mortality at 6 months, the incidence of grade III-IV acute GVHD at 100 days, chimerism at Day 21, 100,180 and 365 and the Incidence of neutrophil engraftment by Day 42. Other transplant related endpoints include the Incidence of platelet engraftment by six months, the incidence of Day 100 grade II-IV and III-IV acute GVHD, the incidence of one year chronic GVHD, the probability of one and two year progression free survival, the probability of one and two year survival and the incidence of one and two year relapse or disease progression.

This is a Minimax two-stage phase II design. Stage 1 will enroll 110 patients. If 54 or fewer develop GVHD, 45 additional patients will be enrolled. After stage 2, if 71 or fewer out of 155 enrolled develop GVHD, CSA/Sirolimus will be considered worthy of further consideration.

11.2 Statistical Analysis

11.2.1 Analysis of Primary Endpoint

Simple proportions will be used to estimate the probability of grade II-IV AGVHD. We do not expect competing risk but if necessary AGVHD will be estimated by cumulative incidence treating non-event death as a

competing risk. Ninety-five percent confidence intervals will help provide inference as well as show a potential upper bound for the primary endpoint around the benchmark rate of 42%.

11.2.2 Analysis Of Secondary and Transplant Related Objectives

Analyses of the secondary and transplant related endpoints emphasize estimation along w/ a measure of precision which includes 95% confidence intervals. Grade III-IV acute and chronic GVHD will be estimated by cumulative incidence treating non-GVHD death as a competing risk. Transplant-related mortality will be estimated by cumulative incidence treating relapse as a competing risk. Kaplan-Meier curves will be used to estimate overall and disease-free survival. Engraftment will also be estimated by cumulative incidence treating non-event death as a competing risk. Ninety-five percent confidence intervals will help provide inference for all endpoints. Chimerism (percentage donor) will be summarized among evaluable patients surviving to each time-point at Days 21, 100, 180 and 365 with descriptive box-plots and statistics such as medians, ranges and interquartile ranges.

Estimation of endpoints is the primary emphasis in this study. However, in the event that investigators desire to compare primary and/or secondary endpoints to an external cohort or wish to look for various risk factors within the cohort, regression methods will be employed. Cox regression will be used for the endpoints of survival and disease-free survival. Fine and Gray regression will be employed for all endpoints that include competing risks. Logistic regression will be employed for binary endpoints. SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.2 (R foundation for Statistical Computing, Vienna, Austria) will be used for all statistical analyses.

11.3 Rationale for Sample Size

The sample size is based on the Minimax two-stage design with a type-I error of 5% and a power of 80%. Using prior data and on advice by investigators, we used a benchmark rate of 42% GVHD to be considered effective and a rate of 52% or higher to be considered ineffective. Based on our design, there is less than a 5% probability of concluding effectiveness if the true rate is ≥ 52%. GVHD less than equal to 42% is considered effective and there is an 80% probability of concluding effectiveness if the true proportion is ≤ 42%. If the trial reaches stage 2, there will be 155 patients enrolled. We do not expect early competing risk for the primary endpoint but if up to 5% of patients have an early competing risk of non-event death, we will conservatively add an additional 8 patients to the study sample for a total enrollment of 163. Based on enrollment

in the similar trial, MT2005-02, we can expect to enroll approximately 15-25 patients per year so enrollment should be complete between 6 and 10 years.

11.4 Safety Monitoring

Sirolimus/MMF has been shown to be safe in protocol MT2005-02 therefore continuous monitoring will not be in place during this study. Instead, safety will be the responsibility of the DSMC committee and the principal investigator. The committee will review safety twice a year with particular attention paid to graft failure by Day 42 post-transplant. Graft failure should be estimated at each review. A failure rate exceeding 25% should raise concern. If this rate is exceeded, the principal investigator and any others deemed necessary by the DSMC committee should be notified.

12 Conduct of the Study

12.1 Record Retention

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

12.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. In the case of minor patients, the parent/guardian will be required to sign and date the parental consent form and the minor, if 8 years or older will be presented with a minor information sheet.

Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

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Appendix I – Eligibility Checklist
Eligibility Checklists are now kept in Oncore

Appendix II – Karnofsky Performance Status and Lansky Play Score

For patients 16 years of age and older:

Karnofsky Performance Scale	
Percent	**Description**
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 to 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 indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

For patients < 16 years of age:

Lansky Score	Play Score
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 activity
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 but 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	No play; does not get out of bed
0	Unresponsive

Appendix III – TBI 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.

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, 10, or 18 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 gives 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.

Updated 10/2015 by Kathryn Dusenbery, MD