UNIVERSITY OF MINNESOTA BONE MARROW TRANSPLANTATION PROGRAM

ALLOGENEIC TRANSPLANT FOR HEMATOLOGICAL MALIGNANCY

MT2001-02

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DATE	PROTOCOL CHANGE	IRB approval
March 21, 2013	Added reference to use of MTX as standard GVHD prophylaxis	
May 30, 2012	add UCB as a stem cell source option for CY/FLU prep; add ATG to the preparative regimen for patients receiving cord blood and who have not had chemotherapy in the prior 3 months; delete oral option for busulfan as no longer given that way; delete MT2004-03 treatment arm as study is closed to accrual; change busulfan dose to 0.8 mg every 6 hours (currently 1.0 mg every 6 hours) Add statement to allow flexibility in treatment based on individual patient needs change to Keppra as seizure prophylaxis (currently Dilantin) update the DSMP add Claudio Brunstein to cover page (officially added as co-Investigator 3/16/12)	5/31/12
January 26, 2010	Eligibility clarification	02/18/2010
July 29, 2008	Added an arm to co-enroll subjects from MT2004-03; added Dr. Jeffrey Miller to the study committee, removed Dr. Juliet Barker and Dr. Norma Ramsay from the study committee	09/25/2008
April 28, 2008	Increased enrollment goal to 350 subjects, updated study to conform to current institutional standards	9/25/2008
June 14, 2005	Section 4.2: If the recipient is $\leq$ 18 years of age with a related donor, they will receive marrow.	
May 3, 2004	Added myelproliferative diseases to the eligibility (section 3.4.5) TBI dose rate changed to 10-19 cGy/min to conform to current equipment in Therapeutic Radiation (section 4.3.1.1) G-CSF dosing for donors changed to 10 mcg/kg/day – section 4.1.3, Appendix 1.	7/7/2004
January 8, 2004	Busulfan pharmacokinetics added (section 4.3.2)	January 8, 2004
November 6, 2002	Eliminated "rest day" from TBI pre-transplant regimen (section 4.3.1)	January 8, 2003
October 2002	1. Amendment Page added 2. Testicular boosts for males with ALL added to the TBI guidelines. (section 4.3.1.1 and Appendix II)	December 5, 2002
December 6, 2001	Protocol revised to reflect that this study is considered "treatment guidelines", rather than a research study, in the eyes of the CPRC. References to this being a "phase II study" have been removed.	CPRC approval, Jan 8, 2002
October 6, 2001	Added Data and Safety Monitoring plan, a schema, and a more complete statistical section (stipulations of CPRC prior to opening study).	October 31, 2001

TABLE OF CONTENTS

Study Schema

Potential BMT candidate

to

Screen for eligibility after New Patient visit or during pre-BMT evaluation

Review eligibility for study with higher scientific priority

to

Present proposed plan to patient; secure written informed consent.

to

Screen donor for appropriate histocompatibility and medical suitability to donate

Present proposed plan to donor; secure written informed consent

to

Prepare patient for BMT using chemotherapy ± total body irradiation

Infuse donor stem cells
(allowable sources – related or unrelated BM or PB or, for BU/CY preparative chemo only, UCB is also permitted)

to

Supportive care

to

Long-term follow-up for listed as well as unexpected complications and survival

1.0 OBJECTIVES

The purpose of this protocol is to study the use of related or unrelated allogeneic stem cell transplantation as therapy for individuals with acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, myelodysplasia or juvenile chronic myelogenous leukemia. Specifically, this study researches the following question.

1.1 With what frequency will allogeneic stem cell transplantation (BMT) along with fractionated total body irradiation (TBI) and cyclophosphamide; or busulfan and cyclophosphamide for patients who are ineligible for TBI, promote long-term disease-free survival in patients with hematological malignancies?

2.0 BACKGROUND AND RATIONALE

Allogeneic bone marrow transplantation has been widely used for treatment of lethal hematologic disorders. Extensive experience with bone marrow as the stem cell source has documented the ability of engrafted marrow to restore hematopoiesis, immunocompetence and protect against malignant recurrence leading to extended disease-free survival for a sizable fraction of children and adults undergoing such transplantation. Over the last 10 years, extensive clinical experience, confirmed in several randomized trials, has suggested that for certain patient populations, G-CSF mobilized peripheral blood from matched related or unrelated donors contains sufficient stem cells for prompt engraftment and sustained hematopoiesis. While questions still remain regarding the incidence, severity and duration of acute and chronic graft-versus-host disease following allogeneic transplantation using blood-derived stem cells, it is well established that these are a viable source of cells for use in allotransplantation. Peripheral blood stem cell allografts have been associated with quicker neutrophil recovery and a shorter time to platelet and red cell transfusion dependence then corresponding grafts using marrow-derived stem cells. This has resulted in lesser early transplant-related toxicity and mortality. Acute graft-versus-host disease has been either similar or slightly less frequent than in marrow grafts, and chronic graft-versus-host disease has been reported as either similar or slightly more frequent than grafts using marrow. Several randomized trials have suggested a survival advantage for blood stem cell transplants, particularly for high risk patients.

Experience at the University of Minnesota with over 100 such allografts confirms quicker engraftment, but similar rates of graft-versus-host disease and disease-free survival, compared to bone marrow transplants at our institution.

Recognizing this advantage for all, but the lowest risk group of patients, this study will evaluate, in prospective fashion, the use of G-CSF mobilized donor blood stem cells in patients undergoing allotransplantation. Those receiving unrelated donor grafts or those whose donors are younger than age 12 will still undergo marrow harvests for stem cell

collection. All patients will receive uniform conditioning with cyclophosphamide and fractionated total body irradiation for busulfan plus cyclophosphamide, if irradiation is not possible. They will receive the multi-modal supportive care provided for all patients undergoing transplantation at our institution. Standard post-transplant outcomes relating to engraftment, graft-versus-host disease complications, malignant relapse and survival will be evaluated.

3.0 ELIGIBILITY AND EXCLUSION CRITERIA

3.1 Donors will be < 75 years of age and in good health.

3.2 Recipients will be $\leq$55 years, will have normal organ function (excluding bone marrow) and will have a Karnofsky activity assessment $\geq$ 90%.

3.2.1 Creatinine $\leq$2.0 mg/dl for adults; or clearance > 50 ml/min for children
3.2.2 Bilirubin, AST, ALK $\leq$2 x normal.
3.2.3 Pulmonary function test > 50% of normal.
3.2.4 MUGA $\geq$ 45% ejection fraction.

3.3 Recipients with related or unrelated donor matched at the HLA A, B, DRB1 loci, or mismatched related or unrelated (if < 35 years old) at a single HLA A, B, DRB1 locus. For the busulfan/cyclophosphamide (BU/CY) prep, UCB is also a permitted stem cell source. If UCB is used, unit(s) 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. 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

3.4 Recipients will be eligible in one of the following disease categories

3.4.1 Chronic myelogenous leukemia in accelerated phase or in post blast crisis; second or greater chronic phase; or in chronic phase but intolerant of or resistant to tyrosine kinase inhibitors.

3.4.1.2 Accelerated Phase: Patients with hematologic peripheral blood or bone marrow findings meeting standard criteria for CML, but who present with or progress to express any of the following findings are considered as having accelerated phase disease:

Leukocytosis (WBC greater than $50x10^9$/L) uncontrolled by single agent chemotherapy.

Thrombocytosis (Platelet count greater than $1x10^{10}$/L) uncontrolled by single agent chemotherapy.

Anemia (hemoglobin less than 8 grams/dl) uncontrolled by single agent therapy.

Peripheral blood blast percentage between 5 and 30%, uncontrolled by single agent chemotherapy.

Cytogenetic abnormalities in addition to the Philadelphia chromosome at presentation, or the development of new cytogenetic abnormalities in addition to the Philadelphia chromosome during observation.

Splenomegaly uncontrolled by single agent chemotherapy.

Extramedullary disease.

Severe, progressive myelofibrosis or osteosclerosis.

Achievement of a "second chronic phase" after blast crisis.

3.4.2 Acute myelocytic leukemia in first or greater remission, or first, second or third relapse.

3.4.3 Acute lymphocytic leukemia in the 2nd or greater bone marrow remission.

3.4.3.1 High risk children will be transplanted in first remission if they meet one of the following criteria:

Infants < 6 months at diagnosis;

Infants < 12 months at diagnosis with one or more of the following:
CD10 negative blasts
WBC > 100,000/Φl at diagnosis
M2 or M3 on day 14 bone marrow (M2 = 5-15% blasts; M3 > 15% blasts)

Children > 12 months <10 years with one of the following:
High risk cytogenetics: t(9;22), t(4;11) or hypodiploidy (< 45 chromosomes)

Children and young adults > 10 years < 21 years of age with one or more of the following:
High risk cytogenetics: t(9;22), t(4;11) or hypodiploidy (< 45 chromosomes)

WBC at diagnosis > 200,000/OI

Any patient with M2 or M3 bone marrow on day 28 of initial induction (i.e. No CR in 4 weeks).

3.4.3.2 Patients 21-30 years old are considered high risk and eligible in 1st CR if they have either:

B-cell ALL (Surface immunoglobulin +) or with t(8;14); t(2;8); or t(8;22).
High risk Cytogenetic features: t(9;22; t(4;11); or hypodiploidy (< 45 chromosomes).
WBC at diagnosis > 20,000/Φl;
No CR by day 28 of initial induction therapy;
Extramedullary leukemia.
All patients > 30 years old.

3.4.4Myelodysplastic syndrome.

3.4.4.1 RAEB: "refractory anemia with excess of blasts" (RAEB)

3.4.4.2 Cytopenia affecting 2 or more myeloid lines.

3.4.4.3 Less than 5% circulating blasts.

3.4.4.4 Bone marrow evidence of dysgranulopoiesis, dyserythropoiesis, and/or dysmegakaryocytopoiesis.

3.4.4.5 5-20% blasts in the bone marrow.

3.4.4.6 A history consistent with the above syndrome for greater than three months prior to bone marrow transplantation.

3.4.4.7 RAEB in Transformation:RAEB as defined above with any of the following modifications:

5% or more blasts in the peripheral blood.
20-30% blasts in bone marrow.
Presence of Auer rods in granulocytic precursors.

3.4.4.8 Severe Cytopenia and Severe Dysmyelopoiesis: Severe cytopenias of 2 or more peripheral blood myeloid cell lines (Hb < 10.0 gm with < 1% retics; absolute granulocyte count < 500/mm^3 platelet count < 20,000/mm^3) associated with dysmyelopoietic changes in the bone marrow.

3.4.4.9 Severe Cytopenia and Clonal Chromosomal Abnormalities: Severe cytopenias of 2 or more myeloid cell lines associated with clonal, chromosomal abnormalities of the bone marrow.

3.4.5 Myeloproliferative Diseases – (i.e. myelofibrosis, CMML)

3.4.6 Juvenile myelomonocytic leukemia

3.4.7 Chronic lymphocytic leukemia -- must have all three:

Rai Stage III/IV

Progression after previous CR or PR

Recent chemotherapy responsiveness

3.4.8 Advanced non-Hodgkin's (NHL).

3.4.8.1 Low-grade NHL (working formulation A, B, C) following progression after initial therapy if asymptomatic at diagnosis ($\geq$ CR2, $\geq$ PR2) or if no CR was achieved ($\geq$ PR1).

3.4.8.2 Mantle zone after initial therapy ($\geq$ CR1, $\geq$ PR1).

3.4.8.3 Intermediate grade lymphoma (> PR2).

3.4.8.4 High-grade NHL (IWF H, I, J) after initial therapy if $\geq$ stage III at diagnosis; after any progression even if localized (stage I, II) at diagnosis.

3.4.8.5 Recent chemotherapy responsiveness

3.4.9 Advanced Hodgkin's disease beyond PR2 ($\geq$ CR3, $\geq$ PR3).

3.4.9.1 Recent chemotherapy responsiveness

3.4.10 Multiple Myeloma after initial therapy.

3.4.10.1 Advanced (III) stage

3.4.10.2 Beta 2 microglobulin > 6

3.5 Donors and recipients will sign informed consent approved by the Committee on the Use of Human Subjects at the University of Minnesota.

4.0 TREATMENT SCHEMA

4.1 Stem Cell Acquisition by Source

4.1.1 Normal related donor priming and apheresis.

- If donor is > 12 years of age, > 100 lb.
- If recipient is not in Chronic Phase CML
- G-CSF administration schedule (donor).

Day -4 through Day 0	Therapy
Transplant day -4	G-CSF, 10 mcg/kg subcutaneously
Transplant day -3	G-CSF, 10 mcg/kg subcutaneously
Transplant day -2	G-CSF, 10 mcg/kg subcutaneously
Transplant day -1	G-CSF, 10 mcg/kg subcutaneously
Transplant day 0	G-CSF, 10 mcg/kg subcutaneously

Apheresis schedule

Transplant day 0	Apheresis
Transplant day +1	G-CSF pre Apheresis if needed.

A target of 5 x 10^6/kg and a minimum of 4 x 10^6 CD34+ cell/kg recipient weight will be collected by apheresis and used for transplant. In most cases this dose will be recovered in a single apheresis; however, a second or rarely third apheresis performed on the following days may be required to achieve the minimum dose. The apheresis product will be administered to the recipient without cryopreservation on each day of collection.

Donors will receive pre-medications for G-CSF consisting of acetaminophen 650 mg. p.o. every 8 h. beginning the day prior to G-CSF administration and ending on the first day of apheresis.

Donors may experience any of the following side effects.

Bone pain	Nausea/vomiting	Rash
Headaches	Insomnia	Edema
Body ache	Dyspnea	
Fatigue	Other complaints	

Donors experiencing intolerable symptoms (grade 3 toxicity, use CALGB criteria) attributed to G-CSF therapy will receive dose reduction to 5.0 mcg/kg/d.

Apheresis procedure.

Peripheral blood progenitor cells will be collected with a blood cell separator (Fenwal CS-3000 plus, Baxter Healthcare Corporation, Deerfield, IL) using a granulocyte separation chamber, a small volume collection chamber and an interface offset of 140. The flow rates will range from 50 to 70 mL/minute and a total of 15 liters of whole blood will be processed over 4-6 hours. The volume of the apheresis product collected should be 50 mL, but following the collection an additional 250 mL of autologous plasma will be collected and added to the apheresis product.

Analysis of CD34+ and CD3 content of blood and aphereses products.

Flow cytometry. Progenitor cell and T-cell (CD3) total content of PBSC grafts will be determined by FACS.

4.1.2 The patient will receive marrow:

- If the recipient is $\leq$ 18 years of age with a related donor.
- If donor is < 12 years of age.
- If recipient is in Chronic Phase CML
- Donor is unrelated.
- Bone marrow will be harvested in accordance with standard procedure.
- Bone marrow dose: 2.0 x 10^8 nc/kg will be collected.
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4.1.3 Umbilical Cord Blood as the cell source (BU/CY preparative regimen only)

Umbilical cord blood is an alternative to marrow or peripheral blood. The unit(s) 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. Co-enrollment on the University of Minnesota UCB registration protocol MT2011-13R for minimally processed cords is required.

4.2 Transplant procedure

4.2.1 Preparatory Regimen Using Total Body Irradiation (TBI) and cyclophosphamide

Day	
-6	cyclophosphamide 60 mg/kg I.V.
-5	cyclophosphamide 60 mg/kg I.V.
-4	TBI AM, PM 165 cGy each dose
-3	TBI AM, PM 165 cGy each dose
-2	TBI AM, PM 165 cGy each dose
-1	TBI AM, PM 165 cGy each dose
0	Stem cell or Bone Marrow Infusion

Total Body Irradiation/cyclophosphamide Regimen

1320 cGy administered in 8 fractions of 165 cGy each with 2 fractions being given each day. Total body irradiation is given at a dose rate of 10-19 cGy/minute prescribed to the midplane of the patient at the level of the umbilicus. The total body irradiation will be delivered with right and left lateral fields, with the patient supine on a specially designed couch. Based on measurements of transverse thicknesses, aluminum compensators will be used to ensure that the dose homogeneity across the field 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). Total body irradiation will be delivered with a linear accelerator using 6, 18 or 24 MV xrays. The energy used will be based on the calculated dose to the midline at points up and down the patient's torso. The lowest energy that gives 90-100% of the prescription 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.

Testicular boosts should be used for all males with ALL (and according to institutional practice for other diseases). The testicular boost is given in a single 400 cGy fraction with either electrons prescribed to Dmax or photons prescribed to the midplane of the scrotum. If electrons are used, the energy for the testicular boost depends on the thickness of the testicles and is chosen so that the D90 corresponds to the posterior surface of the scrotum.

Patients are eligible for any GVHD prophylaxis studies active at the University of Minnesota.

Cyclophosphamide is to be given as a 2 hour infusion with strict attention given to vigorous hydration, fluid balance, and maintenance of urine output.

4.2.2 Alternate preparative therapy for patients not able to receive TBI

Dose and/or schedule modifications based on weight (i.e. for pediatric patients), clinical issues or current institutional practice are permitted at the discretion of the treating physician for any drug.

Cyclophosphamide	50 mg/kg iv once daily x 4 days (total 200 mg/kg)
Busulfan	0.8 mg/kg/dose IV in 4 daily doses x 4 days(total 12.8 mg/kg)

Day	Agent	Dose; Administration
- 10	Begin Keppra	
- 9	Busulfan	0.8 mg/kg/dose IV every 6 hrs
- 8	Busulfan	0.8 mg/kg/dose IV every 6 hrs
- 7	Busulfan	0.8 mg/kg/dose IV every 6 hrs
- 6	Busulfan	0.8 mg/kg/dose IV every 6 hrs
- 5	Cyclophosphamide	50 mg/kg/day iv over 2 hours
- 4	Cyclophosphamide	50 mg/kg/day iv over 2 hours
- 3	Cyclophosphamide ATG* Start GVHD prophylaxis	50 mg/kg/day iv over 2 hours 15 mg/kg IV every 12 hours
- 2	Cyclophosphamide ATG*	50 mg/kg/day iv over 2 hours 15 mg/kg IV every 12 hours
-1	Rest ATG*	 15 mg/kg IV every 12 hours
0	Stem Cell infusion per current institutional guidelines	
+1	Begin G-CSF 5 mcg/kg/day IV until ANC > 2500 x 2 days	

*only for UCB recipients who have not had chemotherapy in the preceding 3 months

Keppra will be administered per institutional guidelines through 1 day after the last dose of busulfan (through day -5).

Busulfan pharmacokinetic monitoring will be done according to institutional guidelines.

UCB recipients who have not had chemotherapy in the preceding 3 months will also receive Equine ATG (ATGAM) 15 mg/kg IV will be administered every 12 hours for 6 doses beginning on day -3 per institutional guidelines. The study team may decide to omit the ATG on an individual patient basis if it is not clinically warranted. 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.

Cyclophosphamide will be given in a two-hour infusion with attention to vigorous hydration, fluid balance and maintenance of urine output.

Mesna will be administered according to support protocol MT(S) 9006 during cyclophosphamide infusion.

Patients will be started on G-CSF support on day +1 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.

Patients are eligible for any GVHD prophylaxis studies active at the University of Minnesota or one of the regimens listed below:

- **Methotrexate** and **Cyclosporine A** as per BMT standard of care protocol MT1990-07S

- **Cyclosporine A and Mycophenolate mofetil** as below

  Cyclosporine A
  Cyclosporine A (CSA) will start day -3 and will be administered PO/IV maintaining a trough level between 200 and 400 ng/mL. For adults the initial dose will be 2.5 mg/kg IV over 1 hour every 12 hours. For children < 40 kg the initial dose will be 2.5 mg/kg IV over 1 hour every 8 hours. CSA dosing will be monitored and altered as clinically appropriate per institutional pharmacy guidelines. Dose adjustments will be made on the basis of toxicity and/or low CSA levels.

  Patients will receive CSA until approximately day +100. If no GVHD, the dose will then be tapered 10% per week and discontinued approximately at 6 months.

  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 1st day of 3 consecutive days of absolute neutrophil count [ANC) > 0.5 x 10^9 /L]).

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).

4.3 Supportive Care

Dose and/or schedule modifications based on weight (i.e. for pediatric patients), clinical issues or current institutional practice are permitted at the discretion of the treating physician for any drug.

4.3.1 All patients will receive allopurinol (300 mg/d or 150 mg/M^2/d p.o.) beginning one day prior to chemotherapy administration and ending one day following the last chemotherapy or TBI administration unless hyperuricemia (>10 mg/dl) persists.

4.3.2 Vigorous intravenous hydration (2000□3000 ml/m^2/day) should be given from 12 hours prior to the first cyclophosphamide dose until 24 hours past the termination of cyclophosphamide therapy. Adequate diuretics should be given and patients urged to urinate every 1-2 hours to ensure urinary output of at least 200 ml/two hours to maintain appropriate fluid balance. Patients should be weighed BID during cyclophosphamide administration to aid in managing fluid balance.

4.3.3 Mesna should be given in total milligram dose equivalent to the cyclophosphamide dose qd (divided in 5 doses: pre, 3 hour, 6, 9 and 12 hours after) beginning at the time of cyclophosphamide administration and continuing until cyclophosphamide therapy is terminated.

4.3.4 All recipients receiving PBSC will receive G-CSF 5 mcg/kg/d administered I.V. over 15 min. starting on day +1 and continuing until ANC $\geq$ 2500/ml. x 2 days.

4.3.5 If WBC <100 at day +21, then add GM-CSF 250 mcg/m^2/day IV in addition to G-CSF. Follow support protocol for "Approach to graft failure."

4.3.6 Patients will be eligible for additional supportive care study protocols including, but not limited to, those related to prophylaxis and treatment of infection, mucositis and/or nutritional support.

4.3.7 All blood product support administered within one week preceding, and following initiation of chemotherapy will be irradiated to prevent inadvertent blood donor lymphoid engraftment.

4.3.8 Standard blood product support techniques will be used, including packed red cell transfusions to maintain hemoglobin $\geq$ 8.0 g/dl, platelet transfusion support to

maintain platelet counts > 10,000/Φl. Leukocyte transfusions will be indicated only under uncommon circumstances after discussion with the attending physician.

5.0 REQUIRED OBSERVATIONS: DONORS

5.1 Anti-HIV, Hepatitis B, surface antigen, anti-HCV, CMV, HSV, EBV serologies, pre-priming.

5.2 CBC, platelet count

5.2.1 CBC platelet count each day of aphereses, day 0 (or 1 or 2 as needed).

6.0 REQUIRED OBSERVATIONS: RECIPIENT

6.1 Anti-HIV, hepatitis B surface antigen, anti-HCV, CMV, HSV, or EBV serologics pretransplant.

6.2 Suitable markers of donor recipient chimerism pretransplant to include cytogenetics, RFLP.

6.3 Engraftment:

6.3.1 Time to first of 3 consecutive days with ANC > 500.

6.3.2 Time to platelet transfusion independence.

6.3.3 Time to RBC transfusion independence.

6.4 Incidence of late graft failure.

6.5 Incidence and severity of acute GVHD.

6.6 Incidence and severity of chronic GVHD.

6.7 Donor chimerism at +3 mos., +6 mos., +12 mos.

7.0 TOXICITIES AND COMPLICATIONS

7.1 Donor

7.1.1 G-CSF. Administration of G-CSF in normal donors can be associated with bone pain, headaches, body aches, fatigue, nausea, vomiting, insomnia, dyspnea and other symptoms. Such symptoms are usually minor, and may be controlled with administration of acetaminophen. However, symptoms can occasionally be dose-limiting or require cessation of G-CSF administration.

G-CSF administered in normal donors has rarely been associated with hypokalemia and hypoglycemia. G-CSF administration may also be associated with elevation of bilirubin, ALT and alkaline phosphatase. These are transient abnormalities.

7.1.2 Apheresis

If antecubital veins are not suitable for apheresis, large-bore, Quinton catheters in neck veins are required for the venous access necessary to perform apheresis and peripheral blood progenitor cell collections. The 4-6 hour collection procedures are occasionally associated with reversible hypotension. Thrombocytopenia may develop transiently following the apheresis especially if several aphereses are performed. G-CSF administration may suppress the marrow response to thrombocytopenia. Hypocalcemia secondary to the citrate anticoagulation may produce tingling or paresthesis. Calcium supplements will be given as needed.

7.2 Recipient

7.2.1 Cyclophosphamide or Busulfan

Hemorrhagic cystitis may occur following the use of cyclophosphamide despite aggressive fluid replacement, frequent voiding and Mesna.

Cyclophosphamide can cause fatal cardiac necrosis with clinical irreversible heart failure. EKG changes are not infrequent and reduction in EKG voltage may be observed. Patients previously treated with anthracyclines or with mediastinal irradiation may be at higher risk. Cyclophosphamide (with or without irradiation) may also induce pericarditis.

Nausea, vomiting and diarrhea are frequent following high doses of cyclophosphamide or busulfan. Aggressive anti-emetic therapy, including Ondansetron, may be helpful in minimizing this problem.

Alopecia is common. It is usually reversible, but changes in hair color or texture after regrowth may occur.

Skin rash may occur, but is infrequent. Busulfan may produce skin hyperpigmentation.

Sterility: Permanent sterility is likely at this dose of cyclophosphamide, particularly when given with other drugs and/or irradiation.

Busulfan may produce lung inflammation (pneumonitis), liver injury leading to veno-occlusive disease and rarely seizures.

7.2.2 Total body irradiation

1320 cGy is administered in 8 fractions over 4 days. Nausea, vomiting and diarrhea are common.

Generalized mild cutaneous erythema is frequently seen.

Parotitis may occur.

Lung: Inflammatory pneumonitis or even respiratory failure may develop in the first three months following TBI. Late respiratory failure has been seen in a small fraction of patients.

Liver: veno-occlusive disease may cause fluid retention, ascites, or renal failure.

Sterility: Sterility is common after this dose of total body irradiation.

Brain damage can develop in a small fraction of treated patients.

7.2.3 Myelosuppression

Both the chemotherapy + TBI, or the chemotherapy only conditioning induce significant myelosuppression requiring reinfusion of viable hematopoietic stem cells for prompt marrow recovery. During the period of myelosuppression and pancytopenia, the patient is highly vulnerable to infection and/or bleeding. Irradiated red cell transfusions will be given to maintain adequate oxygen delivery and platelet transfusions will be given in an attempt to prevent bleeding. Various isolation and prophylactic measures to reduce risks of infection and to vigorously treat any infections will also be required.

7.2.4 Graft Failure

Infusion of allogeneic peripheral blood or bone marrow may be associated with failure to engraft, partial engraftment of one, two, or three cell lineages or late graft failure. Risk of graft failure will be minimized by providing a targeted CD34+ cell dose of 5 x 10^6/kg recipient weight. Graft failure may be treated with growth factors, infusion of additional PBPC or of marrow or PBPC obtained from the original donor after recognition of graft failure.

7.2.5 Graft vs. Host Disease (GVHD)

Infusion of allogeneic PBPC may be associated with development of acute and/or chronic GVHD. An attempt to reduce incidence and severity of GVHD will be made by limiting infusion of peripheral cells to a target dose of 5 x 10^6 34+/kg recipient weight or 2.0 x 10^8 nc/kg of marrow cells and by using GVHD prophylaxis consisting of methotrexate (MTX) and cyclosporine (CSA) or alternative GVHD prophylaxis study approaches.

If Greater than 45kg: Cyclosporine 2.5mg/kg over 2 hours every 12 hours, begin on Day -3.
If Less than 45Kg: Cyclosporine 2.5mg/kg over 2 hours every 8 hours, begin on Day -3.

Cyclosporine Levels every Monday, Wednesday, and Friday beginning Day -1 to Day +7, then Cyclosporine Levels every Monday.

7.2.6 Second Malignancy

The potential carcinogenic effects of the pre-transplant chemotherapy and/or radiation may compound any inherent risks of second malignancy already induced by treatment the patient may have already received. Both late second epithelial malignancies and early treatment-associated neoplasms (particularly post-transplant lympho-proliferative disorders) may develop after transplantation.

8.0 STATISTICAL CONSIDERATIONS

8.1 Patient Accrual

Based on the BMT patient referral pattern of the University of Minnesota, we expect to accrue up to 50 cases to this study each year. The overall case accrual will be 350.

8.2 Statistical Analysis

The major end points of this study are engraftment failure, time to engraftment, incidence and severity of acute and chronic GVHD, persistence or relapse of malignancy and survival of the recipient. Data will be collected by nurse coordinators and the personnel of the Biostatistical Support Group of the University of Minnesota Blood and Marrow Transplant Program using prospective data plans already in place for all patients enrolled in institutional BMT protocols. These standard clinical end points will be evaluated using conventional survival analysis methods, including the Kaplan-Meier or cumulative incidence method and Cox proportional hazard models. Results will be compared to historical data of allogeneic bone marrow transplantation.

Complication rates of recipients (and donors, if any) will be monitored and descriptive statistics will be employed to assess their incidence. These will include pneumonitis, veno-occlusive disease of the liver, hemorrhagic cystitis and serious infection.

Note: Patients enrolled on additional investigational studies including, but not limited to Treg infusions, may have their outcomes analyzed separately

8.3 Study Data & Safety Monitoring

This institutional continuing case series will be monitored by the PI and the Study Committee assisted by the personnel and facilities of the Biostatistical Support Group of the University of Minnesota Blood and Marrow Transplant Program. Major and unexpected serious adverse events will be examined and reviewed periodically. All on study deaths will be reviewed by the PI and as indicated by the study committee and are reported to the IRB. Examination of accrual and survival outcomes will be performed as indicated by study events or as required by regulatory committees including the Cancer Center Protocol Review Committee and the IRB.

DATA AND SAFETY MONITORING PLAN

This study will be in compliance with the University of Minnesota Cancer Center's Data & Safety Monitoring Plan, which can be accessed at http://www.cancer.umn.edu/page/resource/dataplan.html

At the time of the IRB continuing review, the Principal Investigator will provide a copy of the report to the DSMC.

APPENDIX I

SCHEDULE FOR G-CSF (10 mcg/kg/day) ADMINISTRATION to DONOR

Number of G-CSF vials Given per Day

Donor Weight (kg)	1.0 mL (300 µg) Vials	1.1 mL (480 µg) Vials	Daily G-CSF Dose µg/kg/day	Daily G-CSF Dose Response (µg/kg/day)
40 to 48	0	1	480	10 to 12.0
49 to 60	2	0	600	10 to 12.2
61 to 78	1	1	780	10 to 12.8
79 to 90	3	0	900	10 to 11.4
91 to 96	0	2	960	10 to 10.5
97 to 108	2	1	1080	10 to 11.1
109 to 120	4	0	1200	10 to 11.0
121 to 126	1	2	1260	10 to 10.4
127 to 138	3	1	1380	10 to 10.9
139 to 144	0	3	1440	10 to 10.4
145 to 150	5	0	1500	10 to 10.3
151 to 168	4	1	1680	10 to 11.1
169 to 174	1	3	1740	10 to 10.3

APPENDIX TWO: TBI GUIDELINES

Fractionated Total Body Irradiation (In Lateral Position)

1320 cGy administered in an 8 fractions of 165 cGy each with 2 fractions being given each day.

Total body irradiation is given at a dose rate of 10-19 cGy/minute prescribed to the midplane of the patient at the level of the umbilicus.

The total body irradiation will be delivered with right and left lateral fields, with the patient supine on a specially designed couch.

Based on measurements of transverse thickness, aluminum compensators will be used to ensure that the dose homogeneity across the field 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).

Total body irradiation will be delivered with a linear accelerator using 6, 18, 24 MV X-rays. The energy used will be based on the calculated dose to the midline at points up and down the patient's torso. The lowest energy that gives 90-100% of the prescription 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.

Testicular boosts should be used for all males with ALL (and according to institutional practice for other diseases). The testicular boost is given in a single 400 cGy fraction with either electrons prescribed to Dmax or photons prescribed to the midplane of the scrotum. If electrons are used, the energy for the testicular boost depends on the thickness of the testicles and is chosen so that the D90 corresponds to the posterior surface of the scrotum.

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