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

Reduced Intensity Conditioning (RIC) and Transplantation of HLA-Haploidentical Related Bone Marrow (Haplo-BM) For Patients With Hematologic Diseases

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	12/03/13	Original to CPRC/IRB	
1	09/12/2016	Updated disease eligibility and general study inclusion /exclusion criteria to match institutional standard language Updated with current protocol template language	no

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Synopsis

Reduced Intensity Conditioning (RIC) and Transplantation of HLA-Haploidentical Related Bone Marrow (Haplo-BM) For Patients With Hematologic Diseases

MT2013-33C

CPRC #2013OC116

This is a treatment guideline to allow routine clinical data to be collected and maintained in OnCore and the University Of Minnesota Blood and Marrow Database as part of the historical database maintained by the department.

Design: This is a treatment guideline for HLA-Haploidentical hematopoietic stem cell transplant (HSCT) using a reduced intensity conditioning (RIC) regimen. This regimen, consisting of fludarabine, cyclophosphamide and low dose total body irradiation (TBI), is designed for the treatment of patients with advanced and/or high risk diseases

Eligibility:

- Diagnosis of a hematologic disease for which a transplant is indicated but without a 7/8 or 8/8 HLA-matched sibling donor or appropriate UCB unit(s)
- Meets the disease specific criteria found in section 3.2
- Age < 75 years of age
- Available related haploidentical bone marrow donor

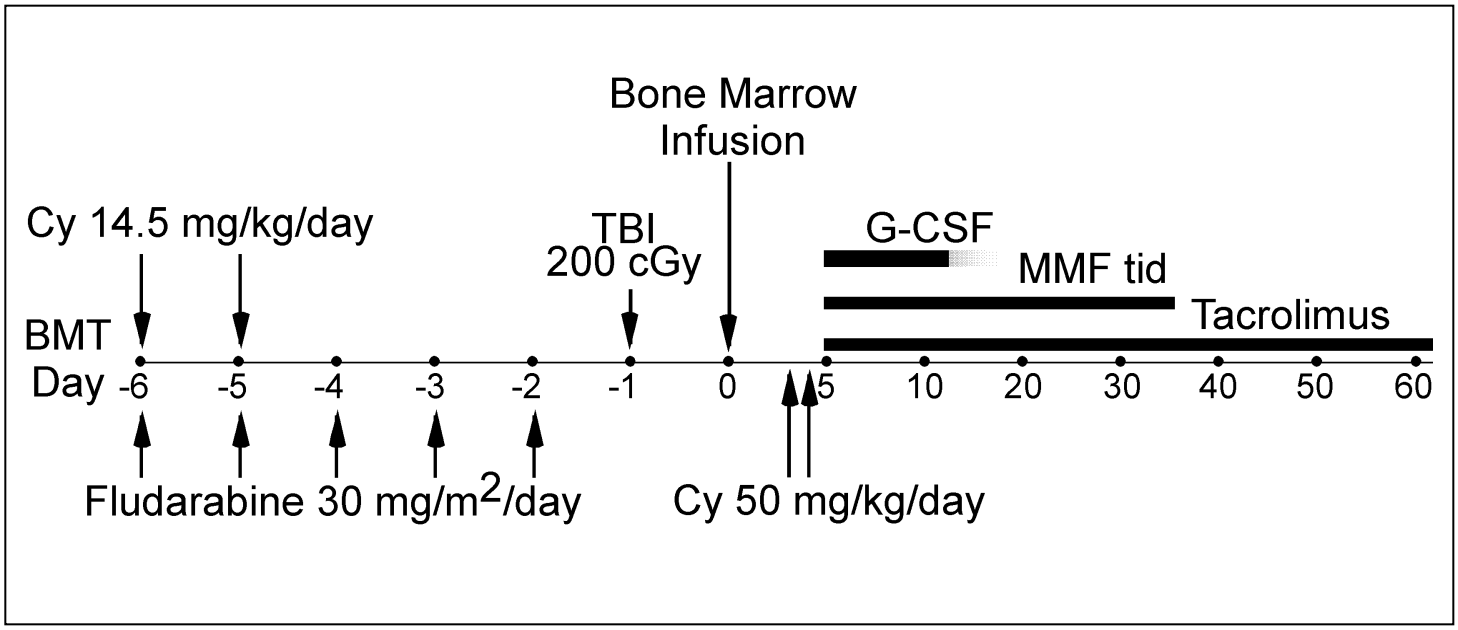
Treatment Plan

treatment day	treatment	protocol section
Day –6, -5	Fludarabine 30 mg/m^2 IV Cyclophosphamide 14.5 mg/kg IV	section 5.1
Day –4, -3, -2	Fludarabine 30 mg/m2 IV over 30-60 minutes	
Day –1	TBI 200 cGy	
Day 0	Non-T-cell depleted bone marrow infusion	section 5.2
Day 3	Cyclophosphamide 50 mg/kg IV	section 5.3
Day 4	Cyclophosphamide 50 mg/kg IV	
Day 5	Begin tacrolimus (or cyclosporine), mycophenolate mofetil, and G-CSF	sections 5.4 and 5.5

Endpoints: Endpoints include survival at 2 years post- transplant, hematopoietic engraftment, chimerism at day 100, 6 months and 1 year, acute GVHD at 100 days, chronic GVHD at 1 year, and transplant related mortality (TRM) at 6 months.

Enrollment: 4 to 5 patients per year

Schema


Bone Marrow
Infusion
Cy 14.5 mg/kg/day
TBI
200 cGy
G-CSF
MMF tid
Tacrolimus
BMT
Day
-6
-5
-4
-3
-2
-1
0
5
10
20
30
40
50
60
Fludarabine 30 mg/m2/day
Cy 50 mg/kg/day

1.0 Introduction

This is a treatment guideline for a haploidentical bone marrow transplant (Haplo-BM) using reduced intensity conditioning (RIC) for patients with a hematologic disease for whom a matched donor or umbilical cord blood is not available. There is no research element except the collection of routine clinical data.

Patients will consent to allow routine clinical data to be collected and maintained in OnCore, the Masonic Cancer Center's (MCC) clinical database, and specific transplant related endpoints in the University Of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

Endpoints include survival at 2 years post-transplant, hematopoietic engraftment, chimerism at day 100, 6 months and 1 year, acute GVHD at 100 days, chronic GVHD at 1 year, and transplant related mortality (TRM) at 6 months.

2.0 Background and Rationale

Allogeneic hematopoietic cell transplantation (HCT) is widely used as a curative therapy for number of hematological diseases. Reduced intensity conditioning (RIC) opened opportunities for older patients and those with comorbid conditions to be eligible for potentially curable transplantation.[1-5] However, donor availability still remains significant challenge for large number of patients as HLA-identical matched sibling (MSD) or adult unrelated donor (MUD) is available only for about 60% of the patients.[6] In addition, the data from the National Marrow Donor Program (NMDP) indicate that median time from donor search to adult MUD transplant is about 3-4 months, this time delay infrequently increases the risk of malignancy relapse in some patients with aggressive diseases.[1,2] Since adult MUD is generally not readily available for many patients with hematological malignancies who are in need for urgent HCT, recent years number of transplant centers widely expended the use of alternative graft sources such as umbilical cord blood (UCB) or haploidentical grafts. [1-5,7-11] Although UCB is timely available for most of the Caucasian patients, its availability is significantly less for ethnic minorities such as African Americans or Asians. Furthermore, significantly high cost of UCB as compared to other donor sources remains an additional limitation. In contrast, lower cost and easy accessibility of haploidentical transplantation (haploHCT) makes it an attractive alternative graft source. First-degree relative haploidentical donor is available for more than 95% of individuals with an average of 2.7 such donors number per patient.[6,12] Initial experience with haploidentical transplantation using T-cell replete allograft was disappointing with unacceptably high incidence of severe graft versus host disease (GVHD) and non relapse mortality (NRM) in about half of the patients.[1314,15] However, when T-cells were depleted and non-myeloablative (NMA) preparative regimen was used

there was an excessive risk of graft failure. Engraftment was improved with the infusion of mega-doses of CD34 + cells (over $10x10^6$ cells/kg) and/or when myeloablative conditioning regimens were used.[9,12,16] On the other hand T-cell depleted myeloablative regimens were associated with significantly increased mortality from serious infections and poor immune reconstitution as reported by the European Group for Blood and Marrow Transplantation (EBMT) [16] Several strategies are still under development to promote T-cell tolerance and reduce the risk of GVHD without affecting immune reconstitution. These approaches include the adoptive therapy of pathogen-specific T-cells,[17-21] T-cells engineered to express suicide genes,[22-24] regulatory T-cells (Tregs),[25,26] alloreactive donor T-cell ex-vivo photodepletion.[27,28], ex vivo anergy induction by costimulation blockade,[29,30] ex vivo selective depletion of T-cells,[31-33] and more recently the administration of high-dose post-transplant cyclophosphamide (PT-Cy).[10,34-37]

PT-Cy approach has become more widely used by many transplant centers in recent years given its ease of administration and low cost. PT-Cy leads to in vivo depletion of alloreactive T-cells that helps reducing both graft rejection and GVHD rates.[38] Recent study by Munchel and colleagues reported 87% sustained engraftment, 27% grades II-IV acute GVHD and 13% chronic GVHD rates among 210 haploHCT recipients with 5-year non-relapse mortality (NRM) of only 18%, relapse incidence of 55% and overall survival (OS) of 35%.[34] Another study by Ciurea and colleagues compared the clinical outcomes of 65 haploHCT recipients with T-cell replete BMT/PT-Cy versus T-cell depleted peripheral blood HCT. They demonstrated superiority of T-cell replete BMT/PT-Cy with significant lower 1-year NRM (16% vs.42%, p=0.03), chronic GVHD rate (8% vs. 18%, p=0.03), and superior progression free (PFS) (45% vs. 21%, p=0.03) and OS (66% vs. 30%, p=0.02).[35] Several recent studies suggest improvement of immune reconstitution with preserved memory T-cells when PT-Cy is used in T-cell replete haploHCT.[34,36] Bashey and colleagues identified comparable relapse rate, DFS and OS were identified between haploHCT/PT-Cy and MSD or adult MUD transplant.[10] Another group of investigators from China retrospectively compared the outcome of 117 patients with various hematological malignancies receiving MSD (n=36) and haploidentical bone marrow transplant (haplo-BM, n=81). They showed higher incidence of grade II-IV acute GVHD in haploHCT group as compared to MSD group (49% v. 24%, p=0.014), but lower 2-year relapse rate (26% vs. 49%, p=0.008), which resulted to better 3-year probability of OS among haploHCT recipients (42% vs. 20%, p=0.048).[39] Brunstein and colleagues reported the outcomes of patients with haplo-BM/PT-Cy (BMT CTN 0603, n=50) and UCB transplantation (BMT CTN 0604, n=50) after RIC in Blood and Marrow Transplant Clinical trials Network (BMT-CTN) 2 parallel multicenter phase 2 trials.[8] Eligibility criteria for the two trials were the identical. The target accrual of 50 patients per trial was achieved in just 20 months (16 months faster than expected). Recipients of haplo-BM were conditioned with Flu 30 mg/m^2/day IV daily from Days -6 to -2 (total dose of 150 mg/m^2), Cy 14.5 mg/kg IV on Day -6 and -5, and 2 Gy TBI in a single

fraction on Day -1 (Figure 1). GVHD prophylaxis consisted of Cy 50 mg/kg IV on Days 3 and 4 followed by MMF and tacrolimus beginning on Day 5, with CsA as an acceptable substitution for tacrolimus. Filgrastim 5 mcg/kg/day was initiated on post-transplantation Day 5 and continued until the ANC was ≥ 1000/μL for three consecutive days.

2.1 Patient Characteristics Receiving Haplo-BM per BMT-CTN0603

Characteristics of the patients enrolled in haploHCT are summarized in Table 1 (BMT CT 0603).

Fifty patients were treated according to the protocol and included in the report. Seventeen donors were siblings of the recipient, 15 were parents and 18 were children. More than three quarters of the HLA-haploidentical related donors were mismatched for four or more HLA loci using high-resolution typing (HLA-A, -B, -C, -DRB1, and –DQB1) in both the graft-versus-host and host-versus-graft directions.

	Haplo
Number of patients	50
Age (yrs)	
Median	48
Range	7 – 70
Weight (kg)	
Median	78
Range	21 – 184
Performance Status	
= 90	38 (76%)
< 90	12 (24%)
Primary Disease	
Acute Lymphoblastic Leukemia	6 (12%)
Acute Myelogeneous Leukemia	22 (44%)
Biphenotypic/ Undifferentiated Leukemia	3 (6%)
Burkitt's Lymphoma	0
Hodgkins Lymphoma	7 (14%)
Large Cell Lymphoma	8 (16%)
Marginal Zone B-cell Lymphoma	1 (2%)
Follicular Non-Hodgkins Lymphoma	3 (6%)
Disease Stage	
Acute Leukemia	
First Complete Remission	15 (48%)
Second Complete Remission	12 (39%)
Third or Subsequent Complete Remission	4 (13%)
Lymphomas	
Complete Remission	7 (37%)
Partial Response	12 (63%)
Resistant	0
Number of Prior Chemotherapy Regimens (Lympl	
Two	4 (21%)
Three	6 (32%)
More Than Three	9 (47%)
Prior Autologous Transplantation	
Yes	11 (22%)

Table 1. Patient characteristics receiving haplo-BM

2.2 Hematopoietic Recovery and Chimerism

After haplo-BM the cumulative incidence of neutrophil recovery ≥500/μL at Day 56 was 96% (95%CI, 90-100%) with a median time to recovery of 16 days (range, 12-83). The cumulative incidence of platelet recovery ≥ 20,000/μL at Day 100 was 98% (95%CI, 93-100%) with a median time to recovery of 24 days (range, 1-92). The corresponding probability for platelets ≥ 50,000/μL was 76% (95%CI, 64-88%) with a median time to recovery of 26 days (range, 1-126). There was one case of primary graft failure. This patient did not receive a second transplant and died on Day 67. Median donor chimerism in marrow or peripheral blood was 100% (range 72-100%) on Day 28 and 100% (range 0-100%) on Day 56 after transplantation.

2.3 Graft-Versus-Host Disease

After haplo-BM transplantation, the cumulative incidence of grade II-IV acute GVHD at Day +100 were 32% (95% CI, 19-45%). There were no reported cases of grade III-IV acute GVHD. The cumulative incidence of chronic GVHD at 1 year was 13% (95% CI, 3-23%).

2.4 Treatment-Related-Mortality, Relapse, and Survival

After haplo-BM, the median follow-up of surviving patients was 357 days (range 103-441). The 1-year cumulative incidence of TRM was 7% (95% CI, 0-15%) and of relapse/progression was 45% (95% CI, 30-61%; Figure 2A). Sixteen patients have died: 13 from relapse, 2 from infection, and 1 from graft failure. Six-month survival, which was the primary endpoint, was 84% (95%CI, 70-92%). The 1-year probability of progression-free survival was 48% (95% CI, 32-62%) and overall survival 62% (95% CI, 44-76%; Figure 2B).

The BMT CTN haplo-BM results (0603) may even be a little better than those initially reported by Johns Hopkins,[11] probably because of inclusion of somewhat better-risk patients in the BMT CTN trial. These results of the RIC followed by haploidentical related (0603) transplantation in multicenter Phase II trials are quite encouraging. This set the stage for current ongoing BMT-CTN 1101 a multicenter, randomized phase III trial that aims to compare 2-year PFS of two standard of care alternative donor platforms; haplo BM with PT-Cy and double UCB grafts. The reproducible outcomes of haploHCT, in particular haplo BM with PT-Cy, has made it yet another viable and effective graft source that is readily and extends allogeneic

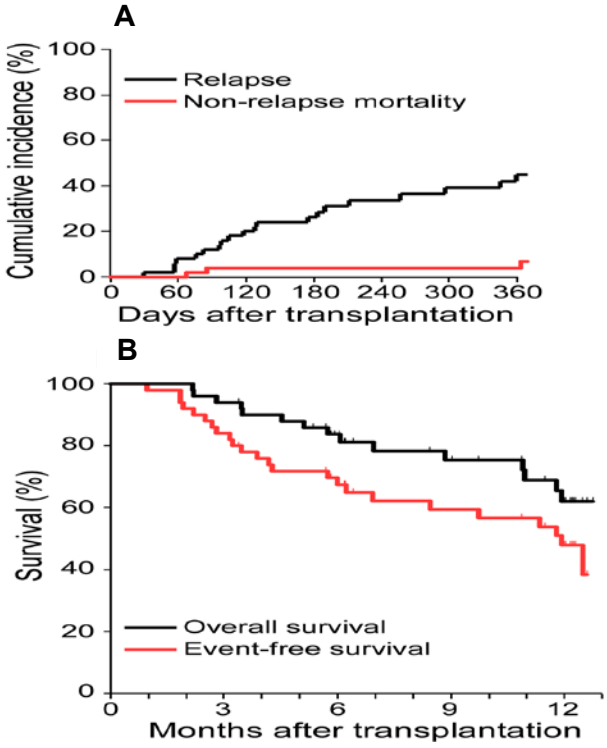


Figure 2. Relapse, NRM (A), overall survival, and event-free survival (B) after RIC and transplantation of Haplo-marrow.

transplantation to almost all patients lacking an HLA-identical donor and for those requiring potentially curative urgent transplantation.

3.0 Patient Selection

3.1 Age, Graft Cell Dose and Graft HLA Criteria

Must be <75 years old with no 7/8 or 8/8 HLA-matched sibling donor. Patients ≥ 70 and ≤ 75 years of age may be eligible if they have a Co-Morbidity score ≤ 2 (http://www.qxmd.com/calculate-online/hematology/hct-ci)

One or more potential related mismatched donors (e.g. biologic parent (s) or siblings (full or half) or children). Low resolution using DNA based typing at HLA-A, -B and –DRB1 for potential haploidentical donors is required.

Patients and donor must be HLA typed at high resolution using DNA based typing at the following HLA-loci: HLA-A, -B, -C and DRB1 and have available:

A related haploidentical BM donor with 2, 3, or 4 HLA-mismatches. A unidirectional mismatch in either the graft versus host or host versus graft direction is considered a mismatch. The donor and recipient must be HLA identical for at least one antigen (using high resolution DNA based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1. 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.

Donors will consent to and be enrolled in the University of Minnesota Procedure Guidelines For Related Hematopoietic Stem Cell Donors (MT2012-14C). Refer to that document for donor related eligibility and procedures.

Donor Prioritization:
In the event that two or more eligible donors are identified, the following order of priority is suggested but NOT mandated:

- For cytomegalovirus (CMV) seronegative recipients, a CMV seronegative donor
- Red blood cell compatibility
- RBC cross-match compatible
- Minor ABO incompatibility
- Major ABO incompatibility

3.2 Eligible Diseases

Acute Leukemias: Must be in remission by morphology (≤5% blasts). Also a small percentage of blasts that is equivocal between marrow regeneration vs. early relapse are acceptable provided there are no associated cytogenetic markers consistent with relapse.

Acute lymphoblastic leukemia (ALL)/lymphoma: second or greater CR; CR1 unable to tolerate consolidation chemotherapy due to chemotherapy-related toxicities; CR1 high-risk ALL.
High risk ALL is defined as having one of the following::

- Adverse cytogenetics such as t(9;22), t(1;19), t(4;11), other MLL rearrangements, *IKZF1*
- White blood cell counts of >30,000/mcL (B-ALL) or >100,000/mcL (T-ALL) at diagnosis,
- 30 years of age or older at diagnosis,
- Slow cytologic response (>10% lymphoblasts in bone marrow on Day 14 of induction therapy)
- Evidence of persistent immonophenotypic or molecular minimal residual disease (MRD) at the end of induction and consolidation therapy

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

Favorable risk is defined as having one of the following:

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

Acute Leukemias in 2nd or subsequent CR

Biphenotypic/Undifferentiated/Prolymphocytic Leukemias in first or subsequent CR, adult T-cell leukemia/lymphoma in first or subsequent CR

Burkitt's Lymphoma in CR2 or subsequent CR

Natural Killer Cell Malignancies

Chronic Myelogenous Leukemia (CML): in chronic or accelerated phase, or CML blast crisis in morphological remission (<5% blasts). Chronic phase patients must have failed at least two different TKIs, been intolerant to all available TKIs or have T315I mutation

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

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

Relapsed Large-Cell Lymphoma, Mantle-Cell Lymphoma and Hodgkin Lymphoma that is chemotherapy sensitive and has failed or ineligible for an autologous transplant.

Lymphoplasmacytic Lymphoma is eligible after initial therapy if chemotherapy sensitive.

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

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

Relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma, follicular lymphoma, which have progressed within 12 months of achieving a partial or complete remission. Patients who had remissions lasting > 12 months, are eligible after at least two prior therapies. Patients with bulky disease should be considered for de-bulking chemotherapy before transplant. Patients with refractory disease are eligible, unless has bulky disease and an estimated tumor doubling time of less than one month.

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

Acquired bone marrow failure syndromes

Myeloproliferative neoplasms/myelofibrosis

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

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

3.3 Organ Function and Performance Status Criteria

Adequate organ function is defined as:

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

Pulmonary: DLCO, FEV1, FVC ≥ 40% predicted, and absence of O2 requirements. For children that are not able to cooperate with PFTs, a pulse oximetry with exercise should be attempted. If nether test can be obtained it should be clearly stated in the provider's note.

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

Renal: serum creatinine ≤2.0 mg/dl (adults) or glomerular filtration rate (GFR) ≥ 40 mL/min/1.73m^2 (peds). Patients with a creatinine > 1.2 mg/dl or a history of renal dysfunction must have glomerular filtration rate (GFR) ≥ 40 mL/min/1.73m^2.

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

3.4 Other Inclusion Criteria

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

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

3.5 Exclusion Criteria

- Available and clinically suitable 5-6/6 HLA-A, B, DRB1 matched sibling donor
- Pregnant or breast feeding. The agents used in this study include Pregnancy Category D: known to cause harm to a fetus. Females of childbearing potential must have a negative pregnancy test prior to starting therapy
- Evidence of HIV infection or known HIV positive serology
- Untreated active infection
- Less than 3 months since prior myeloablative transplant (if applicable); less than 6 months since prior autologous transplant (if applicable).
- Evidence of progressive disease by imaging modalities or biopsy - persistent PET activity, though possibly related to lymphoma, is not an exclusion criterion in the absence of CT changes indicating progression
- CML in refractory blast crisis
- Large cell lymphoma, mantle cell lymphoma and Hodgkin disease that is progressive on salvage therapy.
- active central nervous system malignancy

4.0 Registration in OnCore

Patients will be registered in OnCore after providing written consent.

5.0 Treatment Plan

The information provided in this section is to serve as a guideline for treatment and maybe altered as clinically appropriate on a per patient basis.

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care therapy (i.e. acetaminophen, diphenhydramine, G-CSF, antimicrobials, etc.).

Corticosteroids may not be used as an anti-emetic agent and should not be administered until 24 hours after the completion of post-transplantation cyclophosphamide, unless used for adrenal support or during a medical emergency (e.g. treatment of anaphylaxis).

treatment day	**treatment**	**protocol section**
Day –6	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 14.5 mg/kg IV over 1-2 hours	section 5.1
Day –5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 14.5 mg/kg IV over 1-2 hours	
Day –4	Fludarabine 30 mg/m2 IV over 30-60 minutes	
Day -3	Fludarabine 30 mg/m2 IV over 30-60 minutes	
Day -2	Fludarabine 30 mg/m2 IV over 30-60 minutes	
Day –1	TBI 200 cGy	
Day 0	Non-T-cell depleted bone marrow infusion	section 5.2
Day 3	Cyclophosphamide 50 mg/kg IV Mesna 40 mg/kg IV	section 5.3
Day 4	Cyclophosphamide 50 mg/kg IV Mesna 40 mg/kg IV	
Day 5	Begin tacrolimus (or cyclosporine), mycophenolate mofetil, and G-CSF	sections 5.4 and 5.5

Refer to appendix II for the risks associated with the treatment plan.

5.1 Transplant Preparative Therapy (day -6 through day -1)

All drugs will be prepared and administered per institutional guidelines, with the drugs, doses and scheduled modified as clinically indicated.

Fludarabine

Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2 for a total dose of 150 mg/m^2.

Fludarabine will be dosed according to the recipient's actual body weight. For patients who have an estimated or measured GFR < 70 ml/min/1.73 m^2, prior

CNS disease, prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. The fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

Fludarabine must be administered before cyclophosphamide on Days -6 and -5.

Pre-Transplantation Cyclophosphamide

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/hour for 8 hours post-cyclophosphamide.

Uroprotection is administered according to institutional guidelines. Mesna is recommended to accompany pre-transplantation cyclophosphamide, but is not required. The mesna dose will be based on the cyclophosphamide dose being given. A suggested approach is as follows: divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide. The total daily dose of mesna should be ≥ 80% of the total daily dose of cyclophosphamide.

Cyclophosphamide 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion on Days –6 and –5. Cyclophosphamide 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.

Total Body Irradiation (TBI)

200 cGy TBI will be administered in a single fraction on Day –1 per institutional standards.

5.2 Transplant (day 0)

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, and a recommended minimum yield of 2.5×10^8 nucleated cells/kg of recipient IBW. It is recommended not to take more than 10 mL per aspirate.

In addition to calculating the total nucleated cell dose /kg, a sample of the product to be infused will be sent for flow cytometry to determine the content of CD34+cells.

The use of cryopreserved marrow is not recommended.

5.3 Post-Transplant Cyclophosphamide (days 3 and 4)

Hydration and uroprotection may be given according to institutional standards. See Section 5.1 for a recommended strategy.

Cyclophosphamide 50mg/kg will be given as an IV infusion over 1-2 hours (depending on volume) on Days 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 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.

5.4 Immunosuppressive Therapy (begin day 5)

Tacrolimus will be given at a dose of 1 mg IV daily or 1 mg PO bid, and then will be changed to a PO dosing schedule once a therapeutic level is achieved or as per institutional standards. Tacrolimus prophylaxis will begin on Day 5 post-transplant. 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 trough level of 5-15 ng/mL. Tacrolimus will be discontinued after the last dose around Day 180, or may be continued if active GVHD is present.

Cyclosporine (trough level of 200-400 ng/ml) may be substituted for tacrolimus if the patient is intolerant of tacrolimus or per institutional practice.

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 begin on Day 5 post-transplant and will be discontinued after the last dose on Day 35, or may be continued if active GVHD is present.

5.5 Growth Factor Support (begin day 5)

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 $\geq$ 1,500/mm^3 for three consecutive measurements on two different days. G-CSF may be restarted to maintain ANC > 1,000/mm^3. G-CSF may be given by IV or subcutaneously.

5.6 Supportive Care

Patients will receive standard supportive disease and transplant related care, including antibacterial/antifungal/antiviral prophylaxis according to institutional guidelines or as modified based on clinical parameters.

Patients will be eligible for any supportive care studies regarding infectious disease prophylaxis and management, immunoglobulin support, etc. as appropriate.

5.7 Follow-Up

Follow-up will be according to the current University Of Minnesota BMT follow-up guidelines as outlined in section 6.

6.0 Clinical Evaluations

All clinical evaluations are standard of care and will be done according to current institutional guidelines or as clinically indicated. The table below contains suggested guidelines and may be tailored as appropriate for individual patient's clinical case.

ACTIVITY	PRE-BMT WORK-UP	DAY 1 TO ENGRAFTMENT*	FOLLOW-UP DAYS 31-100	FOLLOW-UP (6 months, 1 and 2 years)
Consent	X			
Medical History	X	daily	weekly	X
Physical Exam	X	daily	weekly	X
Karnofsky/Lansky	X		day 100	X
GVHD Assessment		weekly	weekly, day 100	X (day 180, 360)
CBC/diff/plt	X	daily	weekly	X
PT/PTT	X	weekly		
basic metabolic panel (BMP)		daily		
comprehensive metabolic panel	X	weekly (0mit BMP on these days)	weekly	X
Viral Screen	X			
testing for anti-HLA antibodies	X#			
Urinalysis	X			
GFR for peds or adults with creat > 1.2 or hx or renal dysfunction	X			
Pregnancy test for FOCBP	X			
BM Biopsy chimerism	X (on BM or blood)	BM (day 21)	BM (day 100)	X
Blood chimerism		PB (day 21)	PB (day 60)	
PFT	X			

MUGA or Echo	X			
Chest CT	X**			
Disease Evaluation	X	X (day 28)	X (day 100)	X

obtain as soon as possible once the patient is determined to be a candidate for Haplo-BM transplantation in order to guide donor selection

* engraftment defined as absolute neutrophil count (ANC) $\geq 5 \times 10^8$/L for 3 consecutive measurements

**Patients with a history of MDS or a history of 2 or more consecutive inductions/re-inductions to treat acute leukemia or CML blast crisis or prolonged neutropenia of at least 2 months immediately preceding transplant should have a chest CT without contrast to exclude occult fungal infection prior to transplant.

7.0 Event Reporting

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

Transplant related outcomes and events will be recorded in the Blood and Marrow Transplantation (BMT) database.

Events requiring prompt reporting to the University of Minnesota Institutional Review Board (IRB) and protocol deviations will be documented in OnCore.

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	Report Form	irb@umn.edu

8.0 Data Collection and Statistical Plan

Specific transplant related endpoints include:

- 2 year survival
- Incidence of hematopoietic engraftment
- Incidence of chimerism at day 100, 6 months and 1 year
- Incidence of acute GVHD at 100 days
- Incidence of chronic GVHD at 1 year
- Incidence of transplant related mortality (TRM) at 6 months

All endpoint data will be recorded in the University Of Minnesota Blood and Bone Marrow Database as part of the historical database maintained by the department.

8.1 Trial Size Justification

The primary objective is to record outcomes and patient characteristics in the BMT database for patients who are treated in a standard manner. Based on prior enrollment it is expected this study will accrue 4 to 5 patients per year. Since this treatment plan among these patients has been studied over the last several years, this is now a standard of care protocol. No trial size justification is needed. Safety was closely monitored and assessed in the prior CTN trial as described in section

2.0 using the same preparative regimen and GVHD prophylaxis. The treatment was shown to be safe and efficacious.

8.2 Enrollment Plan

4-5 patients per year

8.3 Analysis of Primary and Secondary Endpoints

Cumulative incidence will be used to estimate TRM, neutrophil engraftment, GVHD and graft failure treating non-events as competing risks. Kaplan-Meier curves will be used to estimate disease-free survival and overall survival. Chimerism will be plotted with box-plots and described over time.

8.4 Safety Monitoring

This regimen has been studied for patients with these diagnoses for the past several years and it has been shown to be safe. Continuous stopping rules are no longer needed. Safety parameters will be monitored on a yearly basis.

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Appendix I – Appendix I – Performance Status Scales

For patients 16 years of age and older:

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

For patients < 16 years of age:

Lansky Score	Play Score
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Appendix II - Expected Risks of the Preparative Regimen, GVHD Prophylaxis and Transplant

Preparative Regimen:

Cyclophosphamide		
Common	**Less Common**	**Rare, but may be serious**
• low white blood cell count with increased risk of infection • hair loss or thinning, including face and body hair (usually grows back after treatment) • nausea • vomiting • loss of appetite • sores in mouth or on lips • bleeding from bladder, with blood in urine • diarrhea • long-term or short-term infertility (inability to have children) in women and men	• low platelet count (mild) with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if you become pregnant while taking cyclophosphamide	• heart problems with high doses, with chest pain, shortness of breath, or swollen feet • severe allergic reactions • skin rash • scarring of bladder • kidney damage (renal tubular necrosis) which can lead to kidney failure • heart damage, with trouble getting your breath, swelling of feet, rapid weight gain • scarring of lung tissue, with cough and shortness of breath • second cancer, which can happen years after taking this drug • death from infection, bleeding, heart failure, allergic reaction, or other causes

Fludarabine		
Common	**Less Common**	**Rare, but may be serious**
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness • tiredness (fatigue) • nausea • vomiting • fever and chills • infection	• pneumonia • diarrhea • loss of appetite • weakness • pain	• numbness and tingling in hands and/or feet related to irritation of nerves • changes in vision • agitation • confusion • clumsiness • seizures • coma • cough • trouble breathing • intestinal bleeding • weakness • death due to effects on the brain, infection, bleeding, severe anemia, skin blistering,

Fludarabine		
Common	**Less Common**	**Rare, but may be serious**
		or other causes • death from infection, bleeding, heart failure, allergic reaction, or other causes

Total Body Irradiation		
Common	**Less Common**	**Rare, but may be serious**
• nausea and vomiting • diarrhea • cataracts • sterility • endocrinopathies • growth failure • intestinal cramps • mucositis	• parotitis • interstitial pneumonitis • generalized mild erythema • veno-occlusive disease	• dysphagia • vertebral deformities • nephropathy • risk of 2nd malignancy years later (when given along with chemotherapy)

Risks of the Transplant Procedure (in general)

The following problems may occur as a result of cord blood or marrow transplant.

- **Slow recovery of blood counts**
- **Graft failure**
- **Graft-Versus-Host Disease (GVHD)**
- **Other complications.** Other complications may include:
  a. **Damage to the vital organs**
  b. **Serious infections**
  c. **Relapse of disease or a new blood cancer**
  d. **Risk to the unborn**

Risks of Using a Haploidentical Donor

Based on previous experience at this instutition and others there is lower transplant related mortality (TRM), a greater chance of disease relapse but similar overall survival when compared with other transplants using a related or unrelated matched donor.

Supportive Care:

Tacrolimus		
Common	**Less Common**	**Rare, but may be 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

It is very important that grapefruit or drinks with grapefruit juice are consumed while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study**.** Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

Mycophenolate mofetil (MMF)		
Common	**Less Common**	**Rare, but may be 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 stool • bloody vomit • change in vision • secondary cancers, such as lymphoproliferative disease or lymphoma • Progressive Multifocal Leukoencephalopathy

filgrastim (G-CSF)		
Common	**Less Common**	**Rare, but may be serious**
• bone or muscle pain • increased levels of liver enzymes and uric acid in the blood • headache • tiredness	• injection site reaction (redness, pain, or swelling) • nausea	• allergic reaction • spleen enlargement or rupture –symptoms of an enlarged spleen include a feeling discomfort, fullness, or pain on the upper left side of the abdomen; this pain may spread to the left shoulder

filgrastim (G-CSF)		
Common	**Less Common**	**Rare, but may be serious**
		• serious lung problems (ARDS) • worsening of skin rashes