UNIVERSITY OF MINNESOTA BONE MARROW TRANSPLANTATION PROGRAM

UNRELATED OR PARTIALLY MATCHED ALLOGENEIC DONOR STEM CELLS FOR LYMPHOMA, MYELOMA, AND CHRONIC LYMPHOCYTIC LEUKEMIA

MT1999-14

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Study Committee

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Protocol Changes and Amendments

May 9, 2008	Cord blood grafts may be single or double Updated protocol for IRB reapplication process (changed enrollment goals, added DSM plan)	8/6/08
January 8, 2004	Busulfan pharmacokinetics added (section 4.1.2)	
September, 2002	Protocol Amendment page added	
November 18, 1999	Radiation guidelines changed at the request of Dr. Katie Dusenbery, Therapeutic Radiation Department (section 4.1.2).	December 10, 1999 (final IRB approval for project)
October 11, 1999	At the request of the CPRC, a schema, drug information, data items, and adverse event procedures were added to this study (items needed before final approval could be granted).	December 10, 1999 (final IRB approval for project)

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1.0 OBJECTIVES

In order to reduce the risk of relapse and to improve long-term survival for chronic lymphoid malignancies this allogeneic donor stem cell study is designed to answer the following questions:

1.1 Can allogeneic transplantation using unrelated or partially matched allogeneic marrow or cord blood donors result in timely, complete and durable engraftment in recipients with advanced lymphoproliferative malignancies?

1.2 What is the incidence and grade of acute and of chronic GVHD observed following such allogeneic transplant?

1.3 Can the augmented graft versus tumor effect accompanying unrelated or partially matched donor allogeneic transplant reduce the incidence of relapse for these high risk malignancies?

2.0 BACKGROUND AND RATIONALE

For many years, histocompatible related donor marrow was used as source of stem cells for almost all allogeneic transplantations. However over the last 15 years, over 8000 patients have undergone unrelated donor allogeneic marrow transplants, and over the last several years, over 1000 have undergone unrelated donor umbilical cord stem cell transplants. Both these sources of stem cells have been able to effect complete myeloid and lymphoid reconstitution, restoring hematopoiesis and defense against infection. The immune systems developing from the unrelated donor marrow or cord blood cells have had variable problems associated with their transplantation including a somewhat higher risk of graft failure or slow engraftment and possibly more frequent Graft versus Host Disease, at least as compared with sibling donor bone marrow. Matched unrelated donor marrow transplants yield results for various diseases that are either similar to or slightly inferior (10 to 15 percent more frequent complications and mortality) compared to sibling donor BMT. However even with the extended resources of the National Marrow Donor Program (NMDP) not all patients have an available sibling or unrelated adult donor marrow available. Umbilical cord blood, perhaps because of its immunologic immaturity and greater ease of establishing immunologic tolerance with tissues of the recipient, might provide allogeneic cells available for transplantation for those patients lacking an unrelated or related adult donor for transplantation. Additionally, UCB might be associated with less risks of Graft versus Host Disease and thus lower peri-transplant related mortality.

As an additional option, partially matched (haploidentical) stem cells from a related donor would provide a source for allo-transplantation for nearly all other patients. Though clinical experience is less, haploidentical BMT yields similarly increased risks of graft failure, GVHD, and post-transplant immunodeficiency yet can be performed promptly, with a large cell dose for nearly all patients using either parents, most siblings or the patient's children as obligate at least halploidentical or better donor.

For treatment of advanced lymphoproliferative disease including non-Hodgkin's Lymphoma, Hodgkin's disease, Multiple Myeloma, and Chronic Lymphocytic Leukemia, both allogeneic and autologous transplantation have been used widely. For early stage patients such as those in PR1 or

CR2 PR2, some categories of Hodgkin's Disease and non-Hodgkin's Lymphoma can be effectively cured in sizable fractions of patients using auto transplantation. For patients with more advanced disease, for low grade lymphoma, for mantle cell lymphoma, myeloma, and CLL, autografting is not widely accepted as potentially curative therapy, though published experience suggests its potential value in achieving extended remission duration.

In contrast, allogeneic transplantation for these advanced lymphoproliferative diseases has resulted in extended relapse free or progression free survival for a substantial number of patients suggesting the curative potential of these allogeneic approaches. In this trial, we propose to evaluate unrelated or partially matched related donor stem cells either from adult unrelated donor marrow available through the NMDP or unrelated donor umbilical cord blood cells to facilitate allogeneic transplantation for patients who are poor candidates for autografting and have no available matched related donor. Evaluation of the success of prompt engraftment, acute and chronic graft versus host disease, overall peri-transplant mortality and extended disease free survival will be evaluated in contrast with other experience using matched related donor hematopoietic stem cells for transplantation.

2.1 Clinical Trial

We propose to perform closely matched unrelated donor transplants using either adult donor marrow or cryopreserved umbilical cord blood stem cells or in some patients, partially matched related donor transplants. Eligible patients will include individuals who have advanced Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, or chronic lymphocytic leukemia. Patients will receive standard acute GVHD prophylaxis with a combination of methotrexate and cyclosporine, or, if eligible, alternative GVHD prophalaxis.

We will assess engraftment, time to engraftment, incidence and severity of acute GVHD, incidence and severity of chronic GVHD, development of unusual GVHD syndromes; post-transplant infections, lymphoproliferative disease and immune reconstitution; survival and persistence or relapse of malignant disease.

3.0 ELIGIBILITY AND EXCLUSION CRITERIA

3.1 Donors will be <55 years of age and in good health as approved by the NMDP donor and collection centers. Related donors will be < 70 years of age.

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

3.2.1 Creatinine $\leq$2.0 mg/dl.
3.2.2 Bilirubin, AST, ALK $\leq$2 x normal.
3.2.3 Pulmonary function test and DLCO > 50% of normal.
3.2.4 MUGA $\geq$45% injection fraction.

3.3 Recipients with unrelated donor matched at the HLA A, B, DRBI loci, or if < 35 years mismatched at a single HLA A or B, or DRBI locus.

3.4 Umbilical cord blood (5) used as an unrelated stem cell source will provide > 2.0 x 10^7 cells/kg and will be matched at 4 - 6 of 6 HLA A, B, and DRBI loci. Cord blood grafts may include a single or pair of cord units depending on the cell dose.

3.5 Partially matched related donors will be at least haploidentical (matched at ≥3 of 6 HLA A, B, DRB1 loci).

3.6 Recipients will fall under one of the following disease categories

3.6.1 Chronic lymphocytic leukemia -- must have all three:

1. Rai Stage III/IV
2. Progression after previous CR or PR including purine antagonist (i.e. fludarabine).
3. Recent chemotherapy responsiveness

3.6.2 Advanced non-Hodgkin's (NHL).

3.6.2.1 Low-grade NHL (Working Formulation A, B, C) following progression after initial therapy if asymptomatic at diagnosis (≥CR2, ≥ PR2; response duration < 1 year from last therapy) or if no CR was achieved (>PR1). At least one prior therapy of intermediate intensity (e.g. CHOP).

3.6.2.2 Mantle zone lymphoma after any progression following initial therapy (>CR1, > PR1). At least one prior therapy of intermediate intensity (e.g. CHOP).

3.6.2.3 Intermediate grade lymphoma (> PR2). Response duration < 1 year from prior therapy.

3.6.2.4 High-grade NHL (IWF H, I, J) after initial therapy if ≥stage III at diagnosis; after any progression even if localized (stage I, II) at diagnosis with prior response duration < 1 year.

3.6.2.5 Recent chemotherapy responsiveness after treatment with ≥ 3 intermediate intensity regimens.

3.6.3 Advanced Hodgkin's disease beyond PR2 (≥CR3, ≥PR3).

3.6.3.1 Recent chemotherapy responsiveness

3.6.4 Multiple Myeloma (> CR2, > PR2) or after initial therapy if no prior PR.

3.6.4.1 Recent chemotherapy responsiveness

3.7 Recipients will sign informed consent approved by the Committee on the Use of Human Subjects at the University of Minnesota.

3.8 Exclusions: No available histocompatible related donor; 2nd BMT, HIV-1 positive; active uncontrolled infection; or resistant malignancy.

4.0 TREATMENT SCHEMA

4.1 Transplant procedure

4.1.1 Preparative therapy.

Day	Therapy
-7	cyclophosphamide 60 mg/kg/day
-6	cyclophosphamide 60 mg/kg/day
-5	Rest
-4	TBI, 165 cGy a.m. and p.m.
-3	TBI, 165 cGy a.m. and p.m.
-2	TBI, 165 cGy a.m. and p.m.
-1	TBI, 165 cGy a.m. and p.m.
0	Infusion of stem cells.

Total cyclophosphamide 120/kg
Total TBI 1320 cGy.

4.1.2 Alternative therapy for patients not eligible to receive TBI.

Day	Therapy
-9	busulfan 4 mg/kg/day po (1 mg/kg po every 6 hrs.) (may be administered intravenously see below)*
-8	busulfan 4 mg/kg/day po (1 mg/kg po every 6 hrs.)
-7	busulfan 4 mg/kg/day po (1 mg/kg po every 6 hrs.)
-6	busulfan 4 mg/kg/day po (1 mg/kg po every 6 hrs.)
-5	cytoxan 50 mg/kg IV

-4	cytoxan 50 mg/kg IV
-3	cytoxan 50 mg/kg IV
-2	cytoxan 50 mg/kg IV
-1	Rest
0	Infusion of stem cells.

Total cyclophosphamide 200 mg/kg.
Total busulfan 16 mg/kg if oral or IV equivalent
* Busulfan (intravenous BUSULFEX) **dose**, **administration** and **phamacokinetic monitoring** to be administered as described in MT2003-19S.

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

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

4.1.5 TBI will be administered in the mid-plane dose of 1,320 cGy in eight fractions of 165 cGy over four days at 10 to 19 cGy/minute prescribed to the midplane at the umbilicus. The two daily fractions are given at least 6 hours apart. Radiation will be administered through bilateral ports. A "beam spoiler" will be used to increase the skin dose. Individually designed compensations are used to keep the dose homogeneity along the axis of the patient to within □ 10% of the prescribed dose.

4.2 Supportive Care

4.2.1 All patients will receive allopurinol (300 mg/d or 150 mg/M^2/d p.o.) beginning one day prior to conditioning and on day zero unless hyperuricemia (>10 mg/dl) persists.

4.2.2 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 b.i.d. during cyclophosphamide administration to aid in managing fluid balance.

4.2.3 Mesna should be given in total milligram dose equivalent to the cyclophosphamide dose q.d. (divided in 5 doses: pre, 1 hour, 3, 6 and 12 hours after) beginning at the time of cyclophosphamide administration and continuing until cyclophosphamide therapy is terminated.

4.2.4 Vigorous hydration should also be administered (approximately 1500 ml/m^2/d) during busulfan or irradiation therapy.

4.2.5 Patients receiving busulfan should also receive phenytoin (po or if needed IV) as anti-convulsant therapy for 11 days, beginning day -10.

4.2.6 Patients will be eligible for additional transplant studies related to unrelated marrow, cord blood, or other allogeneic transplantation.

4.2.7 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.

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

4.2.9 Standard blood product support techniques will be used, including packed red cell transfusions to maintain hemoglobin > 8.0 g/dl, platelet transfusion support to maintain platelet counts > 10,000/:l. Leukocyte transfusions will be indicated only under extraordinary circumstances after discussion with the attending physician.

5.0 REQUIRED OBSERVATIONS

5.1 Pre-transplant: Anti-HIV, hepatitis B surface antigen, anti-HCV, CMV HSV serologies.

5.2 Suitable markers of donor recipient chimerism pretransplant to include cytogenetics, HLA typing, RFLP, *in situ* Y chromosome hybridization as needed.

5.3 Engraftment:

5.3.1 Time to first of 3 consecutive days with ANC > 500/:l.

5.3.2 Time to platelet transfusion independence (platelets > 20,000 with no transfusions for the following 7 days).

5.3.3 Time to RBC transfusion independence (Hb > 9.0 with no transfusions for the following 15 days).

5.4 Incidence of initial and late graft failure.

5.5 Incidence and severity of acute GVHD (grade II/IV; grade III/IV).

5.6 Incidence and severity of chronic GVHD.

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

6.0 TOXICITIES AND COMPLICATIONS

6.1 Cyclophosphamide: **is manufactured and commercially available in the United States.**

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. 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.

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

6.2 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.

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

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

6.3 Busulfan **Oral and IV Busulfan are manufactured and commercially available.**

6.3.1 Action: a bifunctional alkylating agent

6.3.2 Supplied as: 2 mg tablets for oral use only or as IV formulation (busulfex)

6.3.3 Toxicity: myelosuppression, mucositis, diarrhea, alopecia, pulmonary fibrosis, amenorrhea, azoospermia, hepatitis, veno-occlusive disease, seizures

6.4 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.

6.5 Graft Failure

Infusion of allogeneic stem cells may be associated with failure to engraft, partial engraftment of one, two, or three cell lineages or late graft failure. Graft failure may be treated with growth factors, infusion of additional marrow or available stem cells obtained from the original donor after recognition of graft failure.

6.6 Graft vs. Host Disease (GVHD)

Infusion of allogeneic cells may be associated with development of acute and/or chronic GVHD. An attempt to reduce incidence and severity of GVHD will be made by using GVHD prophylaxis consisting of methotrexate (MTX) and cyclosporine (CSA), **which are both commercially available** or other GVHD prophylaxis. Cord blood recipients will receive MMF (mycophenylate mofetil) from day -3 to +30 instead of methotrexate, or other GVHD prophylaxis depending on current institutional standards. **Patients may be enrolled on other study protocols directed toward the prevention of GVHD.** Acute and chronic GVHD will be treated according to established protocols.

6.7 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 myelodysplastic syndrome and/or leukemia) may develop after transplantation.

6.8 Reporting of Adverse Reactions: It is the responsibility of the investigator to report all adverse reactions, or suspected adverse reactions. The principal investigator with the assistance all co-investigators, are responsible for assessing all adverse events, then classifying the toxicity according to the protocol designed toxicity scale.

7.0 EXPERIMENTAL DESIGN AND STATISTICAL CONSIDERATIONS

7.1 Patient Accrual

Based on the BMT patient referral pattern of the University of Minnesota, we expect to accrue 3 cases to this study each year. The overall case accrual will be 15. Other transplant approaches and higher priority clinical trials limit accrual for this transplant study but selected patient populations may have no more promising treatment option.

7.2 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. These end points will be evaluated using standard survival analysis methods, including the product limit method and Cox proportional hazard model. Results will be compared to historical data of bone marrow transplantation from histocompatible related donor allogeneic bone marrow or blood stem cells.

8.0 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

Regular meetings of the study's principal investigator and staff will be held to discuss matters related to the safety of protocol participants (SAE reporting), validity and integrity of the data, enrollment rate, retention of participants, adherence to protocol, and data completeness

The Principal Investigator will provide at least monthly monitoring of patient safety with quarterly reporting to the Clinical Trials Office (CTO) for distribution to the Cancer Protocol Review Committee's (CPRC) Data & Safety Monitoring Council (DSMC).

At the time of the IRB continuing review, the Principal Investigator will report to the CPRC the number of patients entered on the trial, the number of patients, treated, a summary of all adverse events reported to date using CTC grading, a specific list of serious adverse events requiring immediate reporting, and significant literature reporting developments that may affect the safety of participants or the ethics of the study.