Single Arm Phase II Study of Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia (ALL) in Older Patients Using Fludarabine and Total Body Irradiation (FluTBI) Regimen

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Informed Consent Document

TITLE OF RESEARCH: **Single Arm Phase II Study of Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia (ALL) in Older Patients Using Fludarabine and Total Body Irradiation (FluTBI) Regimen**

PROTOCOL NO: **IRB -130515007**
UAB #1285

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SPONSOR: **UAB Comprehensive Cancer Center**

Purpose of the Research

You are being invited to participate in this research trial because you are going to receive a stem cell transplant from a matched brother or sister, or an unrelated donor to treat your leukemia. The goal of this research is to evaluate a pre-transplant (conditioning) regimen for stem cell transplant patients with high-risk disease that provides an anti-leukemia effect with fewer side effects. The conditioning regimen being used in this trial is the drug Fludarabine and total body irradiation (FluTBI). The use of FluTBI for cancer treatment has been approved by the FDA (U.S. Food and Drug Administration). We are studying the combination of Fludarabine and total body irradiation in stem cell transplant patients which has not been FDA approved.

Many transplant centers use full intensity conditioning treatments such as CyTBI (Cyclophosphamide and total body irradiation) as a standard pre-treatment for transplantation, but severe drug-related side effects remain a major cause of death. Fludarabine, though less effective when compared to Cyclophosphamide, has less drug-related side-effects. Fewer drug related side effects is a potential benefit for patients who are older or have high-risk disease.

This study will continue to test if this new conditioning treatment, FluTBI, can lead to a safer and more effective stem cell transplant treatment approach for patients 40 to 65 years of

age and/or younger patients with high risk disease. This is a phase II clinical trial that will enroll approximately 20 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

For your stem cell transplant, you (the recipient) will get FluTBI chemotherapy, 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.

If you decide to take part in this phase 2 clinical research trial you will receive treatment using full-intensity chemotherapy and radiation followed by stem cell transplant. Full intensity means you will receive high doses of chemo-radiotherapy, as a pre-treatment, before your transplant. The high dose chemo-radiotherapy is given to kill as many cancer cells as possible; however it will also destroy your bone marrow's ability to make blood cells. It must be followed by a stem cell transplant to restore your bone marrow function.

You may be eligible to take part in this research study if your disease is in remission. To be eligible you should meet at least the following inclusion criteria:

- 40 to 65 years of age. Participants younger than 40 years of age may participate if they have other medical condition which prevents them from participating in more aggressive conditioning regimens.
- You have a suitable donor available, who may be related or unrelated to you.
- Your heart, lung, liver, and kidney function tests are acceptable.
- You must be well enough to undergo full intensity conditioning.

There are conditions that might exclude you. If you are HIV positive, or 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 research 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 receive FluTBI as your chemotherapy regimen starting 7 days before your transplant. You and your study doctors and nurses will review the clinical information for the transplant. In preparation to receive your stem cell transplant the following test will be performed as 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 to participate.

Pre-Transplant (within 35 days prior to transplant admission)

You will have the following standard evaluations and tests:

- Complete history and physical examination (including blood tests).
- Heart function test (either Echocardiogram or MUGA).
- Lung function test (called Pulmonary Function Tests or PFTs).
- Pregnancy test, if you are a female who could become pregnant.
- Blood sample to check Creatinine, AST, ALT, Alk Phos., and Total bilirubin

Pre-Transplant

You will have a standard procedure called a bone marrow aspirate and biopsy. This is to collect a sample of your bone marrow and evaluate your current disease condition.

Pre-Transplant, Conditioning Regimen

In this research study, subjects enrolled will receive the FluTBI pre-treatment (the conditioning regimen) beginning with Fludarabine for 4 days. Each day's total Fludarabine dose is given on Days -7 to -4, prior to your transplant on Day 0. You will receive total body irradiation (TBI) for 3 days. Total dose of TBI is given on Days -3 to -1, prior to your transplant on Day 0. The FluTBI treatment is summarized in the following table.

	Chemotherapy drugs-FluTBI	
Day, Pre-Transplant	Fludarabine	Total Body Irradiation
Day -7	1st dose IV	
Day -6	2nd dose IV	
Day -5	3rd dose IV	
Day -4	4th dose IV	
Day -3		1st dose
Day -2		2nd dose
Day -1		3rd dose
Day 0	Transplant-Stem cell infusion	

You will receive medication according to the center's institutional guidelines to helps relieve some of the side effects of chemo-radiotherapy.

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 if you are on the study or not.

After Day 0, you will be given: antibiotics, anti-viral and anti-fungal medication to help prevent infections, or if necessary to fight infections; blood transfusions to increase the number

of red blood cells in your system; platelet transfusions to assist in helping your blood to clot; and nutritional and general support, according to the study protocol (and the transplant center's institutional guidelines).

Post-Transplant, Required Observations and Follow-up

Following your transplant you will have regularly scheduled evaluations as part of your standard medical care to monitor your health and how well your transplant has replaced your bone marrow's cells. The follow up visits are scheduled as medically necessary; however, the study will require visits at least once a week visits until day +100 after your transplant.

From day +100 to one year (day +365) clinic visit will be required at least once per month.

For this study, you will be followed for 2 years after your transplant, after which follow-up for your disease is encouraged till at least 5 years post-transplant. The follow-up visits will be determined by your doctors as medically necessary, but with the additional requirements of this study you will have to have the following minimum:

- Acute GVHD (graft-versus-host disease) assessments at least once a week until day +100 and then chronic GVHD assessment at least once per month until 1 year after your transplant.
- Immune reconstitution and chimerism studies will be performed. These studies will monitor how well your body cells are recovering. The recommended timing of the labs is at Day +30 (±7), Day +60 (±7), Day +100 (±14), Day +180 (±21) and at 1 year (±45) post-transplant.
- At least three bone marrow aspirate and biopsy tests after your transplant, on days +30, +100, and at 1 year, if your disease has not relapsed (progressed) by that time and you are able to tolerate the procedure. In addition, a marrow aspirate will also be collected whenever a relapse is suspected. Every effort will be made to do these tests when they are scheduled as part of your standard care.

Your participation in the study will end after the follow-up period is complete 2 years after your transplant.

Drugs for GVHD (graft-versus-host disease) Prevention

GVHD is 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 following drugs, thymoglobulin, (rATG), Atgam, methotrexate, tacrolimus and Leucovorin are permitted under the protocol. Your study doctor may prescribe any combination of these drugs to try to prevent GVHD (GVHD prophylaxis), or help reduce its severity if you do

develop GVHD. The specific drugs that you receive will depend on both your study doctors' judgment for what is best for you and the transplant center's standard medical practice

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 study doctor may prescribe to try to prevent infections. The specific drugs that you receive will depend on both your study doctors' judgment for what is best for you and your transplant's standard medical practices.

Risks and Discomforts

There is a possibility that Fludarabine may be less effective than other chemotherapy regimens in treating your disease. The specific medication used in this study and the known side effects which you may experience are listed below:

Fludarabine

Drug-related side effects observed in more than 10% of adult patients treated with Fludarabine in previous clinical trials include decreased bone marrow function (myelosuppression), fever and chills, infections, nausea and vomiting, pain, weakness, cough, pneumonia, (shortness of breath) dyspnea, diarrhea, anorexia, rash, edema.

Side effects observed in less than 10% of adult patients (general weakness) malaise, (oral inflammation) stomatitis, (muscle pain) myalgia, (abnormal sensations) paresthesia, visual disturbance, gastrointestinal bleeding, upper respiratory infection, (excessive sweating) diaphoresis, (painful urination) dysuria, urinary infection, sinusitis, hearing loss, hyperglycemia, headache, (sore throat) pharyngitis, (spitting blood) hemoptysis, (swelling of the esophagus) esophagitis, mucositis, (blood in urine) hematuria, osteoporosis, (hair loss) alopecia, (serious allergic reaction) anaphylaxis, hemorrhage, dehydration, sleep disorder, depression, (lack of coordination) cerebellar syndrome, impaired mentation, allergic pneumonitis, (nose bleeds) epistaxis, bronchitis, hypoxia, liver failure, abnormal liver function, (gallstones) cholelithiasis, ARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, respiratory failure, constipation, dysphagia, (itching) pruritus, (dandruff) seborrhea, renal failure, abnormal renal function test, (protein in urine) proteinuria, hesitancy, angina, congestive heart failure, arrhythmia, (rapid heart rate) supraventricular tachycardia, myocardial infarction, deep venous thrombosis, (swelling of a vein) phlebitis, transient ischemic attack, aneurysm, (stroke) cerebrovascular accident, (joint pain) arthralgia, tumor lysis syndrome.

Total Body Irradiation

Possible side effects of total body radiation include; loss of appetite, nausea, vomiting, diarrhea, (dry mouth) xerostomia, (difficulty in swallowing) dysphagia, headache, (swelling in the mouth/throat) stomatitis, altered skin integrity, (hair loss) alopecia, swelling, increased risk for infection and/or bleeding, possible lung failure, dry cough, fatigue, anxiety, fever, possible

liver failure, lung scarring, loss of vision, shortness of breath, (permanent dilation of small vessels causing red lesions) telangiectasia, testicular damage, ovarian damage, premature menopause, sterility, heartburn, cystitis, sleep disturbances altered gastrointestinal and genitourinary function, radiation pneumonitis, neuropathy, fistulas, altered endocrine function, and increased risk of a second cancer.

Anti-Graft-Versus-Host Disease Medications

GVHD is due to immune cells (lymphocytes) from the donor attacking the recipient's organs. The acute form of GVHD may cause redness of the skin, nausea, vomiting, diarrhea, and/or liver problems. The chronic form of GVHD may cause dryness of the eyes and/or mouth, and/or breathing problems. It may cause tightness and/or scarring of the skin, weight loss, diarrhea, and/or difficulty swallowing. Either one of the forms of GVHD can range from mild to severe to life threatening. Severe GVHD is commonly the cause of death for patients who have serious and fatal complications, after their transplant.

During your transplant process you will receive standard of care medications to help prevent and/or decrease GVHD. These are listed in the tables below.

Tacrolimus

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
• Low red blood cell counts • Loss of appetite • Diarrhea • High potassium levels • High blood pressure • Nausea • Fever • Headache • High blood sugar	• Hair loss • Vomiting • Tingling sensation in the extremities • Itching • Rash • Abdominal pain	• Confusion • Painful joints • Increased sensitivity to light • Blurred vision • Insomnia(unable to sleep) • Jaundice (yellowing of skin and eyes) • Kidney injury • Seizures

These side effects are usually reversible by reducing the dose or discontinuing the drug.

Methotrexate

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
• High levels of liver enzymes	• Nausea • Vomiting • Loss of appetite • Diarrhea • Mouth sores • Sensitivity to sunlight • Increased risk of sunburns • Decrease number of red and white blood cells and platelets	• Hair loss • Dizziness • Skin redness, tenderness, darkening, and peeling • Blurred vision • Allergic reaction • Damage to nerve tissue • Kidney damage • Seizures • Decreased lung function • Decreased liver function-temporary • Bone and tissue damage • Loss of memory, concentration, balance, and walking

Thymoglobulin

Likely *("Likely" refers to a side effect that is expected to occur in more than 25% of patients.)*	**Less likely but serious** *("Less likely" refers to a side effect that is expected to occur in 25% or fewer patients.)*
• Fever • Chills • Decreased platelets and white blood cells • Pain • Headache • Abdominal pain • Diarrhea • High blood pressure • Nausea • Swelling • Difficulty breathing • Weakness • High potassium • Rapid heartbeat • Infection	• Severe or life threatening allergic reaction • Lymphomas (i.e. cancers of the immune system)

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 subjects must commit to using these precautions throughout their participation in the study. You should talk to your study doctor so they can advise you, based on the program's clinical practices, when it's safe for you to make any changes.

Benefits

You may not receive any personal benefits from being in this study. If you do not benefit personally, you participation in this research study will provide the investigators with important information to help design safer and more effective treatment 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, 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 law 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, your identity will not be given out.

If any part of this study takes place at the University of Alabama Hospital this consent document will be placed in your file at that facility. The document will become part of your medical record chart. Your medical record will indicate that you are on a clinical trial and will provide the name and contact information for the principal investigator. 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 the patient/patient's insurance.

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.

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 study 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. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

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. You will be 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.

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 Comprehensive Cancer Center 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 Dr. Donna Salzman at (205)934-1908 or at UAB paging (205)934-3411.

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 agree to participate in this study. You will receive a copy of this signed document.

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
PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol: Single Arm Phase II Study of Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia (ALL) in Older Patients Using Fludarabine and Total Body Irradiation (FluTBI) Regimen

UAB IRB Protocol Number: IRB-130515007
Principal Investigator: Donna Salzman M.D.
Sponsor: UAB Comprehensive Cancer Center

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected 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 protected health information may be used for the research.

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

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected 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 this 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 protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected 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: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____