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FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE,
DEPARTMENT OF MEDICINE, DIVISION OF ONCOLOGY
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Nonmyeloablative Hematopoietic Cell Transplantation (HCT) for Patients with Hematologic Malignancies using Related, HLA-Haploidentical Donors: A Phase II trial of Peripheral Blood Stem Cells (PBSC) as the Donor Source

Principal Investigator:
Rachel Salit, MD, Assistant Member, Fred Hutch; Assistant Professor, UW
206-667-1317

Biostatistician:
Ted Gooley, Ph.D., Full Member, FHCRC; Affiliate Full Professor of Biostatistics, UW
206-667-6533

Clinical Research Nurse: Nancy Anderson, RN
206-667-6264

Emergency (24 hour) Phone: (206) 598-8902
Fax: (206)-598-4034

1.0 Introduction

Transplantation of haploidentical bone marrow in the nonmyeloablative setting with post-transplant cyclophosphamide prophylaxis of graft-versus-host disease (GvHD) has been shown to be safe therapy of hematologic malignancies. This approach has extended the transplant option to patients without matched related or unrelated donors, especially to ethnic minorities who have comprised about 20% of patients on these studies. Over 200 such transplants have now been performed at this and other centers. The incidence of graft rejection, nonrelapse mortality and survival is similar to that of transplants using matched donors. The incidences of Grades III/IV acute GvHD and extensive chronic GvHD are similar and possibly lower. In many centers, the lack of availability of operating room time and expertise of harvesters or bias in favor of peripheral blood stem cells (PBSC) have been barriers to acceptance of this approach.

Therefore, we propose a phase II trial of PBSC as the donor source in nonmyeloablative HCT from haploidentical donors in an attempt to overcome such barriers.

1.1 Background

Allogeneic blood or marrow transplantation, following either marrow-ablative or nonmyeloablative conditioning, is a potentially curative treatment for a variety of hematologic malignancies and non-malignant hematologic disorders [1]. Of all the potential sources of allografts, those from human leukocyte antigen (HLA)-matched donors have generally produced the best overall and progression-free survival [2]. Unfortunately, HLA- matched donors can be found in only about 70% of transplant candidates. For patients who lack HLA-matched donors alternative sources of allografts are units of umbilical cord blood or HLA-mismatched (haploidentical) related donors [3]. Since any patient shares exactly one HLA haplotype with each biological parent or child and half of siblings, an eligible HLA-haploidentical donor can be identified rapidly in nearly all cases.

Cyclophosphamide (Cy) is a highly immunosuppressive anti-neoplastic agent that has an established role in conditioning for allogeneic transplantation. Typically, the drug is administered prior to transplantation to prevent graft rejection by suppressing the host immune system. In contrast, administration of a properly timed, high dose of Cy after transplantation can inhibit both graft rejection and GvHD. Studies in mouse models of haploidentical bone marrow transplantation have shown that administration of high-dose cyclophosphamide early post-transplant deletes the highly alloreactive clones of T-cells, which in the absence of any other immunosuppressive therapy, would become activated and proliferate in the first few days post-transplant causing severe GvHD [4-7]. Studies at this center and at Johns Hopkins University over the past several years have shown that bone marrow transplanted from haploidentical donors as treatment of high-risk hematologic malignancies can engraft rapidly and stably after nonmyeloablative conditioning that includes post-transplantation Cy [8],[9][unpublished data]. Protocols at this center and Johns Hopkins differed in the dose of post-transplant cyclophosphamide (Cy) administered as GvHD prophylaxis (50 mg/kg at day+3 [FHCRC] or 50 mg/kg on days +3, +4 [JHU]). The only difference in outcomes observed between the two protocols was a higher incidence of extensive chronic GvHD in the group receiving a single dose of post-transplant Cy (25% vs. 5%, respectively) [9].

To date, 48 patients have been transplanted on protocol 1667 at this center (Ref 9] included the first 28 patients). Six of 45 evaluable patients (survival ≥28 d) failed to engraft. Successful donor engraftment (≥95% donor T-cells) was achieved in all patients who survived to day +100. Persistent mixed chimerism of donor T-cells or granulocytes was not observed in any patient. The rate of primary graft rejection was 13%. A fatal outcome secondary to persistent aplasia was observed in two of the 6 patients who rejected their grafts. No secondary graft failures were observed

Other safety endpoints of the study were met by the low and acceptable rates of severe acute GvHD or NRM. Comparison of outcomes after haploidentical transplants to those after related or unrelated donors at this or other centers is shown in Table 1.1. The rates of Grades III/IV GvHD (9%) and of extensive chronic GvHD (23%) were similar to or lower than that observed for matched donors. Some of the difference may be related to the donor source (bone marrow in protocol 1667 vs. peripheral blood stem cells in most current transplants from matched donors) which is known to affect the development of chronic GvHD[10]. The rate of NRM at 1 yr was 23%, also similar to patients transplanted from matched donors. NRM occurred almost exclusively in patients with lymphomas, primarily due to infection. Many of these patients had extensive prior cytotoxic therapy including autologous transplantation for their recurrent diseases and had progressive disease at the time of transplantation. Clearly, special attention to monitoring for infection and prophylaxis and treatment is warranted in such patients.

Although not endpoints of this study, survival data showed that the transplant approach with haploidentical donors can be effective therapy for hematologic malignancies with overall and event-free survival of 36% and 32%, respectively at 3 yr. For a mixed population of advanced hematologic malignancies, these outcomes are not different from those observed with matched donors. In our study, relapse was the main cause of treatment failure. Patients with myeloid or lymphoid malignancies who were long-term survivors were either those with high-risk AML in first complete remission or lymphoma patients who had a very good partial or complete response to salvage chemotherapy. There were no survivors among the 5 patients with AML in second or third complete remissions or among patients with bulky lymphomas. One explanation of this outcome is that the GvL effect may be diminished by post-transplant depletion of T-cells by cyclophosphamide making it is less effective against residual, more aggressive leukemia or lymphoma cells which have undergone genetic selection during disease progression. Treatment failures in patients with refractory disease, particularly lymphomas suggest that eligibility criteria in the current trial should be revised to exclude such patients.

Table 1.1 Comparison of outcomes after nonmyeloablative transplantation for heterogeneous populations of high-risk hematologic malignancies using matched donors or related haploidentical donors

	Haploidentical		Unrelated			Related	
	FHCRC [9][1] (2009)	FHCRC/JHU [9] (2008)	Giralt [10] (2007)	Maris [11] (2003)	Mielcarek [12] (2007)	McSweeney [13] (2001)	Mielcarek [12] (2007)
N	48	68	285	89	184	45	221
Med Age (range)	40 (20-71)	46 (1-71)	53 (18-79)	53	56 (5-75)	56	55 (20-73)
Graft Source							
BM (%)	100	100	52	20	4	0	0
PBSC (%)	0	0	48	80	96	100	100
HLA-matched (%)	0	0	84	61	87	100	100
Rejection (%)	13	13	11	21		20	
Acute GvHD (%)							
II-IV	57	34	39	52	74	50	52
III/IV	9	6	22	10	15	15	15
Chronic GvHD (% at 2 yr)	25	25/5	41	37	67	68	68
NRM (% at 1 yr))	23	15	30	18	20	10	20
Survival (% at 3 yr)							
DFS	30	26	22	33		45	
OS	36	36	28	40	40	60	50

[1]Includes data on an additonal 20 patients

A number of randomized, controlled trials in the myeloablative setting have shown that the incidence of clinically significant acute GvHD after transplantation using PBSC does not differ significantly from that after BMT despite the fact that G-CSF-mobilized PBSC allografts contain ~10-fold greater number of T-cells than marrow allografts [10].

Although there are no such randomized trials in the nonmyeloablative setting, outcomes seen with PBSC in phase II trials are consistent with results in the myeloablative setting (see Table 1.1). The reason that acute GvHD is not increased markedly despite the 10-fold excess of T-cells in the PBSC allograft is thought to be due to a skewing of the T-cell repertoire in PBSC caused by exogenous G-CSF from a Th1 immunophenotype which is known to play a direct role in acute GvHD to an anti-inflammatory Th2 immunophenotype which can suppress acute GvHD [14]. Use of PBSC may have several advantages over bone marrow as the allograft source for haploidentical transplants including (1) ease of collection, (2) more rapid time to platelet-independence (2 wks vs. 3 wks) and (3) decreased relapse in advanced hematologic malignancies, the primary cause of treatment failure in our studies using bone marrow as the allograft source. Disadvantages may include (1) a higher incidence of grades III/IV acute GvHD and (2) a higher incidence of extensive chronic GvHD. No differences would be expected in recovery of neutrophils (median of 12 d in the FHCRC/JHU protocols) or in nonrelapse mortality at 1 yr post-transplant.

2.0 Study Overview

This is a Phase II study to assess the safety of haploidentical peripheral blood stem cell transplantation using a nonmyeloablative preparative regimen and post-transplant cyclophosphamide.

2.1 Primary Endpoints

To demonstrate that use of PBSC in place of marrow as the source of lymphocytes and stem cells for nonmyeloablative transplants from related, haploidentical donors will not result in unacceptable rates of high-grade acute or chronic GvHD, nonrelapse mortality or relapse compared to historical data on nonmyeloablative transplants from unrelated donors.

2.2 Secondary Endpoints

Estimates of the rates of neutrophil and platelet recovery, number of RBC and platelet transfusions, incidences of graft failure, transplant-related toxicities, disease-free survival and overall survival.

2.3 Patient Inclusion Criteria

2.3.1 No age limit.

2.3.2 Molecular based HLA typing will be performed for the HLA-A, -B, -Cw, -DRB1 and –DQB1 loci to the resolution adequate to establish haplo-identity. 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 or low-likelihood of finding a matched, unrelated donor.

2.3.3 Acute leukemias (includes T lymphoblastic lymphoma). 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. If the marrow has < 20% cellularity due to treatment related cytotoxicity, but still has < 5% blasts, an exception may be made to include this patient up to PI discretion.

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

2.3.3.1.1 Adverse cytogenetics including but not limited tot(9;22), t(1;19), t(4;11), MLL rearrangements.

2.3.3.1.2 White blood cell counts >30,000/mcL,

2.3.3.1.3 Patients over 30 years of age

2.3.3.1.4 Time to complete remission >4 weeks

2.3.3.1.5 Presence of extramedullary disease.

2.3.3.1.6 Minimal residual disease

2.3.3.1.7 Other risk factors determined by the patient's attending physician to be high risk features requiring transplantation.

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

2.3.3.2.1 Greater than 1 cycle of induction therapy required to achieve remission,

2.3.3.2.2 Preceding myelodysplastic syndrome (MDS),

2.3.3.2.3 Presence of Flt3 abnormalities,

2.3.3.2.4 FAB M6 or M7 leukemia, or

2.3.3.2.5 Adverse cytogenetics for overall survival such as

2.3.3.2.5.1 those associated with MDS

2.3.3.2.5.2 Complex karyotype (≥ 3 abnormalities)

2.3.4.3.5.3 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)

2.3.3.2.6 Other risk factors determined by the patient's attending physician to be high risk features requiring transplantation.

2.3.3.3 Acute Leukemias in 2nd or subsequent remission

2.3.3.4 Biphenotypic/Undifferentiated Leukemias in 1st or subsequent CR.

2.3.3.5 High-risk MDS status-post cytotoxic chemotherapy

2.3.4 Burkitt's lymphoma: second or subsequent CR.

2.3.5 Lymphoma.

2.3.5.1 Chemotherapy-sensitive (at least stable disease; see response criteria Appendix C) 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.

2.3.5.2 Marginal zone B-cell lymphoma or follicular lymphoma that has progressed after at least two prior therapies (excluding single agent Rituxan).

2.3.6 MM Stage II or III patients who have progressed after an initial response to chemotherapy or autologous HSCT or MM patients with refractory disease who may benefit from tandem autologous-nonmyeloablative allogeneic transplant.

2.3.7 Patients with adequate physical function as measured by:

2.3.7.1 Cardiac: left ventricular ejection fraction at rest must be $\geq$ 35%.

2.3.7.2 Hepatic: bilirubin $\leq$ 2.5 mg/dL; and ALT, AST, and Alkaline Phosphatase **<** 5 x ULN.

2.3.7.3 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.

2.3.7.4 Pulmonary: FEV_1, FVC, DLCO (diffusion capacity) $\geq$ 40% predicted (corrected for hemoglobin); if unable to perform pulmonary function tests, then O_2 saturation > 92% on room air.

2.3.7.5 Performance status: Karnofsky/Lansky score $\geq$ 60%.

2.3.7.6 Patients who have received a prior allogeneic HSCT and who have either rejected their grafts or who have become tolerant of their grafts with no active GVHD requiring immunosuppressive therapy.

2.3.8 Patients will undergo standard pre-transplant work-up as dictated by standard practice guidelines the results of which may be used for screening for this study.

2.4 Patient Exclusion Criteria

2.4.1 HLA-matched, or single allele-mismatched donor able to donate.

2.4.2 Pregnancy or breast-feeding.

2.4.3 Current uncontrolled bacterial, viral or fungal infection (currently taking medication with evidence of progression of clinical symptoms or radiologic findings).

2.4.4 Patients with primary idiopathic myelofibrosis.

2.5 Donor Inclusion Criteria

2.5.1 Donors must be HLA-haploidentical first-degree relatives of the patient. Eligible donors include biological parents, siblings, or children, or half-siblings.

2.5.2 Age ≥ 12 years

2.5.3 Weight ≥ 40 kg

2.5.4 Ability of donors < 18 years of age to undergo apheresis without use of a vascular access device; vein check must be performed and verified by an apheresis nurse prior to arrival at the SCCA

2.5.5 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.

2.6 Donor Exclusion Criterion

2.6.1 Positive anti-donor HLA antibody.

2.7 Donor Prioritization Schema

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

2.7.1.1 For CMV seronegative recipients, a CMV seronegative donor

2.7.1.2 Red blood cell compatibility

2.7.1.2.1 RBC cross-match compatible

2.7.1.2.2 Minor ABO incompatibility

2.7.1.2.3 Major ABO incompatibility

2.8 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* Mesna 14.5 mg/kg in 4 divided doses
Day –4→-2	Fludarabine 30 mg/M^2 IV over 30-60 minutes
Day –1	TBI 200 cGy, donor apheresis
Day 0	T cell replete PBSC

Days 3,4	Cyclophosphamide 50 mg/kg IV Mesna 50mg/kg IV in 4 divided doses
Day 5	Begin tacrolimus ,mycophenolate, and G-CSF

2.8.1 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 Principal Investigator must be consulted.

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

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

(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

2.8.2 Pre-transplantation Cyclophosphamide with Mesna

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 actual body weight unless the patient weighs more than 100% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see below for formulas).

Mesna should be given in 4 divided doses IV per standard practice. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of mesna is equal to 100% of the total daily dose of cyclophosphamide.

2.8.2.1 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

2.8.2.2 Adjusted Ideal Body Weight Formula:

$$AIBW = IBW + [(0.25) \times (ABW - IBW)]$$

2.8.3 Total Body Irradiation

Total body irradiation: 200 cGy will be administered in a single fraction on Day –1 via linear accelerator.

2.8.4 Hematopoietic Stem Cell Infusion

Donors who consent to PBSC donation will receive 5 daily doses of G-CSF, 16 µg/kg/day by subcutaneous injection commencing on day –5. PBSC's will be collected in the afternoon of day -1, stored at 4C overnight, and infused as soon as possible on day 0. If the collection on day –1 contains less than 5.0 X 10^6 CD34+ cells per kg recipient weight, a second collection will be performed the following morning and transfused on day 0.

Quantitation of CD34 and CD3 cells will be performed by the Cellular Therapy Lab. *For all patients, the target number of CD34 cells to be infused should be 5-6 X 10^6 cells per kg recipient weight.* PBSC in excess of 6.0 x 10^6 CD34 cells/kg recipient weight may be cryopreserved.

2.8.5 Post-transplantation Cyclophosphamide with Mesna

Hydration prior to cyclophosphamide may be given according to Standard Practice Guidelines.

Cyclophosphamide [50mg/kg] will be given on Day 3 post-transplant (approximately 72 (+/- 12 hours) after marrow infusion) and on Day 4 post-transplant (approximately 24 (+/- 6 hours) hours after Day 3 cyclophosphamide).

Cyclophosphamide will be given as an IV infusion over 1-2 hours (depending on volume).

Mesna should be given in 4 divided doses IV per standard practice post-cyclophosphamide. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of mesna is equal to 100% of the total daily dose of cyclophosphamide.

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.

2.8.6 Tacrolimus

Tacrolimus will be given at a dose of 1 mg IV daily or 1 mg po twice daily. If tacrolimus is initiated using the IV formulation it will be changed to a PO dosing schedule once a therapeutic level is achieved. Serum levels of tacrolimus will be measured around Day 7 and then should be checked at least 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.

2.8.7 Mycophenolate

Either the sodium salt of mycophenolate or mycophenolate mofetil (MMF) may be used as prophylaxis of GvHD and will be dosed by actual body weight. Only MMF is available as IV formulation. Sodium mycophenolate will be given at a dose of 10mg/kg PO TID rounded to the nearest number of 180mg tablets. MMF will be given at a dose of 15 mg/kg PO TID. The maximum total daily dose should not exceed 2160 mg (sodium salt) or 3 grams (mofetil). Mycophenolate prophylaxis will be discontinued after the last dose on Day 35, or may be continued if active GVHD is present.

2.8.8 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 the absolute neutrophil count (ANC) is $\geq$ 1,000/mm^3 for three consecutive days.

2.8.9 Supportive Care

Patients will receive transfusions, infection prophylaxis and nutritional support according to Standard Practice Guidelines.

2.8.10 Transfusion Support

Platelet and packed red cell transfusions will be given per Standard Practice Guidelines.

2.8.11 Anti-Ovulatory Treatment

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

2.9 Risks and Toxicities

2.9.1 Cyclophosphamide

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

2.9.2 Fludarabine

The most serious side effect is neurotoxicity which may include agitation or confusion, blurred vision, loss of hearing, peripheral neuropathy or weakness. Severe neurologic effects, including blindness, coma, and death have been observed in 36% of patients treated with doses approximately four times greater than specified in this protocol. Other side effects may include anemia, VTE, fever, skin rash, nausea/vomiting, diarrhea , stomatitis, anorexia, chills, peripheral edema, and, very rarely, hemorrhagic cystitis and pulmonary toxicity.

2.9.3 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.

2.9.4 Mycophenolate

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

2.9.5 Tacrolimus

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

2.9.6 Graft Failure

Based on historical data with nonmyeloablative transplants of PBSC, there could be a 15% chance of graft failure.

2.9.6.1 Management of Slow Engraftment and Graft Failure

Slow engraftment or graft failure should be managed according to Standard Practice Guidelines.

3.0 STUDY ENDPOINTS

3.1 Primary Endpoints

3.1.1 Acute GvHD
Incidence of grades III/IV acute GvHD at day +84. GvHD is scored as described in Appendix A.

3.1.2 Chronic Graft-versus-Host Disease. Scored according to the NCI criteria as described in Appendix B. The time to onset of limited and extensive chronic GVHD will be recorded.

3.1.3 Nonrelapse Mortality (NRM)
The cumulative incidence of NRM should be estimated at day +100 and at 1 year. An event for this endpoint is death without evidence of disease progression.

3.1.5 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 of lymphoma progression. When in doubt, the diagnosis of recurrent or progressive lymphoma should be documented by tissue biopsy.

Because malignant cells can sometimes evade immune attack of the GvL effect after haploidentical HCT by mutation to uniparental disomy of the HLA region, HLA-typing of tissue samples: (for example bone marrow, peripheral blood, or lymph node) obtained from patients who experience recurrent disease will be performed whenever possible to direct potential therapy strategies.

3.1.5.1 Relapse of acute leukemia will be diagnosed when there is: (i) reappearance of leukemia blast cells in the peripheral blood, (ii) > 5% blasts in the marrow not attributable to another cause (e.g., bone marrow regeneration), (iii) the appearance of new dysplastic changes within the bone marrow, (iv) the development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid, or (v) clonal cytogenetic abnormalities.

3.1.5.2 Relapse of lymhphoma is diagnosed when there is: (i) 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 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), or (ii) 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, or (iii) at least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

3.1.5.3 Multiple Myeloma. Relapse or progressive disease will be diagnosed when there is: (i)Reappearance or increase in the serum M or urine globulins, or (ii)Appearance of new lytic lesions in bone, or (iii)Bone marrow examination contains >5% abnormal plasma cells

3.2 Secondary Endpoints

3.2.1 Neutrophil Recovery
Achievement of an ANC ≥ 500/mm^3 for three consecutive measurements on different days. The first of the three days will be designated the day of neutrophil recovery.

3.2.2 Primary graft failure
< 5% donor CD3 chimerism as measured at day +84.

3.2.3 Secondary graft failure/rejection: Decline of neutrophil count to <500/ul with loss of donor chimerism after day 55.

3.2.4 Platelet recovery
The first day of a sustained platelet count >20,000/mm^3 with no platelet transfusions in the preceding seven days.

3.2.5 Donor Cell Engraftment
Donor chimerism in the T-cell (CD3-positive) and granulocyte (CD33-positive) fractions of sorted peripheral blood ≥ 50% on day ≥ 84 after transplantation. Donor engraftment also should be tested on day +28.

3.2.6 Progression-free Survival
Progression-free survival is the minimum time interval to relapse/recurrence, to death or to last follow-up.

3.2.7 Infections

Infections will be reported by anatomic site, date of onset, organism and resolution, if any.

4.0 PATIENT ENROLLMENT AND EVALUATION

4.1 Protocol Registration

On the basis of diagnosis and type of transplant, the Clinical Coordinator will assign patients to this protocol. Additional screening will be completed pre-transplant to ensure the patient and donor meet the inclusion and exclusion criteria. Patients will be registered between 8:00 am and 5:00 pm, Monday through Friday.

In addition, for each patient on this study a copy of the signed informed consent and a completed FHCRC Research Subject Registration Form (Appendix D) must be sent to the FHCRC Research Coordinator via email as a PDF or by FAX to 206-667-2011.

4.2 Clinical Evaluation

The follow-up schedule for scheduled study visits is outlined in Table 4.4.5.

4.3 Records

The primary research record includes the medical chart and standard flow sheets on which clinical information and laboratory data are recorded. The medical records department at each site maintains all original inpatient and outpatient chart documents. Patient case report forms will be kept in a locked file cabinet in a secure building. The patient database will be maintained by the study coordinator in a secure computer network at FHCRC. Any publication or presentation will refer to patients in agggregate and not by name.

4.4 Procedures for Data Safety and Monitoring

The PI and research coordinator for this study will closely monitor all patients enrolled on this study. The clinical research nurse and PI will, at a minimum, meet to evaluate patient data after each group of 3 patients has completed the “day 80” departure work-up which is typically performed between days 80 and 100 post-transpant.

The dedicated protocol Data Safety Monitoring Board (DSMB) will consist of two clinical investigators not associated with the study and the study biostatistician. The DSMB will review protocol outcomes annually; at least 2 of the 3 members must be present to hold the meeting. This Committee will be responsible for making a recommendation regarding the continuation or discontinuation of the

current protocol based on these outcomes in comparison to other settings with regard to the safety and potential efficacy of the proposed regimen.

4.4.1 Guidelines for Reporting Serious Adverse Events

Only serious, unexpected and possibly related adverse events will be reported to the IRB according to FHCRC Guidelines for Reporting Adverse Events through 1 year after transplantation. The PI will review all SAE reports to determine if the report should be submitted to the FHCRC IRB prior to continuing review.

Study-wide deaths will be reported to the FHCRC IRB at continuing review.

4.4.2 Protocol Data and Monitoring Plan

A secondary endpoint of this study is to assess toxicity related to this treatment regimen, specifically to evaluate regimen-related toxicity. Toxicities will be assessed up to the time the patient is discharged from the transplant clinic at the SCCA. Toxicities will be documented per CTCAE v3.0 (see http://ctep.cancer.gov/reporting/ctc.html).

The incidence of all non-hematologic adverse events $\geq$ grade 3 will be determined.

The protocol will be reviewed annually by the Data and Safety Monitoring Committee DSMC of the Fred Hutchinson Cancer Research Center and the protocol-specific DSMB Committee. If the PDMC or Review Committee should recommend discontinuation of the protocol, the IRB will be notified immediately.

4.4.3 GVHD Monitoring

GVHD should be monitored in accordance with each participating site's Standard Practice Guidelines. Assessment of acute GVHD should be performed as clinically necessary and reported monthly on the CRFs supplied by the Coordinating Center. Chronic GVHD will be assessed at 1 year (D365) post-transplant.

4.4.4 Ethnic and Gender Distribution Chart

TARGETED / PLANNED ENROLLMENT: Number of Subjects[1]			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2

Not Hispanic or Latino	20	28	48
Ethnic Category Total of All	21	29	50
A. Racial Categories			
American Indian / Alaska	1	0	1
Asian	1	1	2
Native Hawaiian or Other	0	0	0
Black or African American	2	3	5
White	17	25	42
Racial Categories: Total of All	21	29	50

[1]Based on actual data of Protocol 1667 (48/50 patients accrued as of 7/15/09)

4.4.5 Patient Assessments

TABLE 4.4.5 SUMMARY OF PATIENT CLINICAL ASSESSMENTS

Study Assessments/Testing	Baseline	Day 28*	Day 56*	Day 84*	Day 365*
History, physical exam, weight, height, and Karnofsky/Lansky performance status[1]	X	X	X	X	X
Infectious disease titers[2]	X				
EKG and LVEF	X				
DLCO, FEV1 and FEV or O_2 saturation	X				
Bone marrow aspirate for pathology and cytogenetics (as clinically indicated) and/or biopsy[3]	X	X	X	X	X
CT or PET/CT imaging[4]	X			X	X
Chest X-ray[6]	X				
ß-HCG serum pregnancy test (non-menopausal women[7])	X				
Acute GVHD assessments		X	X	X	
Chronic GVHD assessment					X
Chimerism[5]		X		X	X

Notes:

[1] History, height, weight, and Karnofsky/Lansky performance status only required at baseline

[2] 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.

[3] LEUKEMIA and MDS PATIENTS ONLY. Bone marrow aspirate and/or biopsy should be sent to pathology, cytogenetics and hematopathology for flow cytometry.

[4] LYMPHOMA AND CLL PATIENTS ONLY

[5] Chimerism will be measured by STR-PCR on peripheral blood sorted into CD3+ and CD33+ cell fractions.

[6] Chest-Xray is only required in patients not having Chest CT

+/- 14 days from expected. Day 365 evaluations should be done +/- 60 days from expected.

[7] Menopause confirmed by gynecology note

* Day 28 & 56 evaluations should be done +/- 7 days from expected. Day 84 evaluations should be completed

5.0 Statistical Considerations and Termination of the Study

The primary objective of this trial is to assess the safety and potential efficacy of the use of haploidentical PBSC with a nonmyeloabaltive preparative regimen and post-transplant cyclophosphamide. The endpoints that will contribute to this assessment include severe acute GVHD, chronic GVHD, relapse, and NRM. Specific benchmarks for each of these endpoints will not be set, but guidelines for what would be considered

acceptable rates will be drawn from the haploidentical setting where bone marrow is the source of stem cells in addition to data from "matched" unrelated donors. Experience with the regimen proposed in the current protocol with bone marrow as the source of stem cells has led to severe acute GVHD in less than 10% of patients, chronic GVHD in roughly 25% of patients, an estimated probability of relapse by 3 years of approximately 50%, and non-relapse mortality by one year of about 15%. In the unrelated donor setting using PBSC, rates of severe GVHD range from 10-25%, chronic GVHD ranges from roughly 40% to 70%, non-relapse mortality at 1 year 20-30%, and relapse by 3 years in the neighborhood of 50%. A protocol-specific DSMB consisting of two clinical investigators who are not associated with the study and the study biostatistician will meet yearly, and this committee will be responsible for making a recommendation regarding the continuation or discontinuation of the current protocol based on these outcomes in comparison to other settings with regard to the safety and potential efficacy of the proposed regimen.

Fifty patients will be enrolled. This sample size was not chosen based on any statistical arguments or desire to show statistically significant differences with respect to historical benchmarks. Rather it was chosen based on a balance between a number of patients that could be enrolled in a reasonable time frame and a number that provides a reasonably precise estimate of each of the above endpoints. With 50 patients, the estimate of failure for each endpoint will be within at least 0.12 of the true failure rate with 90% confidence. We believe that this level of precision will allow an informed decision as to whether PBSC is an acceptable alternative to BM in this setting.

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APPENDIX A

ACUTE GRAFT-VERSUS-HOST-DISEASE STAGING AND GRADING TABLES

Clinical Stage of Acute GVHD According to Organ System

Stage	Skin	Liver	Intestine [1]
1	Maculopapular rash <25% of body surface	Bilirubin 2-3 mg/dl	>500-1000 mL diarrhea per day or (nausea, anorexia or vomiting with biopsy (EGD) confirmation of upper GI GVHD
2	Maculopapular rash 25-50% of body surface	Bilirubin 3.1-6 mg/dl	>1000 -1500 mL diarrhea per day
3	Maculopapular rash >50% body surface area or Generalized erythroderma	Bilirubin 6.1-15 mg/dl	>1500 mL diarrhea per day
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus

Overall Clinical Grading of Severity of Acute GVHD

Grade	Skin	Liver	GI
I	1-2	0	0
II[A]	3 and/or	1 and/or	1
III[A,B]	4 and/or	2-4 and/or	2-4
IV[A,C]	4 and/or	2-4 and/or	2-4

A. Grade II-IV GVHD with only single organ involvement should be biopsy confirmed.
B. Non-fatal GVHD
C. Fatal GVHD

[1] For pediatric patients the following diarrhea volumes will apply:
Stage 1 - > 10 ml/kg/day
Stage 2 - > 20 ml/kg/day
Stage 3 - > 30 ml/kg/day

APPENDIX B

CHRONIC GRAFT-VERSUS-HOST DISEASE (GvHD)

Chronic GVHD in allogeneic transplant recipients resembles autoimmune disorders such as scleroderma,Sjogren syndrome, primary biliary cirrhosis, lichen planus, wasting syndrome, bronchiolitis obliterans among other manifestations (see below). Approximately 50% of patients will develop this complication within 6 months after the transplant despite continued treatment with immunosuppressive medications. Close monitoring is recommended during the first 2 years after allogeneic stem cell transplantation so that appropriate treatment can be instituted promptly in patients who develop chronic GVHD. Debilitation, joint contractures and profound immunosuppression resulting in recurrent bacterial infections are prominent characteristics of untreated chronic GVHD.

A. Classification of Chronic GVHD

The purpose of this classification is to identify patients with cGVHD who need long-term systemic immunosuppression according to clinical and laboratory findings and risk factors at the time of initial diagnosis. In addition, a morbidity scale has been developed to help grade the severity of manifestation of chronic GVHD (see below) at the time of diagnosis, when changes in treatment are made and when assessing treatment response.

1. Chronic GVHD not requiring systemic treatment: mild abnormalities involving a single site, with platelet count >100,000 and no steroid treatment at the onset of chronic GVHD

a) Oral abnormalities consistent with cGVHD, a positive skin or lip biopsy, and no other manifestations of cGVHD.

b) Mild liver test abnormalities (alkaline phosphatase ≤2 x upper limit of normal, AST or ALT ≤3 x upper limit of normal and total bilirubin ≤1.6) with positive skin or lip biopsy, and no other manifestations of cGVHD.

c) Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of body surface area (BSA), dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of cGVHD.

d) Ocular sicca (Schirmer's test ≤5mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of cGVHD.

e) Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of cGVHD.

2. Chronic GVHD requiring systemic treatment: more severe abnormalities or involvement of multiple sites, or platelet count <100,000, or steroid treatment at the onset of chronic GVHD

a) Involvement of two or more organs with symptoms or signs of cGVHD, with biopsy documentation of cGVHD in any organ.

b) ≥15% base line body weight loss not due to other causes, with biopsy documentation of cGVHD in any organ.

c) Skin involvement more extensive than defined for clinical limited cGVHD, confirmed by biopsy.

d) Scleroderma or morphea.

e) Onycholysis or onychodystrophy thought to represent cGVHD, with documentation of cGVHD in any organ.

f) Decreased range of motion in wrist or ankle extension due to fascitis caused by cGVHD.

g) Contractures thought to represent cGVHD.

h) Oral involvement with functional impairment, refractory to topical treatment.

i) Vaginal involvement with functional impairment, refractory to topical treatment.

j) Bronchiolitis obliterans not due to other causes.

k) Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase >2 x upper limit of normal, AST or ALT >3 x upper limit of normal, or total bilirubin >1.6, and documentation of cGVHD in any organ.

l) Positive upper or lower GI biopsy.

m) Fasciitis or serositis thought to represent cGVHD and not due to other causes

B. Physical manifestations of Chronic GVHD

Manifestations that are distinctive for chronic GVHD can begin before day +100 after the transplant, and manifestations that are typical of acute GVHD can persist long after day +100. For this reason, the differential diagnosis between acute and chronic GVHD cannot be made solely according to the time interval from transplant. The diagnosis of chronic GVHD requires at least one manifestation that is distinctive for chronic GVHD (*identified by italic print below*) as opposed to acute GVHD. In all cases, infection and others causes must be ruled out in the differential diagnosis of chronic GVHD. Karnofsky or Lansky Clinical Performance scores <60%, ≥15% weight loss, and recurrent infections are usually signs of clinical extensive chronic GVHD. Abnormalities that could indicate chronic GVHD are categorized by organ system are listed below (*italic print identifies manifestation more distinct of chronic GVHD):*

1) Skin Erythema, dryness, pruritis, macular-papular or urticarial rash, *pigmentary changes (i.e., hyperpigmentation, vitiligo), mottling, papulosquamous or lichenoid plaques, hyperkeratosis, exfoliation (ichtyosis), nodules, scleroderma, morphea (one or several circumscribed, indurated and shiny lesions)*. The extent of skin involvement and the skin

thickness score for patients with scleroderma needs to be recorded at the time of diagnosis, when changes in treatment are made and when assessing treatment response. Medical photos are also useful for assessing the extent of skin involvement and response to treatment.

2) Nails *Ridging, onychodystrophy, onycholysis*

3) Hair *Premature graying (scalp hair, eyelashes, eyebrows), thinning scalp hair, alopecia, decreased body hair*

4) Mouth Dryness, burning, gingivitis, mucositis, striae, *dryness, atrophy, erythema, lichenoid changes, ulcers, labial atrophy or pigmentary changes, tightness around the mouth, sensitivity to acidic, strong flavors, heat or cold, tooth decay*

5) Eyes *Dryness, burning, blurring, gritty eyes, photophobia, pain*
Vagina/vulva *Dryness, dyspareunia, stricture or stenosis, erythema, atrophy or lichenoid changes not induced by ovarian failure or other causes*

6) Liver Jaundice and elevated liver function tests not due to other causes (see laboratory tests)

7) Lung *Bronchiolitis obliterans (see diagnostic indicators), cough, wheezing, dyspnea on exertion, history of recurrent bronchitis or sinusitis*

8) GI Anorexia, nausea, vomiting, diarrhea, *malabsorption, dysphagia, odynophagia*

9) Myofascial *Stiffness and tightness with restriction of movement, occasionally with swelling, pain, cramping, erythema and induration, most commonly affecting the forearms, wrists and hands, ankles, legs and feet, inability to extend the wrists without flexing the fingers or the elbows, contractures*

10) Muscle *Proximal muscle weakness, cramping*

11) Skeletal *Arthralgia of large proximal girdle joints and sometimes smaller joints*

12) Serosal *Unexplained effusions involving the pleural, pericardial, or peritoneal cavities not due to venocclusive disease of the liver, cardiac insufficiency, malignancy, infection, GM-CSF toxicity or other causes*

C. Laboratory Testing and Diagnostic Indicators of Chronic GVHD

1) Eye *Schirmer's test with a mean value ≤ 5 mm at 5 minutes, or values of 6-10 mm in patients who have sicca symptoms, or keratitis detected by slit lamp examination*

2) Liver Elevated liver function tests not due to other causes (alkaline phosphatase ≥2 x upper limit, of normal, AST or ALT >3 x upper limit of normal or total serum bilirubin ≥1.6)

3) Lung *New obstructive lung defect defined as an FEV1 <80% of predicted with either an FEF 25-75 <65% of predicted or RV >120% of predicted, or a decrease of FEV1/FVC by >12%*

within a period of less than 1 year, thought not to be caused by an infectious process, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux. In the absence of GVHD in any other organ, the diagnosis of bronchiolitis obliterans requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high resolution end-expiratory and end-inspiratory CAT scan of the lungs, or confirmation by thoracoscopic biopsy.

4) Esophagus *Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry*

5) Intestine Endoscopic findings of mucosal edema and erythema or focal erosions with histological changes of apoptotic epithelial cells and crypt cell drop out. Patients with unresolved acute GVHD may have more severe intestinal mucosal lesions including ulcers and mucosal sloughing.

6) Muscle *Elevated CPK or aldolase, EMG findings consistent with myositis with biopsy revealing no other etiological process*

7) Blood Thrombocytopenia (usually 20,000-100,000/_l), eosinophilia (> 0.4 x 103/uL), hypogammaglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

Appendix C

LYMPHOMA RESPONSE CRITERIA

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	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
PR	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	Irrélevant if positive prior to therapy; cell type should be specified
SD	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		
Relapsed disease or 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

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

From Cheson, B.D. et al. [15]

Appendix D
Research Subject Registration Form

Protocol Number: 2372 **Principal Investigator** Rachel Salit, MD

Research Subject Name:_____

Date of Birth: ___ ___/___ ___/ ___ ___ ___ ___
Month Day Year

Ethnicity: *(Choose one)*
- ☐ **Hispanic or Latino** (A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. Term "Spanish Origin" can also be used in addition to "Hispanic" or "Latino"
- ☐ **Not Hispanic or Latino**
- ☐ **Refused to Report**

Race: *(check all that apply)*
- ☐ **American Indian/Alaska Native** (A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment)
- ☐ **Asian** (A person having origins in any of the original peoples of the Far East, Southeast, Asia, or the Indian subcontinent including, for example, Cambodia, China, India Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam)
- ☐ **Native Hawaiian/Pacific Islander** (A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands)
- ☐ **Black/African American** (A person having origins in any of the black racial groups of Africa.
- ☐ **White** (A person having origins in any of the original peoples of Europe, the Middle East or North Africa)
- ☐ **Unknown**
- ☐ **Refused to Report**

Gender:
- ☐ Male
- ☐ Female
- ☐ Unknown

HIPAA Authorization: (check one)

- ☐ Protocol covered under general HIPAA authorization
- ☐ Protocol specific HIPAA authorization required for this protocol. *(Attach and submit with this form)*

Name of person completing form (Please Print)

_____

Name Phone Number

_____

Date Submitted Time

FAX COVER SHEET

*DATE:*_____

TO: Research Coordinator

FAX (206) 667-2011

RE: RESEARCH SUBJECT REGISTRATION FORM

FROM:_____

FAX:_____

PHONE:_____