INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0136 PRINCIPAL INVESTIGATOR: Christopher Kanakry , M.D.

STUDY TITLE: Multi-institutional Prospective Pilot Study of Lupron to Enhance Lymphocyte Immune Reconstitution Following Allogeneic Bone Marrow Transplantation in Post Pubertal Adults with Molecular Imaging Evaluation

Continuing Review Approved by the IRB on 07/10/18
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Recipient

INTRODUCTION

We are asking you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

- Taking part in NIH research is entirely voluntary.
- You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.
- You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

We are conducting a study of allogeneic stem cell transplantation from HLA-matched related and unrelated volunteer donors for cancers of the blood and immune system. Because you have one of the cancers with which we are concerned and for which transplantation is a possible cure, we are inviting you to participate in this pilot trial of lupron to enhance lymphocyte immune reconstitution following allogeneic bone marrow transplantation (BMT) in post-pubertal adults

with molecular imaging evaluation. The cancers with which we are concerned include acute myelogenous leukemia, acute lymphocytic leukemia, and high-risk myelodysplastic syndrome. One of the issues that often develop after BMT is that the new immune cells don't work as well after transplant in the new host (the recipient of the BMT) as they did before in the donor. This can lead to increased risk for severe infections and a disease called graft-versus-host disease whereby the new donor cells can attack and harm healthy organs in the recipient. This study tests whether androgen withdrawal with a medicine called lupron might improve the function of the newly transplanted cells. In addition, some participants in this study may also undergo a type of nuclear medicine imaging (similar to a PET scan) called FLT that may reveal how well the transplant is progressing and whether the cells are growing properly inside the bone marrow.

Why are you being asked to take part in this study?

You are being asked to participate in this study because you have acute myelogenous leukemia, acute lymphocytic leukemia, or high risk myelodysplastic syndrome for which transplantation is a potential cure and you meet the criteria for enrollment. You may receive chemotherapy on this protocol first if either: 1) you are not in remission or 2) if you require a donor search and it is likely that your disease will come back before we can identify a donor. If your doctors have not previously identified an HLA-matched donor, we will perform a search to identify a match. If you have siblings, we will test these individuals first. If you do not have siblings, or they are not a match, we will search the bone marrow donor registries such as the National Marrow Donor Program. To be eligible to proceed to BMT on this study, you must match a relation or an unrelated donor on 8/8 or 7/8 HLA markers.

How many people will take part in this study?

Up to 236 people (118 patients/118 donors) will take part in this research study.

Description of Research Study

Bone Marrow Transplantation and Donor Search

Donor Search
It is first necessary for us to find a suitable (HLA-matched) donor. About 5 to 10 tablespoons of blood will be drawn to check how closely you and your potential donor are genetically matched. Often this blood test has already been performed at your home medical office prior to a visit to the NIH or it will be performed at the NIH Clinical Center. In this study, we will accept recipient patients 9 to 55 years of age.
Rarely, a volunteer donor may become unavailable or the donor center is unable to collect enough stem cells to perform the transplant. If this happens, you will be removed from the study

before transplantation unless we are able to identify another suitable unrelated donor. If you have already received the conditioning chemotherapy, you will still be removed from the study, but we will continue to care for you.

We will explain to you the choice of your donor once we have this information.

Bone marrow transplantation
The process of bone marrow transplantation involves killing your own bone marrow cells and then receiving matched cells from another individual. Bone marrow cells are called hematopoietic (meaning blood) stem cells (meaning immature). These cells live within our bone marrow and produce white blood cells that fight infections, red blood cells that carry oxygen, and platelets that help us clot. When these bone marrow cells are taken from one person (called the "donor") and given to another person (called the "recipient"), it is known as "allogeneic" stem cell or bone marrow transplantation (BMT). Allogeneic BMT benefits many patients with high risk leukemias because: 1) we can rid the body of most of the leukemia cells, 2) the new donor cells may recognize and kill cancer cells, termed graft-versus-leukemia effects.

BMT Preparative regimen
Allogeneic stem cell transplantation (SCT) has been used successfully to treat, and sometimes cure, many kinds of cancer or pre-cancerous conditions that develop in blood or immune system cells. For patients who are receiving a SCT for the first time, to deplete your own cells, we will use a standard preparative regimen including radiation and chemotherapy. The radiation is total body irradiation, meaning that the whole body is exposed to the radiation. The lungs will be protected during this process. The chemotherapy for the BMT will be cyclophosphamide. For patients who have received SCT before and those who can't tolerate radiation therapy, we may use a combination of chemotherapy agents such as busulfan and fludarabine or cyclophosphamide. In this way, your bone marrow cells will die. Then, we will give you new healthy cells from your donor in a blood transfusion that will find their way into your bones and begin to grow into white blood cells, red blood cells and platelets. We call this engraftment.

The side effects of cyclophosphamide chemotherapy as part of BMT are: immediate (within 1-2 days) anorexia, nausea, vomiting, metallic taste, difficulty with salt management and rarely transient blurred visions and heart problems; within 2-3 weeks, lower white blood cell counts, hair loss, and occasionally red blood in the urine can occur; delayed reactions can include gonadal dysfunction (sterility), occasionally lung problems called pulmonary fibrosis, and rarely second cancers and bladder fibrosis.

The side effects of radiation are usually nausea, mucositis, pain with eating, occasionally, hypothyroidism, cataracts, lung problems, kidney problems, and rarely secondary cancers.

BMT Complications
The number one risk of death after BMT is your cancer. If your cancer comes back after BMT, we will try to treat it by either helping the new immune cells work better to kill the cancer or giving other therapies. However, this remains a significant risk even with the BMT.

Rarely, the new cells do not engraft or continue to grow within the recipient. This is called graft rejection. When this happens, one of two things occurs. Either your own cells will manage to grow back, or you will require new donor cells and possibly more chemotherapy to survive.

More commonly, we observe a problem termed graft versus host disease (GVHD). In this disease, the new donor cells recognize pieces of you as foreign and attack your healthy tissues. This can occur early after transplant with one type of disease, and later after BMT with different kinds of problems. Most often when this occurs early after BMT, termed acute GVHD, the donor cells attack the gut leading to diarrhea and weight loss, the skin leading to a rash, or the liver with elevated liver enzymes. When GVHD occurs later after BMT, termed chronic GVHD, patients can develop many symptoms including: dry eyes, dry mouth, rashes and skin changes, liver enzyme elevation, mouth ulcers, diarrhea. Rarely, chronic GVHD can lead to life-threatening complications such as lung GVHD, sclerotic skin GVHD, and liver failure.

The risk of GVHD increases when the donor and recipient are not matched perfectly. Cells are matched by markers are called "human leukocyte antigens", or HLA. A person inherits half of his or her HLA markers from each parent. Your immune system uses HLA proteins on your body's cells to tell the difference between normal, healthy tissues and foreign organisms like bacteria or viruses. Differences in HLA proteins between a donor and recipient make it more likely that one person's immune system will recognize the other person's cells as foreign, causing graft rejection or GVHD. A donor and recipient who share all 8 of their HLA markers are called "HLA-identical". A transplant from an HLA-identical sibling (brother or sister) has a lower chance of graft rejection or GVHD, compared with other donors for allogeneic SCT. Many people have cancers that could be treated with allogeneic SCT, but only 20-30% of people have HLA-identical sibling donors. For some people without HLA-identical sibling donors, an HLA-matched unrelated donor can be used, but the risk of graft rejection and GVHD is higher. Patients on this study with a partial genetic match (7/8 HLA genes) with their unrelated donor may have a modestly higher risk of complications compared to subjects with a full genetic match with their unrelated donor (8/8 HLA genes).

Drugs can prevent GVHD after allogeneic BMT, but they do not work all the time.

Prevention of Graft-Versus-Host Disease

This study will use standard GVHD prophylaxis for myeloablative BMT: methotrexate and tacrolimus. Methotrexate is a chemotherapy agent that is used to diminish rapidly dividing T cells, the cells that have been shown to cause GVHD. Patients will receive 4 doses on 4 days of this medication after BMT. Side effects of methotrexate include: sore throat, chills, fever, signs of infection, unusual bruising or bleeding, excessive tiredness, pale skin, shortness of breath, liver damage, lung damage, mucositis, stomach ulcers, diarrhea, black tarry stools, vomiting, rash, peeling skin, dizziness, drowsiness, headache, swollen tender gums, decreased appetite, reddened eyes, hair loss, blurred vision or sudden loss of vision, seizures, confusion, weakness or difficulty moving one or both sides of the body, loss of consciousness. Tacrolimus is a medication that prevents T cells from attacking foreign organs (GVHD). It may cause: fever, sore throat, cough, extreme tiredness, warm, red, painful skin, increase the rate of infections, headache, uncontrollable shaking in a part of the body, diarrhea, constipation, nausea, vomiting, heartburn, stomach pain, loss of appetite, difficulty falling asleep or staying asleep, dizziness, weakness, back or joint pain, burning, numbness, pain or tingling in hands or feet, hives, rash, itching, difficulty breathing or swallowing, decreased urination, pain or burning on urination, swelling of arms, hands, feet, ankles or lower legs, weight gain, unusual bleeding or bruising, seizures, coma.

BMT Research Design

We are trying to improve the results of allogeneic BMT by improving: 1) the new donor immune system's function; and 2) ways that we identify how well the transplant worked.

The methods we are testing in this research study include:

- Lupron is a drug that suppresses androgen production for a period of time. For females, this means that you will have less estrogen in the blood. For males, this drug lowers testosterone levels. Lupron is already used for females undergoing chemotherapy and BMT. During BMT when the platelet count is lower, it is not safe to have a period. Lupron is one of the agents we use to prevent menses. Lupron also affects the immune system. In mice and men, lupron has been shown to improve the development and function of T cells, a white blood cell that is important for graft-versus-tumor effects, graft-versus-host disease, and to fight infections. All females on this protocol will receive lupron 2 weeks prior to BMT. For first SCT, half of the men will receive lupron 2 weeks prior to BMT. For 2nd SCT, all of the men will receive Lupron. This is delivered as a single shot that lasts for 3 months for men and women younger than 18 and 4 months for those older than 18. We will then perform blood tests and monitor for GVHD to determine whether lupron was helpful in the recovery of the immune system and led to fewer complications of BMT. Patients may receive further doses of lupron if clinically indicated.

- For patients ≥18 years of age; FLT is a nuclear medicine imaging test; it stands for 3'-deoxy-3 ^{18}F-fluorothymidine, the scientific name of the reagent. During this test, patients will receive an injection of a FLT and undergo imaging on a special machine. The pictures will reveal what the cells inside the marrow look like, letting us 'see' whether the new cells are engrafting and recovering after the BMT. This test would be very useful for patients who engraft slowly, to tell us if they are engrafting slowly or not at all. In addition, some patients who are not in remission will be asked to undergo this test to help us learn if we can detect leukemia using this test too. This test has been used in patients who received high doses of chemotherapy and radiation for other cancers.
    1. For BMT whether first or 2nd: 23 patients for first BMT and 16 for 2nd SCT, who are ≥18, will undergo FLT will receive up to 5 FLT images of which 2 will be accompanied by PET/CT. Images will be performed for 1st BMT: on day -1, day +5 or +9 with FLT alone. On day 28 and another time point to be determined by evidence of immunologically important events (such as thymus immune recovery or GVHD), FLT and PET/CT will be performed. After these 23 patients, newly accrued patients will undergo a single FLT scan greater than 1 year after transplant. For 2nd BMT: 2, FLT images will be performed alone on day -1, and include day +28 and +60 with PET/CT as well. If you relapse after the 2nd BMT, we will image at the time of relapse and after immunotherapy (if you receive it) with FLT and PET/CT.
    2. The PET scan is a clinical test that is used to monitor for certain cancers. It requires patients to fast several hours before and then gives a radioactive glucose (sugar) through an IV followed by imaging in a scanner. Because cancer and inflammatory cells have increased metabolism and use more glucose than neighboring cells, these cells will take up more of the radioactive glucose and be easily seen on PET scan. Patients who undergo this PET scan will receive the IV radioactive glucose and then be asked to lie quietly in a darkened room for 30 minutes. Then, the patient will be asked to urinate. After this, we will perform the scan. The scan takes approximately 1 hour and is painless, but you may feel sore after lying in the scan. You will be asked to urinate approximately 90 minutes after the radioactive sugar is given.
    3. The FLT scans are performed in a similar way. This scan involves the use of a radioactive chemical (fluoro-thymidine) injected into an IV, followed by a scan similar to a CT scan. Thymidine is normally found in DNA. Dividing cells will take up the radioactive thymidine, and cells that are not dividing should not take up any thymidine. Because more cancer cells are dividing and new bone marrow transplant cells should also be dividing, these should take up radioactive thymidine more than surrounding cells, and should be easily seen on the FLT PET scan. Patients who undergo this test will receive a dose of FLT through an IV, and then be asked to lie in a darkened room for 30 minutes. After 30 minutes, we

will ask you to urinate. This will help reduce the dose to the bladder. We will then begin the scan. The scan takes approximately 1 hour and is painless, but you may feel sore after lying on the scanner. We will ask you to urinate approximately 90 minutes after the IV dose. Side effects are discussed below (in the side effects section of this document).

What will happen if you take part in this research study?

The following will be done as part of this research study (details are included in later sections):

- First, we will determine if you are in remission and initiate chemotherapy if needed. Some patients may undergo FLT imaging of relapsed leukemia.
- Next, we must establish proof of a full genetic match (8/8 HLA genes) or partial genetic match (7/8 HLA genes) between you and your potential related or unrelated donor.
- We will arrange to have your donor's stem cells collected here if you have a sibling or at a center in cooperation with the National Marrow Donor Program.
- After you have a match and are in remission, you will receive lupron if you are a female or have been randomized to do so as a male.
- Then, all patients will receive the "conditioning regimen," to prepare you for the transplant, which includes cyclophosphamide and total body irradiation.
- If you are a patient with MDS and your counts did not recover after receiving chemotherapy you will receive a lower dose "conditioning regimen" to prepare you for transplant, which includes fludarabine and total body irradiation.
- After this transplant chemotherapy, you will receive the transplant with your unrelated donor's stem cells and immune cells.
- All patients will receive GVHD prophylaxis. Some patients may receive intrathecal chemotherapy (if there was evidence of the leukemia in the spinal fluid).
- Patients who have agreed to undergo FLT imaging will be imaged before the cells are given (BMT) and at 3 time points after.
- You will be hospitalized approximately 4 weeks after your transplant.
- When the study doctors think your condition is stable, you will be discharged from the hospital and be seen frequently at the NIH as an outpatient.
- You will continue on medications at home to lower the risk of GVHD and infections.
- You may receive additional cells from the donor after the transplant; these additional cells are given to help to rebuild or enhance your immune system.
- You will visit our clinic regularly for the first six months after the transplant, and then less often for at least five years.

Pre-Transplant Evaluation

Once it is determined that you have a potential donor, you will be seen at the NIH Clinical Center, at which time you will have a complete medical history and physical examination in the NCI Medical Oncology Clinic. Members of the transplant team will review your medical history and explain the transplant procedure. A blood sample will also be used to check the health of your kidneys and liver. We will also test for exposure to a variety of infections, including hepatitis B and C, syphilis, and a virus called cytomegalovirus (CMV). As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection. You will also be tested for the following viruses: hepatitis A, HTLV-1 and -2, adenovirus, Epstein-Barr virus, herpes simplex virus, and the parasite Toxoplasma. A total of approximately 4-12 teaspoons of blood will be collected. If the study doctor feels it is necessary, you will have a PPD skin test (to test for tuberculosis). You will be asked to collect your urine for 24 hours to measure your kidney function. If you are a woman, you will have a urine test for pregnancy. If you are a woman who is breast-feeding or pregnant, you may not take part in this study because we don't know how the transplant will affect your baby or unborn child. If you think that you or your partner is pregnant, you should tell your study doctor or nurse immediately.

In addition, you will have a special breathing test, a test for heart health, and several X-ray studies, including a CT scan of your chest, abdomen, pelvis, and possibly your neck. You will have a CT scan or MRI of your head. You will also have a bone marrow aspiration and biopsy. This test is performed by numbing the iliac (pelvis) bone with a local numbing medicine called lidocaine. A small cut will be made in the skin, a needle is inserted into the pelvis bone, and about two tablespoons of liquid samples are removed from the bone marrow through the needle. A small fragment of the bone marrow may also be removed with the needle. If you are at risk of having your cancer involve the brain or central nervous system, you may also have a spinal tap (also known as a lumbar puncture). A thin needle is then inserted into your spinal canal and a small amount (about 5 tablespoons) of spinal fluid is removed. You will also be seen by a dentist, and meet with a social worker. You will be encouraged to name someone as your "durable power of attorney". This should be someone whom you trust to make medical decisions for you if you become physically or mentally unable to make your own treatment decisions. You should know that being in this study may keep you from being in other research studies that limit the number or types of treatments that you are allowed to have received previously.

The Central Venous Catheter

If you do not already have one before you enroll in this study, you will receive an intravenous (I.V.) line placed in the upper part of your chest and tunneled under the skin into a neck vein. This line is called a central venous catheter that can be used throughout your transplant procedure and follow-up treatment. This kind of catheter is sometimes called a "Hickman catheter". If the catheter becomes infected or clogged, it can be replaced. It will be flushed once daily to prevent clogging. The nursing staff will teach you how to do this yourself.

The catheter will be used to give you chemotherapy, your transplant, blood transfusions (if needed), and other medications such as antibiotics. It can also be used for drawing blood samples for tests. Since blood will be drawn often during your treatment, the catheter will make it easier and less painful.

Transplantation of the Blood Stem Cells from Your Donor

Before you begin your induction chemotherapy, your related or unrelated donor will have had a medical examination by a doctor at NIH or in the National Marrow Donor Program (NMDP) network and laboratory studies that include extensive testing to make sure they do not have any of the following: HIV, Hepatitis B, Hepatitis C, and possible infectious diseases that may be transmitted by stem cell donation. The donor's exam will also ensure that they remain available and are physically well enough to undergo the donation procedure. The NMDP will notify NIH if there are any abnormalities that increase the risk of transmitting infectious diseases to you during the transplant. These findings will be discussed with you. The donor's medical clearance will be verified by the NIH study doctor before you receive any chemotherapy.

If you have an unrelated donor, the identity of the donor is confidential and the donor will be anonymous. This means that you will not know who your donor is or where they are. You will know the age and gender of the donor and any history or medical exam findings that could possibly change the risk of your transplant. Likewise, the donor will not know who you are or where you are. He/she will know your age, gender, and the type of disease that you have. The donor will be given basic updates about your condition 30 days, 6 months, and 1 year after your transplant. The only information they will receive is whether or not the stem cells "engrafted" (taken hold), and if you have been discharged from the hospital. The donor will also be notified in the event of your death.

Depending on the policy of the particular donor center, you may be able to communicate without revealing your identities in an anonymous manner with your donor beginning at the time of your transplant. In some cases, if both you and the donor agree, you may be able to learn who your donor is after one year. There are some cases when a donor and patient may never communicate or meet. Your transplant coordinator will tell you the details of if and how you may contact the donor once the donor has completed his or her medical exam.

Transplant Procedures

All females and ½ of the male (randomized) will receive lupron 2 weeks prior to BMT.

You will be admitted into the hospital approximately seven days before transplantation. You will receive either 4 days of irradiation followed by 2 days of cyclophosphamide transplant chemotherapy or 3 days of Fludarabine followed by 1 day of irradiation. Two days after completing this chemotherapy you will receive the stem cell transplant. Your donor's stem cells will be infused through your central venous catheter. This is referred to as "day 0".

While you are in the hospital for your transplant, you will be monitored very closely for possible complications, which are described below. You will receive drugs to help prevent and/or treat infections, blood transfusions, and intravenous nutrition (if needed). Blood will be drawn frequently during your treatment. Your blood will be tested to monitor your health during and after the chemotherapy and transplant procedure. In general, 4 to 10 teaspoons of blood will be drawn an average of 2 to 3 times per week. Some blood will be drawn for research purposes. In general, 3 to 4 tablespoons of blood will be drawn for research on average of once per week for the first 100 days after transplant.

The average time you will stay in the hospital is four weeks after transplant, but it could be longer if there any complications.

You will receive methotrexate and tacrolimus to prevent GVHD before and after your transplant. Beginning three days before you receive the stem cell transplant, you will receive tacrolimus to help prevent GVHD. Tacrolimus is given either through an I.V. or by mouth once a day for approximately six months after transplant. Methotrexate is given for four doses intravenously (through the vein) before you are discharged from the hospital, shortly after the transplant.

Some patients will undergo FLT and PET imaging during the preparative regimen, at day 5 post-transplant, at day 28 post-transplant, and at a later time point to correspond with the development of immune system (thymus) or GVHD.

Once the stem cells have taken hold and you are strong enough, you will be discharged from the hospital and followed closely as an outpatient. You will be required to remain in the Washington, D.C. area for approximately three months after transplantation so the NIH doctors can monitor you in case of any complications. You may require re-admission to the hospital for complications. You will be followed by the doctors in the NCI clinic for the first six months after transplant, and then you will be followed less frequently for at least five years.

After the transplant, if tests show that your blood and immune cells have not fully converted to your donor's type ("mixed chimerism"), then the drugs you are taking to prevent GVHD will be lowered to help change your blood and immunity to full donor chimerism. If your cancer is still present or grows after the transplant, tacrolimus may be reduced in an attempt to permit a stronger graft-versus-leukemia effect.

Frequent Follow-up at the NCI in the First Year after Transplant

If you are in good health after the three month period after your transplant, you will then be allowed to return home to the care of your primary physician. You will be required to return to the NIH monthly until approximately six months after transplantation so you can be monitored for late transplant complications including GVHD and infection. Thereafter you will be seen at NIH every three months until you are two years after transplant. At each visit when you return to NIH, you will have a physical exam and blood draws (approximately 4-10 teaspoons of blood will be taken). During some visits you may have a bone marrow aspirate and biopsies, and other appropriate tests (for example: CT, MRI, PET scan) to monitor disease status. Study-related medications will be provided by the NIH during your hospital stay and after you leave the NIH. As part of your post-BMT care, you will be given vaccinations. Because your old immune system is gone, we will need to vaccinate the new immune system which is standard of care. As part of this process, we will test to be sure that your new immune system is mature enough to benefit from the vaccines and we may give another vaccine if the new immune system is not yet mature enough to respond.

Risks or Discomforts of Participation

Risks of Lupron

Lupron has been used in female patients receiving BMT. Male patients will be randomized in this study to receive lupron or not. It is administered as a single intramuscular injection 2 weeks prior to BMT.

Side effects include:

Likely	Less Likely	Rare but Serious
• Testicular Atrophy	• Headache	• Abscess
• Hot flashes/sweats	• Weakness	• Allergic reaction
• Generalized pain	• Injection site reaction	• Blood clot
	• Stomach complaints	• Abnormal heart beat
	• Joint problems	• Gastrointestinal bleeding

Likely	Less Likely	Rare but Serious
	• Dizziness • Flu syndrome • Dehydration • Pins and needles feeling • Breathing issues • Neuromuscular disorders • Skin reaction • Urinary problems	• Low oxygen • Confusion • Neurological problems

Risks of Fludarabine:

Likely	Less Likely	Rare
• low blood counts • lowered level of immune cells • increased risk of infection	• nausea and vomiting • diarrhea • fever • mouth sores • loss of appetite • swelling (edema) • skin rash • muscle aches • headache • agitation • hearing loss • fatigue • weakness • numbness / tingling ("pins and needles")	• GI bleeding • lung damage • kidney damage • severe neurologic (brain and/or spinal cord) toxicity has occurred after very high doses including: blindness, deterioration of mental status, and death.

Risks of Cyclophosphamide:

Likely	Less Likely	Rare
• low blood counts • hair loss	• nausea and vomiting • painful and bloody urination • sterility • water retention	• heart damage • secondary leukemia (a different type of cancer) • skin rash

Risks of Busulfan:

Likely	Less Likely	Rare
• Low blood counts • Hair loss	• Nausea and vomiting • Sterility	• Secondary leukemia (a different type of cancer) • Skin rash

Risk of Radiation (not including the Total Body Irradiation from BMT)

The risks of FLT and FDG scanning are primarily risks of radiation. The radiation exposure that is for research purposes is from PET/CT scanning with FLT and FDG. The maximal amount of radiation you will receive in this study is from 5 injections (maximum 3 mCi per injection) FLT and 2 injections FDG (maximum 5 mCi per injection). The NIH Radiation Safety Committee has reviewed the use of radiation in this research study, and although the radiation exposure exceeds the annual guideline of 5 rem, has approved its use as involving acceptable risk to obtain the information desired. Although each organ will receive a different dose, the maximum amount of radiation exposure that you will receive is equal to a uniform whole-body exposure of 6.2 rem. The average person in the United States receives an annual radiation exposure of 0.3 rem from natural sources such as the sun, outer space and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet an Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of research radiation exposure received in this study is harmful, there is indirect evidence that it might not be completely safe. There may be a very slight risk of cancer; which is less than the risk for the BMT itself.

Please tell your doctor if you have taken part in other research studies or received care at the NIH or other places/hospitals where radiation was used. This way we can make sure that you do not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant or breastfeeding, you will not be permitted to participate in this research study. It is best to avoid radiation exposure to unborn or nursing children, since they are more sensitive to radiation than adults.

Risk of Death from Allogeneic SCT:

Patients undergoing allogeneic SCT are at risk of dying from the transplant procedure and its possible complications. In some studies of allogeneic SCT, as many as half of the patients died as a direct result of the transplant or its complications. In transplant studies similar to this one, up to 50 percent of patients have died from the transplant procedure. The risk of death or other complications can vary greatly, depending on the age of the patient, the way the transplant is performed, and other factors.

Other risks from allogeneic SCT include:

Veno-Occlusive Disease (VOD) - A severe liver complication known as VOD occurs in less than 5 percent of allogeneic transplants. VOD is a chemotherapy side effect that causes blood vessels in the liver to be blocked. Severe VOD can lead to liver failure and death.

Graft Rejection: There is a chance that you may reject your donor's stem cells. There is the rare possibility that your own cells may recover. This may result in prolonged low blood counts, which may result in infection or bleeding and may lead to death. In this event, we would attempt to re-transplant you.

Graft-Versus-Host Disease (GVHD): You will be at risk for the development of GVHD for the rest of your life after transplantation. GVHD occurring within the first 100 days after transplantation is referred to as acute GVHD. Acute GVHD most commonly attacks the liver, intestines, and skin. Symptoms of skin GVHD may be as mild as a rash with itching, or as severe as blistering and loss of the skin. Symptoms of intestinal GVHD may be as mild as heartburn and mild diarrhea, or as severe as cramping abdominal pain and bloody diarrhea. Liver GVHD may be as mild as slight disturbances in liver function, or severe as jaundice (yellowing of the skin) with liver failure. Mild GVHD (skin rash only) can be treated with steroid creams that you apply on your skin. Severe GVHD can be very dangerous and needs to be treated aggressively. Treatment of severe GVHD initially includes weakening of the immune system, usually with intravenous (I.V.) steroids. Weakening of the immune system increases the risk of infection.

A delayed form of GVHD, known as chronic GVHD, may occur after day 100 post-transplant. Some degree of chronic GVHD affects about half of patients after transplantation. It most commonly attacks the skin, the liver and the intestines, but it may also affect other organs such as the lungs, eyes, muscles, joints, and the bone marrow. Symptoms of chronic GVHD may include dryness of the mouth and eyes, a loss of

appetite, weakness, hair loss, weight loss, liver damage (including yellowing of the skin), and lung damage leading to shortness of breath and cough. Patients with severe chronic GVHD are also at increased risk of infection and death. Chronic GVHD is also treated with drugs that weaken the immune system such as steroids. Taking steroids may increase your risk of infection.

Late Transplant Complications: There are other potential complications that can occur long after transplantation. These complications could affect any organ in the body including the heart, lungs, kidneys, liver, muscles, and brain. Rarely, patients who receive an allogeneic SCT are at risk for developing a second cancer such as leukemia or lung cancer.

Other complications are also possible following your transplant. The most common complication is infections. Because you will be receiving drugs (e.g. cyclosporine) that weaken the immune system, you are at greater risk to develop infections from uncommon organisms. These infections can be life-threatening, and could cause death.

There is about a 40 percent chance of death from complications of conventional allogeneic bone marrow transplants. There is also the risk of complications that cannot be predicted.

Bone Marrow Aspiration and Biopsy: This procedure usually causes only mild pain for a short time at the biopsy site. Very rarely, bleeding or an infection may occur at the biopsy site.
Blood Draws: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness and rarely, fainting. When a large amount of blood is drawn, your red blood cell count may drop causing anemia. Anemia can cause a lack of energy and other symptoms. Transfusions of red blood cells are sometimes needed to treat anemia.

Central Venous Catheter: Side effects of placing a central venous line in your chest wall include bleeding, bruising, blood clot, or pain in the area of insertion. This line will be placed by physicians with experience in this procedure. These physicians will discuss the above risks at the time of the line insertion. Rarely, placement of a central venous catheter can result in a collapsed lung. If a collapsed lung occurs, it may require hospitalization and temporary insertion of a plastic tube in your chest to re-expand the lung.

Transplantation Chemotherapy: Potential side effects of chemotherapy and TBI are described above.

Graft-versus-Host Disease Prevention: As described above, you will receive tacrolimus and methotrexate, to prevent GVHD. Side effects are described above.

Stem Cell Infusion: The donor cells may be frozen with a chemical called DMSO to protect them from the effects of freezing. Patients receiving thawed cells often develop side effects from the DMSO. DMSO side effects may include fever and allergic reactions, such as skin rash, itching, difficulty breathing, and low blood pressure. Although not harmful, this agent does have an odor similar to garlic that dissipates in 24 hours. These reactions are usually mild and temporary, and they can be easily treated with IV fluids and medications. Products may also be contaminated with bacteria or red blood cells. Every effort is made to collect cells in sterile fashion and reduce red blood cells (if needed); however, you may need to receive fluids or antibiotics should this be needed.

Other Medications: You will routinely receive several other drugs to prevent or treat various infections and other transplant-related complications. These medications and their common side effects are listed as follows:

Ursodeoxycholic acid: Ursodeoxycholic acid, also known as ursodiol, can cause nausea, vomiting, "heartburn", a metallic taste, abdominal pain, an inflamed gallbladder, constipation, mouth pain, flatulence, diarrhea, itching, rash, dry skin, hives, headache, fatigue, anxiety, depression, and sleep disorders. Less common side effects include sweating, thinning of hair, back pain, muscle and joint pains, runny noses, and cough.

Diphenhydramine may cause tiredness, dizziness, upset stomach, disturbed coordination, dry mouth, flushing, or difficulty urinating.

Valacyclovir can cause nausea, vomiting, headache, dizziness, abdominal pain, bone pain, allergic reactions, mild liver inflammation, kidney injury, and abnormal nervous system function.

Fluconazole can cause nausea, vomiting, headache, skin rash, abdominal pain, and diarrhea. Rare but sometimes serious liver toxicity has also been reported. Fluconazole can increase the blood levels of other drugs, which can increase their effectiveness and/or their side effects.

Trimethoprim/sulfamethoxazole (Bactrim) may cause nausea, vomiting, loss of appetite, allergic skin rashes, and suppression of bone marrow function. Rare but severe reactions may affect the skin and bone marrow; these have sometimes been fatal.

Reproductive Risks: This treatment is likely to result in sterility (the inability to produce children). However, we cannot predict for certain that you will become sterile during this treatment. It is unknown what effects the chemotherapy and other drugs included in this treatment may have on an unborn child, but they would most likely be harmful. For this reason,

if you have not been placed on a contraceptive (birth control) as part of this study, you will need to use an effective form of contraception while on this study, and for one year after transplant (examples include: intrauterine device (IUD), hormonal (birth control pills, injections, or implants), tubal ligation/hysterectomy (self or partner), partner's vasectomy, barrier methods (condom, diaphragm, or cervical cap), or abstinence.

Potential Benefits of Participation

This study has the potential to: 1) cure your cancer; 2) improve your immune system function after transplantation, diminishing the risks of transplant including GVHD and life-threatening infections; 3) improve the ways that we evaluate the success of bone marrow transplantation through imaging.

The chemotherapy you receive may cause improvement in your cancer, although it is not likely to result in a cure by itself. The allogeneic SCT may improve the chance that your disease will enter into a long remission and possibly be cured. However, you should understand that this cannot be guaranteed. In addition, your participation in this study may contribute to understanding and developing new ways of using allogeneic SCT for the treatment of cancer.

Alternative Treatment

To be eligible for this study, you must have already received the standard treatment for your disease and be recommended for BMT because the data suggests that this is a beneficial treatment option, but there are other options other than participating on this trial:

- You may consider other treatments such as other forms of chemotherapy, radiation, surgery, or immune therapies.
- Taking part in another research study
- Instead of participating in a research study such as this, you may also be eligible to receive a standard allogeneic stem cell transplant without the experimental elements of this transplant (lupron and FLT imaging).
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.
- Another option is not to receive any further treatment at all.

You should discuss with your referring doctor and your doctors at the NCI whether or not any of these other treatments might be a reasonable choice for your disease.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- If your doctor believes that it is in your best interest
- If you request to be withdrawn from active therapy
- Completion of 1year protocol therapy
- If new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

Participation in this research study is voluntary. You may stop your participation in the study at any time. There are no penalties for withdrawing from the study. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first. If you withdraw after the transplant chemotherapy ("conditioning regimen") without receiving the infusion of donor stem cells, you would be at high risk for serious complications, including death.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Sponsor or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- The study Sponsor, Dr. Karen Kurdziel, or her agent(s)
- We may share data from this study with a blood and bone marrow registry called: The Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR (www.cibmtr.org) is committed to respecting your privacy and the data we share with is sent without revealing any personal information. The information that is sent to the CIBMTR is combined with information from other transplant centers to better understand how transplants work and to improve patient care.

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

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;

- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.
You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.
We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Christopher Kanakry, M.D., Telephone: 240-760-6171. You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your specimens and data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:	
A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. _____ _____ Signature of Adult Patient/ Legal Representative Date _____ Print Name	**B. Parent's Permission for Minor Patient.** I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) _____ _____ Signature of Parent(s)/ Guardian Date _____ Print Name
C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study. _____ _____ _____ Signature of Parent(s)/Guardian Date Print Name	
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 10, 2018 THROUGH JULY 09, 2019. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	