Phase II Clinical Trial of the Use of Post-Transplant Cyclophosphamide for Graft Versus Host Disease (GvHD) Prophylaxis Following Matched Unrelated Donor (MUD)

Hematopoietic Stem Cell Transplant (HSCT)

PI: OMER JAMY, MD

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Consent Form

TITLE OF RESEARCH:	**Phase II Clinical Trial of the Use of Post-Transplant Cyclophosphamide for Graft Versus Host Disease (GvHD) Prophylaxis Following Matched Unrelated Donor (MUD) and Mismatched Unrelated Donor (MMUD) Hematopoietic Stem Cell Transplant (HSCT)**
SPONSOR:	**UAB Comprehensive Cancer Center**
PROTOCOL NO:	**IRB #F130515006** **UAB #1286**
INVESTIGATOR:	**Racquel Innis-Shelton, M.D.**
CO-INVESTIGATORS:	**Shin Mineishi, MD** **Donna Salzman, MD** **Ayman Saad, MD** **Antonio Di Stasi, MD** **Luciano Costa, MD, PhD** **Lawrence Lamb, PhD** **Ruby Meredith, MD**

Purpose of the Research

You are being invited to participate in this Phase II clinical research trial because you are going to receive a hematopoietic stem cell transplant (HSCT) from a tissue typed matched unrelated donor (MUD) or mismatched unrelated donor (MMUD) to treat your disease. As your doctor has discussed with you, one of the main complications of allogeneic transplant is the risk of graft-versus-host disease (GVHD).

The goal of this research study is to determine if the use of cyclophosphamide after transplant will decrease GVHD in MUD and MMUD patients. The main purpose of this study is to assess the effects of cyclophosphamide in the post-transplant setting to prevent onset of acute GVHD. The research staff will collect data to determine the incidence of grade II-IV acute GVHD following allo HSCT using post-transplant cyclophosphamide for patients receiving transplant from MUD and MMUD donors. Other objectives for this study will be the determination of disease-free survival and overall survival following allo HSCT and to assess the safety of post-transplant cyclophosphamide for MUD and MMUD transplantation as well as observation of immune system recovery over time. In patients that do get GVHD, we will also collect data to determine the time of onset, severity, responsiveness to treatment, and organs involved of acute and chronic GVHD.

Many of the current drugs used to prevent GVHD are effective but can cause severe treatment related side effects which interfere with the benefits of HSCT conditioning regimens.

The use of cyclophosphamide is less likely to interfere with HSCT conditioning regimens and has been shown to have some effect in preventing GVHD.

GVHD is a serious potential complication of transplant where the donor stem cells treat the recipient's body as "foreign" and attack cells in the recipient's body. GVHD is one of the common complications with allogeneic stem cell transplant, (where you receive cells from another person). It can affect organ tissues such as skin, stomach, intestines, lungs, liver and others. The use of cyclophosphamide is approved by the FDA (U.S. Food and Drug Administration) and is regularly prescribed by doctors to treat multiple diseases. The investigational part of this study is the use of cyclophosphamide after you receive your donor cell infusion. This dose of cyclophosphamide is to try to prevent GVHD, or help reduce its severity if you do develop GVHD. The use of cyclophosphamide is not approved by the FDA (U.S. Food and Drug Administration) for the prevention of GVHD. This is a phase II clinical trial that will enroll approximately 48 patients, all of whom will be enrolled at UAB. You will be followed for a minimum of 2 years after your transplant as part of this study; this is the same transplant follow-up as you would have whether you are on the study or not on the study.

Explanation of Procedures

You may be eligible to take part in this research study if you meet at least the following inclusion criteria:

- You are between the ages of 19 to 65 years.
- You have a suitable unrelated donor available.
- Your heart, lung, liver and kidney function tests are acceptable.
- You are well enough to undergo full intensity conditioning.

There are conditions that might exclude you. If you are HIV positive, if you have had a previous stem cell transplant, or if you have any active infections, for example, you would not be eligible for this study. If female, you cannot be pregnant or breastfeeding. You may not take part if you have another active life threatening cancer that requires treatment other than stem cell transplant, or if your disease involves the central nervous system (CNS) which is your brain and spinal cord. Your doctor will review with you in more detail the eligibility criteria that may apply to you

If you decide to participate in this study you will be given cyclophosphamide on day +3 after your transplant. Clinical information about your transplant will be reviewed by the study doctors and nurses. Since you are having a stem cell transplant you will receive workup tests as part of your transplant standard of care whether you are on the study or not. We will use the information from your medical record to evaluate this trial only if you decide that you want to participate.

Depending upon your disease and your age you will get one of the chemotherapy regimens listed below as a conditioning regimen followed by an infusion of blood stem cells collected from a donor who is a suitable match. You will have a separate consent form that describes the transplant process and you will be able to ask your doctors and nurses questions about that consent before you make your decision.

Your transplant doctors have determined that the regimen marked below is the best conditioning regimen for you based on your disease, age, and current status:

☐ **Fludarabine and Busulfan**: Busulfan will be given intravenously (IV) though a central vein beginning 8 (+/- 2 days) days before your scheduled transplant day, this is called Day -8. Fludarabine is also given IV beginning 6 days before your scheduled transplant, this is called Day -6. You will get Busulfan on days -8, -6, -4, -3, and -2 and you will receive Fludarabine on days -6, -5, -4 and -3. You will get one dose of cyclophosphamide 3 days after your stem cell infusion, which is called day +3.

The standard Flu/Bu regimen targets the busulfan to a total dose of 20,000 to 24,000 AUC (area under the concentration curve) and the fludarabine is dosed at 40 mg/m2. Since we are adding post-transplant cyclophosphamide we will use the lower end of the standard busulfan target of 20,000 AUC. The Fludarabine dose is unchanged.

	Fludarabine and Busulfan	
Days Pre-Transplant	Fludarabine	Busulfan
Day -8 (+/- 2 days)		1st Dose IV
Day -7 (+/- 2 days)	Admit to BMT Unit	
Day -6 (+/- 2 days)	1st dose IV	2nd Dose IV
Day -5 (+/- 2 days)	2nd dose IV	
Day -4 (+/- 2 days)	3rd dose IV	3rd Dose IV
Day -3 (+/- 2 days)	4th dose IV	4th Dose IV
Day -2 (+/- 2 days)		5th Dose IV
Day -1 (+/- 2 days)		
Day 0	Transplant-Stem cell infusion	
Day +3	Cyclophosphamide IV	

☐ **Total body irradiation (TBI) and Cyclophosphamide:** Cyclophosphamide will be given IV beginning day -3 and TBI beginning day -6 (+/- 2 days). You will get cyclophosphamide on days -3 and -2 and you will receive TBI on days -6, -5 and -4. You will get one dose of cyclophosphamide 3 days after your stem cell infusion, which is called day +3.

The standard TBI/Cy regimen is TBI 1,200 cGy and cyclophosphamide 60 mg/kg x 2 days. In this study the TBI dosing will be the same. The cyclophosphamide dosing schedule is changed to 35 mg/kg x 2 days with the addition of post-transplant cyclophosphamide of 50 mg/kg on Day +3. Thus keeping the total dose of cyclophosphamide unchanged.

	TBI and Cyclophosphamide	
Days Pre-Transplant	Cyclophosphamide	Total Body Irradiation
Day -6 (+/- 2 days)		1st day of radiation (x 2 doses)
Day -5 (+/- 2 days)		2nd day of radiation (x2 doses)
Day -4 (+/- 2 days)		3rd day of radiation (x2 doses)
Day -3 (+/- 2 days)	1st dose IV	
Day -2 (+/- 2 days)	2nd dose IV	
Day -1 (+/- 2 days)		
Day 0	Transplant-Stem cell infusion	
Day +3	Cyclophosphamide IV	

☐ **TBI and Fludarabine:** Fludarabine will be given IV beginning day -7 (+/- 2 days) and TBI will be given beginning day -3. You will receive Fludarabine on days -7, -6, -5 and -4 and you will receive TBI on days -3, -2 and -1. You will get one dose of cyclophosphamide 3 days after your stem cell infusion, which is called day +3.

The standard TBI/Flu regimen is TBI 1,200 cGy and fludarabine at 40 mg/m2 x 4 doses. In this study the TBI dose is reduced to 1,000 cGy and the fludarabine dose is unchanged. This lower dose of radiation is still high enough to prepare your body for your donor cell infusion. This regimen is expected to achieve the same level of disease control as it is still greater than doses commonly used in the non-transplant setting.

	TBI and Fludarabine	
Days Pre-Transplant	Fludarabine	Total Body Irradiation
Day -7 (+/- 2 days)	1st dose IV	
Day -6 (+/- 2 days)	2nd dose IV	
Day -5 (+/- 2 days)	3rd dose IV	
Day -4 (+/- 2 days)	4th dose IV	
Day -3 (+/- 2 days)		1st day of radiation (x 2 doses)
Day -2 (+/- 2 days)		2nd day of radiation (x 2 doses)
Day -1 (+/- 2 days)		3rd day of radiation (x 1 dose)
Day 0	Transplant-Stem cell infusion	
Day +3	Cyclophosphamide IV	

☐ **Fludarabine and Melphalan:** Fludarabine will be given IV beginning Day -5 (+/- 2 days) and Melphalan will be given on Day -1 (+/- 2 days). You will get Fludarabine on Days -5, -4, -3, and -2 for a total of 4 doses and you will receive one dose of Melphalan on Day -1. You will get one dose of cyclophosphamide 3 days after your stem cell infusion, which is called day +3.

If your disease is not in complete remission at the time of transplant, your physician may add an additional drug called rituximab which is standard for some lymphoma patients during transplant.

	Fludarabine and Melphalan	
Days Pre-Transplant	Fludarabine	Melphalan
Day -5 (+/- 2 days)	1st dose IV	
Day -4 (+/- 2 days)	2rd dose IV	
Day -3 (+/- 2 days)	3th dose IV	
Day -2 (+/- 2 days)	4th dose IV	
Day -1 (+/- 2 days)		1st Dose
Day 0	Transplant-Stem cell infusion	
Day +3	Cyclophosphamide IV	

In addition to the Day +3 dose of cyclophosphamide, you will also receive the standard drugs used to reduce the potential for GVHD. You will receive medications according to standard of care guidelines to help relieve some of the side effects of chemotherapy and radiation.

Transplant Day

On Day 0, the day of your transplant, you will receive your donor stem cell (cells which will eventually develop into white blood cells, red blood cells and platelets). Donor stem cells may be from a donor's blood or bone marrow. Your transplant is performed exactly the same way it would be done if you are on the study or not.

Post-Transplant, Required observations and follow-up

Following your transplant you will be given medications that help prevent and fight infections and to help reduce and prevent side effects of treatment. You may need blood transfusions to increase the number of red blood cells in your system or platelet transfusions to assist in helping your blood to clot. Following transplant you will also have regularly scheduled evaluations and blood draws as part of your standard medical care to monitor your health and how well you are recovering from transplant. After transplant, patients will have the standard follow up visits; at least once a week until day +100, then monthly till day +365.

Your transplant team will follow you annually for at least 5 years after transplant. For this study you will be followed for 2 years after your transplant. Your participation in the study

will end after the follow-up period is complete 2 years after your transplant. The follow-up visits will be determined by your doctors as medically necessary, but you will have the following assessments at a minimum:

- Acute GVHD (graft-versus-host disease) assessments at least once a week until day +100 and then chronic GVHD assessments at least once per month until 1 year after your transplant.
- At least three bone marrow aspirate and biopsy tests are performed after your transplant to determine your disease status. These are done on approximately days +30, +100, and at 1 year. A bone marrow aspirate will also be collected whenever a disease relapse is suspected.

Drugs for GVHD (graft-versus-Host Disease) prevention

The following drugs, mycophenolate mofetil (MMF, Cellcept) and tacrolimus (FK-506) are permitted under the protocol to help prevent GVHD. Cyclophosphamide will be administered on Day +3 IV single dose. MMF will be administered starting day +5 and continue until day +35 unless there is active GVHD. Tacrolimus will start on day +5 and continue until day +180 with taper starting on +100 unless there is active GVHD.

Drugs for prevention of infection

After your transplant your immune system is severely weakened and slowly improves over many weeks or months. There are a number of different drugs available that your doctor may prescribe to try to prevent, and to treat, infections. The specific drugs that you receive will depend on what is best for you determined by your doctor.

Risks and Discomforts

The known or expected physical risks related to participating in this study are the same risks you will be taking whether you have your transplant on study or off study. You will receive medications that will help protect you from the negative side effects of cyclophosphamide. Post-transplant cyclophosphamide may have the potential to prolong the period of time your blood cell count is low. This could increase your risk of infection. Your doctors will follow you very closely and you will receive medications that will help reduce infection risk. There is a risk of loss of confidentiality since information about your treatment will be reviewed for research purposes. The BMTCT program research staff has processes in place to help reduce that risk.

Post-transplant cytoxan may have the potential to prolong (make longer) the time that your immune system will be weakened and could possibly increase the risk of engraftment delay or failure of your donor cells. We have adjusted the dose of post-transplant cytoxan to reduce that risk.

These risks may vary depending upon the conditioning regimen that your doctor has prescribed for you. Conditioning regimens #1 (FLU/BU), #3 (TBI/ FLU), and #4 (FLU/MEL) will each receive a dose of cytoxan that is not always given off study. You may experience the common side effects (noted below) due to the addition of post-transplant cytoxan. For conditioning regimen #2 (TBI/CY), there is no expectation of increasing the risk of common side

effects of cytoxan due to the fact that the overall total dose of cytoxan you will receive on study is less than or equal to the overall dose that patients normally receive off-study.

The common side effects of cyclophosphamide are listed below:

Cyclophosphamide:

Cyclophosphamide is used to kill cancer cells. Side effects most common in patients that receive cyclophosphamide include: nausea, vomiting, hair loss, decrease in white blood cells, lung scarring, allergic reaction, absence of menstruation, blood in urine and pain while urinating, low sperm count, and immune suppression.

Less common side effects of taking cyclophosphamide include: developing a cancer different than that you are being treated for, congestive heart failure, swelling of heart muscles, bleeding around the heart, and possible cross sensitivity with other alkylating agents.

Information for Women of Childbearing Potential or Men Capable of Fathering a Child

If you are a female of childbearing age, you must not be pregnant at the time you enter the study, or at any time during the study. This study could potentially harm your unborn child. You must avoid becoming pregnant during the study. Before you enter the study, the study doctor will discuss the most appropriate methods to use to avoid pregnancy. All female subjects must commit to using these precautions throughout their participation in the study. If you enter the study and then think you might be pregnant you must tell the study doctor right away. After your participation in the study is complete, if you plan on becoming pregnant you should speak with your study doctor regarding when it is safe to proceed.

For females, if there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use at least TWO types of birth control (one from each list below or two from the "highly effective" list below)AT THE SAME TIME. You must use two types at the same time for medical reasons. You must talk to the doctor before changing any birth control pills. You should not breastfeed an infant while on the study.

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Tubal ligation (Tubes Tied)	Diaphragm
Partner's vasectomy	Cervical Cap

For males, all men must use medically acceptable birth control while taking part in the study, as the effects on sperm are not known. Male patients should not donate blood, semen or sperm during therapy. It is possible you may be a candidate to freeze (cryopreserve) sperm for future use. Discuss this option with the doctor. Cryopreservation is not part of this study.

Again, all participants must commit to using these precautions throughout their participation in the study. You should talk to your doctor so they can advise you.

Benefits

Our hope is that the use of cyclophosphamide after HSCT will reduce GVHD in patients that receive stem cells from matched or mismatched unrelated donors. You may not receive any personal benefits from being in this study. The possible benefit from the study, if any, will be in the control of GVHD. If you do not benefit personally, your participation in this research study will provide the investigators with important information to help design safer and more effective treatment options for other patients with the same types of cancers.

Alternatives

If you decide not to participate in the study, you may still be able to undergo allogeneic stem cell transplantation and receive post-transplant cyclophosphamide if your doctor feels it is the best treatment option for you, but not as part of this study.

If you decide not to undergo allogeneic stem cell transplantation, you may choose to continue chemotherapy or other non-transplant treatment. Or, you may choose to receive palliative care (to relieve suffering and improve you quality of life, but not to cure your disease). Your doctor will discuss these choices and what other options may be available.

Confidentiality

Any information gathered during this procedure will be kept confidential to the extent permitted by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of UAB Bone Marrow Transplantation and Cellular Therapy Program; the U.S. Food and Drug Administration (FDA); and the Office for Human Research Protections (OHRP). The information from the research may be published for scientific purposes; however, you will not be identified in any way if the doctors use your medical records for any research, publication in scientific journal, or presentation at any scientific meetings.

This consent will be placed in your medical record file at the University of Alabama Hospital. This document will become part of your medical record chart. Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System affiliated entities and its billing agents so that the costs for clinical services can be appropriately paid for by either the study account or by you or your insurance company for clinical services and procedures provided to you for treatment of your disease during the course of this study.

Study records that have your name will be kept private. You will not be identified by name in any publications related to this study. Your records will be given a unique code number. The key to the code will be kept in a locked file in the Research and Data Management offices of the BMTCT program. Any computer that is used to store information about you is protected by the University of Alabama's computer security firewall. Individual sign on codes and password protections are used on any electronic files.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by the U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Voluntary Participation and Withdrawal

Taking part in this study is completely voluntary. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drugs and referred for follow-up care.

You may be removed from the study without your consent if the investigator ends the study, if the doctor decides it is not in the best interest of your health, or, if you are not following the study rules.

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. If you decide to withdraw from the research study, the research staff may ask if they can use the data that has already been collected from you.

You may withdraw your consent by writing the BMT research Office at UAB BMT Research office-West Pavilion Room 392-619 19th Street South – Birmingham, AL 35249-6979.

Cost of participation

There is no cost to you to participate in this research study. The study will pay for any research-related items or services that are provided only because you are in the study.

You are responsible for the cost of standard of care treatment for your disease. The charges for your transplant will be billed to you and/or your insurance provider in the usual manner. Your insurance provider may not cover all or part of these costs.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Participation in Research

You will not receive any payment for taking part in this research study.

Payment for Research-Related Injuries

UAB and the UAB BMTCT program have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by your doctor or study staff if new information becomes available that might affect your choice to stay in the study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

Questions

If you have any questions, concerns or complaints about the research or a research-related injury including available treatments, please contact one of the BMT physicians at (205) 934-1908 or at UAB paging (205) 934-3411. If you have any questions about your treatment plan, you can ask any of your BMT physician and/or BMT staff.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the Office of the IRB (OIRB) at (205) 934-3789 or 1-855-860-3789. Regular hours for the ORIB are 8:00a.m. to 5:00p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

Print Name of Participant	Date
Signature of Participant	Date
Signature of Principal Investigator or Other Person Obtaining Consent	Date
Signature of Witness	Date

University of Alabama at Birmingham

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant Name:_____	UAB IRB Protocol Number: F130515006
Research Protocol: **Phase II Clinical Trial of the Use of Post-Transplant Cyclophosphamide for Graft Versus Host Disease (GvHD) Prophylaxis Following Matched Unrelated Donor (MUD) and Mismatched Unrelated Donor (MMUD) Hematopoietic Stem Cell Transplant (HSCT)**	Principal Investigator: **Racquel Innis-Shelton, M.D.**
	Sponsor: **UAB Comprehensive Cancer Center**

What health information do the researchers want to use? All medical information and personal identifiers, including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have the right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____