

TITLE: CHP 894 REDUCED INTENSITY CONDITIONING (RIC) FOR NON-MALIGNANT DISORDERS – AMENDMENT # 6

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ABBREVIATIONS AND DEFINITIONS OF TERMS

RIC	Reduced intensity conditioning
HSCT	Hematopoietic stem cell transplant
ALG	anti-lymphocyte globulin
ATG	Anti-thymocyte globulin
IPEX	immune dysregulation, polyendocrinopathy, enteropathy, X-linked
SCID	Severe combined immune deficiency
CVID	Common variable immunodeficiency
HLH	Hemophagocytic lymphohistiocytosis
IEM	Inborn error of metabolism
LCH	Langerhans cell histiocytosis
CGD	Chronic granulomatous disease
MRD	Matched related donor
MUD	Unrelated donor
MMRD	Mismatched related donor
UCB	Unrelated cord blood
CR	Complete remission.
MMF	Mycophenolate mofetil
VNTRs	Variable nucleotide tandem repeats
GVHD	Graft vs. host disease
VOD	Veno-Occlusive Disease
SAE	Serious adverse event
NCI	National Cancer Institute
CTC	Common Toxicity Criteria

PROTOCOL SYNOPSIS

STUDY TITLE	Reduced intensity conditioning (RIC) regimen for patients with non-malignant disorders
SPONSOR	Investigator Initiated
CLINICAL PHASE	Phase II pilot study
STUDY RATIONALE	Allogeneic hematopoietic stem cell transplant (HSCT) is curative for many non-malignant diseases, including immunodeficiencies and hemoglobinopathies. Standard myeloablative therapy to establish complete donor chimerism usually includes busulfan, cyclophosphamide +/- thymoglobulin. This approach may result in full donor engraftment with complete immune reconstitution. However, this approach has been associated with a poor outcome in patients with significant organ dysfunction, and is associated with significant organ morbidities including veno-occlusive disease. Late complications include gonadal failure and secondary malignancies. Recently, reduced intensity conditioning (RIC) regimens have been used for both adult patients with leukemias and pediatric patients with non-malignant diseases. These regimens are better tolerated, resulting in less transplant related morbidity and mortality. Stable mixed chimerism, while insufficient for eradication of leukemias, may be sufficient to cure patients with non-malignant diseases. There are three conditioning regimens in this protocol for children ≥ 6 months. They differ by the timing and dosing of Alemtuzumab (Campath). The “distal” Campath regimen proposed is identical to the regimen proposed by the Clinical Trials Network for patients with sickle cell disease with unrelated donors and has been used successfully in patients with IPEX. The “proximal” Campath regimen protocol is used extensively in the UK for immune deficiencies, and is currently in use internationally for HLH and LCH. The third regimen is designed specifically for the treatment of patients with Beta Thalassemia Major. These subjects have shown to have an increased rate of autologous reconstitution and studies show that they required more conditioning. Patients with Thalassemia Major Autologous will receive the “distal” conditioning regimen with the addition of hydroxyurea and thiotepea. Reconstitution (graft loss) may be increased with RIC, but life-threatening aplasia from graft failure is rare. The conditioning regimen for children with immunodeficiencies < 6 months omits melphalan, and substitutes two days of busulfan. This regimen is successfully used in the UK, and has been successful in a 3 month old infant at CHOP who engrafted with a haploidentical donor.
STUDY OBJECTIVE(S)	Evaluate engraftment of patients with non-malignant disorders using a reduced-intensity conditioning regimen. Evaluate event free survival.
STUDY DESIGN	This is a Phase II pilot study to evaluate engraftment and toxicity of patients with non-malignant diseases using a reduced intensity conditioning regimen.

SUBJECT POPULATION	Inclusion Criteria Patients up to 25 years with non-malignant diseases, including immune deficiencies, hemoglobinopathies. Hematopoietic stem cell sources will include matched related and unrelated donors and cord blood.
NUMBER OF SUBJECTS	75patients
STUDY DURATION	Annual accrual of 3-6 patients, the study is expected to accrue for 4 years with minimum follow up of one year for all patients.
SAFETY EVALUATIONS	Chimerism studies by VNTRs (variable nucleotide tandem repeats) following engraftment (approximately day +28), then monthly until 1 year. Repeat at 2 years post HSCT. Weekly PCR for CMV, EBV, and adenovirus as per BMT Standard Operating Procedures for unrelated donor transplants, when applicable.
STATISTICAL AND ANALYTIC PLAN	The primary endpoints will be engraftment and event free survival at 1 year post-transplant. Event-free Survival: Event-free survival is defined as the time interval to either primary or late graft failure, disease recurrence, or death. <u>Accrual</u> The projected number is 75 patients/ 4 years. <u>Overall mortality</u> Overall mortality is projected to be $\leq 15\%$ at 100 days. <u>Failure to engraft</u> by chimerism analysis should occur in $<42\%$ of patients. If graft failure exceeds 20% by day 100, the stopping rule will be triggered.
DATA AND SAFETY MONITORING PLAN	Patients on this protocol are monitored and discussed at the weekly BMT program meeting in accordance with the QMP” Toxicity monitoring is done in accordance with the determination made by the Clinical Research Quality Assurance Committee (CRQA) .

Schedule of Study Procedures**Distal Campath (Alemtuzumab) Protocol**

<u>Schedule</u>	<u>Patient</u>	<u>Donor</u>	<u>Therapy</u>	<u>Tests</u>
	-Disease eligibility - Organ criteria	- HLA typing - Unrelated donor search if necessary ¹		
Day -22	Admit for central venous catheter	Xx	Alemtuzumab test dose (SQ/IV)	
Days -21to -19			Alemtuzumab	CBC, chemistry panel
Days -18 to -8	Outpatient	Xx	Bactrim, diflucan prophylaxis	CBC, chemistry panel weekly as per pt clinical status
Days -7 to -3	Inpatient	Xx	Fludarabine IV	As per BMT SOP
Day -2	Inpatient	Xx	Melphalan IV	“
Day -1	Inpatient	Xx	Cyclosporine infusion	“
Day 0	Inpatient	Donor collection/cord blood thawing	Infusion of stem cells	“
Day +1	Inpatient	Xx	Mycophenolate mofetil	“
Engraftment				Day +28 (approx), monthly x 12, 24 months

1. Patients with severe combined immunodeficiency less than 12 months without a suitable matched related (or unrelated donor available urgently) we will use a haploidentical donor

Thalassemia Major: Distal Campath (Alemtuzumab) Protocol

	<u>Patient</u> -Disease eligibility - Organ criteria	<u>Donor</u> - HLA typing - Unrelated donor search if necessary ¹	<u>Therapy</u>	<u>Tests</u>
Day -50 to -22	Outpatient	Xx	Hydroxyurea orally	CBC,Chemistry panel`
Day -22	Admit for central venous catheter	Xx	Alemtuzumab test dose (SQ/IV)	
Days -21to -19			Alemtuzumab	CBC, chemistry panel
Days -18 to -8	Outpatient	Xx	Bactrim, diflucan prophylaxis	CBC, chemistry panel weekly as per pt clinical status
Days -7 to -3	Inpatient	Xx	Fludarabine IV	As per BMT SOP
Day -3	Inpatient	Xx	Thiotepa IV	“
Day -2	Inpatient	Xx	Melphalan IV	
Day -1	Inpatient	Xx	Cyclosporine infusion	“
Day 0	Inpatient	Donor collection/cord blood thawing	Infusion of stem cells	“
Day +1	Inpatient	Xx	Mycophenolate mofetil	“
Engraftment				Day +28 (approx), monthly x 12, 24 months

Intermediate Campath (Alemtuzumab) Protocol

<u>Schedule</u>	<u>Patient</u> -Disease eligibility - Organ criteria	<u>Donor</u> - HLA typing - Unrelated donor search if necessary	<u>Therapy</u>	<u>Tests</u>
Day -14 to day-10		Xx	Alemtuzumab (SQ/IV)	CBC, chemistry panel
Days -7 to -3	Inpatient	Xx	Fludarabine IV	
Day -2	Inpatient	Xx	Melphalan IV	
Day -1	Inpatient	Xx	Cyclosporine infusion starts	
Day 0	Inpatient	Donor collection/cord blood thawing	Infusion of stem cells	“
Day +1	Inpatient	Xx	Mycophenolate mofetil po	“
Engraftment				+28, q month x 12, 24 months x

Protocol < 6months

<u>Schedule</u>	<u>Patient</u> -Disease eligibility - Organ criteria	<u>Donor</u> - HLA typing - Unrelated donor search if necessary	<u>Therapy</u>	<u>Tests</u>
Day -8	Admit for central venous catheter	Xx	Alemtuzumab	CBC, chemistry panel
Day -7	Inpatient		Alemtuzumab	
Days -6 to -5	Inpatient	Xx	Alemtuzumab. Busulfan Fludarabine IV	
Day -4	Inpatient	Xx	Alemtuzumab Fludarabine IV	
Day -3	Inpatient	Xx	Fludarabine	
Day -2	Inpatient	Xx	Fludarabine, cyclosporine infusion	
Day -1	Inpatient	Xx	Rest	
Day 0	Inpatient	Donor collection/cord blood thawing	Infusion of stem cells	“
Day +1	Inpatient	Xx	Mycophenolate mofetil po	“
Engraftment				+28, q month x 12, 24 months x

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

This is a phase II single institution pilot study. It is designed to estimate the efficacy and toxicity of RIC for patients with non-malignant diseases.

1.2 Name and Description of Investigational Product or Description of Intervention

Reduced intensity conditioning prior to hematopoietic stem cell transplant.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Clinical Studies

Allogeneic hematopoietic stem cell transplant (HSCT) is curative for many non-malignant diseases, including immunodeficiencies and hemoglobinopathies. Standard myeloablative therapy to establish complete donor chimerism usually includes busulfan, cyclophosphamide +/- thymoglobulin. This approach may result in full donor engraftment with complete immune reconstitution. However, this approach has been associated with a poor outcome in patients with significant organ dysfunction, and is associated with significant organ morbidities including veno-occlusive disease. Late complications include gonadal failure and secondary malignancies. Recently, reduced intensity conditioning (RIC) regimens have been used for both adult patients with leukemias and pediatric patients with non-malignant diseases. These regimens are better tolerated, resulting in less transplant related morbidity and mortality. Stable mixed chimerism, while insufficient for eradication of leukemias, may be sufficient to cure patients with non-malignant diseases.

Non-myeloablative or reduced intensity conditioning regimens must be significantly immunosuppressive to allow for sustained donor chimerism, particularly in heavily transfused patients(1). Most recent studies have used fludarabine, a lymphotoxic agent, in addition to other immunosuppressive agents in RIC. Additional immunosuppression is added with either anti-lymphocyte globulin (ALG), anti-thymocyte globulin (ATG) or alemtuzamab (Campath). A prospective multicenter trial using fludarabine and 200 cGy total body irradiation in heavily transfused patients was insufficient immunosuppression to achieve stable donor engraftment (2). Interpreting results of these studies poses some difficulty, due to the small numbers of patients with various diseases and donor sources (Table 1). However, it is apparent that this approach is successful for many patients and may result in sustained donor chimerism. The distal Campath conditioning regimen in this study is identical to the one proposed by the NIH sponsored Clinical Trials Network for patients with sickle cell disease with unrelated donors and has been used successfully here and elsewhere for IPEX. The proximal Campath RIC is used in the UK and in Children's Hospital of Cincinnati. It is also proposed for multi-organ Langerhans cell histiocytosis. Of note, while autologous reconstitution (graft loss) is increased with RIC, life-threatening aplasia from graft failure is rare.

Of the seven evaluable patients at CHOP who received proximal Campath, five have required donor lymphocyte infusions and/or second transplants for falling chimerism. The reason for this may be the close proximity of the Campath in relation to the bone marrow infusion, resulting in almost complete T depletion of the graft. This may increase the risk of autologous reconstitution. Moving the Campath to day -14 will allow decreased levels at the time of infusion and may reduce the need for DLI. This has been done at Cincinnati Children's (personal communication).

Addition of Hydroxyurea and Thiotepa for Beta Thalassemia Major Patients:

Recent trials of stem cell transplantation for Beta Thalassemia Major patients using reduced intensity conditioning regimens have been complicated by very high rates of incomplete engraftment, graft rejection, and ultimate autologous reconstitution¹. These high rates of graft failure in Thalassemia major patients have been postulated to be due to: 1) the intact immune system in Thalassemia patients pre-transplant, and 2) the hypercellular expanded marrow space caused by ineffective erythropoiesis in thalassemia increasing the probability of autologous reconstitution. Whereas the combination of alemtuzumab, fludarabine, and melphalan, the conditioning regimen used in the current CHP 894 protocol, has been shown to provide sufficient immune suppression and host stem cell eradication to allow for sustained donor engraftment in sickle cell disease (prior results from the CHP 894 study²) and other non-malignant hematologic disorders,^{3,4} this regimen alone has not previously been demonstrated to induce sustained engraftment in Thalassemia Major patients.

In our current CHP 894 experience, we have performed unrelated donor SCT using alemtuzumab, fludarabine, and melphalan on 2 patients with Thalassemia Major. One patient achieved 100% sustained donor engraftment; however the second patient sustained complete graft failure followed by autologous reconstitution, suggesting that this regimen may be insufficient to consistently achieve successful thalassemia-free survival. The addition of hydroxyurea and thiotepa to this alemtuzumab, fludarabine, and melphalan backbone has recently been shown to allow for reliable sustained donor engraftment for Thalassemia Major patients undergoing unrelated umbilical cord blood transplantation.⁵ In addition a recently completed multi-institutional trial (the URTH trial: NCT01005576) utilizing hydroxyurea and thiotepa in addition to alemtuzumab, fludarabine, and melphalan for unrelated donor marrow and cord blood transplantation recently completed accrual and is currently in the follow-up phase⁶. According to the Principal Investigator of the URTH trial, only 1 of 26 patients on this study experienced graft rejection (Shalini Shenoy, personal communication and Abstract from the 2013 American Society of Hematology Annual Meeting).

Therefore, we propose to amend the current CHP 894 protocol through the addition of hydroxyurea (Days -50 to -22: 30mg/kg/day po) and thiotepa (8mg/kg IV Day -3) to the current conditioning regimen of alemtuzumab, fludarabine and melphalan, specifically for patients with Thalassemia Major undergoing unrelated donor stem cell transplantation.

Immunodeficiencies

Allogeneic hematopoietic stem cell transplant (HSCT) is curative for congenital immunodeficiencies. The optimal strategy for these varied diseases is controversial. For patients with severe immunodeficiencies who lack a matched related donor, haploidentical T-depleted Husks are often used without conditioning. The primary advantage to this approach is the ready availability of the donor and avoidance of morbidity and potential mortality from conditioning, but graft failure and incomplete immune reconstitution often result. Patients with SCID with NK cell activity and ADA deficiency are at high risk for these complications (3); (4). Standard myeloablative therapy to establish complete donor chimerism usually includes busulfan, cyclophosphamide +/- thymoglobulin. This approach may result in full donor engraftment with complete immune reconstitution. However, the toxicities associated with myeloablative conditioning may preclude its use in these patients. Many of these patients present with life threatening infections and organ dysfunction that would preclude the use of a myeloablative conditioning. The UK group at Great Ormond Street has extensive experience using the proximal Campath RIC regimen for patients with immunodeficiencies. In a recent UK study, the outcomes of RIC for immunodeficiencies was compared to retrospective controls who received myeloablative conditioning. All children had primary engraftment, and there was no difference in the rate of immune reconstitution or GVHD risks between the two groups. Overall survival was significantly better in the RIC group (31/33- 94%) vs. 10/19 (53%) in the myeloablative group (19). However, they have noted increased morbidity in patients <6 months, and

therefore, this regimen is not recommended for children <6 months until further data is available (Rao, Great Ormond Street, personal communication). The UK group has eliminated melphalan for the infants <6 months, and have substituted busulfan or treosulphan (not available yet in the US). We have also successfully utilized this busulfan/alemtuzumab/fludarabine regimen to engraft a three month old with an immunodeficiency with a haploidentical donor. Also, patients with MHC class II deficiency (bare lymphocyte syndrome) have superior outcome with a myeloablative conditioning (Veys, Great Ormond Street, personal communication).

IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) has been associated with a poor outcome with conventional myeloablative therapy(5). A recent study of four patients with IPEX demonstrated successful engraftment with both unrelated and related donors using a non-myeloablative regimen of Alemtuzumab, fludarabine and melphalan(6). The regimen was well tolerated, even when used for second transplants in two patients. We have also used this regimen successfully in a 15 month old male with IPEX at CHOP. He had no regimen related toxicity, and has complete donor chimerism with unrelated donor bone marrow.

Alemtuzumab (Campath)

Alemtuzumab is a humanized monoclonal antibody against CD52, an antigen expressed predominantly on the surface of lymphocytes and macrophages. Its use in RIC is to deplete host lymphocytes that mediate graft rejection. In addition, by depleting host antigen presenting cells, it may decrease the risk of GVHD (7). One study by Chakraverty et al used alemtuzumab within 10 days of stem cell infusion in 44 patients with malignancies. Graft failure occurred in 2/44 patients and GVHD occurred in only 3/44 (8). However, while this timing may be valid for patients with malignancies, the prolonged serum concentrations of the drug may pose disadvantages for immunocompetent patients. Pharmacokinetic studies have shown that alemtuzumab concentrations of up to 0.5 ug/mL may be detected to 56 days post HSCT if the drug is given within one week of transplant (9). Depletion of donor T cells as a result of the prolonged serum concentration may increase the risk of graft failure. In addition, prolonged serum concentrations post HSCT delay immune reconstitution and increase the risk of viral infections(10);(11);(12). Giving Alemtuzumab several weeks prior to stem cell infusion alleviates these problems for patients with hemoglobinopathies and IPEX. The modified dose schedule proposed in this study has been used by other centers (13); (6) and is identical to the NIH sponsored Clinical Trials Network study (proposed) for unrelated donors for sickle cell transplants. In the event of falling chimerism, donor lymphocyte infusions will be considered. A second transplant with myeloablation will be considered in the event of autologous reconstitution.

Study	Patients	Regimen	Donors	Outcome
Children's Memorial (14)	13- SCD/thal- 4 Immune def: 5 IEM- 3 CGD- 1	Busulfan/fludarabine/ATG	MRD-4 MUD-6 MMRD-1 UCB-2	9- donor chimerism 85-100% 4- NE or no engraftment
UCSF (15)	15 Immune def- 4 AA-2 IEM- 3 Thal- 2 CGD-3	Busulfan */fludarabine/ATG *Busulfan full dose	MRD- 5 MUD-9 UCB-1	Graft loss- IEM – 4
Great	8- Immune def	Fludarabine,	MRD- 2	1-HLH relapse

Ormond Street(16)	1- HLH	melphalan, ALG	MUD- 6	7- well
Children's Hosp of NY(17)	6 AA- 2 HLH- 1 Thal-2 WAS- 1	Alemtuzumab or ATG, fludarabine, cyclophosphamide	MRD- 2 UCB- 4	3- CR toxicity 2-autoreconstitution (thal)
Great Ormond Street(18)	12- HLH	Alemtuzumab or ATG, fludarabine, melphalan	MRD- 1 MMRD-3 MUD- 8	3 deaths; 9 alive, remission
Great Ormond Street(19)	33 6- SCID Immune def, non-SCID- 27	Fludarabine, melaphalan, alemtuzumab or ATG	MUD- 33	31- alive and well
Washington U (13)	16 HLH/LCH-3 IEM-3 AA-5 SSD-1 Other heme-4	Fludarabine, melaphalan, alemtuzumab	MRD-8 MUD-3 UCB-5	>95% donor chimerism in 14 pts 4 deaths
Japan(20)	6 Immune def- 4 CGD- 2	Fludarabine, melphalan, ATG	MRD- 3 MUD- 1 UCB- 1 MMRD- 1	5- alive, CR 1- dead (SCID)
Washington U, National Children's, Cinti(6)	4- IPEX	Alemtuzumab, fludarabine, melphalan	MRD-1 MUD- 3	All alive, engrafted

Immune def- immune deficiency (including severe combined immune deficiency, Wiskott-Aldrich syndrome); IEM: inborn error of metabolism; HLH- hemophagocytic lymphohistiocytosis; LCH: Langerhans cell histiocytosis; A- aplastic anemia; thal- thalassemia; CGD- chronic granulomatous disease; MRD- matched related donor; MUD- unrelated donor; MMRD- mismatched related donor; UCB- unrelated cord blood; CR- complete remission.

1.4 Selection of Drugs and Dosages

The drugs and doses proposed in this study have extensive clinical experience. The “distal” Campath regimen proposed is identical to the regimen proposed by the Clinical Trials Network for patients with sickle cell disease with unrelated donors and has been used successfully in patients with IPEX. The “intermediate” Campath regimen protocol is similar to the protocol used extensively in the UK for immune deficiencies, and is currently in use internationally for HLH and LCH. However, due to the increased risk of falling chimerism necessitating donor lymphocyte infusions and/or second transplants, the Campath will be given prior to the start of the other drugs. Autologous reconstitution (graft loss) may be increased with RIC, but life-threatening aplasia from graft failure is rare.

1.5 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH). Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report adverse events in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

1.6 Relevant Literature and Data

References to literature are at the end of this document.

2 STUDY OBJECTIVES

- Evaluate engraftment of patients with non-malignant disorders using a reduced-intensity conditioning regimen.
- Evaluate event free survival.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is a Phase II study to evaluate engraftment and toxicity of patients with non-malignant diseases using a reduced intensity conditioning regimen

3.1.1 Screening Phase

Referred patients are discussed at the weekly BMT meeting and potential eligibility discussed at that time.

3.1.2 Follow-up Phase

Patients will be followed for two years post-transplant for evaluation of engraftment and toxicity.

3.2 Randomization and Blinding

N/A

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study

Patient enrollment over four years. Patients will be followed for two years post-transplant for evaluation of engraftment and toxicity.

3.3.2 Total number of subjects projected: 75

3.4 Patient Eligibility

- Age ≥ 6 months- 25 years
 - Diseases eligible for Distal Alemtuzumab:
 - ✓ IPEX syndrome,
 - ✓ Sickle cell disease:
 - Neurologic: history of stroke or any neurologic defect lasting >24 hours accompanied by infarct on MRI; or abnormal transcranial Doppler, or abnormal MRI with cerebral vasculature stenosis. OR
 - minimum 2 episodes of acute chest syndrome in preceding 2 year period
 - or history 3 or more severe pain events/year in the 2 years prior to transplant.
 - ✓ Thalassemia major
 - ✓ Bone marrow failure, including Kostmann's, amegakaryocytic thrombocytopenia, Blackfan-Diamond syndrome
 - Diseases eligible for Intermediate Alemtuzumab
 - ✓ Hemophagocytic lymphohistiocytosis other macrophage activation syndromes, severe Langerhans histiocytosis
 - ✓ Severe combined immune deficiency, adenosine deaminase deficiency, common variable immunodeficiency
 - ✓ Wiskott-Aldrich syndrome
 - Age <6 months with immunodeficiencies: Eligible for "mini" busulfan, fludarabine, alemtuzumab
 - ✓
- Organ criteria:
- ✓ Cardiac: Echocardiogram shortening fraction $\geq 27\%$
 - ✓ Pulmonary: for those with pulmonary function tests: DLCO/VA $>40\%$
If DLCO/VA is not reported this is considered inability to perform the test. In this case Pulse Ox and Respiratory Exam will be used as evaluation criteria.
 - ✓ Renal: Serum creatinine ≤ 1.5 x upper limit of normal for age
 - ✓ Hepatic: ALT and AST <5 x upper limit of normal
 - Infection: No active infections.
 - Exclusion criteria
 - ✓ Uncontrolled bacterial, fungal or viral infections.
 - ✓ Bare lymphocyte syndrome (MHC class II deficiency)

Donor Eligibility

- Donor bone marrow preferred. Priority:
 - Matched related donor and/or cord blood
 - Unrelated donor 6/6 matched by high resolution typing.
 - Unrelated donor 5/6 with one allele mismatch.
 - Unrelated donor 5/6 with one antigen mismatch.
 - Unrelated cord blood mismatch at single locus with DRB1 match. Cord blood unit must be at least $3.7 \times 10^7/\text{kg}$ TNC and/or $1.7 \times 10^5/\text{kg}$ CD34+ recipient weight.

Patients with severe combined immunodeficiency less than 12 months without a suitable matched related (or unrelated donor available urgently) we will use a haploidentical donor. These patients will receive complete T depletion by CD34+ selection of donor peripheral stem cells per our standard of care

4 STUDY PROCEDURES

4.01 Pre-transplant evaluation.

1. Organ evaluation as per BMT SOP.
2. Sickle cell disease, thalassemia or other chronic transfusions:
 - Serum ferritin
 - Liver biopsy (optional), Liver MRI for iron evaluation
 - Prior neurologic event: MRI, transcranial Doppler;
 - Desferal or any other chelating agents to be discontinued one week prior to fludarabine administration
3. Hemophagocytic lymphohistiocytosis
 - Spinal tap (prior CNS involvement), bone marrow (prior involvement)

4.02 Conditioning Regimen (s)

There are 4 Conditioning Regimens.

1. Distal Campath (with two dosing schemes one for <10 kg, and another for >10 kg), fludarabine/melphalan
 2. Distal Campath with conditioning to include Hydroxyurea, Fludarabine, thiotepa and melphalan for Beta Thalassemia Major patients
 3. Intermediate Campath, fludarabine/melphalan
 4. “Mini” busulfan, fludarabine and Campath for patients < 6months with immunodeficiencies
-

RIC: Distal Campath (Alemtuzumab) - Treatment for patients that are <10 kg

**<12 months fludarabine 1 mg/kg; melphalan 4.7 mg/kg

Day	Treatment <10 kg
-22	Alemtuzumab test dose 3 mg IV over 2 hours
-21	Alemtuzumab 10 mg
-20	Alemtuzumab 10 mg
-19	Alemtuzumab 10 mg
-7	Fludarabine ** 30 mg/m ² IV
-7	Fludarabine **30 mg/m ² IV
-5	Fludarabine ** 30 mg/m ² IV
-4	Fludarabine ** 30 mg/m ² IV
-3	Fludarabine ** 30 mg/m ² IV
-2	Melphalan ** 140 mg/m ² IV
-1	Cyclosporine infusion begins
0	Stem cell infusion
+1	Mycophenolate mofetil begins

PLEASE REFER TO SECTION 4.3 FOR ALEMTUZUMAB PRE MEDICATION, GVHD PROPHYLAXIS AND POST TRANSPLANT STUDIES.

RIC: Distal Campath (Alemtuzumab) - Treatment for patients that are >10 kg

**<12 months fludarabine 1 mg/kg; melphalan 4.7 mg/kg

Day	Treatment >10 kg
-22	Alemtuzumab test dose 3 mg IV over 2 hours
-21	Alemtuzumab 10 mg
-20	Alemtuzumab 15 mg
-19	Alemtuzumab 20 mg
-7	Fludarabine ** 30 mg/m ² IV
-6	Fludarabine ** 30 mg/m ² IV
-5	Fludarabine ** 30 mg/m ² IV
-4	Fludarabine ** 30 mg/m ² IV
-3	Fludarabine ** 30 mg/m ² IV
-2	Melphalan ** 140 mg/m ² IV
-1	Cyclosporine infusion begins
0	Stem cell infusion
+1	Mycophenolate mofetil begins

PLEASE REFER TO SECTION 4.3 FOR ALEMTUZUMAB PRE MEDICATION, GVHD PROPHYLAXIS AND POST TRANSPLANT STUDIES.

RIC: Distal Campath (Alemtuzumab) for Thalassemia Major- Treatment for patients that are >10 kg

**<12 months fludarabine 1 mg/kg; melphalan 4.7 mg/kg

Day	Treatment >10 kg
-50 to -22	Hydroxyurea 30 mg/kg/day orally
-22	Alemtuzumab test dose 3 mg IV over 2 hours
-21	Alemtuzumab 10 mg
-20	Alemtuzumab 15 mg
-19	Alemtuzumab 20 mg
-7	Fludarabine ** 30 mg/m ² IV
-6	Fludarabine ** 30 mg/m ² IV
-5	Fludarabine ** 30 mg/m ² IV
-4	Fludarabine ** 30 mg/m ² IV
-3	Fludarabine ** 30 mg/m ² IV Thiotepa 8mg/kg IV
-2	Melphalan ** 140 mg/m ² IV
-1	Cyclosporine infusion begins
0	Stem cell infusion
+1	Mycophenolate mofetil begins

Intermediate Campath (Alemtuzumab) – Alemtuzumab dosing does not change for weight, use mg per kg dosing.

**<12 months fludarabine 1 mg/kg; melphalan 4.7 mg/kg

Day	Treatment
-14 to d-10	Alemtuzumab 0.2 mg/kg SQ/IV
Day -7 through-3	Fludarabine **30 mg/m ² IV
-2	Melphalan ** 140 mg/m ² IV
-1	Cyclosporine infusion begins
0	Stem Cell Infusion
+1	Mycophenolate mofetil begins

PLEASE REFER TO SECTION 4.3 FOR ALEMTUZUMAB PRE MEDICATION, GVHD PROPHYLAXIS AND POST TRANSPLANT STUDIES.

“Mini” busulfan, fludarabine and alemtuzumab for patients < 6months with immunodeficiencies

Day	Treatment
-8	Alemtuzumab 0.2 mg/kg SQ/IV
-7	Alemtuzumab 0.2 mg/kg SQ/IV
-6	Alemtuzumab 0.2 mg/kg SQ/IV Busulfan* Fludarabine 1 mg/kg IV
-5	Alemtuzumab 0.2 mg/kg SQ/IV Busulfan * Fludarabine 1 mg/kg IV
-4	Alemtuzumab 0.2 mg/kg SQ/IV Fludarabine 1 mg/kg IV
-3	Fludarabine 1 mg/kg IV
-2	Fludarabine 1 mg/kg IV Cyclosporine infusion begins
-1	Rest
0	Stem Cell Infusion
+1	Mycophenolate mofetil begins

* Busulfan dosing

< 3 months old: 1mg/kg/dose. as a starting dose q 6 hours x 8 doses

> 3 months old but < 10 kg: 0.8 mg/kg/dose as a starting dose q 6 hours x 8 doses

>10 kg but 1.0 mg/kg/dose as a starting dose q 6 hours x 8doses

Dosing will be adjusted according to pharmacokinetic assessments.

PLEASE REFER TO SECTION 4.3 FOR ALEMTUZUMAB PRE MEDICATION, GVHD PROPHYLAXIS AND POST TRANSPLANT STUDIES.

4.03 Supportive Care Guidelines

Alemtuzumab (Campath) Pre medication

- (begin 12 hours prior to first dose):
- Methylprednisolone or prednisone 0.5 mg/kg IV or po q 6 hours

Prior to alemtuzumab infusion:

- Diphenhydramine 1mg/kg IV or po prior to infusion
- Acetaminophen 10-15 mg/kg po prior to infusion
- Meperidine 0.5 mg/kg q 4-6 hours as needed for rigors

Continue prednisone and diphenhydramine for 48 hours after last dose of Alemtuzumab.

- Filgrastim: begin 5 mcg/kg subcutaneously starting day +7. Continue until ANC >2000.

GVHD prophylaxis :

a. Day -2: Begin cyclosporine infusion 3mg/kg day with levels 200-400 ng/ml. Transition to oral tacrolimus prior to discharge and continue until 3 months post SCT. Wean over 2 months in the absence of GVHD.

b. Day + 1: Mycophenolate mofetil (MMF).

- Dosing: ^^^^
 - Children ≥ 50 kg: 1 gm po or IV q 8 hours
 - Children <50 kg: 15 mg/kg/dose q 8 hours
 - MMF levels suggested weekly.
 - Discontinue day +45 in the absence of GVHD.

Note: MMF dosing will be decreased to q 12 hours if there is an increase in GI toxicity after engraftment.

c. Cord blood: as per SOP: at day + 7: methylprednisolone 1 mg/kg/day in two divided doses and continued until day +28 or engraftment.

Post transplant studies

a. Chimerism studies by VNTRs (variable nucleotide tandem repeats) Upon engraftment (approximately day +28), then monthly until 1 year. Repeat at 2 years post HSCT.

- T cell chimerism: At engraftment, 3, 6 months post HSCT.

b. Infection monitoring: as per BMT SOP

c. Immune reconstitution: as per BMT SOP

d. Disease evaluation:

- Sickle cell (prior neurologic event): MRI, MRA, at 2 years.
 - Hb electrophoresis day +100, 6, 12, 24 months post SCT.
- History chronic transfusions: Serum ferritin, liver MRI for iron at 24 months

4.1 Screening Visit

Referrals made and discussed at BMT weekly meeting. Referrals to the Blood and Marrow Transplant program come from CHOP; other pediatric oncology/hematology practices from New Jersey, Delaware and the world. The director is contacted by the patient's primary physician or parents to determine if transplant is an option for the child's disease. Patients are presented and discussed at the BMT weekly meetings mentioned above and the team determines if the risk of the transplant is in the patient's best interest/outcome.

HLA typing of patient and siblings.

4.2 Subject Completion/Withdrawal

Patients can be taken off the study for any of the following reasons:

- The investigator decides that continuing in the study would not be in the subject's best interest.
- Subject becomes pregnant and the study treatment could be harmful to the fetus
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH)

4.2.1 Early Termination Study Visit

Subjects will be offered other treatment options including continuing with conventional medicine and/or transfusions or undertaking a fully myeloablative conditioning treatment.

5 STUDY ENDPOINTS AND EVALUATIONS

The primary endpoint will be event-free survival at 1 year post-transplant.

Event-free Survival: Event-free survival is defined as the time interval to either primary or late graft failure, disease recurrence, or death.

Graft Failure

Primary Graft Failure

Primary graft failure is defined as the presence of < 20% donor cells assessed by bone marrow or peripheral blood chimerism assays on Day 42. Infusion of a second stem cell product on or prior to Day 42 will be considered primary graft failure.

Late Graft Failure

The presence of < 20% donor derived hematopoietic cells in peripheral blood or bone marrow after Day 42 in a patient with prior evidence of > 20% donor cells will be considered late graft failure. Infusion of a second stem cell product beyond Day 42 will be considered late graft failure. Screening and Baseline Evaluation

5.1 Evaluations prior to Transplant

Routine pre-HSCT evaluation including:

Cardiac: Echocardiogram shortening fraction $\geq 27\%$

Pulmonary: for those with pulmonary function tests: DLCO/VA $> 40\%$

☐ If DLCO/VA is not reported this is considered inability to perform the test. In this case Pulse Ox and Respiratory Exam will be used as evaluation criteria.

Renal: Serum creatinine ≤ 1.5 x upper limit of normal for age

Hepatic: Bilirubin < 2 x upper limit of normal for age; ALT and AST < 5 x upper limit of normal

Patients who have been receiving chronic transfusion therapy -liver MRI with assessment of iron. Liver biopsy optional.

Infection: No active infections. CT scans of sinuses, chest, abdomen when clinically indicated.

A urine pregnancy test will be performed for female subjects who are ≥ 11 years of age or are < 11 years and are physically capable of becoming pregnant.

5.2 Efficacy Evaluations

Chimerism studies

- Chimerism studies by STRs (sequence tandem repeats) should be obtained following engraftment (approximately day +28), then monthly until 1 year. Repeat at 2 years post HSCT.
 - T cell chimerism: At engraftment, 3, 6 months post HSCT.
-

5.3 Safety Evaluation

Subject safety will be monitored by tracking severe and unexpected adverse events, including admissions to the PICU, grade IV graft vs. host disease, and death.

6 STATISTICAL CONSIDERATIONS

Accrual The projected number is 75 patients/4 years.

Analysis will include mortality, graft failure (initial failure to engraft or late graft failure). These are the major anticipated toxicities based upon the literature.

Overall toxicity rate Overall toxicity rate is projected to be $\leq 15\%$ at 100 days.

The following stopping rules have been modified to account for the patients already enrolled on study. The baseline proportions for toxicity (unacceptable TRM and graft failure) are 15%. The table below summarized the probability of observing greater or equal to R events assuming a true toxicity rate of 15%. Under the specified stopping rule, the study will be stopped with probability of 0.93 under a true toxicity rate of 15%, with probability of 0.63 under a true toxicity rate of 10%, and with probability of 0.14 under a true toxicity rate of 5%.

Stopping Rule for Overall Toxicity by Day 100

Number of patients	Stop if event occurs in	Probability of observing $\geq R$ events
35	4	0.79
40	4	0.87
45	5	0.83
50	5	0.89

6.1.1 Safety Analysis

All subjects entered into the study will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail. Analysis of engraftment and outcome (event free survival) at 1 and 2 years post transplant

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.2 Sample Size and Power

The sample size of 75 patients over a 4 year period is a realistic number based on our past patient experience and referral numbers for these disorders.

Note: As of March 2016, accrual has been better than expected and the toxicity less than expected resulting in expansion of the sample size. We have not made a modification to the stopping rules to reflect the new sample size.

7 SAFETY MANAGEMENT

The frequencies of AEs by type, body system, severity and relationship to the study will be summarized.

Tracking of the following AE's will be ongoing for subject's enrolled on this study:

Infection- bacterial, fungal, and viral-

Acute and chronic GVHD

Organ toxicity

Late effects- including sterility, organ dysfunction, secondary cancers

Graft Loss

Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

7.1 Adverse Event Reporting

All fatal or life-threatening serious adverse events occurring from initiation of transplant conditioning to 28 days after infusion of stem cells that are considered to be related to protocol therapy must be promptly reported to the institution's IRB as per institutional guidelines.

The Table below details the adverse event reporting plan. Serious adverse events must be followed until resolution or deemed irreversible. The minimum information required at initial reporting is the patient identifier, description of the event, and the investigator's opinion of its attribution to one of the following: i) the study intervention (RIC) ii) other transplant related cause or iii) relapse.

We will follow standard regulatory SAE reporting guidelines as per 21 CFR 812.150. The treating physician and Medical Director will define attribution (in their opinions) for all expected and unexpected SAEs and will define any potential device effect as per 21 CFR 812.3(s).

Adverse events (AE's) will use the descriptions and grading scales found in the revised national Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 4, which can be found at <http://ctep.cancer.gov/forms/CTCAEv4.pdf>.

7.2 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event. All unexpected Grade 4 and Grade 5 adverse events regardless of attribution will be reported to the IRB by phone or email within three days and in writing within 10 days of becoming aware of the event. We will also notify the IRB expeditiously of any expected Grade 4 and Grade 5 events regardless of attribution. Expected toxicities such as infection, mucositis, fever, hematologic toxicities or non-constitutional events related to the underlying disease will not be reported. All deaths and non-hematological and non-constitutional events unrelated to the underlying disease or to infection will be reported expeditiously for 30 days after transplant and then only unexpected related serious adverse event will be assessed and included in the annual report.

Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE. Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

7.3 IRB/IEC Notification of SAEs

The Investigator is responsible for promptly notifying the IRB of all study on-site SAEs and other unanticipated problems related to research using the CHOP Internal SAE reporting form and in accordance with the following timeline.

Type of Internal Adverse Event	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 5 calendar days
Internal (on-site) SAEs All other SAEs	72 hours	Within 5 calendar days
Unanticipated Problems Related to Research	72 hours	Within 5 calendar days
All other AEs	N/A	Summary of AEs Reported at Time of Continuing Review

7.3.1 Follow-up report

If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. All SAE should be followed until either resolved or stable.

7.4 Medical Emergencies

Please refer to the Risks of BMT, section 8.9.2.

7.5 Data Collection and Management

A data base of patient entry, data, including engraftment, acute and chronic GVHD, and outcomes, will be kept at the Children's Hospital of Philadelphia. The database will include the following fields:

UPN – Unique Patient Identifier

Age

Sex

Disease

Donor type and match grade

Fe (for sickle cell)

Chimerism

GVHD

Outcome

The database is kept in the Oncology server which is password protected. We will do our best to keep personal information private and confidential. All Children's Hospital employees who handle or have access to patient information in their jobs must take care to protect that information so that it remains confidential.

Patient identity will be kept private in any publication or presentation about the study.

7.6 Regulatory and Ethical Considerations

7.6.1 Data and Safety Monitoring Plan

Patients on this protocol are monitored and discussed at the weekly BMT program meeting in accordance with the QMP". The BMT/Hemoglobinopathies Committee meets monthly to review subject eligibility, donor options, and follow up of subjects. Toxicity monitoring is done in accordance with the determination made by the Clinical Research Quality Assurance Committee (CRQA)

In addition the University of Pennsylvania Cancer Center will monitor all cell therapy trials on a annual basis.

NCI Common Toxicity criteria will be used for adverse event reporting and toxicity grading.

7.6.2 Risk Assessment

The main Risks following a HSCT include:

Infection- bacterial, fungal, viral- can be life threatening

Acute and chronic GVHD

Organ toxicity- can be life threatening

Late effects- including sterility, organ dysfunction, secondary cancers

With RIC: increased risk of autologous reconstitution (graft loss)

Increased rejection with cord blood product infusion.

Risks of drugs used in protocol:**FLUDARABINE:**

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving Fludarabine Phosphate, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Vomiting, loss of appetite • Tiredness, fever • Pain • Bruising, bleeding • Cough • Increased risk of unusual infections lasting more than 6 months
OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving Fludarabine Phosphate, from 4 to 20 may have:
• Anemia, kidney problems which may cause tiredness, bruising, or swelling • Nausea, chills • Feeling of "pins and needles" in arms and legs • Damage to organs which may cause tiredness, changes in thinking or shortness of breath • Confusion
RARE SIDE EFFECTS, AND SERIOUS In 100 people receiving Fludarabine Phosphate, 3 or fewer may have:
• Kidney damage which may require dialysis

BUSULFAN:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Busulfan, more than 20 may have:

- Anemia which may require blood transfusions
- Abnormal heartbeat
- Constipation, diarrhea, heartburn, nausea, vomiting, loss of appetite
- Sores in mouth which may cause difficulty swallowing
- Chills, fever
- Pain
- Swelling of the body
- Damage to the liver
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Bruising, bleeding
- Dizziness, headache, tiredness
- Difficulty sleeping
- Worry
- Cough, stuffy nose
- Rash
- High blood pressure which may cause blurred vision
- High or low levels of certain salts in the body which may require you to take another medicine to correct the salt level

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Busulfan, from 4 to 20 may have:

- Cloudiness of the eye, visual disturbances
- Seizure
- Blood in urine
- Loss or absence of sperm
- Menopause
- Internal bleeding which may cause coughing up blood
- Scarring of the lungs

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Busulfan, 3 or fewer may have:

- Infection, especially when white blood cell count is low
- Fluid around heart
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Cancer of bone marrow caused by chemotherapy
- Low blood pressure which may cause feeling faint

CAMPATH:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Campath, more than 20 may have:

- Chills
- Fever
- Nausea
- Vomiting
- Rash
- Low blood counts
- Severe infection
- Pain

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Campath, from 4 to 20 may have:

- Low blood pressure
- Fatigue
- Hives
- Itching
- Shortness of breath
- Headache
- Diarrhea
- Loss of appetite

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Campath, 3 or fewer may have:

- Dizziness
- Trembling
- Fast heartbeat
- Abdominal pain
- Constipation
- Difficulty sleeping

HYDROXYUREA:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving hydroxyurea, more than 20 may have:

- Decrease in the number of red and white blood cells and platelets made in the bone marrow

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving hydroxyurea, from 4 to 20 may have:

- Nausea
- Vomiting
- Mouth sores
- Low number of red blood cells

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving hydroxyurea, 3 or fewer may have:

- Rash
- Redness of the skin on the face
- Painful and difficult urination
- Kidney damage
- Headache
- Dizziness
- Yellow-colored appearance of the skin and eye due to abnormal flow of bile
- Worsening of side effects due to radiation treatments
- Seeing or hearing things that are not really there
- Seizures
- Diarrhea
- Temporarily increased levels of liver enzymes
- Darkening of the skin
- Nail changes

THIOTEPA:

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Thiotepa, more than 20 and up to 100 may have:

- Nausea
- Vomiting
- Loss of appetite
- A feeling of extreme tiredness or weakness
- Fewer white blood cells, red blood cells and platelets in the blood.
 - A low number of red blood cells can make you feel tired and weak.
 - A low number of white blood cells can make it easier to get infections.
 - A low number of platelets causes you to bruise and bleed
- Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
- Absence or decrease in monthly periods and could affect your ability to become pregnant
-
- With High Doses used before marrow transplants:
- Inflammation and/or sores in the mouth, throat and/or esophagus (the passage between the throat and stomach)

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Thiotepa, from 4 to 20 may have:

- Pain at the injection site
 - Dizziness
 - Headache
 - Blurred vision
 - Hives, skin rash
 - Wheezing
 - Sudden high fever
 - Pain in the abdomen
 - Difficulty emptying the bladder
 - Feeling the urgency to urinate or pain on urination
 - Hair loss
 - Inflammation and reddening of the eye
 - Inflammation of the skin where the drug comes into contact with the skin
 -
 - With High Doses used before marrow transplants:
 - Inappropriate behavior
 - Confusion
 - Drowsiness
 - Elevation in the blood of certain enzymes and/or bilirubin found in the liver
 - Bronze discoloration or darkening of the skin
-

RARE SIDE EFFECTS, AND SERIOUS In 100 people receiving thiotepa, 3 or fewer may have:
• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Swelling and tightening of the throat which can cause difficulty with breathing • A new cancer or leukemia resulting from this treatment

MELPHALAN (intravenous)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Melphalan, more than 20 and up to 100 may have:
• Sores in mouth which may cause difficulty swallowing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Melphalan, from 4 to 20 may have:
• Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis or require blood transfusions • Infection, especially when white blood cell count is low • Bruising, bleeding • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Hepatitis which may cause yellow eyes and skin, tiredness • A new cancer resulting from treatment of earlier cancer • Cancer of bone marrow caused by chemotherapy • Kidney damage which may cause swelling, may require dialysis • Scarring of the lungs which may cause shortness of breath

RARE, AND SERIOUS In 100 people receiving Melphalan, 3 or fewer may have:
• Heart stops beating • Swelling and redness at the site of the medication injection • Abnormal or absence of menstrual period, menopause • Loss or absence of sperm

FILGRASTIM (G-CSF):

COMMON SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving filgrastim (G-CSF), more than 20 may have:

- Nausea, vomiting
- Pain in bone

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving filgrastim (G-CSF), from 4 to 20 may have:

- Anemia which may cause tiredness, or may require transfusion
- Damage to the lungs which may cause shortness of breath
- Internal bleeding which may cause coughing up blood
- Swelling or tenderness of vessels

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving filgrastim (G-CSF), 3 or fewer may have:

- Rupture of the spleen leading to bleeding in the belly
-

Medicines used to prevent Graft vs. Host Disease
CYCLOSPORINE A/ TACROLIMUS
COMMON SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus,
more than 20 and up to 100 may have:

- Headache
- Nausea and vomiting
- High blood pressure
- Loss of desire to eat or appetite
- Reduced ability of the body to fight infection
- Diarrhea or constipation
- Fever
- Tremor (shakiness usually of the hands)
- Increases in the levels of certain chemicals in the blood because the kidney is not working as well as normal which may require lowering the dose
- Fewer red blood cells in the blood_
 - a low number of red blood cells can make you feel tired and weak
- Difficulty sleeping or falling asleep
- A feeling of weakness and/or tiredness
- Pain which may be in the abdomen (belly), back and/or other parts of your body
- High levels of sugar in the blood that may require treatment
- Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or vein
- Low (*or High*) levels of certain salts in the body like potassium and phosphate which may require treatment
- Numbness and tingling in the fingers and toes

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus, from 4 to 20 may have:

- Chest pain
 - Hair loss
 - Dizziness
 - Elevation in the blood of certain enzymes or bilirubin found in the liver which may mean the liver is not working as well
 - Bladder or kidney infection
 - Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight
 - Rash that may itch
 - An increase in the levels of lipids (fats) and cholesterol in your blood which if prolonged could lead to heart problems later in life
 - Acid or upset stomach (heartburn)
-

OCCASIONAL SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus, from 4 to 20 may have:

- Difficulty or discomfort on swallowing
- Inflammation of the stomach or esophagus (the tube that leads from the mouth to the stomach)
- Too much gas produced in the intestines
- Shortness of breath and/or a tight feeling in the chest with wheezing and shortness of breath (asthma)
- Increased cough
- Flu type symptoms with fever, tiredness, aches and pains
- Changes in your brain function such that you have difficulty in thinking clearly, are sleepy, depressed, anxious, have strange dreams, are nervous, have changes in your mood which may include severe depression, feelings of suicide, feelings of aggressiveness and violent behavior or see or hear things that are not there
- Fewer white blood cells and platelets in the blood
- a low number of white blood cells can make it easier to get infections
- a low number of platelets causes you to bruise and bleed more easily
- Greater than normal numbers of white or red blood cells in the blood
- Aches and pains in the joints or muscles
- Skin changes including pimples, change in color, increased tendency to sun burn and skin sores
- Wounds may be slower to heal
- Excessive hair growth such as on the face, eyebrows, arms and legs
- Bleeding or tender gums, overgrowth of gum tissue
- Changes in your vision or a decrease in vision
- Ear pain or ringing in the ears
- Gallstones

RARE SIDE EFFECTS, AND SERIOUS

In 100 people receiving Cyclosporine A/ tacrolimus,
3 or fewer may have:

- Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
- Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen which makes it look larger.
- Inflammation of the lungs which could lead to chest pain and discomfort
- A new cancer or leukemia resulting from this treatment

MYCOPHENOLATE (Cellcept)

Likely	Less Likely	Rare, but Serious
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“Likely” refers to a side effect that is expected to occur in more than 20% of patients	“Less likely” refers to a side effect that is expected to occur in 20% or fewer of patients	These possible risks have been reported in rare occurrences, typically less than 2/100 patients. They may be serious if they occur
Diarrhea Stomach pain Nausea Difficulty falling asleep or staying asleep	Pain in back, muscles, joints Constipation	Swelling of the hands, feet or lower legs Difficulty breathing Shaking hands Headache Fast heartbeat Tiredness Dizziness Blood in stools Gum swelling Vision changes Rash Low blood counts

7.6.3 Potential Benefits of Trial Participation

The primary advantage to participation in this trial is the possibility of decreased morbidity and mortality from RIC as compared to a fully myeloablative regimen. There may be decreased risk of sterility compared with a myeloablative regimen.

7.6.4 Risk-Benefit Assessment

The benefits of the RIC to establish stable mixed chimerism outweigh the risks. The primary risk of RIC is autologous reconstitution. Life threatening aplasia is a rare complication. The risks of life threatening organ toxicity are significantly reduced, and transplant related mortality is decreased by 1/3-1/2 compared to myeloablative conditioning protocols. When achieved, stable chimerism is sufficient to cure these patients with non-malignant diseases without the toxicity of myeloablative conditioning. If autologous reconstitution were to occur, patients could be considered for a myeloablative conditioning regimen to establish complete donor chimerism.

Recruitment Strategy

Patients referred to BMT are discussed and reviewed at the weekly BMT meeting regarding suitability for BMT. This study will be “advertised” to outside referring physicians as well as CHOP Hematology and Immunology.

7.7 Informed Consent/Assent

Patients have a family meeting regarding transplant to obtain consent. The family meeting is a 1.5 to 2 hour meeting scheduled well in advance of the admission for transplant. We also provide additional educational materials including “Bone Marrow and Blood Stem Cell Transplants, A guide for patients”

Patients are assigned a Primary Nurse Practitioner (this is standard delivery of care and the NP's are not caring for these patients specifically because they are enrolled on this trial) who coordinates the admission for transplant, and provides education on an ongoing basis about the transplant process, complications and the transplant study the patient is enrolled on.

The physician is responsible for obtaining consent.

7.8 Payment to Subjects/Families

No payment will be made to the subject or their family for participation in this study. The subject's insurance company must agree to reimbursement for the treatment before hospital admission.

7.9 Confidentiality

Information from medical records and from the procedures, interviews and tests that are part of this research will be collected. We will do our best to keep personal information private and confidential. However, we cannot guarantee absolute confidentiality. Personal information may be disclosed if required by law. The results of this study may be shown at meetings or published in journals to inform other doctors and health professionals. Patient identity will be kept private in any publication or presentation about the study. People and organizations that may inspect and/or copy research records to assure the quality of the data and to analyze the data include:

- Members of the research team at CHOP;
- Medical staff who are directly or indirectly involved in your care related to this research;
- People who oversee or evaluate research and care activities at CHOP
- People from agencies and organizations that perform independent Accreditation and oversight of research;
- The Food and Drug Administration;
- The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research, organizations involved in research on blood and marrow transplantation and in the coordination of this study
- The National Heart Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

There is no set time for destroying the information that will be collected for this study. We will continue to analyze data for many years and it is not possible to know when they will be completely done.

8 PUBLICATION

We will keep the identity private in any publication or presentation about the study.

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