BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning (NST) and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies

BMT CTN PROTOCOL 0603
VERSION 3.0

Study Chairpersons

Ephraim Fuchs, M.D.[1] -
Paul O'Donnell, M.D., Ph.D.[2] -

Protocol Team

Claudio Anasetti, M.D.[3]
Karen Ballen, M.D.[4]
Juliet Barker, M.D.[5]
Claudio Brunstein, M.D., Ph.D. [6]
Shelly Carter, Sc.D.[7]
Jennierose D'Elia[7]
Mary Eapen, M.D.[8]
Mary Horowitz, M.D., M.S.[8]
Mary Laughlin, M.D.[9]
Charles Linker, M.D.[10]

Sponsored by the National Institutes of Health

National Heart, Lung and Blood Institute -
National Cancer Institute -

[1] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
[2] Fred Hutchinson Cancer Research Center
[3] H. Lee Moffitt Cancer & Research Institute
[4] Massachusetts General Hospital
[5] Memorial Sloan-Kettering Cancer Center
[6] University of Minnesota
[7] The EMMES Corporation
[8] Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin
[9] Case Western Reserve University
[10] University of California, San Francisco

Core Study Participants:

City of Hope
Dana Farber Cancer Institute
Fred Hutchinson Cancer Research Center
Johns Hopkins University
Memorial Sloan-Kettering Cancer Center
Oregon Health & Science University
University of California, San Diego/SCRIPPS
University of Florida College of Medicine
University of Nebraska Medical Center
Washington University, Barnes Jewish Hospital

Affiliate Study Participants:

Baylor University Medical Center
BMT Group of Georgia/Northside Hospital
Intermountain BMT
Kapi'olani Medical Center for Women and Children
Medical University of South Carolina
Temple University, Fox Chase
University of Kansas Medical Center
University of Maryland
University of Texas, Southwestern
Vanderbilt University

PROTOCOL SYNOPSIS – BMT CTN 0603

A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies

Principal Investigators: Ephraim Fuchs, M.D., Paul O'Donnell, M.D., Ph.D.

Study Design: This study is a Phase II, multi-center study of nonmyeloablative conditioning and transplantation of bone marrow from partially HLA-mismatched, related donors.

Primary Objective: The primary objective is to determine overall survival 180 days after HLA-haploidentical bone marrow transplantation using a nonmyeloablative preparative regimen and post-transplantation cyclophosphamide.

Secondary Objectives: Patients enrolled in this study will also be followed for the following endpoints: neutrophil and platelet recovery, graft failure, acute graft-versus-host disease (GVHD), chronic GVHD, incidence of infection, treatment-related mortality, time to relapse/progression, overall survival, and current progression-free survival.

Study Design: This study is a Phase II, multi-center study of non-myeloablative conditioning, transplantation of partially HLA-mismatched bone marrow and post-transplantation cyclophosphamide in patients with:

1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, and Burkitt's lymphoma in remission.
2) Relapsed lymphoma, including marginal zone B cell lymphoma, follicular lymphoma, and chemotherapy-sensitive large-cell or Mantle Cell Hodgkin lymphoma.

Accrual Objective: The target sample size is 50 patients

Accrual Period: The estimated accrual period is three years.

Eligibility Criteria: Patients 21-70 years of age, or 1-21 years old and ineligible for BMT CTN #0501 with the diagnosis of a hematologic malignancy and with a partially (< 5/6) HLA-mismatched donor.

Adequate organ function defined as: 1) left ventricular ejection fraction > 35%; 2) DLCO, FEV_1, FVC > 50% predicted; 3) total bilirubin ≤ 2.5 mg/dl, and ALT, AST, and alkaline phosphatase all

< 5 x upper limit of normal (ULN); 4) serum creatinine within normal range for age, or if serum creatinine outside normal range for age, then renal function (creatinine clearance or GFR by Cockroft-Gault formula) > 40 mL/min/1.73m^2; 5) Karnofsky/ Lansky performance score 60 to 100; and 6) if applicable, > 3 months since a previous autologous transplant.

Treatment Description: The preparative regimen will consist of:
- Fludarabine 30 mg/m^2 IV Days –6, –5, –4, –3, –2
- Cyclophosphamide (Cy) 14.5 mg/kg IV Days –6, –5
- Total body irradiation (TBI) 200cGy Day –1
- Day 0 will be the day of infusion of non-T-cell depleted bone marrow.

The GVHD prophylaxis regimen will consist of:
- Cy 50 mg/kg IV Days 3, 4
- Tacrolimus (IV or po) beginning Day 5 with dose adjusted to maintain a level of 5-15 ng/mL
- Mycophenolate mofetil (MMF) 15 mg/kg po TID beginning Day 5, maximum dose 1 g po TID
- G-CF 5 mcg/kg/day beginning Day 5 until ANC ≥ 1,000/mm^3 for 3 consecutive days

Study Duration: - Patients will be followed for one year after transplantation.

TREATMENT SCHEMA*

Days –6, –5: Fludarabine 30 mg/M^2 IV daily
Cyclophosphamide (Cy) 14.5 mg/kg IV daily
Mesna 11.6 mg/kg IV daily**
Begin antibiotic prophylaxis

↓

Days –4 → –2: Fludarabine 30 mg/M^2 IV daily

↓

Day –1: TBI 200 cGy

↓

Day 0: Infuse non-T cell-depleted marrow

↓

Days 3, 4: Cy 50 mg/kg (IBW) IV daily
Mesna 40 mg/kg IV daily**
(First dose of Cy must be administered 60-72 hour after infusion of marrow)

↓

Day 5: Begin tacrolimus 1mg IV qd** or 1 mg po bid** and
MMF 15 mg/kg PO TID with maximum daily dose 3 gm/day -
Begin G-CSF 5 mcg/kg/day SC or IV, continue until ANC ≥ 1000/mm^3 x 3 days -

↓

Day ~28: Assess chimerism in peripheral blood

↓

Day 35: Discontinue MMF (optional if GVHD is active)

↓

Day ~56: Assess chimerism in peripheral blood

↓

Day 180: Discontinue tacrolimus (optional if GVHD is active)
Assess chimerism in peripheral blood
Evaluate disease

↓

1 yr,: Evaluate disease
Assess chimerism in peripheral blood

* Refer to Section 2.5 for complete instructions on medication administration.
** Or as per institutional standards.

TABLE OF CONTENTS

LIST OF APPENDICES

CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Allogeneic blood or marrow transplantation (alloBMT) is a potentially curative therapy for a variety of hematologic malignancies, including the acute and chronic leukemias, myelodysplasia, lymphoma, and multiple myeloma[1]. Clinical data now confirm that T cells contained within the donor graft are capable of exerting a "graft-versus-malignancy" effect[2, 3]. However, successful application of alloBMT to patients with hematologic malignancies is limited by the toxicity of myeloablative conditioning, graft-versus-host disease (GVHD), opportunistic infection, and by the lack of histocompatible siblings in the majority of patients. Substantial progress has been made recently in the development of reduced intensity conditioning regimens that facilitate the sustained engraftment of donor stem cells with less toxicity[4]. However, the problem of donor availability remains. For the 70% or so of patients who lack an HLA-identical sibling, an acceptable alternative is the transplantation of stem cells from an HLA-identical unrelated donor. Still, only half of patients who might benefit from a transplant are able to find an HLA-identical sibling or unrelated donor. This proportion is lower among patients belonging to racial or ethnic minorities, since unrelated donor registries contain relatively fewer individuals belonging to these minorities[5]. Development of an alternative to HLA-identical sibling or unrelated donor transplantation could therefore expand the availability of this procedure to patients who need it, especially those belonging to minority groups.

One potentially attractive alternative source of stem cells is a partially HLA-mismatched or HLA-haploidentical relative. There are at least two advantages of HLA-haploidentical relatives as compared to unrelated donors. First, since all biological parents and children and half of siblings share one HLA haplotype, there is a high likelihood of identifying an eligible donor. Second, donors can be identified promptly, whereas the time from initiation of search to unrelated donor identification takes a median of 49 days[6]. The major drawbacks of HLA-haploidentical stem cell transplantation, especially after myeloablative conditioning, have been high rates of graft rejection and severe graft-versus-host disease (GVHD)[7, 8]. We have been investigating the effect of administering high dose, post-transplantation cyclophosphamide (Cy) on the incidence and severity of these complications, first in animal models[9, 10] and then in humans[11]. The immunobiologic rationale for administering Cy after transplantation is that recently activated, alloreactive T cells (the cells most responsible for GVHD) are selectively sensitive to the toxic effects of this drug[12]. Pre-clinical studies demonstrated that engraftment of major histocompatibility complex (MHC)-mismatched bone marrow could be achieved by conditioning mice with the combination of pre-transplantation fludarabine and low dose (200 cGy) total body irradiation, and post-transplantation Cy[9]. Additional studies demonstrated that post-transplantation Cy reduced the incidence and severity of GVHD in the setting of MHC-mismatched alloBMT after myeloablative conditioning (unpublished data).

Based upon the encouraging results in the pre-clinical model, two independent clinical trials, one at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (n=60) and the other at

the Fred Hutchinson Cancer Research Center (n=28), evaluated the safety and efficacy of high-dose, post-transplantation cyclophosphamide (Cy) to prevent graft rejection and GVHD after outpatient nonmyeloablative conditioning and T cell-replete bone marrow transplantation from partially HLA-mismatched related donors. Eighty-eight consecutive patients were accrued to these trials between 1999 and 2006. Eligible patients were 0.5-70 yr of age with high-risk hematologic malignancies or paroxysmal nocturnal hemoglobinuria (PNH; n=1) for whom standard allogeneic (HLA-matched, related or unrelated) or autologous BMT was unavailable or inappropriate. Eligible hematologic malignancies included interferon- or imatinib-refractory chronic myeloid leukemia (CML) in first chronic phase or any CML in second chronic phase (n=9), poor-risk acute leukemia in first complete remission (CR) or any acute leukemia in CR$\geq$2 (n=40), advanced myelodysplastic syndrome (MDS; n=6), poor-risk chronic lymphocytic leukemia (n=3), and lymphoma or multiple myeloma in resistant relapse (not responsive to conventional salvage therapy prior to transplantation) or in relapse after autologous transplantation (n=29). Twenty-three patients (26%) had failed at least one autologous stem cell transplantation (SCT), including 12 of 13 patients with Hodgkin lymphoma (HL), 5 of 11 patients with non-Hodgkin lymphoma (NHL), 3 of 34 patients with acute myeloid leukemia (AML), and one patient each with CML, chronic lymphocytic leukemia (CLL), and multiple myeloma. Two additional patients had received autologous BMT for a malignancy prior to a diagnosis of therapy-related MDS. Twenty-five percent of patients were from ethnic minority groups.

Patients on the two protocols were treated in three separate groups designated Hopkins A, Hopkins B and Seattle, which differed by postgrafting immunosuppression (Figure 1.1). The intent was to treat all patients as outpatients. Transplantation conditioning consisted of Cy 14.5 mg/kg/day IV on Days –6 and –5, fludarabine 30 mg/m^2/day IV on Days –6 to –2, and 200 cGy of TBI on Day –1. On Day 0, patients received donor marrow, which was obtained in a targeted collection of 4 x 10^8 nucleated cells/kg recipient weight and depleted of red blood cells by processing on a Gambro Spectra apheresis instrument. On Day 3, 50 mg/kg Cy was administered over 90 min together with Mesna (80% dose of Cy in 4 divided doses over 8 hr) by IV infusion (Hopkins A and Seattle groups). The Hopkins B group received an additional dose of Cy on Day 4. Pharmacologic prophylaxis of GVHD was initiated on the day following completion of post-transplantation Cy. All patients received tacrolimus, which was initiated at a dose of 1 mg IV daily, adjusted to achieve a therapeutic level of 5-15 ng/ml, and then converted to oral form until discontinuation. If there was no active GVHD, tacrolimus was tapered after Day 90 (Seattle) or discontinued on Day 50 or 180 (Hopkins A and B, respectively). All patients received mycophenolate mofetil until Day 35 at a dose of 15 mg/kg PO twice daily (Hopkins group A) or thrice daily (Hopkins B and Seattle groups), with a maximum daily dose of 3 g in the Hopkins B group. Patients received filgrastim, 5 μg/kg/day by subcutaneous injection starting on Day 1 (Hopkins) or Day 4 (Seattle) and continuing until recovery of neutrophils to >1000/μL for three days.

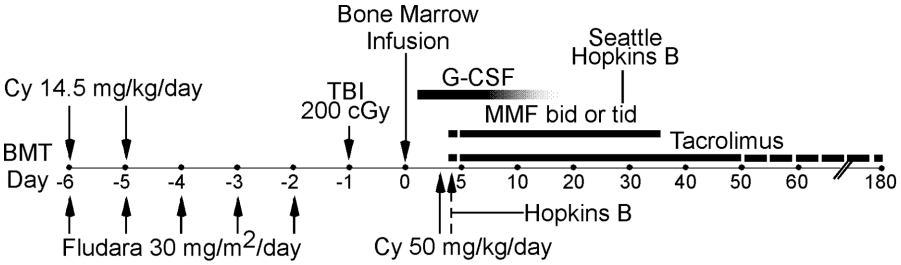

Figure 1.1 Treatment Schema

Engraftment and chimerism. Forty-four 44 of 88 donors were siblings, 22 were parents and 22 were children of the patients. By high resolution typing, donors differed from their recipients by a median of 3 of 8 (HLA-A, -B, -Cw, and DRB1) HLA alleles in both the host-versus-graft (HVG) and graft-versus-host (GVH) directions. About one-third of donor-recipient pairs were mismatched for all four of these HLA antigens. The three groups did not differ with respect to the age of the donors, the relationship of donors to the patients, or the total number of HLA allele mismatches in either the HVG or GVH directions.

Median times to recovery of neutrophils and platelets were 15 and 24 days, respectively. The median times to neutrophil recovery (Fig. 1.2A) were 15, 12, and 16 days and the median times to platelet recovery (Fig. 1.2B) were 30, 18, and 26 days for the Hopkins A, Seattle, and Hopkins B groups, respectively. Compared to patients in the Hopkins A group, patients in the Seattle group had significantly faster recoveries of neutrophils (HR 2.74, 95% CI 1.38-5.44, p=.004) and platelets (HR 2.59, 95% CI 1.26-5.34, p=.01). Factors in multivariate analysis that were associated with significantly delayed recoveries of neutrophils and platelets were lower graft $CD34^+$ cell content and administration of a second dose of post-transplantation Cy. Increasing mismatch in the HVG direction was associated with delayed platelet but not neutrophil recovery.

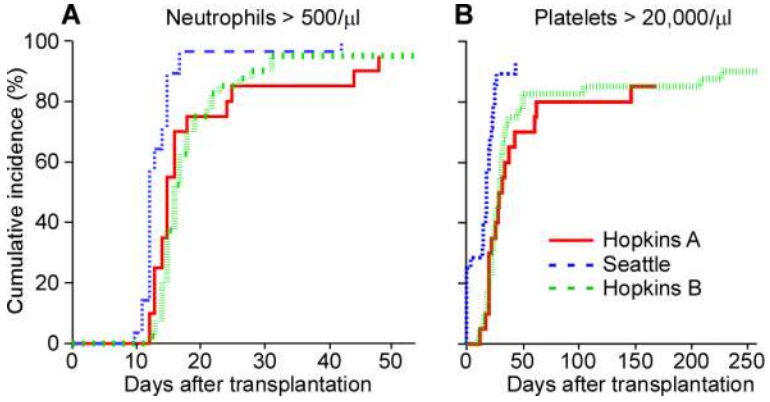

Figure 1.2 Neutrophil and Platelet Recoveries

Graft failure occurred in 15 of 84 evaluable patients (18%): 6 of 19 (32%) in the Hopkins A group, 3 of 26 (12%) in the Seattle group, and 6 of 39 (15%) in the Hopkins B group. Primary and secondary graft failure occurred in 13 and 2 patients, respectively, and all but two patients with graft failure had recovery of autologous hematopoiesis with median times to neutrophil and

platelet recovery of 24 days (range 11-48 days) and 44 days (range 15-395 days), respectively. Adjusting for group, transplantation of female donor marrow into a male recipient increased the probability of graft failure (OR=6.08, 95% CI 1.6-22.8, p=0.01) while increasing numbers of prior regimens decreased the risk of failure (OR=0.61, 95% CI 0.38-0.96, p=0.03).

Measurable disease was present in 11 of 15 patients with graft failure; of these, five achieved objective clinical responses, including 3 of 5 patients with MDS (1 CR x 1193 days, 2 PR) and 2 transient molecular CRs in 3 patients with CML. These data are consistent with pre-clinical and clinical data suggesting that graft rejection is associated with an immunologic anti-tumor effect.

Engrafting patients achieved full donor chimerism rapidly (Fig. 1.3). Analysis of peripheral blood that was either (i) unfractionated (Hopkins groups) or (ii) separated into T-cell (CD3-positive) or granulocyte (CD33-positive) fractions (Seattle group) showed that with few exceptions, donor chimerism in patients with sustained engraftment was virtually complete (>95%) by 2 months after transplantation.

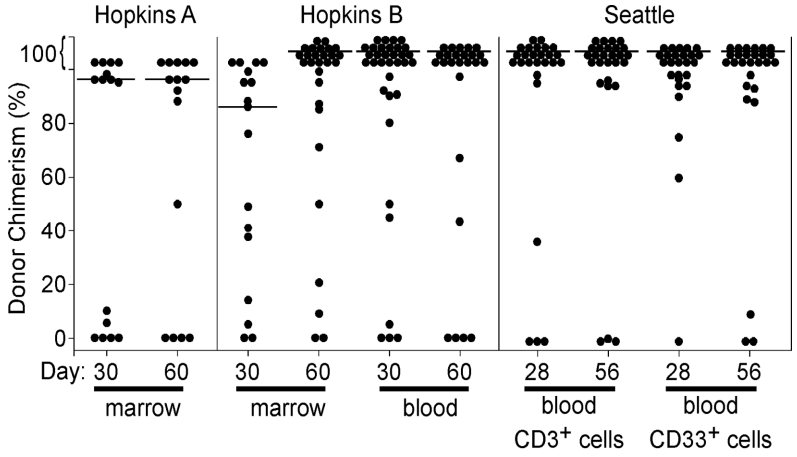

Figure 1.3 Donor Chimerism after Transplantation

Hospitalizations and infections. All patients received their initial treatment in the outpatient department and were discharged to their referring oncologist between 60 and 90 days after transplantation, unless complications requiring admission to the hospital supervened. The median number of hospitalizations prior to Day 60 was 1 (range 0-4) for each patient group, and the median length of stay was 4 days (range 0-44). Neutropenic fever accounted for 56% of the admissions; non-neutropenic fever accounted for 33%; other causes, including acute GVHD, accounted for the remaining 11%. Thirty-six patients (41%) did not require hospitalization within the first 60 days of transplantation.

Patients who are seropositive for cytomegalovirus (CMV) are known to be at high-risk for reactivating CMV after transplantation, regardless of the serologic status of the donor[13]. In this study, CMV reactivation was observed in 20 of 60 (33%) high-risk patients. The incidence of reactivation but not the median time to onset differed across the groups. Acute GVHD was diagnosed in 10 of 20 (50%) patients on or about the time of CMV reactivation. CMV

pneumonia developed in only one patient and there was no CMV-associated mortality. Proven or probable invasive mold infections, all caused by *Aspergillus sp*, were observed in 6 of 88 (6.8%) patients of whom two had infection prior to transplant. Two patients died from *Aspergillus* infection, one while persistently neutropenic following graft failure.

Graft-versus-host disease. The cumulative incidences of grades II-IV and III-IV acute GVHD by Day 200 were 35% and 10%, respectively (Fig. 1.4A). The groups did not differ significantly in the incidence of grades II-IV or III-IV acute GVHD. The combined incidence of graft failure and severe acute GVHD in the Hopkins A group was 55% by 1 year, which prompted the addition of the second dose of post-transplantation Cy on Day 4 and the change to thrice daily MMF in the Hopkins B group.

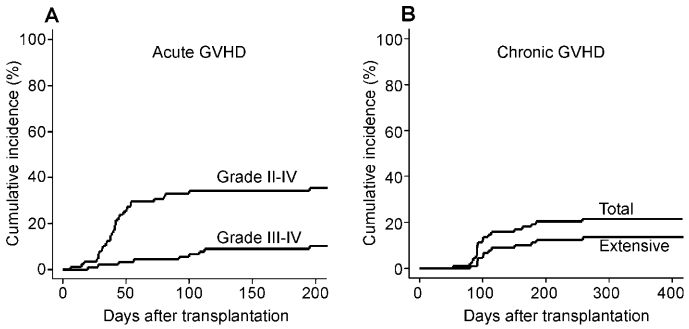

Figure 1.4 Graft-versus-host Disease

The cumulative incidences of overall and extensive chronic GVHD in the first year after transplantation were 22% and 14%, respectively (Fig. 1.4B). At one year after transplantation, the cumulative incidences of chronic GVHD were 15%, 46%, and 8% in the Hopkins A, Seattle, and Hopkins B groups, respectively; corresponding incidences of extensive chronic GVHD were 15%, 25%, and 5%. The incidence of chronic GVHD in the Seattle group was significantly higher than in both the Hopkins B (HR 7.95; 95% CI 2.29-27.6; p = .001) and Hopkins A groups (HR 3.86; 95% CI 1.14-13.08; p=.03). The incidence of extensive chronic GVHD was significantly higher in the Seattle group than in the Hopkins B group (HR 5.66; 95% CI 1.21-26.43, p = .03) but not significantly higher than in the Hopkins A group (HR 1.77; 95% CI 0.47-6.74; p = .4).

Non-relapse mortality (NRM), relapse, and overall and event-free survival (EFS). The cumulative incidences of NRM at 180 days and 1 year after transplantation were 13% and 19%, respectively. The cumulative incidences of relapse at 1 and 2 years after transplantation were 50% and 57%, respectively (Figure 1.5A and data not shown). There were no significant differences in the cumulative incidences of either NRM or relapse among groups. In a stratified multivariate analysis, patients with lymphoid malignancies had a significantly lower risk of relapse than patients with myeloid malignancies (HR 0.46, 95% CI .25-.88, p =.02). In the same analysis, increasing age, graft $CD3^+$ cell dose, and number of prior regimens were not associated with a significantly increased incidence of relapse.

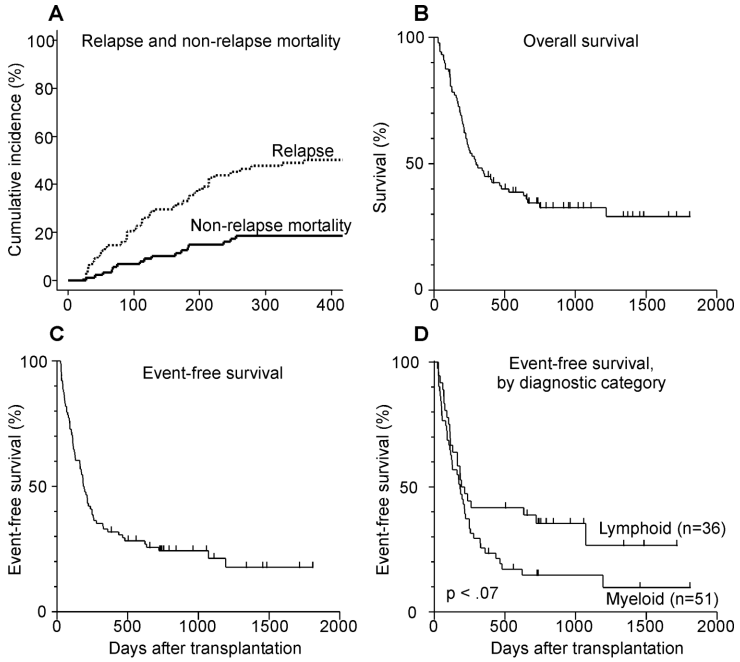

Figure 1.5 Non-relapse Mortality, Relapse, Overall and Event-free Survival

At a median follow-up of survivors of 817 days (range, 112-1808 days), the actuarial overall survivals of the entire group at 1 and 2 years were 45% and 35%, respectively (Figure 1.5B). The actuarial EFS at 1 and 2 years were 32% and 24%, respectively (Figure 1.5C). Survival and EFS did not differ significantly among groups. However, compared to patients with myeloid malignancies, patients with lymphoid malignancies showed a trend toward a higher EFS at 1 year (42% versus 24%) and at 2 years after transplantation (36% versus 15%; $p < .07$; Figure 1.5D). Fifty-eight patients have died; among these patients, post-transplantation relapse or progression of the underlying disease was diagnosed in 41. GVHD accounted for five of the 16 deaths in the Hopkins A group but for only two out of 42 deaths in the other two treatment groups. Only four patients died of infection without GVHD.

Multivariate analysis of risk factors for EFS was performed. Compared to patients with AML, patients with NHL and HL had higher EFS. Interestingly, an increasing number of HLA-antigen mismatches in the HVG direction was associated with improved EFS, whereas an increasing graft dose of $CD3^+$ cells was associated with worse EFS. Also, a donor-recipient mismatch of two or more HLA antigens in the GVH direction was associated with a lower risk of relapse and improved overall and event-free survival compared to lesser degrees of HLA mismatch in the same direction (data not shown).

In summary, HLA-haploidentical BMT after non-myeloablative conditioning and using 2 doses of post-transplantation Cy followed by TID MMF is a well-tolerated procedure that can be administered largely in an outpatient setting. The toxicity of the procedure compares favorably to the toxicity of non-myeloablative transplantation using unrelated or even HLA-identical sibling donors. The major cause of treatment failure in this high-risk population is relapse, occurring in approximately 60% of patients. Sustained disease responses were seen primarily in patients with AML and lymphoma.

To place these results in context, the table below compares major outcomes of patients in the 3 cohorts described above to those in a report containing the largest number of patients receiving unrelated donor grafts after non-myeloablative conditioning (n= 89)[14]. The table demonstrates that the two procedures appear roughly equivalent in terms of time to neutrophil engraftment and the incidences of sustained donor chimerism, acute GVHD, and NRM. The recipients of unrelated grafts fared somewhat better in terms of overall and disease-free survival at 1 year, but it is not possible in this retrospective comparison to know whether these differences are attributable to the relative efficacies of the treatment or to differences in the patient populations.

	HLA-haploidentical (n=88)	**Unrelated (n=89)***
Median age (years)	48	53
Time to ANC > 500/mL (days)	16	15
Time to platelets > 20K/mL (days)	24	4
Sustained donor engraftment (total)	85%	79%
Among recipient of PBSCs	-	85%
Among recipients of marrow	85%	55%
aGVHD II-IV	35%	52%
aGVHD III-IV	10%	10%
1 year non-relapse mortality (NRM)	19%	17%
1 year survival	45%	52%
1 year disease-free survival (DFS)	32%	38%

*Maris MB et al, Blood 102: 2021-2030, 2003

Based upon the encouraging safety and efficacy data from the Hopkins and Seattle trials, we wish to test the safety and anti-tumor efficacy of HLA-haploidentical BMT after nonmyeloablative conditioning with post-transplant Cy in a national, multicenter phase II trial.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is a multi-center, Phase II study to assess the safety and efficacy of haploidentical bone marrow transplantation using a nonmyeloablative preparative regimen and post-transplant cyclophosphamide. The purpose is to determine whether results in a single center setting can be duplicated in a multi-center setting. If the results of this therapy are acceptable, a randomized trial comparing it to unrelated donor transplantation would be planned.

2.1.1. Hypotheses and Specific Objectives

2.1.1.1. Hypotheses

Primary Hypothesis: 180 day survival after non-myeloablative haploidentical bone marrow transplantation is higher than 60%, similar to what is observed after non-myeloablative unrelated donor bone marrow/peripheral blood transplantation.

Secondary Hypotheses:

1. - More than 80% of engrafting patients will achieve ≥ 95% donor chimerism by Day 56 after BMT.
2. - The incidence of Grades III-IV GVHD will be less than 30%.

2.1.1.2. Study objectives

The primary objective is to determine overall survival 180 days after HLA-haploidentical bone marrow transplantation using a non-myeloablative preparative regimen and post-transplant cyclophosphamide. Secondary objectives include estimating overall and progression-free survival one year after transplantation, treatment-related mortality, incidence of neutrophil and platelet recovery, incidence of graft failure, cumulative incidence of acute and chronic GVHD, incidence of infections, and cumulative incidence of relapse/progression. The proportion of patients able to find acceptable donors and the proportion proceeding to transplant will also be described.

2.2. Patient Inclusion Criteria

Patients fulfilling the following criteria will be eligible to enroll on this study:

1. - Age: Subjects 21-70 years old. Subjects 1-21 are also eligible if they are ineligible for BMT CTN #0501.
2. - Donor must be ≥ 18 years of age.

3. - HLA typing will be performed at high resolution (allele level) for the HLA-A, -B, Cw, DRB1, and –DQB1 loci. A minimum match of 5/10 is required. An unrelated donor search is not required for a patient to be eligible for this protocol if the clinical situation dictates an urgent transplant. Clinical urgency is defined as 6-8 weeks from referral to transplant center or low-likelihood of finding a matched, unrelated donor.

   The donor and recipient must be identical, as determined by high resolution typing, at at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1. Fulfillment of this criterion shall be considered sufficient evidence that the donor and recipient share one HLA haplotype, and typing of additional family members is not required.

4. - Patients must have received cytotoxic chemotherapy within 3 months of consent date (measured from the start date of chemotherapy).

5. - Acute Leukemias (includes T lymphoblastic lymphoma) in 2nd or subsequent CR (see remission definition in Chapter 3).

   a. - Acute Lymphoblastic Leukemia in high risk CR1 as defined by at least one of the following:

      i. - Adverse cytogenetics such as t(9;22), t(1;19), t(4;11), MLL rearrangements,

      ii. White blood cell counts of greater than 30,000 wbc/mcL,

      iii. Patients over 30 years of age, or

      iv. Time to Complete Remission was greater than 4 weeks.

   b. - Acute Myelogeneous Leukemia in high risk CR1 as defined by at least one of the following:

      i. - Greater than 1 cycle of induction therapy required to achieve remission,

      ii. - Preceding myelodysplastic syndrome (MDS),

      iii. - Presence of Flt3 abnormalities,

      iv. - FAB M6 or M7 leukemia, or

      v. - Adverse cytogenetics for overall survival such as

         - those associated with MDS
         - Complex karyotype (≥ 3 abnormalities)
         - Any of the following: inv(3) or t(3;3), t(6;9), t(6;11), + 8 [alone or with other abnormalities except for t(8;21), t(9;11), inv(16) or t(16;16)], t(11;19)(q23;p13.1)

   c. - Acute Leukemias in 2nd or subsequent CR (see remission definition in Chapter 3).

   d. - Biphenotypic/Undifferentiated Leukemias in 1st or subsequent CR.

6. - Burkitt's lymphoma: second or subsequent CR.

7. - Lymphoma.
    a. - Chemotherapy-sensitive (complete or partial response; see response criteria in Chapter 3) large cell, Mantle Cell or Hodgkin's lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are ineligible for an autologous transplant.
    b. - Marginal zone B-cell lymphoma or follicular lymphoma that has progressed after at least two prior therapies (excluding single agent Rituxan).
8. - Patients with adequate physical function as measured by:
    a. - Cardiac: Left ventricular ejection fraction at rest must be ≥ 35%, or shortening fraction > 25%.
    b. - Hepatic: Bilirubin ≤ 2.5 mg/dL; and ALT, AST, and Alkaline Phosphatase < 5 x ULN.
    c. - Renal: Serum creatinine within normal range for age, or if serum creatinine outside normal range for age, then renal function (creatinine clearance or GFR) > 40 mL/min/1.73m^2.
    d. - Pulmonary: FEV_1, FVC, DLCO (diffusion capacity) > 50% predicted (corrected for hemoglobin); if unable to perform pulmonary function tests, then O_2 saturation > 92% on room air.
9. - Performance status: Karnofsky/Lansky score ≥ 60%.

2.3. Patient Exclusion Criteria

Patients fulfilling the following criteria are ineligible for registration onto this study:

1. - HLA-matched, related or 7 or 8/8 allele matched (HLA-A, -B, -Cw, -DRB1) related donor able to donate.
2. - Autologous hematopoietic stem cell transplant < 3 months prior to enrollment.
3. - Pregnancy or breast-feeding.
4. - Evidence of HIV infection or known HIV positive serology.
5. - Current uncontrolled bacterial, viral or fungal infection (currently taking medication with evidence of progression of clinical symptoms or radiologic findings).
6. - Prior allogeneic hematopoietic stem cell transplant.
7. - Patients with a history of primary idiopathic myelofibrosis.

2.4. Donor Selection Criteria

2.4.1. Inclusion Criteria

1. - Donors must be HLA-haploidentical first-degree relatives of the patient. Eligible donors include biological parents, siblings, or children, or half-siblings.
2. - Age ≥ 18 years.
3. - Donors must meet the selection criteria as defined by the Foundation for the Accreditation of Cell Therapy (FACT) and will be screened per the American Association of Blood Banks (AABB) guidelines.

2.4.2. Exclusion Criterion

1. - Positive anti-donor HLA antibody.

2.4.3. Donor Prioritization Schema

Also see Appendix D, Guidelines for Donor Typing and Selection.

In the event that two or more eligible donors are identified, the following order of priority:

1. - For CMV seronegative recipients, a CMV seronegative donor
2. - Red blood cell compatibility
   a. - RBC cross-match compatible
   b. - Minor ABO incompatibility
   c. - Major ABO incompatibility

2.5. Treatment Plan

Day –6, -5	Fludarabine 30 mg/M^2 IV over 30-60 minutes Cyclophosphamide 14.5 mg/kg IV over 1-2 hours*
Day –4→-2	Fludarabine 30 mg/M^2 IV over 30-60 minutes
Day –1	TBI 200 Cgy
Day 0	T cell replete BMT
Days 3,4	Cyclophopshamide 50 mg/kg IV Mesna 40 mg/kg IV
Day 5	Begin tacrolimus, mycophenolate mofetil, and G-CSF

*Uroprophylaxis per institutional preference (see 2.5.3 below)

2.5.1. Indwelling Central Venous Catheter

Placement of a double lumen central venous catheter will be required for administration of IV medications and transfusion of blood products.

2.5.2. Fludarabine

Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2. Fludarabine will be dosed according to the recipient's actual body weight, unless the actual body weight is greater than or equal to two times their ideal body weight, in which case the Protocol Team must be consulted for instruction.

For decreased creatinine clearance (< 61 mL/min) determined by the Cockcroft Formula:

$$C_{Cr} = \frac{(140 - \text{age}) \times \text{ideal body weight (IBW) (kg)}}{P_{Cr} \times 72} \times 0.85 \text{ (for women)}$$

Fludarabine dosage should be reduced as follows:

C_{Cr} 46-60 mL/min, fludarabine = 24 mg/m^{2} -
C_{Cr} 31-45 mL/min, fludarabine = 22.5 mg/m^{2} -
C_{Cr} 21-30 mL/min, fludarabine = 19.5 mg/m^{2} -
C_{Cr} < 20 mL/min, fludarabine = 15 mg/m^{2} -

2.5.3. Pre-transplantation Cyclophosphamide

Cy 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion with a high volume fluid flush on Days –6 and –5. Cy will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see below for formulas). Uroprotection can be administered according to institutional guidelines. Mesna is recommended to accompany pre-transplantation Cy, but is not required.

Ideal Body Weight (IBW) Formulas:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet -

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet -

Adjusted Ideal Body Weight Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2.5.4. Total Body Irradiation

Total body irradiation: 200 cGy will be administered in a single fraction on Day –1. Radiation sources and dose rates will also be defined by the institution. TBI may be delivered from either linear accelerator or Cobalt sources. Bone marrow may be infused on the same day as TBI

administration as long as there is 4-6 hours between administration of TBI and infusion of bone marrow.

2.5.5. Bone Marrow Transplantation

On Day 0, patients will receive unprocessed marrow unless there is a major ABO incompatibility, in which case red blood cells will be depleted from the donor marrow using institutional practices. Institutional practices will determine if there will be processing for minor ABO incompatibilities. Donor bone marrow will be harvested with a target yield of 4×10^8 nucleated cells/kg recipient IBW. Sample of the product to be infused will be sent for flow cytometry to determine the content of $CD34^+$ $CD3^+$, $CD4^+$, and $CD8^+$ cells.

2.5.6. Post-transplantation Cyclophosphamide with Mesna

Hydration prior to cyclophosphamide may be given according to institutional standards. A recommended approach is as follows: Patients are instructed to increase fluids overnight before cyclophosphamide administration. Hydration with normal saline at 3 ml/kg/hr IV will be started 2 hours prior to cyclophosphamide, then the rate will be reduced to 2 ml/kg/hr for 1 hour pre-cyclophosphamide and continued at 2 ml/kg/hr for 8 hours post-cyclophosphamide.

Mesna will be given in divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide or administered per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of mesna is equal to 80% of the total daily dose of cyclophosphamide.

Cyclophosphamide [50mg/kg IBW] will be given on Day 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be given as an IV infusion over 1-2 hours (depending on volume).

It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes corticosteroids as anti-emetics.

2.5.7. Tacrolimus

Tacrolimus will be given at a dose of 1 mg IV qd or 1 mg po bid, then will be changed to a PO dosing schedule once a therapeutic level is achieved or as per institutional standards. Serum levels of tacrolimus will be measured around Day 7 and then should be checked weekly thereafter and the dose adjusted accordingly to maintain a level of 5-10 ng/mL. Tacrolimus will be discontinued after the last dose around Day 180, or may be continued if active GVHD is present. Cyclosporine (target concentration 200-400 ng/ml) may be substituted for tacrolimus if the patient is intolerant of tacrolimus.

2.5.8. Mycophenolate Mofetil (MMF)

MMF will be given at a dose of 15 mg/kg PO TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g PO TID). MMF prophylaxis will be discontinued after the last dose on Day 35, or may be continued if active GVHD is present.

2.5.9. Supportive Care

Patients will receive transfusions, infection prophylaxis and nutritional support according to institutional guidelines. Infection prophylaxis should include, but is not limited to, agents or strategies (e.g., PCR screening and preemptive therapy) to prevent herpes simplex, cytomegalovirus (CMV), Pneumocystis carinii, and fungal infections.

2.5.10. Transfusion Support -

Platelet and packed red cell transfusions will be given per current institutional recommendations. -

2.5.11. Anti-Ovulatory Treatment -

Menstruating females should be started on an anti-ovulatory agent prior to the initiation of the preparative regimen.

2.5.12. Post-BMT Evaluation

Patients will be followed at the institution that performed the BMT at least until the chimerism/disease evaluation performed on Day ~56 after BMT. Additional follow-up at 6 months and 1 year after transplantation should be performed at the treating institution. Any biopsy taken to evaluate suspected GVHD must be interpreted by pathologists at the institution performing the BMT.

2.6. Risks and Toxicities

Cyclophosphamide:

Cyclophosphamide side effects include: nausea/vomiting, cardiomyopathy, skin rash, mucositis, stomatitis, sterility, diarrhea, hemorrhagic cystitis, fluid weight gain/edema, alopecia and hemolytic/anemia.

Fludarabine:

a. - Neurotoxicity: Agitation or confusion, blurred vision, loss of hearing, peripheral neuropathy or weakness have been reported. Severe neurologic effects, including blindness, coma, and death are seen in 36% of patients treated with doses approximately four times greater than recommended; severe CNS toxicity is rarely seen with doses in the recommended range for nontransplant therapy of hematologic malignancies. Effect of chronic use on the CNS is unknown, although patients have received recommended doses for up to 15 courses. The dose used in this study is approximately 1.5 times the

usual one-course dose given in non-transplant settings. Doses and schedules such as those used in this study have been used in adult and pediatric patients and increased neurotoxicity has not been observed.

b. - Anemia: Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported after one or more cycles of therapy in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission; no mechanisms for development of this complication have been identified. Corticosteroids may or may not be effective in controlling these episodes. The majority of patients re-challenged developed a recurrence of the hemolytic process.

c. - Cardiovascular: Deep venous thrombosis, phlebitis, transient ischemic attack, and aneurysm (1%) are reported.

d. - Fever: 60% of patients develop fever.

e. - Skin Rash: 15% of patients develop a skin rash, which may be pruritic.

f. - Digestive: Gastrointestinal side effects include: nausea/vomiting (36%), diarrhea (15%), stomatitis (9%), anorexia (7%), GI bleeding and esophagitis (3%), mucositis (2%), liver failure, abnormal liver function test, constipation, dysphagia (1%) and mouth sores.

g. - Some other effects are: Chills (11%), peripheral edema (8%), myalgia (4%), osteoporosis (2%), pancytopenia, arthralgia (1%), dysuria (4%), urinary tract infection and hematuria (2%); renal failure, abnormal renal function test, and proteinuria (1%); and, very rarely, hemorrhagic cystitis and pulmonary toxicity.

Total Body Irradiation:

TBI can cause: nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self-limited), generalized mild erythema, hyperpigmentation, fever, mucositis, and alopecia.

Late effects include: possible growth retardation, vertebral deformities, cataracts, probable increased risk of secondary malignant neoplasms, sterility, nephropathy, interstitial pneumonitis and veno-occlusive disease.

Mycophenolate Mofetil:

Side effects include: pancytopenia, nausea, vomiting, diarrhea, hypertension, headache, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, and leg cramps/bone pain.

Tacrolimus:

Side effects include: reversible renal insufficiency, hypertension, hyperglycemia, hypomagnesemia, hypokalemia, and neurologic toxicity.

Graft Failure:

Based on historical data, there could be a 15% chance of graft failure. Recovery of autologous hematopoiesis occurred in 14 out of 16 patients experiencing graft failure in the original Johns Hopkins/Seattle trial.

2.7. Growth Factor Support

G-CSF will be given beginning on Day 5 at a dose of 5 mcg/kg/day (rounding to the nearest vial dose is allowed), until absolute neutrophil count (ANC) is $\geq$ 1,000/mm^3 for three consecutive days. G-CSF may be given by IV or subcutaneously.

2.8. Management of Slow Engraftment and Graft Failure

Slow engraftment or graft failure shall be managed according to institutional practices, and may include the administration of colony stimulating factors and prophylactic antibiotics.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is overall survival at 180 days from the time of transplantation.

3.2. Secondary Endpoints

3.2.1. Neutrophil Recovery

Neutrophil recovery is defined as achieving an ANC $\geq$ 500/mm^3 for three consecutive measurements on different days. The first of the three days will be designated the day of neutrophil recovery. The only competing event for neutrophil recovery is death without neutrophil recovery.

3.2.1.1. Primary graft failure -

Primary graft failure is defined as < 5% donor chimerism on all measurements. -

3.2.1.2. Secondary graft failure

Secondary graft failure is defined as initial recovery followed by neutropenia with < 5% donor chimerism. If no chimerism assays were performed and ANC is < 500/mm^3, then it will be counted as a secondary graft failure.

3.2.1.3. Platelet recovery

Platelet recovery is defined by two different metrics as the first day of a sustained platelet count >20,000/mm^3 or >50,000/mm^3 with no platelet transfusions in the preceding seven days. The first day of the sustained platelet count will be designated the day of platelet engraftment.

3.2.2. Donor Cell Engraftment

Donor cell engraftment is defined as donor chimerism $\geq$ 5% on Day $\geq$ 56 after transplantation. Chimerism should be evaluated on Days ~28, ~56, ~180, and ~365 after transplantation. Chimerism may be evaluated in whole blood or mononuclear fraction.

3.2.3. Acute Graft-versus-Host Disease

The cumulative incidences of grade II – IV and III – IV acute GVHD will be determined. Acute GVHD will be graded according to the BMT CTN MOP. The time to onset of acute grades II-IV GVHD and grades III-IV GVHD will be recorded, as well as the maximum grade achieved.

3.2.4. Chronic Graft-versus-Host Disease

Chronic GVHD will be scored according to the BMT CTN MOP. The time to onset of limited and extensive chronic GVHD will be recorded.

3.2.5. Progression-free Survival

Progression-free survival is defined as the minimum time interval of the times to relapse/recurrence, to death or to last follow-up.

3.2.6. Treatment-Related Mortality (TRM)

The cumulative incidence of TRM will be estimated at Day 100, 180, and at 1 year. An event for this endpoint is death without evidence of disease progression. Documented diseased progression is a competing risk.

3.2.7. Infections

Infections will be reported by anatomic site, date of onset, organism and resolution, if any. For definitions, see the BMT CTN MOP. Patients will be followed for infection for 1 year post-transplant.

3.2.8. Relapse and Residual Disease

Relapse of Malignancy – Testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of acute leukemia consistent with pre-transplant features, or radiologic evidence (including the recurrence of fluoro-deoxyglucose [FDG]-avid lesions on PET scan) of progressive lymphoma. When in doubt, the diagnosis of recurrent or progressive lymphoma should be documented by tissue biopsy.

Minimal Residual Disease – Minimal residual disease is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot, or Western blot, or polymerase chain reaction (PCR), or other techniques, in absence of morphological or cytogenetic evidence of disease in blood or marrow. Since the frequency of testing for minimal residual disease is highly variable among centers, and the sensitivity is highly variable among laboratory techniques, evidence of minimal residual disease will not be sufficient to meet the definition of relapse in the context of this study. Data on tapering immunosuppression, administering chemotherapy or biological agents to in response to detection of minimal residual disease will be captured in the case report forms.

Acute Leukemia – Relapse will be diagnosed when there is:

1. - The reappearance of leukemia blast cells in the peripheral blood; or,
2. - > 5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration); or
3. - The appearance of new dysplastic changes within the bone marrow; or,
4. - The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.

Lymphoma – Relapse will be diagnosed when there is:

1. - Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. - At least a 50% increase from nadir in the sum of the product diameters (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
3. - At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. - Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<.1.5 cm in its long axis by CT).

TABLE 3.2 RESPONSE CRITERIA FOR LYMPHOMA

Table 2. Response Definitions for Clinical Trials

sponse	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
ed disease PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

lations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, the product of the diameters; SD, stable disease; PD, progressive disease.

From Cheson, B.D. et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 5:579-586, 2007.

Acute Leukemia - Remission is defined as < 5% blasts with no morphological characteristics of acute leukemia (e.g., Auer Rods) in a bone marrow with > 20% cellularity, peripheral blood counts showing ANC >1000/µl, including patients in CRp.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

Patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC^{SM}). The following procedures should be followed:

1. - Prior to initiation of conditioning regimen, but no more than 14 days prior to initiation of conditioning regimen, an authorized user at the transplant center enters the patient demographics and Segment A of the Enrollment Form in AdvantageEDC. The eligibility screening (Segment A) includes a question confirming that the patient (or legal guardian) signed the informed consent.
2. - If the patient is eligible, a study number is generated and a treatment assignment is displayed.
3. - A visit schedule based on treatment start date is displayed for printing and is referred to as 'Segment A Follow-up.'

4.2. Study Monitoring

4.2.1. Follow-up Schedule

The follow-up schedule for scheduled study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide.

TABLE 4.2.1: FOLLOW-UP SCHEDULE

Study Visit	Target Day Post-Transplant
1 week	7 ± 2 days
2 week	14 ± 2 days
3 week	21 ± 2 days
4 week	28 ± 2 days
5 week	35 ± 2 days
6 week	42 ± 2 days
7 week	49 ± 2 days
8 week	56 ± 2 days
6 month	180 ± 28 days
12 month	365 ± 28 days

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths: Recipient death information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment of BMT CTN #0603 must be indicated on the SCTOD pre-transplant registration form, if applicable. Additionally, CIBMTR pre- and post- transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

Weekly GVHD Monitoring: GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day 56 post-transplant for GVHD. After Day 56 patients will be assessed at each follow-up visit (Day 180 and 365) for the presence of GVHD.

4.2.2. Adverse Event Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule.

4.2.3. Patient Assessments

Table 4.2.3 summarizes patient clinical assessments over the course of the study.

4.2.3.1. Pre-transplant evaluations

The following observations are considered standard evaluations for transplant eligibility and should be determined < 4 weeks before initiation of conditioning therapy, unless otherwise noted.

1. - History, physical examination, height and weight.
2. - Karnofsky/Lansky performance status.
3. - CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST.
4. - CMV antibody test, hepatitis panel (HepA Ab, HepB Sab, HepB Sag, HepB Core Ab, HepC Ab), herpes simplex, syphilis, HIV and HTLV1 I/II antibody, and varicella zoster virus.
5. - HLA typing, if not already performed.
6. - EKG, < 6 weeks before initiation of conditioning therapy.
7. - Left ventricular ejection fraction or shortening fraction, < 6 weeks before initiation of conditioning therapy.
8. - DLCO, FEV1, and FVC or O_2 saturation. < 6 weeks before initiation of conditioning therapy.
9. - Bone marrow aspirates for pathology and cytogenetics and/or biopsy.
10. β-HCG serum pregnancy test for females of childbearing potential.
11. Chest imaging (Chest X-Ray or Chest CT) as clinically indicated.
12. Peripheral blood for pre-transplant RFLP analysis, to establish a reference profile of host hematopoiesis.
13. Lymphomas (large -cell, B- cell, and Hodgkin): Whole Body PET/CT as clinically indicated.

4.2.3.2. Post-transplant evaluations

The following evaluations are considered standard evaluations for transplant recipients:

1. - History and physical exam to assess GVHD and other morbidity weekly until Day 56 post-transplant, then at six months and one year post-transplant. GVHD evaluation and grading to be in keeping with BMT CTN MOP.
2. - CBC at least three times a week from Day 0 until ANC > 500 mm^3 for 3 days after nadir reached. Thereafter CBC twice per week until Day 28, then weekly until 12 weeks, then at six months and one yearpost-transplant.
3. - Creatinine, bilirubin, alkaline phosphatase, ALT, AST, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests twice a week until Day 28 (or four weeks) and then weekly until 12 weeks, and then at six months and one year post-transplant.

4. - Peripheral blood on Day ~28, ~56, ~180, and ~365 for post-transplant chimerism assay.
5. - Immunizations will be given per institutional guidelines.
6. - Toxicity assessments at Day 28, 56, 6 months, and 1 year.
7. - Disease status evaluation required at Day 60, 6 months, and 1 year. Testing to determine disease status should follow pre-transplant evaluation process. Disease status evaluation before Day 60 should follow institutional practices.

TABLE 4.2.3: SUMMARY OF PATIENT CLINICAL ASSESSMENTS

Study Assessments/ Testing	Baseline	Days after Transplantation									
		7	14	21	28	35	42	49	56	180	365
History, physical exam, weight, height, and Karnofsky/Lansky performance status	X	X	X	X	X	X	X	X	X	X	X
CBC[1], differential, platelet count, and blood chemistries[2]	X	X	X	X	X	X	X	X	X	X	X
Infectious disease titers[3]	X										
EKG, LVEF, or shortening fraction	X										
DLCO, FEV1 and FEV or O_2 saturation	X										
Bone marrow aspirate for pathology and cytogenetics and/or biopsy[4]	X[4]				X[4]				X[4]	X[4]	X[4]
Chest X-ray	X										
ß-HCG serum pregnancy test (females only)	X										
GVHD and other morbidity assessments[5]		X	X	X	X	X	X	X	X	X	X
Toxicity assessments	X				X				X	X	X
Chimerism[6]	X				X				X	X	X

Notes:

[1] CBC performed at least three times a week from Day 0 until ANC >500 mcL for three days after nadir. CBC performed twice weekly until Day 28. CBC performed weekly after Day 28 until 12 weeks post-transplant.

[2] Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests (where standard of care should be according to institutional guidelines). Blood chemistries performed twice weekly until Day 28. Blood chemistries performed weekly after Day 28 until 12 weeks post-transplant.

[3] Infectious disease titers include: CMV, Hepatitis panel (HepA, Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.

[4] LEUKEMIA PATIENTS ONLY. Bone marrow biopsy and aspirates to pathology and aspirate for cytogenetics. Flow cytometry required on aspirate. Baseline, Day 56 and Day 365 are required; Day 28 and Day 180 are optional.

[5] GVHD and other morbidity assessments performed weekly until Day 56 post-transplant, and then at Day 180 and 365.

[6] Chimerism will be measured by RFLP or microsatellite analysis of a peripheral whole blood sample..

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design

The study is a Phase II, non-randomized, multi-center trial. It is designed to assess overall survival 180 days after bone marrow transplantation using a nonmyeloablative preparative regimen and post-transplantation Cy using a partially HLA-mismatched first-degree relative (parent, sibling, or child) as a donor. The sample size is 50 patients. Patients with acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, marginal zone B-cell lymphoma, follicular lymphoma, and chemotherapy-sensitive Burkitt, large-cell, and Hodgkin lymphoma are eligible. A primary purpose of this study is to determine if results from a single center study can be duplicated in a multi-center setting.

5.2. Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Accrual will be reported by race, ethnicity, gender, and age.

5.3. Study Duration

Patients will be followed by BMT CTN personnel for a minimum of one year post-transplant. Additional follow-up will be available through routine CIBMTR mechanisms (see Section 4.2.1).

5.4. Randomization

There is no randomization in this trial.

5.5. Primary Objective

The primary endpoint is the proportion of patients who survive for 180 days after transplantation. The choice of this endpoint is based on CIBMTR registry data reported by Giralt et al (Biol Blood Marrow Transpl 2007; 13:1083) for unrelated adult donor transplants. In this study the probability of 6-month survival was 60%. The primary analysis will include all transplanted patients. Death from any cause is the event for this endpoint. The study is designed to rule out survival percentages below 40%.

5.6. Sample Size and Power Considerations

The sample size is 50 patients. Table 5.6.1 provides 90% confidence intervals for a variety of observed proportions. For example if 30 of the 50 patients survive (60% observed survival percentage) the length of the confidence interval is 22.8%. The percentages above and below 60% are intended to represent other plausible survival rates.

This is an exploratory study with a decision rule that a further Phase III study would be warranted if the lower bound of a 90% confidence interval for the survival estimate is above 40%. The probability to rule out survival percentages of a certain size is known as "power". Table 5.6.2 provides the probability (or power) that the lower bound of a 90% two-sided confidence interval for the overall survival probability will be greater than a threshold of 70%, 65%, 60%, 55%, 50% or 45%. Based on the table below, there is 84% power at $\alpha = .05$to reject the null if the true percentage is < 40%.

TABLE 5.6.1: CONFIDENCE INTERVAL LENGTHS AND POSSIBLE CONFIDENCE INTERVALS FOR VARIOUS OBSERVED OVERALL SURVIVAL PROBABILITIES

N	Overall Survival (OS) %	Length of 95% Confidence Interval	Possible Confidence Intervals	
50	70	21.3	59.3	80.7
50	65	22.2	53.9	76.1
50	60	22.8	48.6	71.4
50	55	23.1	43.4	66.6
50	50	23.3	38.4	61.6
50	45	23.1	33.4	56.6
50	40	22.8	28.6	51.4

The OS probability estimate will be based on the Kaplan-Meier product limit estimator using Greenwood's formula as the variance estimate. In the absence of censoring, the Kaplan-Meier estimate reduces to the simple binomial proportion.

TABLE 5.6.2: PROBABILITY OF RULING OUT A THRESHOLD OF SIZE T FOR VARIOUS TRUE UNDERLYING OVERALL SURVIVAL PERCENTAGES

N	True Overall Survival %	Probability of Ruling Out Overall Survival Percentages of Size T						
		T=70%	T=65%	T=60%	T=55%	T=50%	T=45%	T=40%
50	70		0.14	0.33	0.68	0.86	0.98	0.99
50	65	0.19		0.12	0.39	0.62	0.88	0.96
50	60	0.44	0.16		0.16	0.34	0.67	0.84
50	55	0.71	0.39	0.13		0.13	0.39	0.61
50	50	0.90	0.6	0.34	0.16		0.16	0.34
50	45	0.98	0.87	0.61	0.39	0.13		0.13
50	40	0.99	0.97	0.84	0.67	0.34	0.16	

5.7. Interim Analysis and Stopping Guideline

Interim analyses for efficacy will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately six-month intervals. Monitoring of key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as trigger for consultation with the DSMB for additional review.

Two safety endpoints for this study are treatment-related mortality (TRM) and graft failure. The rate of TRM will be monitored up to 100 days post-transplant and the rate of graft failure will be monitored up to 56 days post-transplant. Monitoring will be performed monthly beginning after the third month of enrollment until enrollment is closed. At least three events must be observed in order to trigger review. Each month, the null hypothesis that the 100-day TRM rate is less than or equal to 30% is tested. Similarly, the null hypothesis that the 56-day graft failure rate is less than or equal to 12% is tested. Primary graft failure, secondary graft failure and second transplants will be counted as events for this stopping guideline. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for each endpoint, as described in greater detail below and in Appendix E.

This sequential testing procedure conserves type I error across all of the monthly examinations for a single endpoint, but not across the multiple safety endpoints. Thus for a single endpoint, the type I error is approximately 5%, and across two safety endpoints, the study-wide type I error is < 10%. The rationale for not conserving type I error across multiple safety endpoints is

twofold. First, adjusting the size of the test for multiple comparisons would reduce statistical power to detect adverse outcomes, which seems imprudent. Secondly, the procedure is a guideline for requiring additional review by the Data and Safety Monitoring Board, and is not a formal "stopping rule" that would mandate automatic closure of study enrollment.

The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of endpoints (e.g., patients experiencing TRM). The continuation region of the SPRT is defined by two parallel lines. Only the lower boundary will be used for monitoring to protect against excessive 100-day TRM. If the graph falls below the lower boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the maximum of 50 patients.

This procedure assumes a censored exponential distribution for the time until failure, e.g., the time until TRM, during the first 100 days, and censors follow-up time after 100 days. Only TRMs that occur on or before the patient has been followed for 100 days are counted. Total time on study is computed as time from registration to event, or to 100 days, whichever comes first, summed for all patients on study.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRTs:

- A SPRT contrasting 30% versus 50% 100-day rate of TRM results in decision boundaries with a common slope of 0.54 and the intercepts are –1.74 and 1.46 with nominal type I and II errors of 10% and 15%, respectively
- A SPRT contrasting 12% versus 30% 56-day rate of graft failure results in decision boundaries with a common slope of 0.69 and the intercepts are –1.43 and 1.20, with nominal type I and II errors of 10% and 15%, respectively.

The actual operating characteristics of the truncated test, shown in Table 5.7.1, were determined in a simulation study that assumed uniform accrual of 50 individuals over a three-year time period, and exponential time to failure after registration. Since 100,000 replications were used, the estimates have two digits of precision.

TABLE 5.7.1: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 100,000 REPLICATIONS

TREATMENT-RELATED MORTALITY

True 100-Day Rate	30%	35%	40%	45%	50%
Probability Reject Null	0.07	0.20	0.41	0.66	0.86
Mean Month Stopped	34.5	32.3	28.5	23.5	18.5
Mean # Endpoints in 100 Days	13.8	15.0	15.1	14.0	12.1
Mean # Patients Enrolled	48	45	40	33	26

GRAFT FAILURE

True 56-Day Rate	12%	15%	20%	25%	30%
Probability Reject Null	0.07	0.16	0.44	0.72	0.90
Mean Month Stopped	34.5	32.6	27.3	21.1	15.6
Mean # Endpoints in 56 Days	5.6	6.6	7.4	7.1	6.3
Mean # Patients Enrolled	48	45	38	30	22

For example, the testing procedure for TRM rejects the null hypothesis in favor of the alternative 7% of the time when the true 100-day TRM rate is 30%, and 86% of the time when the rate is 50%. This corresponds to a type I error rate of $\alpha = 0.07$ and a type II error rate of $\beta = 0.14$. When the true 100-day TRM rate is 50%, on average, the DSMB will be consulted 18.5 months after opening, when 12 events have been observed in 26 patients.
The testing procedure for graft failure rejects the null hypothesis in favor of the alternative 7% of the time when the true 56-day graft failure rate is 12%, and 90% of the time when the rate is 30%. This corresponds to a type I error rate of $\alpha = 0.07$ and a type II error rate of $\beta = 0.10$. When the true 56-day graft failure rate is 30%, on average, the DSMB will be consulted 15.6 months after opening, when 6 events have been observed in 22 patients.

5.8. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, HLA match, disease type and stage, remission status and number, number of prior treatments, prior autologous transplantation (yes or no), serum bilirubin level, serum creatinine level, donor age, donor gender, and donor ethnicity.

5.9. Analysis of Primary Endpoint

The primary analysis will consist of estimating the 180 day overall survival probability based on the Kaplan-Meier product limit estimator. The 180 day overall survival probability and confidence interval will be calculated. All registered patients will be considered for this analysis.

5.10. Analysis of Secondary Endpoints

1. - **Overall survival**: The overall survival distribution at one and two years after transplantation will be estimated by the Kaplan-Meier curve. All patients will be followed for a minimum of two years post-transplant for mortality.
2. - **Neutrophil recovery**: To assess the incidence of neutrophil recovery from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to neutrophil recovery will be considered a competing risk.
3. - **Platelet recovery:** To assess the incidence of platelet recovery from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to platelet recovery will be considered a competing risk.
4. - **Chimerism**: The degree of donor chimerism will be assessed on Days 28, 56, 180, and 365 after transplantation.
5. - **Graft failure**: To assess the incidence of primary and secondary graft failure a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to graft failure will be considered as a competing risk.
6. - **Acute GVHD:** To assess the incidence of grades II-IV and grade III-IV acute GVHD from day of transplant. The first day of acute GVHD onset at a certain grade will be used to calculate a cumulative incidence curve for that acute GVHD grade. An overall cumulative incidence curve will be computed along with a 95% confidence interval at 100 days post-transplant with graft failure, disease progression, and death considered a competing risk.
7. - **Chronic GVHD:** To assess the incidence and severity of extensive chronic GVHD from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval at one and two years post-transplant. The first day of clinical onset of extensive chronic GVHD will be used. Death, disease progression, or graft failure prior to occurrence of chronic GVHD will be considered competing risks.
8. - **Treatment-related mortality**: Treatment-related mortality at 100 days, six months, and one year will be estimated. Disease progression is considered a competing risk.
9. - **Relapse/progression**: To assess the incidence of relapse/progression from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to relapse or progression will be considered a competing risk.
10. **Progression-free survival**: To assess current progression-free survival, the one and two year progression-free survival probability after transplantation and 95% confidence interval will be calculated based on the Kaplan-Meier product limit estimator.

5.11. Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures. The type and severity of adverse events will be described.

APPPENDIX A

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient, donor and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principle investigator or other designated physician.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of leukemia and lymphoma in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

APPENDIX B

CONSENT FORMS

PATIENT INFORMED CONSENT

Informed Consent to Participate in Research

A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning and - Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with - Hematologic Malignancies -

Your name:_____

Introduction

You are being invited to participate in a clinical trial. A clinical trial is a research study to answer specific medical questions. The information from this study may help future patients. This form tells you about the study. In addition, the study doctor (the person in charge of the research) will explain the study to you.

You are being asked to take part in this study because you have been found to have a cancer of the blood or lymph glands that may be treatable with stem cell transplantation from a relative or an unrelated donor. We and other transplant centers have the most experience using a donor who is a "perfect" or close to perfect "tissue match". However, tissue typing shows that a completely matched donor is unavailable within your family, although you do have a family member who is a partial match. While an unrelated donor transplant is an option, we either have not been able to find a good match or we are concerned that your disease may worsen in the time it takes to find one.

The investigators of this study want you to understand that patients in clinical trials include only those who are completely informed and choose to participate. Please take your time to make your decision. We encourage you to discuss your decision with your doctor, family, and friends.

It is important that you know:

- You will not be paid to be in this study.
- You or your insurance company will pay the bills for your medical treatment except that,
- You will not be charged for research tests.
- You will face the same risks and benefits as any other bone marrow transplant patient.

Principal Investigator Contact Information at your Institution
Name/Title/Phone number/

Contact information for emergencies after hours or on weekends or holidays:
Name/Phone number/

Who is conducting this study?
The research in this study is paid for by the National Institutes of Health (NIH), which supports the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The BMT CTN will direct the research study. All decisions about how the study is done are made independently by the BMT CTN and NIH.

Why is this study being done?
This study is being done because at the present time there are no curative therapies for your disease outside of blood or marrow stem cell transplantation. Because of your age or underlying health and the fact that you do not have a matched donor, you have a higher likelihood of experiencing harm from a conventional stem cell transplant. We are hoping to test whether the method of reduced intensity transplantation (sometimes referred to as a "nonmyeloablative") from partially mismatched donors is safe enough to allow further analysis in more detailed clinical trials.

There is no guarantee or promise that this procedure will be successful.

How many people will take part in the study?
A total of 50 patients will participate in this study. This study will be done many different medical centers in the United States, including [Center Name/Location].

What will happen if I take part in this research study?
In this study, we will use a partially mismatched donor from your family for a new type of bone marrow transplant called "nonmyeloablative transplant" which does not require using high doses of chemotherapy or radiotherapy. You will be treated first with a type of chemotherapy called fludarabine (also called Fludara®), which is given intravenously through your catheter daily for five days. You also will be given cyclophosphamide (also called Cytoxan®) intravenously, which is commonly used to treat cancer, on your first and second day along with fludarabine. After the chemotherapy is completed, you will receive a small dose of radiation to your whole body in a single exposure. The next day, Day 0, your donor's marrow will be harvested and given to you through your catheter. High doses of cyclophosphamide will be administered intravenously on the 3rd and 4th day after the transplantation to help prevent two complications, graft rejection and graft-versus-host disease (GVHD), an attack by donor cells on your normal tissues. Beginning on the 5th day after transplantation, we will give you two other approved drugs, called tacrolimus (also called FK-506 or Prograf®), and Mycophenolate mofetil (also called MMF or CellCept®), after the transplant to help prevent GVHD. In certain cases where patients do not tolerate tacrolimus, they

may be given cyclosporine, another approved drug that helps prevent GVHD. GVHD is explained in greater detail on page B-9.

You will continue to take MMF for about 5 weeks and tacrolimus for about 6 months. Also beginning on the 5th day after transplantation, you will also be given a growth factor called G-CSF (also called filgrastim or Neupogen®) by daily injection through the catheter or under your skin which may help to speed up the recovery of white blood cells. The daily injections of G-CSF will be stopped when the white blood cells have recovered. To make sure your donor's bone marrow is growing back, blood or marrow samples will be obtained from you at about 1, 2, 6, and 12 months after transplant.

The chemotherapy, radiotherapy, and even the supportive care you will receive are associated with many potential side effects, some of which may be life threatening. These side effects are listed below in the section of risks of the study. There can be additional risks associated with the use of antibiotics, which your doctor can discuss with you.

You will receive treatment for any infections according to medical standards.

Blood tests will be performed frequently to evaluate your response to treatment and possible side effects of treatment. If necessary, platelet and red cell transfusions will be given to maintain adequate levels and antibiotics will be given to treat or prevent infection. You may also require intravenous nutritional support and pain medications during or after transplantation. You will be monitored closely for any signs and symptoms of GVHD.

How long will I be in this study?
Your treatment will last approximately 2-3 months at this center but possibly longer if there are complications. We would like to see you in clinic for follow-up at 6 months, if possible, and then 1 year post-transplant.

However, we would like to keep track of your medical condition for the rest of your life. We will do this by contacting you and the doctor providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us know whether there are any unexpected long-term side effects of treatment. Many transplant centers include this type of long-term follow-up as part of their regular care.

Can I stop being in this study?
Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. If you decide to withdraw from the study, we ask that you tell your doctor. If you withdraw, there will be no penalty or loss of benefit to which you are entitled and you will continue to receive medical care. If you do not want this, you must specifically tell your doctor.

If you have any questions about your rights as a study subject, you may contact the Institutional Review Board (IRB) office at /number/.

Can the Principal Investigator withdraw me from this research study?
You can be taken off the study (with or without your consent) for any of these reasons:

- The study treatment does not work for your type of cancer
- You develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications
- You are unable to meet the requirements of the study (for example, you cannot take the medicine as prescribed or you refuse follow up)
- New information about the study drugs or other treatments for cancer becomes available
- The study is cancelled

What side effect or risks can I expect from being in the study?

Likely Side Effects	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely Side Effects	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare Side Effects	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Cyclophosphamide (Cytoxan®)

Likely	Less Likely	Rare, but Serious
• Decreased white blood cell count with increased risk of infection • Temporary hair loss • Nausea • Vomiting • Loss of appetite • Sores in mouth or on lips • Diarrhea • Stopping of menstrual periods in women • Decreased sperm production in men • Decreased platelet count (mild) with increased risk of bleeding • Blood in urine	• Anemia • Temporary tiredness • Damage to the fetus if you become pregnant while taking drug	• Scarring of lung tissue, with cough and shortness of breath • Severe heart muscle injury and death at very high doses • Secondary cancers

Fludarabine (Fludara®)

Likely	Less Likely	Rare, but Serious
• Decreased white blood cell count with risk of infection • Decreased platelet count with increased risk of bleeding • Anemia • Tiredness • Nausea • Vomiting	• Diarrhea • Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet • Changes in vision	• Pneumonia • Agitation/nervousness • Confusion • Cough • Difficulty breathing • Weakness • Severe brain injury and death

G-CSF (Neupogen®)

Likely	Less Likely	Rare, but Serious
• Ache or pain inside the bones • Increased levels of liver enzymes and uric acid in the blood • Low number of platelets in the blood • Headache • Tiredness	• Local irritation (skin) at the injection site • Nausea	• Allergic reaction • Low fever • Enlargement or rupture of the spleen • Worsening of pre-existing skin rashes

Mycophenolate mofetil (MMF; CellCept®)

Likely	Less Likely	Rare, but Serious
• Miscarriage • Birth defects • Diarrhea • Damage to unborn baby • Limited effectiveness of birth control • Stomach pain • Upset stomach • Vomiting • Headache • Tremors • Low white blood cell count with increased risk of infection • Increased blood cholesterols • Swelling of the hands, feet, ankles, or lower legs	• Anemia • Rash • Difficulty falling asleep or staying asleep • Dizziness • Uncontrollable hand shakes	• Difficulty breathing • Unusual bruising • Fast heartbeat • Excessive tiredness • Weakness • Blood in stools • Bloody vomit • Changes in vision • Progressive Multifocal Leukoencephalopathy

Total Body Irradiation (TBI)

Likely	Less Likely	Rare, but Serious
• Fatigue • Nausea	• Vomiting • Cataracts • Low white blood cell count with increased risk of infection • Low platelet count with increased risk of bleeding • Anemia	• Diarrhea • Secondary cancers

Tacrolimus (Prograf®; FK-506)/Cyclosporine

Likely	Less Likely	Rare, but Serious
• Kidney problems • Loss of magnesium, calcium, potassium • High blood pressure • Tremors • Increases in cholesterol and triglyceride	• Nausea • Vomiting • Liver problems • Changes in how clearly one can think • Insomnia • Unwanted hair growth • Confusion	• Seizures • Changes in vision • Dizziness • Red blood cell destruction

Risks and Toxicities Related to Standard Transplant Procedures

Risks of Bone Marrow Transplantation
The following problems may occur as a result of transplantation of bone marrow. These are risks that would be present whether such a transplant was done as part of the study or not:

1. **Slow Recovery of Blood Counts.** The red blood cells, white blood cells, and platelets can be slow to recover after bone marrow transplantation. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. Although infections can be treated with drugs, they can be very dangerous or fatal. To speed the recovery of the white cells as much as possible you will receive growth factor, a hormone that tells the bone marrow to make white blood cells.
2. **Graft Failure.** The bone marrow stem cells (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 15% chance of graft failure. If graft failure occurs, this may result in low blood counts for a long period of time. Graft failure can be fatal.

3. **Graft-versus-host Disease (GVHD).** This condition results from the bone marrow cells recognizing your body as foreign and attacking it. In most cases, GVHD can be successfully treated. Sometimes GVHD is severe or difficult to treat and may lead to death. You will be watched closely for this complication and given medication to prevent and/or treat it.

   There are two forms of GVHD: acute GVHD (occurs in the first 3 months after transplant) and chronic GVHD (after the first 3 months). Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a biopsy (i.e. taking a small sample of tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

4. **Other Complications.** Other complications that can result from the transplantation procedure not specifically related to one specific drug or the bone marrow stem cells or this study include:

   a. **Damage to the vital organs in your body.** This could result in problems in any body organ, such as heart, lungs, liver, gut, kidneys and bladder, brain, etc. The lungs and the liver are particularly vulnerable. Some patients will experience severe lung problems due to infections and/or due to a reaction of the lungs to the chemotherapy and radiation. Rarely patients can suffer veno-occlusive disease of the liver (VOD). This complication results from high doses of chemotherapy and/or radiation. Patients with VOD become jaundiced (yellowish skin), have liver function abnormalities, abdominal swelling, and abdominal pain. Although many patients recover completely, these complications may cause permanent damage or even death.

   b. **Serious infections.** Full and complete recovery of your immune system may take many months following the initial recovery of your cell counts. During this time, there is an increased risk of infections. You will be prescribed certain medications to reduce the chance of those infections. However, preventative treatments are not always effective. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections may result in death.

   c. **Recurrence of disease, or development of a new blood cancer.** Your leukemia or lymphoma may come back even if the transplant is initially successful. In rare cases a blood cancer may arise from cells of the donor. Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10 years after treatment, or 6 years on average. The risk of developing a new blood cancer after allogeneic BMT is probably less than 2%. However, since your donor's marrow is exposed to cyclophosphamide after the transplant, there is a risk that a blood cancer may develop in your donor's blood cells. This risk is unknown, but it may be as high as 5-10%. If cancer develops in your donor's blood cells, you may require additional treatment with

chemotherapy or another bone marrow transplantation procedure.

d. Risk to the unborn. The treatments in this study have NOT been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant must use some form of effective birth control while receiving chemotherapy, TBI, and GVHD prophylaxis. Effective birth control is defined as the following:

1) Refraining from all acts of vaginal intercourse (ABSTINENCE)
2) Consistent use of birth control pills -
3) Injectable birth control methods (Depro-Provera, Norplant) -
4) Tubal sterilization or male partner who has undergone a vasectomy -
5) Placement of an IUD (intrauterine device) -
6) Use, with every act of intercourse, of a diaphragm with contraceptive jelly - and/or condoms with contraceptive foam.

e. - **Sterility and future childbearing potential for men and women.** Chemotherapy and/or irradiation may affect your ability to have children. Male patients may become sterile (unable to produce sperm) and should discuss with their doctor regarding sperm banking prior to transplantation. Female patients who have attained puberty may find that their menstrual cycle becomes irregular or stops permanently. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use some effective method of birth control during transplant and afterwards until you are off GVHD prophylaxis. Damage to reproductive tissue may result in infertility (inability to have children). It is not known if the damage could result in birth defects. You should discuss these risks and options in detail with your doctor before entering this study.

5. - **Unknown or Unexpected Side Effects.** As with any treatment, there may be unknown and/or unexpected side effects from a nonmyeloablative bone marrow transplant. We many learn new things about nonmyeloablative bone marrow transplants that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study.

6. - **Additional information regarding MMF**

a. - MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.

b. - MMF can limit the effectiveness of birth control pills and thus increase your chances of becoming pregnant while you are taking it.

c. - In this trial you will be assigned to receive MMF for approximately 5 weeks and therefore you should not become pregnant during that time. If you think you might be pregnant or could be become pregnant during the upcoming 5 weeks, you should not enroll in this trial.

Are there benefits to taking part in the study?
This research study is examining the treatment results of chemotherapy and radiation given before and after a bone marrow transplant from a partially mismatched related donor. The knowledge gained from this study may help future patients who need a bone marrow stem cell transplant, but you may not benefit from participating in the study.

As a result of the bone marrow transplant, your disease may be put in remission or continue in remission.

What other choices do I have if I do not take part in this study?
Participation in this study is entirely voluntary. You don't have to be in this study. What you decide will not affect current or future health care you receive at this institution. Before you decide to be in this study, you and the medical staff will discuss other options available to you, including:

- Chemotherapy
- A transplant of cord blood cells
- Transplantation from an adult unrelated donor, if one can be identified that would be a good match for you
- No therapy to try and control your leukemia/lymphoma but treatment to make sure you remain comfortable for the remainder of your life.

What are the costs of taking part in this study?
You and/or your insurance company will pay all medical expenses relating to, or arising from, bone marrow transplantation. You will not be billed for tests that are only done for research purposes.

You will not be paid to be in this study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What if I am injured as a result of being in this study?
In the event that this research activity results in an injury, treatment will be available. This treatment includes first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed to your insurance company. If you think you have suffered a research related injury, let the study doctors know right away. Unexpected side effects or accidents might result in your getting sicker than anticipated. All available medical care will be provided to you, but you and your insurance company are responsible for the costs of all such care.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you. You will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information that may effect your health or your willingness to stay in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will my medical information be kept private?
Your participation in this research study will be kept private and confidential. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

<u>Organizations with access to your research and medical records:</u>

- /Institution/
- The National Institutes of Health (NIH)
- The National Heart, Lung, and Blood Institute (NHLBI)
- The National Cancer Institute (NCI)
- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)

- Institutional Review Boards (IRBs) responsible for this study
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- Study investigators

Scientific and medical findings resulting from a study may be presented at meetings. They may be published so that the information can be useful to others. You will not be identified in these presentations and publications.

Information related to or resulting from your transplant will be reported to the CIBMTR. The CIBMTR is a voluntary organization of basic and clinical scientists working together to gather results of blood stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

For questions about access to your medical records, please contact /name/ at /number/.

HIPAA[1] authorization to use and disclose individual health information for research purposes

Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled: *A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies*

Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results).

1 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(list hospitals, clinics or providers from which health care information can be requested)

_____

_____

_____

Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigators and the researcher's staff at the Johns Hopkins University and Fred Hutchinson Cancer Research Center
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples
- National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.
- Others:

_____

_____

_____

Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

This authorization does not have an expiration date.

****

Is there an expiration date for keeping my records?
Study records will be kept indefinitely by the transplant center for re-analysis and follow-up. If you have questions about the keeping of your research records or access to your files, please call /name/ at /number/.

Will researchers benefit from me being in this research study?
Your doctors have no money invested and will not get any financial gain from this study. Presenting research results may help the career of a doctor. Therefore, the doctors running this research study may benefit when the results are presented at scientific meetings or in the scientific press.

****

Consent for Treatment:

I have been informed about this study's purpose, procedures, possible benefits and risks. I have been given a chance to ask questions and have had them answered to my satisfaction. I understand that I can ask more questions at any time.

I voluntarily agree to participate in this study.

By signing this consent form, I have not given up any of the legal rights which I otherwise would have as a subject in a research study.

_____ _____
Signature of Subject *Date*

_____
Print Name of Subject

_____
Signature of Legally Authorized Representative *Date*

Certification of Counseling Healthcare Professional

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this information have been answered.

_____ _____
Counseling Healthcare Professional *Date*

Use of an Interpreter: Complete if the subject is not fluent in English and an interpreter was used to obtain consent:

Print name of interpreter: _____ Date: _____

Signature of interpreter: _____

An oral translation of this document was administered to the donor in _____ (state language) by an individual proficient in English and _____ (state language). See the attached short form addendum for documentation.

ASSENT FORM

A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies

You have leukemia or lymphoma. Leukemia and lymphoma are cancers of the blood cells made in your body's "blood factory", which is called the bone marrow. These diseases are treated with special medicines. These medicines are called chemotherapy. They kill cancer cells. If chemotherapy doesn't kill all of the cancer cells, a special and stronger treatment called a transplant may be needed.

During some transplants, you receive a very large amount of chemotherapy medicines and radiation therapy to kill the cancer cells in your body. These chemotherapy drugs are so strong that they also kill many normal cells in your blood and bone marrow. In a mini-transplant you will still get chemotherapy medicines and radiation therapy, but you will get smaller doses of these medicines. A smaller amount of your cancer cells will be killed, but your body will be able to heal itself faster and attack the cancer cells. Your doctors think that a mini-transplant is the best treatment for you. They believe that it will increase your chance of cure.

Cells from the donor's bone marrow can be used in a transplant. Bone marrow contains blood-forming cells that can help re-grow your bone marrow after treatment with chemotherapy medicines and radiation. Bone marrow cells can be donated by a volunteer in your family who has a similar type of bone marrow as you do.

Transplant Procedure
Before the transplant, you will be given the drugs cyclophosphamide and fludarabine. These drugs will be given through a central line – an IV that will be placed in your chest. If you do not already have a central line, we will put one in as a surgical procedure (you will be asleep for this). A central line makes it easier for you to receive drugs and for drawing blood for tests (you will not be poked for blood or receive shots). You will also get radiation to your whole body the day before your transplant. After you have received these drugs and radiation, bone marrow will be given through your central line. When the blood gets into your body, you may feel sick to your stomach but that will go away quickly. You will be in the hospital for about four weeks after the bone marrow is given to you while we are waiting for the bone marrow cells to grow up inside your body and for you to recover from the chemotherapy and radiation. You will need to be on a number of medications during your transplant, which will either be given through your line or will be taken by mouth.

It will be necessary to check your blood and bone marrow after the transplant to make sure the bone marrow cells are growing in your body. Your doctors will do blood tests and bone marrow tests. Blood tests will also be done by taking blood through your line.

Risks/Discomforts
The drugs and radiation may cause hair loss, nausea and vomiting, and diarrhea. Your blood counts will fall and you may get fevers, infections or start bleeding. You may also get mouth sores. These are temporary and you will feel better as your new bone marrow grows.

During the period your new bone marrow is growing back after the bone marrow transplant, you may need to get antibiotics since you will not be able to fight infections. You may also need to get blood transfusions since your new bone marrow will not be making new blood cells right away. It is possible that your new bone marrow will not grow back. This is unlikely but if it did happen, it may even be necessary to do a second transplant. You may get graft-versus-host disease (GVHD), which happens when transplanted cells attack your body causing skin rash, vomiting, diarrhea and liver problems. These problems could be mild, or they could be very serious. Your doctors will do their best to make you feel better and keep you safe.

The above information has been explained to me. My questions have been answered.

I agree to participate in this study.

_____ _____
Patient Parent

_____
Physician

_____ _____
Witness Date

APPENDIX C

LABORATORY PROCEDURES

1. HLA TYPING

HLA typing will be performed for all patients and donors in American Society of Histocompatibility and Immunogenetics (ASHI)-approved laboratories designated by the transplant centers. HLA typing must be performed by DNA methods for HLA-A, -B, -Cw, DRB1, and DQB1 at high resolution (allele level).

2. CHIMERISM

Prior to transplantation, a sample of peripheral blood from the patient and from the donor is collected for chimerism studies according to institutional standards. Patient samples are also collected on Day ~28, ~56, ~180 and ~365 after transplantation. Chimerism will be measured by RFLP or microsatellite. Donor chimerism after transplantation shall be measured on samples of whole blood or mononuclear fraction.

APPENDIX D

GUIDELINES FOR DONOR TYPING AND SELECTION

An HLA-haploidentical donor is defined as a family member who shares one complete HLA haplotype with the recipient, and is variably HLA mismatched on the non-shared haplotype. A transplant recipient is HLA-haploidentical to each parent, to each child, and each sibling has a 50% chance of being HLA-haploidentical to the recipient. Typing all siblings, parents, and children is neither practical nor economically feasible. Siblings are always typed first in the attempt to find an HLA-matched donor.

If an HLA-matched donor is unavailable (Section 2.4), the following sequence is recommended:

1. - Review HLA-typing of siblings and perform extended family typing, as appropriate, to ascertain parental haplotypes. If an HLA-haploidentical donor is identified, then proceed with criteria for "preferred donor" below. If no HLA-haploidentical donor is identified and there are additional siblings or half-siblings willing to be typed for potential donation, then perform HLA and ABO typing and determine CMV serologic status of the remaining siblings or half-siblings.
2. - If a *preferred donor* (defined below) is not identified from the siblings or half-siblings, then consider performing HLA and ABO typing and determining CMV serologic status of parents that are ≤ 60 years of age and children ≥ 18 years of age. If typing of parents and children is not performed, and no HLA-haploidentical sibling meets the criteria for a *preferred* donor, then choose a *suitable donor*, defined as the HLA-haploidentical sibling who meets most of the criteria for preferred donor, in the order listed. If typing of parents and children is performed but no preferred donor is identified, then choose the most suitable donor.
3. - If a preferred or suitable donor is still not identified, perform HLA and ABO typing and determine CMV serologic status of parents ≥60 years old.

A *preferred donor* is defined as one who meets all the following criteria:

1. - Medically and psychologically fit and willing to donate.
2. - If the patient is CMV seronegative, then the donor should be CMV seronegative.
3. - No major ABO incompatibility:
    a. - If the patient is blood type "O", then the donor should be type "O".
    b. - If the patient is blood type "A", then the donor should be type "A" or "O"
    c. - If the patient is blood type "B", then the donor should be type "B" or "O"

If more than one preferred donor or more than one suitable donor is identified and there is no medical reason to prefer one of them, then the following guidelines are recommended:

1. If the patient and family express a strong preference for a particular donor, use that one
2. If the donor is a sibling, choose the youngest sibling
3. If the donor is not a sibling, choose a parent over a child (for psychological reasons)

APPENDIX E

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1) / f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B < 1 < A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$, and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N \mid \theta_j) \equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0) \le \alpha$ and $\Pr_1(\text{reject } H_0) \le \beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2, ...$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1 (> \theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A = (1-\beta)/\alpha$ and $B = \beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1) = (A^{h(\theta)} - 1)/(A^{h(\theta)} - B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int (f(x;\theta_1)/f(x,\theta_2))^{h(\theta)} f(x;\theta) dx = 1$.

The formula $E(N;\theta) = [[(1 - O(\theta)] \log A + O(\theta) \log B] / E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N) \approx [E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Uncensored Exponential Survival Times

For example, we wish to construct a sequential test for the composite null hypothesis that the rate of treatment-related mortality (TRM) at 100 days is less than or equal to 30% versus the alternative hypothesis that it is greater than or equal to 50%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 5%, and that the test provide 80% power to reject the null hypothesis under a specified alternative that the true rate is 50%. A maximum sample size of 50 patients will be permitted.

Let us assume that the survival times, $T_1, T_2, ..., T_n$, are completely observed (uncensored) and are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, a 100-day survival rate of 70% translates into a mean survival of 0.768 years ($\theta_0 = 1.303$), and 50% translates into a mean survival of 0.395 years ($\theta_1 = 2.532$).

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, - $H_0 : \theta = \theta_o = 1.303$ versus $H_1 : \theta = \theta_1 = 2.532$. However, since the log-likelihood ratio for the exponential, $\log\prod_i^n f(x_i;\theta_1) - \log\prod_i^n f(x_i,\theta_0) = n(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, is a monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ. Thus the SPRT is a one-sided level .05 test of a composite null ($H_0 : \theta \le \theta_o = 1.303$) versus a composite alternative ($H_1 : \theta \ge \theta_o = 1.303$), with power of $1 - \beta = .80$ at the selected alternative $\theta = \theta_1 = 2.532$.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\log\theta_0 - \log\theta_1)/(\theta_0 - \theta_1) = 0.541$, and intercepts $\log A/(\theta_0 - \theta_1) = -2.256$ and $\log B/(\theta_0 - \theta_1) = 1.270$, for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the cumulative sum of failure times, $\sum_i^n T_i$, is recomputed, and plotted against the current sample size, n. When this graph crosses the lower boundary, the null hypothesis is rejected.

The maximum sample size of 50 patients requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 50 patients, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 50 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. However, we consider it reasonable to assume the hazard for TRM is constant over the first 100 days post-transplant, and

we will restrict our attention to this time interval. Furthermore, it is not practical to conduct a clinical study by putting each individual on trial, and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from transplant to failure, or to the 100 day time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number of individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times, $T_1, T_2, ..., T_n$, with censored failures times, $x_1, x_2, ..., x_n$, and the current sample size, n, with the number of observed failures, d.

Now we relax the second assumption, and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 50 patients to the study, and that the final analysis takes place 100 days after the last patient is entered. Putting all of this together, we propose a modified truncated SPRT, where at any interim time point, s, ranging from 0 to 3 years 100 days, the sum of observed time on study, $\sum_i^n X_i(s)$ is plotted against the number of observed failures, $d(s)$. In practice, monitoring will be scheduled monthly after the start of enrollment to the study. A further modification to the SPRT was to only use the lower boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 100-day TRM rates.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

Recall that the uncensored SPRT targeted a drop in survival at Day 100 from 70% to 50%, with type I and II errors of 5% and 20%. Since only the lower boundary is used for monitoring, the continuation region of the test was bounded below by a line with a slope of 0.541 and intercept of –2.256. The effect of truncation is to reduce the power of the test. In order to compensate for this, we raise the lower boundary to make it easier to cross. Under the further assumption of uniform accrual over a three year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study. These simulation show that an intercept of –1.741, corresponding to setting parameters α and β to 10% and 15%, result in empirical type I and II error rates of about 5% and 20%.

Table E-1 Operating Characteristics of Sequential Testing Procedures from a Simulation Study with 100,000 Replications

Treatment-Related Mortality (TRM)

True 100-Day Rate	30%	35%	40%	45%	50%
Probability Reject Null	0.07	0.20	0.41	0.66	0.86
Mean Month Stopped	34.5	32.3	28.5	23.5	18.5
Mean # Endpoints in 100 Days	13.8	15.0	15.1	14.0	12.1
Mean # Patients Enrolled	48	45	40	33	26

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true rate of TRM on or before Day 100 was 30%, the test crossed the lower boundary in 7119 of 100,000 replications, for an estimated type I error rate of 7%. When the true rate of TRM on or before Day 100 was 50%, the test failed to cross the boundary in 14226 of 100,000 replications, for an estimated type II error rate of 14%. And on average, the boundary will be crossed at 18.5 months, when 26 patients will be enrolled to the study.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at 100 days, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the 100 day failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first 100 days were high, the exponential test would reject faster than the binomial test, but have not conducted simulation studies to demonstrate this.

APPENDIX F

REFERENCES

[1] Thomas' Hematopoietic Cell Transplantation (ed 3rd). Malden, MA, Blackwell Publishing, 2004.

[2] Weiden PL, Flournoy N, Thomas ED, et al.: Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. N Engl J Med 300:1068-1073, 1979.

[3] Weiden PL, Sullivan KM, Fournoy M, et al.: Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. N Engl J Med 304:1529-1533, 1981.

[4] Sandmaier BM, Mackinnon S, Childs RW: Reduced Intensity Conditioning for Allogeneic Hematopoietic Cell Transplantation: Current Perspectives. Biology of Blood and Marrow Transplantation 13:87-97, 2007.

[5] Kollman C, Abella E, Baitty RL, et al.: Assessment of optimal size and composition of the U.S. National Registry of hematopoietic stem cell donors. Transplantation 78:89-95, 2004.

[6] Barker JN, Krepski TP, Defor TE, et al.: Searching for unrelated donor hematopoietic stem cells: Availability and speed of umbilical cord blood versus bone marrow. Biology of Blood and Marrow Transplantation 8:257-260, 2002.

[7] Anasetti C, Amos D, Beatty PG, et al.: Effect of HLA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. N Engl J Med 320:197-204, 1989.

[8] Anasetti C, Beatty PG, Storb R, et al.: Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. Hum Immunol 29:79-91, 1990.

[9] Luznik L, Jalla S, Engstrom LW, et al.: Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. Blood 98:3456-3464, 2001.

[10] Luznik L, Engstrom LW, Iannone R, et al.: Posttransplantation cyclophosphamide facilitates engraftment of major histocompatibility complex-identical allogeneic marrow in mice conditioned with low-dose total body irradiation. Biol Blood Marrow Transplant 8:131-138, 2002.

[11] O'Donnell PV, Luznik L, Jones RJ, et al.: Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 8:377-386, 2002.

[12] Mayumi H, Umesue M, Nomoto K: Cyclophosphamide-induced immunological tolerance: an overview. [Review] [74 refs]. Immunobiology 195:129-139, 1996.

---

[13] Junghanss C, Boeckh M, Carter RA, et al.: Incidence and outcome of cytomegalovirus infections following nonmyeloablative compared with myeloablative allogeneic stem cell transplantation, a matched control study. Blood 99:1978-1985, 2002.

[14 -] Maris MB, Niederwieser D, Sandmaier BM, et al.: HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative conditioning for patients with hematologic malignancies. Blood 102:2021-2030, 2003.