Post Transplant Cyclophosphamide for Unrelated and Related Allogeneic Hematopoietic Stem Cell Transplantation for Hematological Malignancies

Principal Investigator
John L. Wagner, MD
Department of Medical Oncology

Co-Investigators
Seyfettin Alpdogan, MD
Matthew Carabasi, MD
Beth Colombe, PhD
Neal Flomenberg, MD
Usama Gergis, MD
Dolores Grosso, DNP, CRNP
Chetan Jeurkar, MD
Margaret Kasner, MD
Lisa Kearns, CRNP
Joanne Filicko-OHara, MD
William O'Hara, Pharm-D
Weyin Shi, MD
Ubaldo Martinez-Outschoorn, MD
Thomas Klumpp, MD
Neil Palmisiano, MD
Pierluigi Porcu, MD
Shaik Rashid, MD
Maria Werner-Wasik, MD

Statistician
Inna Chervoneva, PhD

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1.0 Introduction and Objectives

1.1 Introduction

Post transplant cyclophosphamide has been utilized in a number of trials as a means to reduce graft versus host disease (GVHD) after allogeneic marrow transplantation. At Thomas Jefferson University (TJU), we have developed an approach where the transplant is administered in two separate steps, one being the lymphoid portion of the graft and the second being the stem cell portion of the graft. These protocols which have been quite successful to date administer cyclophosphamide after the lymphoid portion but before the stem cell portion of the graft. These trials use an investigational device for stem cell separation requiring an Investigational Drug Exemption (IDE) from the Food and Drug Administration (FDA). The entry criteria are quite restrictive, disenfranchising many patients who would otherwise be reasonable transplant candidates. In addition, recipients of unrelated donor transplants cannot be treated in this fashion because of the extra logistics that are required for donation which are not feasible in the unrelated donor setting. This protocol attempts to enfranchise these various patient groups using a simpler post transplant cyclophosphamide approach.

1.2 Primary

This study will encompass two patient groups – those transplanted using related donors and those transplanted using unrelated donors and recruitment to both arms will start simultaneously. The principle objective of the related donor arm is to determine whether post-transplant cyclophosphamide can be used to successfully engraft patients with Human Leukocyte Antigen (HLA) identical or HLA mismatched related donors after preparation with either an ablative or nonmyeloablative conditioning regimen who are not candidates for the TJU two step protocols for the reasons specified above. The objective of the unrelated donor arm of the study is to determine if patients with HLA matched unrelated donors and, if successful, patients with one or two antigen mismatched unrelated donors can successfully engraft using cyclophosphamide post transplant. Since one patient has successfully engrafted using a matched unrelated donor (on study) and two patients have successfully engrafted (off study) using one antigen mismatched unrelated donors we will consider after one additional patients with one antigen mismatched unrelated donors have engrafted using patients with two antigen mismatched unrelated donors

1.3 Secondary

1. Assess incidence of Grade III-IV GHVD; goal is less than 10%.
2. Assess incidence of GVHD unresponsive to corticosteroids and photopheresis; goal is less than 15%.
3. Assess day 100 transplant related mortality; goal is less than 15%.

2.0 Rationale

High-dose chemoradiotherapy followed by hematopoietic allogeneic stem cell transplantation (HSCT) is a potentially curative modality for a variety of hematological disorders, including acute and chronic leukemia, myelodysplastic syndrome (MDS), multiple myeloma (MM), and lymphoma that are incurable with conventional dose chemotherapy.[1] The ability of HSCT to control an underlying hematological malignancy is based on three variables, the intrinsic sensitivity/resistance of the malignancy, treatment

regimen intensity, and graft versus tumor (GVT) effects. Disease sensitivity/resistance is not something that can be changed when patients present for treatment, and transplant regimen intensity can be further increased only over a narrow additional range since treatment intensity is near maximal in many transplant regimens. Consequently, it is difficult if not impossible to manipulate the first two variables to effect substantial improvements for many HSCT candidates. Thus the third variable the GVT effect may be the easiest variable to manipulate. Therefore manipulating the GVT effect will be a major focus of this trial and expanding the pool of potential candidates for transplant will be the second focus of this trial.

Just as there are three major variables to determine the ability of an HSCT to control an underlying hematological malignancy so too there are three traditional therapeutic components of a conventional allogeneic HSCT. The first component is the use of a high-dose myeloablative-conditioning regimen to eradicate the underlying malignancy and to suppress the host immune system in preparation to receive the donor stem cell graft. This is followed by the infusion of donor stem cells to both rescue the host from the lethality of the conditioning regimen as well as to eliminate residual tumor cells and host resistance to donor stem cells by graft-versus-tumor reactions (GVT). The third component is pre-grafting T-cell depletion of donor stem cells or post-grafting immunosuppression to regulate the development of graft-versus-host disease (GVHD). [2, 3] While a variety of agents can be used for the conditioning regimen, the dose intensity may be limited by the patient's condition at presentation for an HSCT. The second and third components can be altered by either strategies that involve graft engineering or by the use of a variety of immunosuppressive agents. The consequence to one degree or another, of all types of transplants, is a period of immunosuppression either from post-grafting immunosuppressant medication or the removal of T-cells from the donor inoculum.

It is now understood that, in some diseases such as follicular lymphoma, a GVT effect, not regimen intensity, is the primary mechanism for long-term disease control after allogeneic transplantation. In other diseases, both treatment intensity and GVT effects contribute to disease eradication. This principle has been firmly established by analysis of transplant outcomes from identical twins[4], the success of reduced intensity HSCT[2] and disease eradication after donor lymphocyte infusions[3]. Unfortunately, despite the potent GVT effects associated with HSCT, death due to relapsed disease remains the greatest barrier to long-term survival for patients with resistant disease undergoing matched donor HSCT. For patients without HLA matched related donors GVHD also remains a significant problem. For all of these reasons this trial was conceived.

In recent years, administration of cyclophosphamide (CY) after a T replete (i.e. non T cell depleted) marrow graft in order to preferentially eliminate proliferating alloreactive T cells has been successfully utilized in non-myeloablative haploidentical HSCT[5, 6]. With this approach, patients avoid profound immunoincompetence due to the remaining donor T cells which, because they are not alloreactive and proliferating early after transplant, are less affected by CY. In contrast, stem cells are not affected by CY due to their high levels of aldehyde dehydrogenase which rapidly metabolizes the active CY derivatives. This approach was described in a reduced intensity conditioning murine model by Luznik et al.

[7]. In this experiment mice received pretransplant CY or fludarabine and TBI with cyclophosphamide post stem cell infusion. The use of CY post transplant was described in a phase I clinical trial at Johns Hopkins University by O'Donnell et al.[5]. In this study ten patients with partially mismatched related donors received conditioning with fludarabine and low dose TBI followed by post transplantation cyclophosphamide. All patients initially engrafted although two patients later rejected. Six patients developed GVHD that was fatal in one patient. A larger study was later published by the same group (with patients added from Seattle) with 68 patients [6]. In this study nine of the 66 patients (14% of the evaluable patients) rejected. The incidence of grade II-IV and III-IV acute GVHD was 34% and 6% respectively. Like the initial phase I trial this study used only reduced intensity conditioning and used only related donors.[5]

Recently another study by Meade et al. at University College London Medical School was published using a different reduced intensity regimen with alemtuzumab, fludarabine, and melphalan and using HLA matched and mismatched unrelated donors.[8] This trial of 50 HLA mismatched unrelated transplants compared to 107 HLA matched unrelated donor transplants was limited to patients under 70 and most had chemosensitive disease. In addition the study used only a nonmyeloablative conditioning regimen and 29 of 157 patients required donor lymphocyte infusions for disease relapse. The graft failure rate was 8% and the incidence of grade II-IV acute GVHD was 22%.

In order to improve upon the results of the above haploidentical trials (for example lack of a published myeloablative regimen), we developed a 2-step myeloablative approach to HSCT from haploidentical donors at TJU which we have successfully applied to patients with hematological malignancies. We refer to this as a 2-step approach because the lymphoid and stem cell portions of the graft are collected and administered at different time points during the conditioning regimen. Our approach does not involve *ex vivo* T cell depletion, but uses CY to tolerize donor lymphocytes. We have been sufficiently pleased with the outcomes of this trial that we now use haploidentical family donors as our alternative donor of choice when a matched related donor is not available, rather than searching for unrelated donors. Our results from the myeloablative portion of those trials are as follows: Of the first 27 patients only two rejected (7%) and both had preformed anti-donor antibodies and only 8% developed grade III-IV acute GVHD.[9] For this trial we would like to include additional potential patients using the Hopkins' approach as well as what we have learned from our two step approach. Thus we will use cyclophosphamide post stem cell infusion as in the Hopkins trial[5] and at the same time allow both myeloablative and nonmyeloablative conditioning regimen as we do in our 2-step trials. Furthermore, we will include an unrelated arm as well as was in the University College London Medical School trial[8] for two reasons. One is that not everyone has an HLA-matched or even an HLA mismatched related donor. Furthermore, despite the fact that there are now over 13 million potential donors in the various unrelated donor registries, many patients still cannot find a fully matched unrelated donor. Therefore, if three patientswith HLA one antigen mismatched unrelated donors engraft then patients with unrelated donors with two antigen mismatches will be entered on the study. If successful this will allow more patients to have access to unrelated donors. This is important especially if we can demonstrate a mortality risk similar to the TJU 2-step protocol which currently is

similar to what one might expect using matched sibling donors.[9] As has been shown in a large National Marrow Donor Program study a single antigen mismatch causes a 9% increase in mortality.[10] The TJU 2-step protocol would not be feasible for patients with unrelated donors as the donor would have to go through two separate collection processes, one for lymphocytes and a second for hematopoietic stem cells. The ability to engraft patients with two antigen mismatched unrelated donors with minimal GVHD would greatly increase the number of potential unrelated transplants especially for minorities (from 30% to greater than 90%).[11]

We are allowing patients with related donors with slightly more/worse comorbidities than on our 2-step study into this study to see if we can offer haploidentical related transplants to more patients as well. The entry criteria required by the FDA are quite strict and exclude patients who would otherwise be deemed appropriate candidates here at TJU. Furthermore a one-step approach if successful would allow more centers without CD34 selection devices to perform haploidentical transplants. We will also exclude people with resistant disease until we have a better understanding of the engraftment rate, GVHD incidence, etc.

January 14, 2015 Update

The Substitution of Alkylating Agents
This protocol opened in 2011 and 13 patients has been treated to date on the current conditioning regimen of Fludarabine, Thiotepa, 2 Gy TBI and CY. Thiotepa has been used in the 2 step RIC approaches since 2008 and in cancer chemotherapy for over 50 years. It was designated as an orphan drug in 2007, and a critical shortage of Thiotepa was identified in 2013, originating from market forces which have affected many oncology medications. The drug is no longer manufactured in the United States and purchasing the drug from overseas has been associated with increasing cost. Therefore, the current expense of the drug makes its use in HSCT at TJUH (and most other centers) no longer feasible, and a drug substitution in the regimen is required. Busulfan has been used in HSCT for over 30 years and is commonly used in RIC HSCT.

3.0 Patient Selection

3.1 Inclusion Criteria

Any patient with a hematological or oncological diagnosis in which allogeneic HSCT is thought to be beneficial.

- Patients without morphological or molecular evidence of disease or
- For patients with “indolent diseases” if the patient has evidence of disease the disease burden must be minimal (at least PR) and the disease must be chemoresponsive. Thus for example patients with acute leukemia (not an indolent disease) must be in a morphological CR or CRp.

For patients with MDS the inclusion criteria is specifically as follows:

- For patients with RA or RARS or isolated 5q- they can proceed to transplant without any treatment.
- For patients with RAEB-1, RCMD+/-RS, or MDS NOS must have stable disease for 6 months (as documented by serial bone marrow examinations)

in the absence of any therapy but growth factors or transfusion support. Patients who require treatment to "control their disease" must show chemo-responsiveness.
    - For patients with CMML or RAEB-2 they must demonstrate chemo-responsiveness.
    - Chemo-responsiveness is defined as a blast percentage decrease by at least 5 percentage points and there must be less than 10% blasts after treatment and at the time of transplant, if there are more than 10% blasts at any point during the disease course.
    - Chemo-responsiveness must also include at least one of the following if applicable
        - A cytogenetic response
        - A well-documented decrease in transfusion requirements.

Patients must have a related donor who is zero, one, two, three, or four antigen mismatched at the HLA-A; B; C; DR loci or an unrelated donor up to a two antigen mismatch. DNA will be retained by the tissue typing laboratory for possible typing for DQ and DP. When multiple related donor options are available donor selection will be determined the same as in the TJU two-step protocols. When multiple unrelated donors are available care will be made to avoid HLA-A and HLA-B mismatches if possible based on data from the Japanese Marrow Donor Registry studies.[12, 13] An HLA antibody screen will be performed on each patient.*The hematopoietc progenitor cells from unrelated donors may be cryopreserved prior to infusion as circumstances require such as during the COVID-19 pandemic. Recently published data has shown that cryopreservation has no adverse effect on survival.* [13A]

All patients must have adequate organ function:

1) Patients with related donors must have an LVEF of $\geq$35%. Patients with unrelated donors must have an LVEF $\geq$45%. Patients with LVEF $\leq$50% and all patients with symptoms or history of heart failure or coronary artery disease must have a stress echo or equivalent test and a cardiological evaluation.
2) Patients with related donors must have a DLCO $\geq$35% of predicted corrected for hemoglobin. Patients with unrelated donors must have a DLCO $\geq$45% of predicted corrected for hemoglobin. *For related donors if the DLCO is less than 45% the EF must be greater than 45% and vice versa.*
3) Patients with related donors must have an adequate liver function as defined by a serum bilirubin $\leq$3.0, AST and ALT $\leq$3.0X upper limit of normal. Patients with unrelated donors must have an adequate liver function as defined by a serum bilirubin $\leq$1.8, AST and ALT $\leq$ 2.5X upper limit of normal. Exceptions may be granted for patients with "benign" liver disorders such as Gilbert's disease.
4) Patients with related donors or with unrelated donors must have a creatinine clearance of $\geq$ 60 ml/min/1.73 m^2.
5) Patients with related donors must have a performance status $\geq$ 60% (TJU Karnofsky[14]) (Appendix A). Patients with unrelated donors must have a Performance status $\geq$ 70% (TJU Karnofsky).

6) Patients with related donors must have a HCT-CI Score[15] ≤ 6 Points (Appendix B). Patients with unrelated donors must have a HCT-CI Score ≤ 5 Points.
7) Patients must be willing to use contraception if they are of childbearing potential.
8) Patients must be able to give informed consent or have a care-giver who can give consent.

3.2 Patient Exclusion Criteria

1) Patients with related donors who have a combination of Performance status of ≤ 70% (TJU Karnofsky) and an HCT-CI of 4 points or more. Patients with unrelated donors with a combination of Performance status of ≤ 80% (TJU Karnofsky) and an HCT-CI of 4 points or more.
2) Patients with active involvement of the central nervous system with malignancy. This can be documented as an abnormal neurological exam and/or a positive CSF analysis.
3) Patients with a psychiatric disorder that would preclude patients from complying with the protocol even with a caregiver.
4) Pregnancy
5) Patients with life expectancy of ≤ 6 months for reasons other than their underlying hematological/oncological disorder.
6) Patients who have received alemtuzumab or ATG within 8 weeks of the transplant admission.
7) Patients with evidence of another malignancy, exclusive of a skin cancer that requires only local treatment, should not be enrolled on this protocol.
8) Patients with clinically significant preformed antibodies to their donors.
9) Patients who require supplemental oxygen other than for sleep apnea will be excluded.

4.0 Informed Consent

Patients referred for the trial will have their eligibility criteria verified. On meeting the eligibility for the trial as outlined, informed consent will be obtained using forms approved by the Thomas Jefferson University Hospital Institutional Review Board and following guidelines related to the use of human subjects in research. The risks and hazards of the procedure, as well as alternative forms of therapy will be presented to the patient in detail. In addition, donors will be asked to sign a consent form after they have been fully informed about the procedures and risks of donating. Patients will receive a signed copy of the consent form after the consent interview.

5.0 Treatment Plan

While the days of radiation and drug administration are fixed, the exact timing of these treatments on the day they are due is not specified because of expected variations in clinical care.

Schema For Myeloablative HSCT

	-3	-2	-1	0	+1	+2	+3	+4	+5

AM	TBI 1.5 Gy	TBI 1.5 Gy	TBI 1.5 Gy	TBI 1.5 Gy	Rest	Rest	Cy 60 mg/kg	Cy 60 mg/kg	Tacrolimus &MMF*
PM	TBI 1.5 Gy	TBI 1.5 Gy	TBI 1.5 Gy	TBI 1.5 Gy HSCT					

Schema For Reduced Intensity HSCT**

	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
AM	Fludarabine 30 mg/m^2	Fludarabine 30 mg/m^2	Fludarabine 30 mg/m^2	Fludarabine 30 mg/m^2	Rest	TBI 2 Gy	Rest	Rest	Cy 60 mg/kg	Cy 60 mg/kg	Tacrolimus & MMF*
PM		Busulfan 3.2 mg/kg	Busulfan 3.2 mg/kg			HSCT					

*Mycophenolate Mofetil (MMF)

**Patients will receive ablative transplants or nonmyeloablative transplant depending on their disease type (per TJU standard practice guidelines). Patients who have received a previous transplant, patients who have received dose limiting radiation, and patients with a DLCO <45% will receive the reduced intensity conditioning regimen. The cyclophosphamide will be administered on days +3 and +4 after the stem cell infusion.

5.1 **Administration of Immunosuppressive Agents during Conditioning**

There should be no administration of agents that suppress lymphocyte reactivity from admission until day -1 in this protocol. This includes steroids, calcineurin inhibitors, MMF, or monoclonal antibodies that affect lymphocyte number or function. Absence from the medication list of these agents serves as documentation that they were not given. Patients must be off steroids (aside from premedication for transfusion) for at least 7 days prior to admission. If patients have previously required steroids as a premedication for transfusion, they may receive a dose of steroid equivalent to 5 mg of prednisone on the first day of TBI. After this, no steroids at all should be given through day -1 of the transplant regimen. Diphenhydramine and meperidine may be used if necessary. Any use of steroids after the first day of TBI through day -1 should not be administered without approval from the PI.

6.0 Study Measurements

The tables below outline the measurements and time points specific to this study. Only the day +28 studies are mandatory. The other elements are recommended. The attending physican may perform assessments/labs more or less frequently based on the patient's unique course.

General Testing for all patients:

	Baseline assessment	During conditioning	After Condition-ing through Day + 28	Days 28-90	Days 90-180	Day 180	Days 180-365
History and physical with vital signs, including SPO_2. Assessment of infectious signs, pregnancy test for females of childbearing potential done on baseline assessment	X	Every 1-2 days	Daily if in hospital weekly until day 28 after discharge	Monthly	As clinically indicated		As clinically indicated
Laboratory Studies*	X	Every 1-2 days	Daily if in hospital weekly until day 28 after discharge	Twice monthly or as clinically indicated	As clinically indicated		As clinically indicated
Quantitative cytomegalovirus CMV by polymerase chain reaction PCR		Weekly or as clinically indicated	Weekly until discharge or as clinically indicated	Twice monthly or as clinically indicated	As clinically indicated		Monthly or as clinically indicated
Viral throat gargle/sputum culture and sensitivity C&S		If respiratory symptoms	If respiratory symptoms	If respiratory symptoms	If respiratory symptoms		If respiratory symptoms
Stool culture (cx), viral screening & cx & fungal cx	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated		If clinically indicated

Study specific testing for patients on Non-Myeloablative Arm:

	Baseline assessment	During condition-ing	Day + 28	Days 28-90	Days 90-180	Day 180	Days 180-365
GVHD Assessment Presence and degree of skin rash, presence and amount of diarrhea, LFT's	N/A	Daily after engraftment until discharge and then weekly as indicated	X	Twice monthly	As clinically indicated		As clinically indicated
Chimerism/ Disease Assessment							
Peripheral blood for CD3+ chimerism & Buffy coat chimerism			X	Twice monthly until >95% donor chimerism	Once d+90	X	As clinically indicated
Bone marrow exam (morphology, flow cytometry, cytogenetics, buffy coat chimerism)			X	Day +90 Marrow	Day +180 Marrow Is optional	Day +270 Marrow Is optional	Day +365 Marrow Is optional
Immune Reconstitution Studies							
Flow cytometry for lymphocyte subsets			X	Monthly	Monthly	X	Quarterly

Study specific testing for patients on the Myeloablative Arm:

	Day + 28	Day + 90	Day +180	Day + 270	Day +365
GVHD Assessment Presence and degree of skin rash, presence and amount of diarrhea, LFT's	X	X	X	X	X
Chimerism/ Disease Assessment					

Peripheral blood for Total, MNC & CD3+ chimerism	X	X	X	X	X
Bone marrow exam (morphology, flow cytometry, cytogenetics, chimerism)	On day +28	At day +90	Day +180 Marrow is optional	Day +270 Marrow is optional	Day +365 Marrow is optional
Flow cytometry for lymphocyte subsets (IRP)	X	X	X	X	X

*Laboratory studies include a complete blood count with differential, comprehensive metabolic panel, lactic and GVHD prophylaxis drug levels when applicable.

The day +28 peripheral blood, marrow studies and IRP can be obtained within 1 week before day 28 (i.e. day +21 through day +28) and within 2 weeks after day +28 (i.e. day +28 through day +42) to account for scheduling factors and failed testing.

Other post transplant studies (d+90, d+180, d+270, d+365) should be performed within one month of their due date.

6.1 Hematopoietic engraftment:
Will be defined as:
ANC ≥ 0.5x10e9/L for at least 3 days.
Platelet engraftment >20,000 with no transfusions X 7 days.

6.2 Toxicity Criteria:
Regimen-related toxicity will be graded according to the NCI Common Toxicity Criteria, version 4.0. These criteria can be found on the Thomas Jefferson University Hospital BMT website at http://bmt.tju.edu

The NCI Common Toxicity Criteria can also be found at the following website: http://ctep.cancer.gov/reporting/ctcnew.html

6.3 Disease Response:
Disease response will be measured according to the National Comprehensive Cancer Network Guidelines (NCCN). The guidelines are disease specific and the guidelines for each disease can be found at:

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

6.4 GVHD Scoring:
Acute GVHD will be staged and graded according to standard criteria contained in Appendix D.

6.5 Adverse event reporting:
All patients will be followed for adverse events (AEs) (serious and nonserious), regardless of relationships to study treatment, from the time of enrollment until d +100

after transplant. The following events are expected side effects of high-dose chemotherapy and transplant and will be recorded but will not be reported except as noted:

Alopecia, dry skin

Emesis from chemotherapy or other agents unless refractory to standard supportive care, nausea and anorexia

Weight loss, cough, dry mouth and headache

Neutropenia/uncomplicated neutropenic fever, grades 1-3 infectious sequellae

Thrombocytopenia, petechiae, ecchymoses, minor vaginal bleeding, epistaxis, hemorrhoidal bleeding, or other similar bleeding eventsill not be reported. (Bleeding events requiring transfusion and/or intervention such as endoscopy or radiologic evaluation will be reported.)

Anemia

Grades 1-3 electrolyte imbalances

Grades 1-3 abnormalities in alkaline phosphatase, AST and ALT

Grades 1-3 Rash

Grades 1-3 Fatigue

Grade I - III Mucositis

Grade I - III Diarrhea

Allergic or other common reactions to drugs used for supportive care unless grade 4-5.

After d+100, only SAEs that are considered by the investigator to be possibly or probably associated with the treatment regimen or deaths will be reported.

6.6 Study Endpoint:

The primary endpoint of this study is percentage of patients who engraft.

This study is eligible for final closure when the last enrolled patient is three months post transplant.

7.0 Supportive Care

7.1 Avoidance of Infection

Patients who are post HSCT are susceptible to infection. BMT Clinical Program SOPs CP:P050.01 and CP:P001.04 address infectious prophylaxis and management of suspected infection.

It is recommended that IVIG 0.5 g/kg IV will be administered monthly post transplant to support immune function, until the IgG level is ≥ 500 mg/dL ("trough" level) on two consecutive monthly measurements. The first dose will be targeted for administration on day +13. It is recognized that fluid overload, changes in renal function, or outpatient lack of coverage for the IVIG may prohibit or delay this therapy.

7.2 Infectious Prophylaxis-General Guidelines

Patients post allogeneic transplantation will be maintained on antifungal prophylaxis. It is at the discretion of the treating attending physician and/or BMT clinical pharmacist to change agents as clinically indicated.

Patients post allogeneic transplantation will be maintained on HSV prophylaxis. It is at the discretion of the treating attending physician and/or BMT clinical pharmacist to change agents based on culture results and sensitivities.

Patients post allogeneic transplantation will be maintained on PCP prophylaxis. It is at the discretion of the treating attending physician and/or BMT clinical pharmacist to change agents based on culture results or drug intolerance.

Specific medications and dosages of prophylactic antibiotics may change in response to changes in standard practice guidelines. These agents will be discontinued with adequate immune recovery/response to vaccinations at the discretion of the treating BMT physician.

7.3 Growth Factor and Transfusion Support

To prevent inadvertent 3rd party lymphoid engraftment, all mature blood cell products must be irradiated.

G-CSF 5μg/m2 can be substituted for GMCSF in the event of a GM-CSF shortage or if a patient has a deleterious reaction to GMCSF as determined by the BMTU attending physician.

All red cell and platelet products will be leukodepleted to prevent alloimmunization and decrease the possibility of infectious complications.

Packed red blood cell transfusions will be given as necessary to keep the hemoglobin ≥ 8 g/L. A higher hemoglobin (≈10) will be maintained during cyclophosphamide administration per TJU BMT program guidelines.

Platelet transfusions will be used as needed to keep the morning count ≥ 20x10e9/L, with ≥10x10e9/L used for situations without an excessive bleeding risk.

GM-CSF 250µg/m^2 will be administered daily beginning on day +5. GM-CSF will be weaned/discontinued at the discretion of the attending physician. Every effort should be made to keep the ANC ≧ 1000 for all patients post transplantation.

Red cell growth factors are permissible after transplantation.

8.0 Drug Information and Administration
(Note TBI will be given as described in Appendix C)

8.1 Cyclophosphamide
Mechanism: A multistep process activates it by conversion to 4-hydroxycyclophosphamide by the liver microsomal oxidase system and to aldophosohamide by tautomerization in the peripheral tissues. Aldophosphamide spontaneously degrades into acrolein and phosporamide mustard, which cause cellular glutathione depletion and DNA alkylation. This results in inhibition of DNA replication and transcription. Cells expressing high levels of aldehyde dehydrogenase (e.g. stem cells, L1210 leukemia cells) resist cyclophosphamide-mediated cytotoxicity as aldophosphamide is inactivated by this enzyme. The drug also does not affect quiescent cells and therefore stem cells are generally protected, an important factor if autologous hematopoietic recovery is relied on in the event of graft failure.

Metabolism: Cyclophosphamide is broken down as described above and the break-down products are excreted by the kidneys.

Incompatibilties: Phenobarbital or rifampin may increase the toxicity of cyclophosphamide. Concurrent allopurinol (administered only if the patient has a high tumor burden going into transplant which is unlikely on this study or on it to prevent gout) or thiazide diuretics may exaggerate bone marrow depression May prolong neuromuscular blockade from succinylcholine Cardiotoxicity may be additive with other cardiotoxic agents (cytarabine, daunorubicin, doxorubicin). The drug may decrease serum digoxin levels. Additive bone marrow depression with other antineoplastics or radiation therapy can occur. It may potentiate the effects of warfarin. May decrease antibody response to live-virus vaccines and increase the risk of adverse reactions. It prolongs the effects of cocaine.

Toxicity: Nausea, vomiting, water retention due to inappropriate secretion of anti-diuretic hormone (SIADH), cardiomyopathy with myocardial necrosis and congestive heart failure, hemorrhagic cystitis, alopecia, skin rash, pulmonary fibrosis, sterility and secondary malignancies.

Administration: In this protocol, patients will receive two doses of cyclophosphamide 60 mg/kg IV, on days +3 and +4. The dose of cyclophosphamide will be calculated according to the dosing body weight. MESNA (sodium-2-mercaptoethane sulfonate) will be administered prior to cyclophosphamide infusion and ending approximately 24 hours after the last dose of cyclophosphamide. The dose of MESNA will also be calculated based on dosing body weight.

Reference: Skeel R & Lachant N. Handbook of Cancer Chemotherapy, 4th Ed. Little, Brown & Co.: Boston.

8.2 Busulfan

Mechanism: Busulfan is an alkylating agent which reacts with the N-7 position of guanosine and interferes with DNA replication and transcription of RNA. Busulfan has a more marked effect on myeloid cells than on lymphoid cells and is also very toxic to hematopoietic stem cells. Busulfan exhibits little immunosuppressive activity, and therefore in this protocol is given with fludarabine and TBI both of which have lymphopenic affects. Busulfan interferes with the normal function of DNA by alkylation and cross-linking the strands of DNA.

Metabolism: Extensively hepatic; glutathione conjugation followed by oxidation
Incompatibilties: Busulfan does not have an extensive list of medications that cause problematic interactions. However, there are a few drugs, commonly used with Busulfan that may affect its metabolism. Phenytoin may decrease the serum concentration of Busulfan and Azoles may decrease the metabolism of Busulfan. Acetominophen and Metronidazole may increase the serum concentration of Busulfan.

Toxicity: Side effects of Busulfan include but are not limited to: tachycardia, hypertension, insomnia, anxiety, headache, fever, vomiting, mucositis, diarrhea, anorexia, myelosupression, hyperbilirubinemia, VOD, weakness, and arthralgias.

Administration: Busulfan is administered for 2 days on days -4 and -3 at a dose of 3.2 mg/kg/day IV. The infusion can be started upon the completion of the fludarabine.

Reference:
http://online.lexi.com.proxy1.lib.tju.edu/lco/action/doc/retrieve/docid/patch_f/6487#f_adverse-reactions

8.3 Fludarabine

Mechanism: Fludarabine phosphate is fluorinated nucleotide and analog of antiviral agent vidarabine, that is relatively resistant to adenosine deaminase deamination. It is actively dephosphorylated to 2-fluoro-ara-A and phosphorylated further by deoxycytidine kinase to 2-fluoro-ara-ATP, then acts by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase resulting in DNA synthesis inhibition.

Metabolism: Renal Excretion
In a pharmacokinetic study of patients treated with fludarabine for rheumatoid arthritis, the mean total clearance was 14.01 L/hr following a dose of 20 mg/m(2)/day, and 13.4 L following a dose of 30 mg/m(2)/day (Knebel et al, 1998). The median total body clearance was 9.6 L/hr after intravenous or subcutaneous fludarabine 30 mg/m(2) for 3 days in 5 patients with lupus nephritis (Kuo et al, 2001).

Incompatibilities: Fludarabine has drug interactions with several vaccines and its simultaneous use with Rotavirus vaccine is contraindicated.

Toxicities: Common: Endocrine/Metabolic: Shivering, Gastrointestinal: Loss of Appetite, Nausea, Vomiting, Neurologic: Asthenia, Other: Fatigue, Malaise**,** Serious: Cardiovascular: Edema (frequent), Dermatologic: Aplasia of skin (rare), Hematologic: Autoimmune Hemolytic Anemia, Graft versus host disease, Transfusion-associated, with non-irradiated blood (rare), Myelosuppression (frequent), Neurologic: Neurotoxicity, Respiratory: Pneumonia (frequent), Other side effects: Fever (frequent), infections.

Administration: In this protocol, Fludarabine is administered for 4 days on days -5 through – 2 at a dose of 30 mg/m^2 IV daily. Creatinine should be checked prior to each dose of fludarabine. If renal insufficiency develops, the attending physician must be notified in cases where a dose adjustment needs to be made.

Reference: MicroMedex Health Care Series, Thomson

8.4 G-CSF

Mechanism: G-CSF is a human granulocyte colony-stimulating factor produced by recombinant DNA technology. It is a glycoprotein which acts on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and some end-cell functions.

Metabolism: Absorption and clearance of G-CSF follows first-order pharmacokinetic modeling without apparent concentration dependence. The elimination half-life in both normal and cancer patients is 3.5 hours.

Incompatibilties: Safety and efficacy of G-CSF when used simultaneously with chemotherapy or radiotherapy has not been evaluated. Donors receiving either of these 2 modalities will not be permitted on study.

Toxicities: Allergic reactions consisting of rash, wheezing and tachycardia. Splenic rupture, ARDS, and exacerbation of sickle cell disease have been reported rarely.

Administration: In this protocol, G-CSF will be administered to healthy donors at a dose of 10 µg/kg (actual weight) subcutaneously on days -5 through day -1.

Reference: Physician's Desk Reference, Edition 58, 2004.

8.5 GM-CSF

Mechanism: GM-CSF is a recombinant human granulocyte-colony stimulating factor produced by recombinant DNA technology in a yeast expression system. It supports survival, clonal expansion, and differentiation of hematopoietic cells. GM-CSF is also capable of activating mature granulocytes and macrophages, and is a multilineage factor with effects on the myelomonocytic, erythroid, and megarkaryocytic lines.

Metabolism: GM-CSF is detected in the serum at 15 minutes after injection. Peak levels occur about 1 to 3 hours after injection, and it is detectable in the serum for up to 6 hours after injection.

Incompatibilities: Interactions between GM-CSF and other drugs have not been fully evaluated. Drugs which may potentiate the myeloproliferative effects of GM-CSF, such as lithium and corticosteroids, should be used with caution.

Toxicities: Allergic and anaphylactic reactions have been reported. A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope and or tachycardia has been associated with the first administration of GM-CSF in a cycle. These signs have resolved with treatment.

Administration: In this protocol, GM-CSF will be given to the patients beginning on Day +5 in the PM.

Reference: Physician's Desk Reference, Edition 58, 2004.

8.6 Mycophenolate Mofetil (MMF)

Mechanism: Inhibits the enzyme inosine monophosphate dehydrogenase, which is involved in purine synthesis. This inhibition results in suppression of T- and B-lymphocyte proliferation.

Metabolism: Following oral and IV administration, mycophenolate is rapidly hydrolyzed to mycophenolic acid (MPA), its active metabolite. Distribution is unknown. MPA is extensively metabolized; <1% excreted unchanged in urine. Some enterohepatic recirculation of MPA occurs. Half Life: *MPA*¾17.9 hr.

Incompatibilities: Combined use with azathioprine is not recommended (effects unknown). Acyclovir and ganciclovir compete with MPA for renal excretion and, in patients with renal failure, may increase each other's toxicity. Magnesium and aluminum hydroxide antacids decrease the absorption of MPA (avoid simultaneous administration). Cholestyramine and colestipol decrease the absorption of MPA (avoid concurrent use). Toxicity may be increased by salicylates. May interfere with the action of oral contraceptives (additional contraceptive method should be used). May decrease the antibody response to and increase risk of adverse reactions from live-virus vaccines, although influenza vaccine may be useful. When administered with food, peak blood levels of MPA are significantly decreased. MPA trough levels (goal 2-4 μg/ml) will be measured on day +7 and dose adjusted accordingly.

Toxicities: GI: Bleeding, Diarrhea, Vomiting, Hematopoietic: Leukopenia Miscellaneous: Sepsis, Increased Risk of Malignancy

Administration: In this protocol, MMF will be administered at a dose of 1 gram IV BID beginning on day +5. MMF will be discontinued on day +28 +/- 3 days in the absence of

GVHD. MMF may be stopped earlier if there is count suppression from the drug or other unforeseen circumstances in which the drug is felt to be deleterious to the plan of care.

8.7 Tacrolimus

Mechanism: Tacrolimus, it is a macrolide immunosuppressant. It inhibits lymphocytes by forming a complex with FKBP-12, calcium, calmodulin leading to the decrease in the phosphatase activity of calcineurin. This in turn prevents generation of NF-AT, a nuclear factor for initiating gene transcription for lymphokines like interleukin-2 and interferon. This drug is used with corticosteroids for prophylaxis of organ rejection in patients receiving allogeneic liver transplants. Its use is also currently being investigated in kidney, bone marrow, cardiac, pancreas, pancreatic island cell and small bowel transplantation.

Metabolism: This drug is well absorbed orally. It is metabolized in the liver by unknown mechanisms and demethylation and hydroxylation has been proposed based on *in vitro* studies. The metabolized products are excreted in the urine.

Incompatibilities: Nephrotoxic drugs, antifungals (azoles), calcium-channel blockers, cimetidine, danazol, erythromycin, methylprednisone and metoclopramide increase the bioavailabilty of tacrolimus. On the other hand phenobarbital, phenytoin, rifamycins and carbamazepine decrease tacrolimus levels.

Toxicities: Adverse reactions include: tremor, headache, neurotoxicity; diarrhea, nausea; hypertension; TTP and renal dysfunction.

Administration: Tacrolimus will be started on day +5. Tacrolimus dosing should be titrated to maintain a target level of 8ng/ml +/- 2, although it is recognized that there may be variations beyond the target range due to interpatient variability. The tacrolimus wean can be initiated by day +60 in the absence of GVHD. Tacrolimus may be discontinued earlier if there is count suppression or other significant side effects thought to be due to the drug. Because of the variability in patient outpatient office visit times and need for GVHD assessment, it is not mandatory that the taper begins on day +60.

9.0 Evaluation of Safety

Specification of Safety Parameters

Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

Safety Assessment and Follow-Up

The PI will follow adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 0 Safety Assessment and Follow-Up.

Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

Safety Reporting

Reporting to IRB

Unanticipated Problems

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 0 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

Adverse Events

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

Serious Adverse Events

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

Reporting to SKCC DSMC

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

For expedited reporting requirements, see table below: DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

10.0 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

11.0 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

12.0 Statistical Analyses

12.1 Study Design

This study is a two arm single center study. The first arm will recruit 18 (13+5) patients with related donors and will utilize the Simon optimal two-stage design. The total of 13 patients with half-matched related donors will be recruited and included in the analysis population. Approximately five additional patients with related donors other than haploidentical will be included in the study but will only be analyzed descriptively. The second arm will recruit three to 23 patients with unrelated donors using the standard two-stage accrual design ("3+3 design") typically used for dose escalation studies. For the purpose of this study, the number of antigen mismatches (0 to 2) is analogous to the escalating dose.

The primary endpoint is the percentage of patients who engraft. The secondary endpoints are the incidence of grade III-IV GVHD and the incidence of GVHD nonresponsive to corticosteroids and photopheresis. The study is designed to evaluate the primary and secondary endpoints separately in each arm, and there is no plan to compare the outcomes in two arms. The data from each arm will be analyzed separately. Within each arm there will be two subgroups of patients, one receiving a reduced intensity conditioning regimen and one receiving a myeloablative transplant. The treatment will depend on the disease type (per TJU standard practice guidelines).

We will compute the **exact** 90% bimonial confidence interval for the rejection r**ate** in the 2 antigen mismatched based on at least 10 patients. If zero rejections are observed in 10 patients, there will be 90% confidence that the true rejection rate is at most 26% (upper limit of exact binomial confidence interval). Otherwise, if 1 rejection is observed in 10 patients, there will be 90% confidence that the true rejection rate is at most 39.4%.

12.2 Design and statistical analysis of the arm with related donors

The majority of the patients in this arm will be patients with half-matched related donors. Only these patients will be included into analysis population to evaluate the primary and secondary endpoints. The total sample size of 13 patients was determined for the half-match related donors only. Approximately five patients with related donors other than haploidentical will be included in the study but not analyzed jointly with the analysis population of patients with haploidentical donors.

The Simon optimal two-stage design[16] is used with the potential for early termination in case of a poor engraftment rate. Choice of design is guided by a desire to stop the trial early if the actual engraftment rate is 65% or less. If the successful engraftment rate is 90% or greater, we would like to have a low probability of failing to conclude the treatment effective. The target Type I error rate is 10% and the target power is 80%.

The Simon optimal two-stage design is:

Look after this number of patients	Stop if number of successes is less than
6	5
13	11

With this design, we have no more than 18% chance of concluding ineffective (≤65% success rate) when the successful engraftment rate is at least 90%. Similarly, we have no more than 9.7% chance of concluding effective (≥90% successful engraftment rate) when it is ineffective. If the actual engraftment rate is 65% or worse, we have at least 68% probability that the trial will stop after the first 6 subjects.

The estimates of the engraftment and incidence rates will be presented with corresponding 90% binomial confidence intervals. For engraftment rates, the method of Atkinson and Brown[17] will be used to allow for the two-stage design. In secondary analysis, we will evaluate the engraftment rate by treatment group (ablative versus nonmyeloablative group), provided that both groups have non-trivial number of patients, and evaluate any possible treatment differences in engraftment rates using Fisher's exact test. This analysis is exploratory and adjustment for two-stage design is not planned. For incidence rates, one-sided exact binomial confidence interval will be computed. If no events of grade III-IV GVHD or GVHD nonresponsive to corticosteroids and photopheresis are observed in 13 patients, we will have 90% confidence that the true incidence rate is at most 16%.

12.3 Design and statistical analysis of the arm with unrelated donors

For the second arm, we will use a two-stage accrual design for each number of the antigen mismatches considered (0, 1, or 2). We will transplant three patients with full one antigen

mismatched unrelated donors (either on or off study). If none of the three fails to engraft i.e., all three engraft then we will proceed with recruitment of patients with unrelated donors who are a two antigen mismatch. If one patient of the first three fails to engraft, then an additional three patients will be recruited with fully HLA matched unrelated donors. If a second patient of the first six with one antigen mismatched donors fails to engraft then the study for this arm will be closed to patient with only mismatched unrelated donors. If five of the first six engraft then we will recruit patients with unrelated donors who are a two antigen mismatch. If at any time there are two or more patients with the same number of antigen mismatches fail to engraft, then there will be no further recruitment of patients with that or higher number of antigen mismatches. Data analysis of this arm is descriptive. All estimates of engraftment and incidence rates will be presented with corresponding confidence intervals using the exact method.

12.4 Accrual and Study Duration

It is estimated that 126 month of accrual will be necessary to enroll 23 patients with unrelated donors and 18 patients with related donors at the approximate rate of six patients per year. Up to ten additional patients will be accrued to the study in either cohort,, at the approximate rate of 2-3 patients per year. Patients will be followed for a minimum of 3 months post-transplant.

As of March 2017, the related arm is closed and will no longer accrue patients. An additional 30 patients will be enrolled onto the mismatched arm of this trial. Of these 30 patients, up to 10 will be accrued to the 2 antigen mismatch arm. The trial will stop accruing when the enrollment total of 81 has been reached.

Patients who are enrolled on the study but do not receive treatment will be considered inevaluable and will be replaced.

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14.0 Appendices

Appendix A

Modified Karnofsky Performance Scale-Web Based Tool

The modified KPS is a Web-based tool developed in our program that builds upon the original KPS.[14] The tool was developed to characterize each patient's performance status in more depth than what was possible with the original KPS in order to determine the suitability of the patient for transplant. The performance status is calculated based on the information entered into the program. At the following website: http://ser0608.kcc.tju.edu/transplant_check/karnofsky/summary.php

The categories "Not on immune suppression" and "At home, not self sufficient" are not further subdivided. The other three categories subdivide into additional questions. An example this further characterization is given below for the "Self sufficient at home" category.

Karnofsky questionnaire

Patient name:

MR number: Find name

Location: ◉ Clinic ○ Admission

Which category best describes the patient?

Can perform some of the following activities:

- ☐ Working at least 50% of the time
- ○ ☐ Run household without help (shop, cook, clean)
- ☐ Drive / walk outside home independently without O_2
- ☐ Exercise actively

At home, this patient:

- ○ **Is fully independent**, can ambulate around the home independently (including stairs) without O_2; is out of bed except to sleep
- ○ **Requires occasional assistance** with stairs, meal preparation, or toileting; is out of bed except to sleep
- ○ **Requires frequent or considerable assistance**; requires the presence/support of another adult most of the time; spends more than 2 daytime hours in bed

- ◉ **Self sufficient at home.** (Can dress, feed self, go to bathroom, but unable to run the household or function outside the home for extended periods of time.)
- ○ **At home, not self-sufficient.** (Requires virtually continuous supervision or assistance; minimally or not ambulatory.)
- ○ **Hospitalized.** (Transplant is not permitted unless patient meets all criteria.)

Other criteria:

- ☐ **Not on immune suppression** except for up to 10 mg of prednisone for 7 days prior to transplant admission

Submit

Appendix B

The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI)[15]

Comorbidity	Definitions of the Comorbidity	HCT-CI Weighted Scores
Arrhythmia	Atrial Fibrillation/Flutter, Sick Sinus Syndrome, Or Ventricular Arrhythmias	**1**
Cardiac	Coronary Artery Disease, CHF, MI Or EF $\leq$ 50%	**1**
Inflammatory Bowel Disease	Crohn Disease or Ulcerative Colitis	**1**
Diabetes	Requiring Treatment with Insulin or Oral Agent but not Diet Alone	**1**
Cerebral Vascular Disease	Transient Ischemic Attack or Cerebral Vascular Accident	**1**
Psychiatric Disturbance	Depression or Anxiety Requiring Psychiatric Consult or Treatment	**1**
Hepatic-Mild	Chronic Hepatitis, Bilirubin > ULN to 1.5 X ULN Or AST/ALT > ULN to 2.5 X ULN	**1**
Obesity	Patients with Body Mass Index > 35 kg/m2	**1**
Infection	Requiring Continuation of Antimicrobial Treatment after Day 0	**1**
Rheumatologic	SLE, RA, Polymyositis, Mixed CTD Or Polymyalgia Rheumatica	**2**
Peptic Ulcer	Requiring Treatment	**2**
Moderate/Severe Renal	Serum Creatinine > 2 mg/dL, on Dialysis, Or Prior Renal Transplantation	**2**
Moderate Pulmonary	DLCO and/or FEV_1 66%-80%, Or Dyspnea on Slight Activity	**2**
Prior Solid Tumor	Treated at any Time Point in the Patient's Past History, Excluding Nonmelanoma Skin Cancer	**3**
Heart Valve Disease	Except Mitral Valve Prolapse	**3**
Severe Pulmonary	DLCO and/or $FEV_1 \leq 65\%$, or Dyspnea At rest or Requiring Oxygen	**3**
Moderate/Severe Hepatic	Liver Cirrhosis, Bilirubin > 1.5 X ULN, Or AST /ALT > 2.5 X ULN	**3**

Appendix C

Radiation Guidelines (For myeloablative regimen except as noted)

Modality

Photon irradiation is to be used for the TBI in all patients. Areas beneath lung blocks will be supplemented with electrons to maintain the homogeneity criteria.

Energy

Either a linear accelerator or Cobalt source may be used. Dose to superficial tissues near skin surface will be increased by using a beam "spoiler" lucite plate close to the patient. Since neoplastic infiltrates may be found in the skin, it is necessary for the superficial dose to satisfy the same total dose requirements as other locations.

Geometry

The treatment configuration shall be such that the patient is entirely included within the treatment beam. It is essential that the correlation between the light field and the radiation field be established and verified for extended TBI distances.

Dose Rate

A dose rate of 0.05 to 0.25 Gy/minute at the prescription point shall be utilized. The physicist of record, involved with TBI treatments, shall be consulted to achieve correct range of treatment dose rate.

Calibration & Beam Data Verification

The calibration of the output of the machine, used for this protocol, shall be verified on a daily basis prior to start TBI treatments. All dosimetric parameters, necessary for the calculation of dose delivered during TBI treatments, shall be measured at the appropriate treatment distance. They shall be documented and made available for calculation of every patient treatment.

Treatment Volume

The patient shall be entirely included within the treatment beam. Care should be taken to guarantee that all of the patient is within the 90% decrement line at each depth. The 90% decrement line is defined as the line in each plane perpendicular to the central axis connecting the points which are 90% of the central axis dose, in that plane.

Diagnostic Determination

CT scans through the chest and abdomen will be done prior to initiating irradiation. An average chest wall thickness (both anteriorly and posteriorly) will be calculated and used in determination of electron energy for supplementing the chest wall beneath the lung blocks. The abdominal scan, renal ultrasound, or intravenous pyelogram will be used to localize the kidneys for proper placement of renal shielding.

Treatment Dose

Prescription Point

The prescription point is defined as the midplane point along the longitudinal axis at the level of the umbilicus.

Dose Units
All doses shall be specified in Gray (Gy) to muscle tissue.

Tissue Inhomogeneity Considerations
No inhomogeneity corrections shall be made in the calculation of the dose to the prescription point.

Prescription Point Dose
The total dose shall be 12.0 Gy. A hyperfractionated regimen over 4 consecutive days shall be used. For the nonmyeloablative regimen a single dose of 2 Gy will be given.

Time-Dose Considerations
Hyperfractionation
For patients receiving 2 fractions per day, there is a required minimum time interval of 6 hours between the fractions.

Chest Wall Supplement
Supplementing the chest wall dose with electrons (both anteriorly and posteriorly) shall be done once a day on 2 treatment days, immediately preceding or following treatment to the entire body. The area beneath the lung blocks shall receive an additional 6.0 Gy to d_{max} in a total of 2 fractions.

Total Number of Treatment Days
There shall be a total 4 consecutive treatment days for the myeloablative regimen and one day for the nonmyeloablative regimen.

Treatment Interruptions
An interruption in the radiotherapy regimen shall not be allowed.

Dose Homogeneity
The total absorbed dose along the patient's head to toe axis (in the midplane of the patient) shall not deviate more than 10% from the prescribed dose.

Treatment Technique
Treatment Fields
Equally weighted parallel opposed portals shall be used. AP/PA fields shall be used.

Field Size
The collimation and treatment distance shall be such that the patient will be entirely included within the treatment beam and that no part of the patient extends beyond that region. The agreement of the light field and the radiation field should be checked periodically for the extended TBI treatment distance.

Treatment Position
The patient shall be treated in any position that is compatible with the homogeneity requirement, allowing for the reproducibility of the patient setup and dosimetry.

Field Shaping

Customized blocking to the lungs is required. Customized blocking to the liver and/or kidneys is optional, at the discretion of each participating center with the approval of the coordinating center radiation oncologist.

Patient specific, individually fabricated shielding blocks are required for the lung from both the anterior and posterior directions. A partial transmission block corresponding to a total dose of 8.0 Gy at midplane of the patient under the blocks shall be used. No corrections for inhomogeneity shall be used.

Patient specific, individually fabricated shielding blocks are optional for the liver from both the anterior and posterior directions. A partial transmission block corresponding to a dose reduction to 90% of the central axis dose shall be utilized.

Patient specific, individually fabricated shielding blocks are optional for the kidneys from the posterior direction only. A partial transmission block yielding a total dose of 10.8 Gy to the midplane of the kidney shall be used.

Customized electron cut-outs shall also be constructed corresponding to the size of the lung block plus appropriate margins in all directions.

Superficial Tissue Supplement Technique

The portion of the chest wall shielded by the partial transmission lung blocks will be supplemented with customized (or shaped) low energy electron fields. A total of 6.0 Gy to d_{max} in 2 fractions will be given to the anterior and posterior chest wall. Electron energy will be determined by chest wall thickness as determined by a chest CT scan, with the depth of the 90% dose relative to d_{max} used to determine the electron energy. The dose prescription point will be at d_{max}.

Calculations

Central Axis Dose

It is recommended that the dose calculation method be based upon measurements that are made in a unit density phantom with the following minimum dimensions:
Length equal to top of shoulder to the bottom of the pelvis.
Width equal to the patient width at the level of the umbilicus.
Thickness equal to the typical patient thickness at the umbilicus.
All measurements should be made at the appropriate extended SSD.

Superficial Dose

For the radiation beam with the Plexiglas plate in place, data should be available demonstrating that the skin dose is within 5% of the prescribed dose.

Normal Tissue Sparing-Lung Dose

Lung Dose

Each patient must have a calculation performed which shows that with the lung shielding and chest wall supplement, the TBI delivers between 9.0 Gy and 10.0 Gy to the mid-lung

region without inhomogeneity corrections. The calculation will be repeated using inhomogeneity corrections approved by the physicist at the coordinating center.

Quality Assurance Documentation

For purposes of quality assurance the following must be performed on every patient undergoing TBI:

A check of the monitor unit calculation by a second physicist and a radiation oncologist prior to first treatment.

Simulation films documenting lung, liver and kidney blocks in both the anterior and/or posterior projections shall be taken.

Portal films (both AP & PA) verifying the position of the lung, liver and kidney blocks shall be taken and must be approved by the supervising radiation oncologist prior to delivery of the first

Appendix D

Acute GVHD Staging and Grading[18]

Clinical Staging of Acute Graft-Versus-Host Disease			
Stage	Skin	Liver	Gut
+	Maculopapular rash <25% of body surface	Bilirubin 2-3 mg/dl	Diarrhea 500-1000 ml/day or persistent nausea
++	Maculopapular rash 25-50% of body surface	Bilirubin 3-6 mg/dl	Diarrhea 1000-1500 ml/day
+++	Generalized erythroderma	Bilirubin 6-15 mg/dl	Diarrhea >1500 ml/day
++++	Desquamation and bullae	Bilirubin > 15mg/dl	Pain +/- ileus

Clinical Grading of Acute Graft-Versus-Host Disease				
Overall Grade	Skin	Liver	Gut	Functional Impairment
0 (none)	0	0	0	0
I (mild)	+ to ++	0	0	0
II (moderate)	+ to +++	+	+	+
III (severe)	++ to +++	++ to +++	++ to +++	++
IV (life-threatening)	++ to ++++	++ to ++++	++ to ++++	+++