

INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0224 PRINCIPAL INVESTIGATOR: Nancy M. Hardy, M.D.

STUDY TITLE: Pilot Study of Radiation-Enhanced Allogeneic Cell Therapy for Progressive Hematologic Malignancy After Allogeneic Hematopoietic Stem Cell Transplantation

Continuing Review Approved by the IRB on 05/13/13
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Recipient

INTRODUCTION

We invite 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.

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

You have been diagnosed with a cancer of the blood system (such as: Hodgkin's or non-Hodgkin's lymphomas, leukemias, and multiple myeloma) that has not been controlled with allogeneic hematopoietic stem cell transplantation (allotransplant), meaning that the cancer cells have continued to grow or, if you did achieve a remission, that the cancer has come back after transplant. Your allogeneic transplant was performed because chemotherapy (drug therapy) and/or immunotherapy and/or radiation therapy did not adequately control your cancer growth. For blood system cancers that are not helped with allogeneic transplantation, there are no treatment options that have been proven to cure the cancer or to help patients live longer. Treatment for persistent blood system cancer after allogeneic transplantation is primarily aimed at improving quality and perhaps length of life. Unfortunately, many blood system cancers quickly develop resistance to standard treatment options and ultimately stop responding to them. Thus, there is a need to find new approaches for the treatment of blood system cancers. You should discuss with your referring doctor and the NIH doctors

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other treatment options that might be available to you so that you feel that you have made the best choice for your disease at the time.

Information on Cancer and the Immune System

The immune system plays many important roles in the body such as helping the body fight infections. The immune system is also known to affect cancer cells. "T" lymphocytes or T cells, are a type of white blood cell and a major component of the immune system. T cells have been shown to be capable of recognizing and destroying a number of different tumors, particularly types of blood system cancers. Unfortunately, most tumors have developed ways of escaping the monitoring by the immune system for foreign or abnormal cells and continue to grow in an uncontrolled manner. Thus, we are looking at ways to manipulate the immune system, in particular the T cell component, so that it will more efficiently recognize and kill tumor cells.

Information on Allogeneic Hematopoietic Stem Cell Transplantation (Allotransplant)

You have received an allogeneic stem cell transplantation. Allogeneic (from a donor) Stem Cell Transplantation has been shown to be a potentially curative therapy for types of blood system cancers - meaning that they originate in bone marrow or lymph nodes - such as leukemias, lymphomas and multiple myeloma. Stem cells are essentially the "seeds" of the bone marrow from which red cells, white cells and platelets can grow.

After transplantation, a new immune system grows from the transplanted donor stem cells and lymphocytes. Donor lymphocytes, unlike the patient's own lymphocytes, are often capable of recognizing the patient's tumor cells as being "foreign" and destroying them. This attack of the donor's immune system against any tumor cells left in the body after transplantation is called the "graft versus tumor" effect. This "graft-versus-tumor" effect is seen in patients treated with allotransplant and is not seen in patients undergoing autologous stem cell transplantation - where your own stem cells are given back. This is probably the main reason why some patients are cured of their tumor with an allotransplant.

You received an allotransplant with the intention of curing your blood system cancer. Although tumor control is observed after allotransplant, relapse and tumor progression remain major problems for many patients with blood system cancers. Further, allotransplant is still associated with significant, potentially life-threatening side effects. Additionally, it is not known how, exactly, the new immune system fights the tumors. We believe cancers respond as a result of donor T lymphocytes, or T cells. T cells are a part of the immune system involved in cancer prevention - people without functioning T cells are more likely to develop some cancers. T cells are part of the donor lymphocyte infusions patients receive after transplantation, and tumor shrinkage seen after donor lymphocyte infusion is further evidence that T cells may be active in tumor control. T cells have been found in some tumors, including B cell malignancies, from patients that have not received any therapy. It is unclear what the T cells are doing in these tumors, but some studies show that patients with tumors that have T cells are better able to keep tumor growth in check.

How many people will take part in this study?

A maximum of 99 people (46 patients, 38 donors and 15 control participants) will be enrolled in this research study.

Description Of Experimental Treatment

The research question being tested in this protocol is whether a single dose of radiation will help donor immune cells control cancer that has not been controlled with allotransplant without causing an excess of side-effects, such as increased rates or severity of graft-versus-host disease (GVHD), lowering of blood cell counts or inflammation from

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radiation. It has been found that a single dose of radiation can improve the potency of cell-based immune therapies. This is probably because the tumor tissue is damaged in such a way that immune cells are attracted to the new tumor proteins that are exposed on the damaged tissue. The damaged tissue also has other ways of activating the immune cells, by substances that are not normally released when tissues are healthy or intact. By giving only a single dose of radiation, the immune cells that are attracted to the tumor are allowed to survive and function in their usual way, growing, expanding, and recruiting other immune cells to tumor sites as well. Some research has shown that this improved tumor control can be widespread, so that the educated immune system has improved ability to control the tumors that have not been radiated as well.

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

All study participants will receive radiation given as a single dose of 8 Gy (a dose that has been proven safe to give in a single dose to patients with metastatic cancers). The radiation will be given to the greatest amount of tumor that can safely be irradiated. We will intentionally leave some tumor that will not be radiated so that we can evaluate whether there is a widespread – or systemic – response to the treatment. There are two treatment arms on the study. Study participants who have donor cells available and who have not had to take medicines to treat GVHD will be given a dose of donor cells to provide an additional boost to the donor immune response (Arm A). Patients who do not have a source of donor cells or who have had significant GVHD or received an allotransplant from a relative who was only partially matched ("haploidentical") will receive a single dose of radiation to boost the donor immune response, but will not receive additional donor cells (Arm B). All study participants will be followed closely for side effects (GVHD, lowering of blood cell counts or inflammation from radiation) and also for tumor response to radiation with or without donor lymphocyte infusion (DLI). We will look to see whether there are signs of an active immune response with research studies, including PET scans, tumor biopsies, bone marrow samples and blood draws. We will be comparing the donor lymphocytes in your tumor, blood and bone marrow to lymphocytes from "control" participants – patients who receive standard therapy with DLI (without radiation) to treat persistent cancer after allotransplant. We are trying to better understand the mechanisms and effectors of GVT, and the reasons some patients tumors are controlled with allotransplant while others are not. The major goal is to improve the success rates of allotransplant, and to better predict which patients will benefit from the therapy.

If your donor was your sibling, with your permission, we may ask your donor to volunteer to have a collection of some of their immune cells, to give to you and to study in the laboratory as a comparison to your immune cells. This may help us understand how these cells change and how to improve their tumor-fighting ability.

Treatment will take place as follows (details follow in later sections):

- We will collect immune cells from your blood (a procedure called apheresis, described in later sections)
- You will have a PET Scan, a radiology test that can measure how active the cells are in tumor and inflamed tissue.
- If you have tumor that can safely and easily be reached with a needle, you will have a needle biopsy to remove some of the tumor.
- To see whether there is tumor in your bone marrow, you will have a bone marrow biopsy and aspiration – where the liquid bone marrow is collected - through a standard bone marrow procedure. Additional liquid marrow will be removed through the same needle to examine for research studies.
- You will receive a single session of radiation, during which the most tumor that can safely be included will be radiated.
- Arm A: If you have a donor who is available to give more cells or you have other donor cells available, and you do not have a high risk of GVHD, you will receive an infusion of your donor's lymphocytes (donor lymphocyte infusion, "DLI"). The DLI will be given 24-48 hours after completing radiation.

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- ARM B: If you do not have a source of additional donor cells available or you have a high risk of GVHD, you will not receive additional donor cells (DLI).
- We will monitor the status of your tumor before and after radiation cell therapy, to see whether the tumor shrinks. This will include an additional PET Scan a few days after radiation, and routine tumor restaging studies every four weeks for at least three months.
- We will evaluate your immune cells in the laboratory, collecting them with a second apheresis procedure a few days after you receive radiation, and with routine blood draws for both standard tests for toxicity and research tests to see the effects of therapy on the immune cells in your blood.
- Four or more weeks after completing treatment, you will be asked to permit a needle biopsy and possibly surgery to remove a sample of remaining tumor for research studies.
- You will have frequent follow-up at the NCI in the first year following infusion therapy.

Preliminary Evaluation

You will have a complete medical history and physical at the NCI Outpatient Clinic at the National Institutes of Health Clinical Center. You will have blood drawn to check your blood counts and blood clotting factors and the function of your kidneys and liver to determine that they are adequate to proceed with apheresis, radiation and (Arm A) a DLI. Your blood may also be tested to see whether you have ever had the following infections, if we do not have results available from previous testing: Hepatitis A, B, and C; *T. Cruzi* (Chagas agent); CMV (cytomegalovirus); adenovirus; EBV (Epstein-Barr Virus); HSV (Herpes Simplex Virus); and toxoplasmosis. If you are Hepatitis B or C positive, you may still participate in this study. 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 may still 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 newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of your HIV infection. If you are a woman, you will undergo a blood or urine test for pregnancy. Approximately 20 teaspoons of blood will be collected. Knowing which of these infections you have had will help us determine how to protect you from having problems with these infections if you require treatment to suppress your immune system.

The extent of your blood system cancer needs to be determined before proceeding with this experimental therapy. This will include computed tomograms or CT scans of the chest, abdomen and pelvis, and a CT scan or MRI of the head. A CT of the neck may be done, if the doctor feels it is needed. If you have acute leukemia or multiple myeloma, these tests may not be done, and blood work or plain x-rays may be substituted. You will have a PET scan, either at the time of initial evaluation or just prior to radiation. You will also have a bone marrow evaluation, including an aspiration of the liquid bone marrow in the pelvic bone and a needle biopsy of the bone and marrow. The bone marrow will be examined for tumor in the bone marrow and a portion of the liquid marrow will also be used for research purposes, to determine whether there is evidence of an immune response to the tumor. The procedure and its risks are described below. You will be asked to sign an additional consent form at the time of this procedure, which will detail the specific technique and risks. If you have a form of blood system tumor (ALL, aggressive Non-Hodgkin's Lymphoma) that has a tendency to spread to the lining of the brain or spinal cord (called the leptomeninges) or if there is any concern that this might have occurred, you will have a lumbar puncture (also called a spinal tap), to determine whether you would require special therapy that should not be delayed while participating on an experimental protocol. Approximately three teaspoons of the fluid that bathes the spinal cord (called the cerebrospinal fluid) would be removed and examined for tumor cells. The procedure is done with local anesthesia to numb the skin in the lower back, and a very thin needle is used to draw fluid from the area below the spinal cord. There is very minor discomfort when the numbing medicine is injected into the skin, and 1/3 or fewer patients may experience some headache while the body replenishes the fluid that is removed. You will be asked to sign an additional consent form at the time of this procedure, which will detail the specific technique and risks.

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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You should know that being in this study may keep you from being in other research studies that limit the number or type of treatments that you are allowed to have had previously. You should always remember that your doctors are available to discuss all available treatment options and we encourage these discussions.

The Central Venous Catheter

If you have a catheter or a port-a-cath inserted in your vein it may be used to receive the DLI infusion for this protocol (Arm A). If you do not have a central venous catheter, a temporary catheter in the vein in arm would be placed for the cell infusion. You will therefore not require an additional central venous catheter.

Apheresis

Twice during the study period we will collect immune cells from your peripheral blood with a procedure called apheresis. The first apheresis will be before the radiation treatment. The second will be at a later time point, about 4 days after radiation. Apheresis is the process where blood is withdrawn from a vein and circulates through the apheresis machine. The machine will collect a portion of your white blood cells into a collection bowl, and the red blood cells and platelets will be returned to your body. Apheresis is a standard procedure that is performed by trained personnel in the NIH Department of Transfusion Medicine. Apheresis requires two needle sticks to temporarily place catheters (plastic tubes) into veins in each arm. On rare occasions the veins in your arms may not be adequate to place the catheters. In that case a temporary catheter will be placed in a vein in your thigh. The apheresis procedure typically requires less than two hours of collection. These immune cells will be used for research to study how your immune system is affected by the cell therapy, a graft-versus-tumor response and graft-versus-host disease (if it occurs).

FDG-PET/CT Scan

You will be receiving radiology tests, including PET-CT scans, as part of your medical care. A PET-CT scan is the same test that is used to measure many types of cancers. A sugar that has been tagged in such a way that it can be tracked and measured is injected into your vein, and pictures are taken to see where the sugar is being used. The use of the "tag" and the scan itself involve radiation exposure to your body. This research study involves exposure to radiation from one additional PET-CT scan. The PET-CT for research will be done about 1 week after your radiation treatment. This additional PET-CT scan which will use a 15 mCi dose of radioactive material. This radiation exposure, from the additional PET-CT scan, is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 1.75 rem, which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year 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 exposure received from participating in this study is harmful, there is indirect evidence that it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes 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.

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If you are pregnant you will not be permitted to participate in this research study. If you are breastfeeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Radiation Therapy

You will be meeting with the doctors in the NCI Radiation Oncology Branch (ROB) during screening evaluation for the protocol (before you sign on to the study) and also while you are a study participant. Your consultation with the doctors at the NCI ROB will include an examination and history taking. In addition to procedures described in this consent, the ROB doctors may need to perform certain additional procedures, scans or tests to determine whether the planned radiation therapy would pose additional risk of side effects. These may include additional radiology studies (for instance, MRI or CT scans) and/or procedures, such as pulmonary function tests. If you need to have a procedure or test done that is not described in this consent, a separate consent will be obtained to address the specific details including a description of the procedure/tests, the purpose of the procedure/test, and its risks. Once the results of the procedure/test are available, the doctor will present them to you and discuss the treatment plan. This information will also be communicated to your primary physician.

You will then be scheduled for a "simulation" or treatment planning session. During this visit, body measurements are taken, CT images are made and some markings may be placed on your body to help the radiation oncologists determine the "field" or area that will be treated. Through this planning session, we want to make sure that all necessary areas are covered by the radiation beam without undue damage to vital organs such as the heart or kidneys. The radiation therapy will be delivered external to your body by a machine that produces x-rays. At no time will you be "radioactive." Radiation therapy will be given one time on one day. The treatment takes about 20 minutes and you must remain very still.

Donor Lymphocyte Infusion

Participants on Arm A will receive a donor lymphocyte infusion (DLI). DLI are lymphocytes that are taken from your donor, then frozen and stored for administration to patients. The DLI used in this study are given in a standard dose that is used to treat persistent tumor after allotransplant. You will be closely watched during the DLI for signs of a reaction. While DLI have been given to other patients with cancer after allotransplant, treating patients after radiation is a new approach that is being evaluated in this protocol. You will need to come in to our "Day Hospital" for the DLI, at one and three days after you receive the infusion; if you do not live close to the Clinical Center or do not have someone who could stay with you, your doctors may recommend that you stay overnight in the hospital after receiving the infusion. You will also be asked to return to the Clinical Center at 1, 2 and 4 weeks after radiation, for blood work and a brief visit with one of our doctors. You will have a physical exam and routine blood work done at these visits. There is a chance that the infusion will cause you to have a reaction or that the cells could cause graft-versus-host disease (GVHD). Risks are described below.

Tumor Biopsies

At each of the time points listed below, if it is safe to do so, we may attempt to biopsy both a lesion that will have/has had radiation, and a lesion that will not have/has not had radiation.

Pre-Radiation Biopsies:

- 1) During the study period we may attempt to obtain tumor samples by needle biopsy and/or surgical removal at up to three time points. Prior to radiation, we will evaluate the safety of obtaining a needle biopsy of a site that will be radiated and a site that will not be radiated. These biopsies are done so the study doctors can verify that the lesions are tumors (clinical reason), and also to serve as a basis for comparison of tumor changes after radiation (research reason). Your biopsies would be taken before you have radiation. The

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procedure for needle biopsy depends on the location of the tumor, and you will have an explanation of the procedure that is planned for you, including its specific risks, before the procedure. You will be asked to sign a separate consent for the procedure. The tissue from this biopsy will be sent for routine pathology examination and will also used for research purposes, to determine whether there is evidence of an immune response to the tumor. Risks are described below.

Please read the statement below regarding the pre-radiation biopsies. Check "yes" or "no" and initial next to your answer. No matter what you decide to do, it will not affect your care on this study. You can change your mind at any time.

If considered safe, I am willing to undergo a biopsy/biopsies before radiation for research purposes. As I will be asked again for specific permission, I understand that I may decline the biopsy procedure at that time.

 Yes No Initials**Post-treatment Biopsies:**

2) Between 4 and 7 days after radiation, if you have tumor in or just below the skin that can be removed with minor surgery, we will ask you for permission to have a biopsy of up to two of these tumors that are in or just below the skin. This biopsy would be used primarily for research studies, to evaluate whether there are early signs that the radiation has helped your donor immune cells to fight your tumor. If safe and possible to perform with local anesthesia, we will ask the surgeons or dermatologists to remove the tumor. The tissue from this biopsy will be sent for routine pathology examination and will also used for research purposes, to determine whether there is evidence of an immune response to the tumor. Risks are described below.

Please read the statement below regarding the post-treatment biopsies. Check "yes" or "no" and initial next to your answer. No matter what you decide to do, it will not affect your care on this study. You can change your mind at any time.

If considered safe, I am willing to undergo a biopsy/biopsies after radiation for research purposes. As I will be asked again for specific permission, I understand that I may decline the biopsy procedure at that time.

 Yes No Initials

3) Four weeks after treatment, as part of a comprehensive evaluation for tumor and side effects, we will determine whether there is any tumor that could safely be sampled with surgery or a needle biopsy. If so, we will ask your permission to obtain up to two biopsies of your tumors. If you have tumor that appears to be surgically accessible, without major risk of bleeding or discomfort to you or requirement for general anesthesia, the biopsy would include surgical removal of tumor(s). In this case, you would be evaluated by the Surgery Consult Service to determine the safest and easiest way to remove tumor. The surgeons, in consultation with Dr. Hardy or one of the other physician investigators on this protocol, will decide on the exact procedure that will be required to safely remove a sample of your tumor with minimal discomfort and risk. The surgery may take place in the operating room, with sedation if necessary, and local anesthesia. The surgeon will explain the specific details of the operation to you before the surgery takes place, and you will be asked to give a separate consent for the surgical procedure. This surgery may be an outpatient procedure, or you may need to stay in the hospital for a brief period of time. If you do not have a tumor that would be surgically accessible, a needle biopsy would be performed if the risk of bleeding, other complication or discomfort is small. The procedure for needle biopsy

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depends on the location of the lesion, and you will have an explanation of the procedure that is planned for you, including its specific risks, before the procedure. You will be asked to sign a separate consent for the procedure. While we will have these biopsies submitted for clinical pathological exam, the primary purpose for these biopsies is for research. We will compare the tumors before and after radiation therapy to study whether there are changes that indicate that the radiation has boosted your donor's cells' ability to fight your cancer. Risks are described below.

Please read the statement below regarding the additional post-treatment biopsies. Check "yes" or "no" and initial next to your answer. No matter what you decide to do, it will not affect your care on this study. You can change your mind at any time.

If considered safe, I am willing to undergo a biopsy/biopsies after radiation for research purposes. As I will be asked again for specific permission, I understand that I may decline the biopsy procedure at that time.

_____ Yes

_____ No

_____ Initials

Biopsies of New Lesions: If new lesions are identified after you have received the radiation therapy, a biopsy may be performed, to determine whether the new lesion(s) are from spread of your tumor. The main reason for this biopsy would be to assess whether it is from your tumor and determine treatment options (clinical reason). If there is enough tissue leftover, some may be used for research. You will be evaluated to determine whether there is any lesion that could safely be sampled with surgery or a needle biopsy. If you have a lesion that appears to be surgically accessible, without major risk of bleeding or discomfort to you, the biopsy would include surgical removal of lesion(s). In this case, you would be evaluated by the Surgery Consult Service to determine the safest and easiest way to remove the lesion. The surgeons, in consultation with Dr. Hardy or one of the other physician investigators on this protocol, will decide on the exact procedure that will be required to safely remove a sample of the new lesion with minimal discomfort and risk. The surgery may take place in the operating room, with sedation or anesthesia if necessary. The surgeon will explain the specific details of the operation to you before the surgery takes place, and you will be asked to give a separate consent for the surgical procedure. This surgery may be an outpatient procedure, or you may need to stay in the hospital for a brief period of time. If you do not have a lesion that would be surgically accessible, a needle biopsy would be performed if the risk of bleeding, complication or discomfort is small. The procedure for needle biopsy depends on the location of the lesion, and you will have an explanation of the procedure that is planned for you, including its specific risks, before the procedure. You will be asked to sign a separate consent for the procedure. The tissue from this biopsy will be sent for routine studies to determine the cause of the new lesion. If the biopsy shows tumor, the tissue sample would also be used for research purposes, to compare with other tumor biopsies in order to better understand whether or how this treatment approach works. Risks are described below.

Blood Samples

Routine blood tests and research blood samples will be drawn on the day you receive the radiation and at 24 and 48 hours after radiation, and at 1 week, 2 weeks and 4 weeks following the radiation. Between 1 and 3 tablespoons of blood will be drawn at each collection. If your physician determines that it would not be safe for you to have an apheresis procedure, an additional 4-5 tablespoons of blood may be drawn at that time to substitute for the apheresis.

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Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control when you enroll on this study and remain on birth control until you have completed the apheresis procedures. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- barrier methods (condoms, spermicide, diaphragm, cervical cap)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Follow-Up

You will be seen at 1 and 4 days, 1, 2 and 4 weeks; and 2, 3, 6, 9, 12 months after the radiation for routine blood work and a clinic visit. After 1 year, you will be seen in the clinic every 6 months for up to five years in this study. At the clinic visits from four weeks and after, your tumor will be measured with the blood tests and radiology studies that are required to follow your cancer and possible response. These may include CT scans, blood work, urine tests and/or plain x-rays, and possibly also with a PET scan or bone marrow aspiration and biopsy. You will also continue to see your home oncologist, who will receive a detailed summary of your records, blood tests and other tests that need to be performed while you are at the NIH. We encourage early communication of any problems with us so that we can assist in deciding the best treatment approach.

ALTERNATIVE APPROACHES OR TREATMENTS

To be eligible for this protocol, you must have already received an allogeneic HSCT. Prior to this, you had received most of the conventional therapies for your disease. You may consider other treatments such as:

- Other forms of chemotherapy, radiation, surgery, or immune therapies, without being in a study.
- You may be eligible for other experimental therapies.
- Another option is not to receive any further therapy at all, other than comfort care, also called palliative care. This type of care reduces tiredness, appetite problems and other problems caused by the cancer. It does not treat cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

You should discuss with your referring doctor and the NIH doctors whether any of these treatments might represent a reasonable treatment option for your disease.

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RISKS OR DISCOMFORTS OF PARTICIPATIONRadiation Therapy

The side effects of radiation therapy depend on the site that is treated. A separate radiation consent will be obtained to address the specific details of receiving radiation to the site(s) of your blood system cancer. Patients usually tolerate the single dose of administration that will be used in this study very well, however, the risk of radiation may increase with increasing numbers of radiated sites. In general, however, radiation can cause tiredness, lowered blood counts, skin reddening, and sometimes nausea. These side effects tend to go away soon after the radiation therapy is completed. However, there are some long-term or chronic side effects that primarily affect the small bowel, liver, kidneys, and spinal cord. Many of these side effects take months to years to develop. Rarely, treatment with radiation may also lead to developing other types of cancer, usually years after receiving the treatment. It is possible that you may experience some, all, or none of the side effects described above. It is also possible that your specific treatment may cause some side effects that we cannot anticipate. For example, it is possible that you will be more sensitive to some of the side effects because you have had an allotransplant. Evaluating the safety of the combination of radiation and allotransplant is a major part of this research study. Therefore, you will be watched closely while you are receiving treatment for any signs that might signal the earliest stage of toxicity so that we can treat them early.

Reproductive Risks

If you are female and able to get pregnant, you will be given a pregnancy test before you begin the radiation treatment part of this study to make sure that you are not pregnant. If there is a chance that you could become pregnant during the treatment part of this study, you should not be in the study. If sexually active, you must use an appropriate and effective method of birth control while you are receiving radiation on study. If you become pregnant while taking part in the radiation treatment part of this study, you must notify the one of the doctors listed on this form immediately.

Donor Lymphocyte Infusion

Participants in Arm A will receive a donor lymphocyte infusion (DLI). The major risk of DLI is GVHD, described in detail below. Like the cells you received at the time of your transplant, the DLI are 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. These reactions are usually mild and temporary, and they can be easily treated with IV fluids and medications. In addition to these known side-effects of donor cells, it is possible that, when DLI are given in conjunction with radiation therapy, additional, unanticipated side-effects may occur. The radiation in this study is being given to try to activate the DLI; activated donor lymphocytes have the potential to cause inflammation and injury, even to places that did not receive radiation.

One subject treated on this study developed bleeding in the lungs two days after receiving the DLI. The lungs had not received radiation. While it is not certain that the treatment caused the bleeding, it may have been, given that it happened so soon after treatment. This type of bleeding, called "Diffuse Pulmonary Hemorrhage" or "DAH," is a critical condition, often requiring intensive care monitoring, including breathing support with a respirator, and is life-threatening. It is possible that you could develop DAH after treatment on this study. The cause of DAH is poorly understood, but is probably due to injury of the delicate tissues in the microscopic airspaces of the lungs. Approaches to treatment include steroids and/or medicines that help with blood clotting.

Graft-Versus-Host Disease (GVHD)

Early (acute) GVHD, which generally occurs in the first 100 days after transplantation, sometimes occurs (in about one-third of patients) after DLI. Mild acute GVHD (skin rash only) can be treated with steroid lotions that you can apply on your skin. More severe acute GVHD can cause blistering of the skin, abdominal pain and diarrhea, disturbances in liver

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function and jaundice (yellowing of the skin) and require stronger treatment including steroids, which are given intravenously (through the vein). Occasionally, severe acute GVHD can be fatal.

Delayed or chronic GVHD may also occur. Typically occurring after the first 100 days following transplantation, it also can occur after DLI. The risk of chronic GVHD seems to be about the same as the risk for acute GVHD, and about one-third of patients treated with DLI may develop chronic GVHD. Symptoms include dryness of the mouth and eyes, skin rash, joint stiffness, weight loss, liver damage (including jaundice), and lung damage leading to cough and shortness of breath. This is treated with drugs that suppress the immune system, such as cyclosporine and steroids given by mouth. Chronic GVHD can at times be present for the rest of your life. Both acute and chronic GVHD, and the drugs we use to treat them, can place patients at significant risk for infections, which can be life threatening, and even cause death.

In patients whose tumors shrink after DLI, the risk of acute and chronic GVHD appears to be higher. About half of the patients whose tumor responds after DLI also develop some GVHD.

Participants in Arm A will receive a donor lymphocyte infusion the day after radiation. It is possible that radiation may increase the risk of GVHD. Participants in Arm B, will not be receiving donor lymphocyte infusion. It is possible that radiation, even without donor lymphocyte infusion, could activate the existing donor immune system, and so could potentially cause GVHD to develop or, if you already have GVHD, for it to get worse. Determining the safety of radiation, including risk of GVHD, in patients who have an allotransplant with or without DLI is an important part of this study. You will be carefully monitored for any signs of new or worsening GVHD. If you develop GVHD, you will receive treatment as soon as possible in an attempt to limit its severity.

Tumor Sampling

Needle Biopsies: During the study period we may attempt to obtain tumor samples by needle biopsy. Prior to radiation, we will evaluate the safety of obtaining a biopsy of a site that will be radiated and a site that will not be radiated. Your biopsies would be taken prior to radiation. The primary risks of biopsy depend on the site where the biopsy is taken. In general, risks include pain from the needle insertion and a slight risk of infection, bleeding, or injury to the nearby tissue. If you develop one of these complications you could require close monitoring, blood products, antibiotics or a surgical procedure to repair tissue injury. Specific risks of the procedure required for your tumor sampling would be discussed with you, and you will be asked to sign a separate consent form outlining these risks at the time of the procedure.

Tumor Removal Surgery: If it can be done safely and comfortably, you will have additional biopsies of these same tumors four weeks after radiation. If the tumor(s) can be removed with a minor surgical procedure, without significant risk of complications or discomfort, and without general anesthesia, we will ask the surgeons to remove the tumor. If minor surgery is not feasible, we will see whether it is safe for you to have additional needle biopsies, as done before radiation. Any biopsies will only be done if relatively easy and safe to do. However, all biopsy procedures carry some risk of infection, bleeding and/or discomfort. Abdomen and lung biopsies will not be performed for research unless they are done for a clinical reason.

The specific risks will be detailed for you prior to surgery or needle biopsy and you will be asked to sign a separate consent form outlining these risks. We will do our best to minimize these risks.

Superficial Tumor Sampling: If you have tumor in the skin or in the tissue just below the skin, you will have additional biopsies one or up to two of these superficial tumors. If it is safe and possible to perform with local anesthesia, we will ask the surgeons or dermatologists to remove the tumor with minor surgery. However, all surgical procedures carry some

MEDICAL RECORD**CONTINUATION SHEET for either:**

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risk of infection, bleeding and/or discomfort. The specific risks will be detailed for you prior to the superficial tumor biopsy and you will be asked to sign a separate consent form outlining these risks. We will do our best to minimize these risks.

Blood Draws - Blood will be drawn frequently during your treatment. Most of the blood draws will be to monitor your health during and after the radiation. In addition, some blood samples will be drawn for research purposes. These samples will be used to study how your immune system is affected by the radiation therapy, a graft-versus-tumor response and graft-versus-host disease (if it occurs). In general, 20 to 70 ml of blood (4 to 12 teaspoons) will be drawn at each clinic visit or hospital stay. Side effects of repeated blood sampling depend in part on how the blood is drawn. If your blood is drawn through a central venous catheter, risks include contamination of the catheter which would result in a serious blood stream infection, requiring admission to the hospital and giving you antibiotics through the vein; if blood is drawn through a needle into your skin, side effects could include pain and bruising in the area where the blood was drawn. Other side effects could include lightheadedness or, rarely, fainting. If you have too many blood samples taken, over time, your red blood cell count could drop (this is called "anemia"). As a precaution, we will check your red blood cell level, and give you iron treatment or a blood transfusion if needed.

Apheresis -The most common side effects of the apheresis procedure include pain and bruising at the IV sites. You may experience fleeting low blood pressure during the apheresis procedure; if this occurs, the settings on the apheresis machine can be modified to treat this problem. Other side effects include chills, numbness and tingling sensations ("pins and needles") of your mouth, fingers, and toes, anxiety, mild muscle cramps, and nausea; these side effects are due to the anti-coagulant (blood thinner) used to prevent your blood from clotting while you are on the apheresis machine. More serious, although uncommon side effects due to the blood thinner lowering your calcium levels include: low blood pressure, seizures, weakness and muscle spasms. These discomforts can be treated with calcium (Tums) by mouth or by stopping the procedure. After the donation, it is common to experience fleeting thrombocytopenia (low platelet count). Platelets help your blood to clot, however, your platelet count will not drop low enough from this procedure to be harmful.

Bone Marrow Aspiration and Biopsy - All patients will have a bone marrow examination, including biopsy and aspiration, as part of the initial evaluation for eligibility for the study and at four weeks after radiation. Additional bone marrow procedures will only be done if necessary to evaluate your tumor or a new problem with your blood counts. Bone marrow biopsy and aspiration is considered a minor procedure and is done routinely as part of evaluation for blood system cancers or other blood disorders. The skin and bone are numbed with an injection of local anesthetic, and needles are inserted through the skin in to the bone in your pelvis to remove a piece of bone (biopsy) and withdraw some of the liquid bone marrow (aspirate). While considered minor, any procedure in which the skin is broken carries a risk of bleeding or infection. The risks with this procedure, which is done under sterile conditions, are small. Additionally, because the skin and marrow are both quite sensitive, there will likely be brief pain at the time of injection of the numbing medicine and during the removal of the liquid marrow. Uncommonly, a bruise may form under the outer lining of the bone that remain tender up to a couple of weeks after the procedure.

Other Risks - Because this is an experimental therapy, there is also the risk of complications that cannot be foreseen. There is a risk that your cancer will continue to grow while we are evaluating this therapy. While you are on this study, we will avoid giving you other forms of cancer treatment if it is possible to do so, ideally for at least three months. This will allow us to evaluate whether the treatment is helping to control your cancer. However, if your cancer grows and threatens to cause a major problem for you, the study doctors may recommend that you be given standard therapy (chemotherapy, radiation therapy, immune therapies) to help control your cancer in addition to the radiation therapy and DLI being studied. You may have side effects from the standard therapy. If the doctors decide you should receive standard therapy in addition to the radiation and DLI therapy on this research study, the risks of the standard therapy you will receive will be discussed in detail with you, and you will be asked to sign an additional consent to receive the therapy. It is possible

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NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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that your cancer may get worse in spite of additional therapy, and this may lead to other complications, and possibly death.

Optional Studies

We would like to keep some of the tissue, blood and/or bone marrow that is left over [or that is collected] for future research. These specimen(s) will be identified by a number and not your name. The use of your specimen(s) will be for research purposes only and will not benefit you. It is also possible that the stored specimen(s) may never be used. Results of research done on your specimen(s) will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your tissue, blood and/or bone marrow can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and/or blood, then any tissue, blood and/or bone marrow that remains will be destroyed.

Please read the sentence below and think about your choice. After reading each sentence, check "yes" or "no" and initial next to the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My tissue, blood and/or bone marrow may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials _____

POTENTIAL BENEFITS OF PARTICIPATION

It is unknown at this time whether radiation with or without additional donor lymphocytes will improve survival or have any benefit for patients with blood system cancers. It is likely that the radiation will help shrink the areas that are included in the radiation. It is possible that the radiation will "train" your donor immune system to recognize tumors that are not radiated, and decrease the amount of your cancer even in areas that do not receive radiation. Your participation in this experimental treatment may also help us advance the understanding and treatment of blood system cancers, find new ways to improve the safety and effectiveness of allotransplant, and identify which patients are most likely to benefit from allotransplant.

RESEARCH SUBJECT'S RIGHTS

Participation in this experimental treatment is voluntary. You will be given a copy of the consent form for your records. . You may ask our staff to answer any and all questions about the experimental treatment and your disease, and we invite you to do so. Any new findings that relate to your experimental treatment will be discussed with you.

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.

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- 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 even if your insurance company does not cover them.
- 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.

Stopping Therapy

You may stop participating at any time. There are no penalties for stopping the experimental treatment. Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- 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.

You can stop taking part in the study at any time. 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.

Revision Copy

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OTHER PERTINENT INFORMATION

1. Confidentiality. When results of NIH research 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 for 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, Nancy M. Hardy, M.D., telephone: 301-451-1406. Other researchers you may call are: the Lead Associate Investigator, Deborah Citrin, M.D., telephone: 301-496-5457 or Deborah Citrin, M.D, telephone: 301-496-5457. For questions about Optional Studies, or if you choose to withdraw from participating in optional studies, please contact the Clinical Director, NCI at 301-496-4251. You may also call the Clinical Center Patient Representative at 301-496-2626.

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

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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.	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 Adult Patient/Legal Representative	_____ Date	_____ Signature of Parent(s)/Guardian	_____ Date
_____ Print Name	_____ 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		_____ Print Name	
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 13, 2013 THROUGH MAY 12, 2014.			
_____ Signature of Investigator	_____ Date	_____ Signature of Witness	_____ Date
_____ Print Name	_____ Print Name		