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
Amendment Approved by the IRB on 12/13/11 (C) Date Posted to Web: 06/01/13
DLI Control

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 is this study being done?
You have had an allogeneic hematopoietic stem cell transplantation (allotransplant) for a blood system cancer that had not responded to other therapies. While you may have had some response as a result of the new immune system, at this time you have tumor that is not being completely controlled by the transplant. Your doctor is planning to give you an infusion of your donor's lymphocytes in an attempt to boost your transplant's tumor activity.

Why are you being asked to take part in this study?
You are being asked to participate in this study to evaluate the immune cells in your blood before and after you receive the infusion of your donor's lymphocytes. We would like to compare the changes in your immune system with patients who are receiving radiation prior to the donor lymphocyte infusion. In this study, participants who are receiving treatment will have a single dose of radiation in hopes of boosting the donor immune system's power to fight the tumor. Patients without significant graft-versus-host disease (GVHD) and who have a way to get additional donor lymphocytes for

infusion, will receive the donor cells one day after the radiation. Because you will not receive radiation prior to the donor lymphocyte infusion, you will be in the control group of this study. In a clinical trial, the control group is the group that does not receive the new treatment (radiation) being studied. The control group will be compared to the group that receives the new treatment, to see if the new treatment works.

Description of Research Study

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 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?

Your participation as a Donor Lymphocyte Infusion (DLI) Control Subject will take place as follows (details follow in later sections):

- You will receive a DLI just as would if you were not on study.
- We will collect immune cells from your blood with a blood draw on the day of your DLI, before you receive the infusion, and about 3, 7, 14 and 28 days after the DLI. On Day 3, you will also have your immune cells collected through a procedure called apheresis, described in later sections)
- If you have biopsies as part of your treatment on another NIH protocol, that tissue may be used for research as a comparison to participants being treated with radiation on this study.
- Your medical records will be reviewed to determine whether you had a response to your treatment and/or had any problems from the DLI, such as graft-versus-host disease. You or your physician may be contacted 3 – 6 months after your DLI if we need to clarify any information.

Donor Lymphocyte Infusion: Participants who are enrolled as DLI Control Subjects 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 be monitored closely signs of toxicity from the DLI. You will need to come in to our "Day Hospital" for the DLI, three days after you receive the infusion, and at 1, 2 and 4 weeks after the infusion, 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.

Apheresis: Three days after you receive donor lymphocytes, your immune cells will be collected by a process known as apheresis three days after you receive donor lymphocytes. During apheresis, blood is withdrawn from a vein in your arm 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, it is not considered experimental, however, the comparison that will be made between the immune cells in your relative's blood and tumor to the immune cells that remain in your blood is considered research. Apheresis requires two needlesticks 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 groin area. This catheter would be removed after your immune cells are collected. The apheresis procedure typically requires less than two hours of collection. These stem cell collections will be processed and frozen, but they will be used for research rather than given to your sibling.

To donate cells by apheresis, you must be in generally good health. You must not have any personal medical history of psychiatric disorder, stroke, myocardial infarction (heart attack), or severe heart disease. If you are a woman, you will undergo a urine or blood test for pregnancy. Because of health risks to the fetus or baby, pregnant or lactating women will not be allowed to participate on this study.

On your next visit to the NIH Clinical Center, you will be seen by a physician and other members of the NCI transplant team. This visit can be coordinated with the collection date. The doctor will take your medical history, perform a physical exam, and explain the procedure. Additional tests will be performed on your blood to determine the health of your kidneys and liver, your ability to clot your blood, your blood levels, and your blood type.

You will also have blood draws to look at your immune cells before DLI, and three, seven and 14 days after DLI. Between two and five teaspoons of blood will be collected at these times.

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

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)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Alternative Approaches

If you choose not to enroll in this research study, you will still receive all planned therapy under your primary treatment protocol. Information about your immune system, tissue samples from any biopsies you have had or will have, and subsequent treatment response or GVHD after DLI treatment will not be evaluated under this protocol.

Risks or Discomforts of Participation

Donor Lymphocyte Infusion
DLI Control Subjects 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.

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 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. 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.

Blood Sampling: Side effects of repeated blood sampling include pain and bruising in the area where the blood was drawn, lightheadedness, or rarely, fainting. If you have too much blood taken over a prolonged period, your red blood cell count may drop (this is called "anemia"). However, the amount of blood you will donate (a total of approximately 100 ml or 20 teaspoons) is not going to make you anemic if you have normal production of red blood cells. As a precaution, we will check your red blood cell level, and give you iron treatment if this is indicated. If you take "over-the-counter" medications, such as aspirin, Advil (ibuprofen), or naproxen, it is important to tell your physician and stop these at least 72 hours prior to the apheresis procedure.

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 a fleeting drop in your platelet count. Platelets help your blood to clot; however, it is highly unlikely that your platelet count would drop low enough from this procedure to be harmful.

Intravenous Catheter Placement: Side effects of placing a temporary intravenous catheter in your femoral vein in your groin (if this is required), include bleeding, bruising, blood clot, infection, or pain in the area of insertion. This catheter will be placed by physicians with experience in this procedure; the above risks will be discussed by these physicians at the time of the catheter insertion. A separate consent form will be used if a femoral catheter is necessary.

Optional Studies

We would like to keep some of the blood that is left over from your apheresis procedure for future research. If you have had biopsies as part of your treatment on another NIH protocol, that tissue may be used for research as a comparison to participants being treated with radiation on this study. 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 specimen(s) 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 specimen(s). Then any specimen(s) that remain will be destroyed.

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

1. My blood and/or tissue may be kept for use in research to learn about, prevent, or treat cancer.
   □ Yes □ No Initials _____

Potential Benefits of Participation

Participation on this protocol will not directly benefit you. Hopefully, your donation of cells will contribute to our understanding of how the transplant immune system fights cancers. In addition, your participation in this research may contribute to the development of new approaches to allogeneic cell treatments for cancer. Another potential benefit includes possible diagnosis of a previously unknown medical condition that may discovered at the time you are screened to participate in this study.

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 even 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.

Participation in this research study is voluntary. You may discontinue your participation at any time. You will be given a copy of the consent for your records. There are no penalties imposed for withdrawing from the research study. You may ask questions of the staff, and indeed are encouraged to do so.

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, Nancy 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. 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.

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 MAY 13, 2013 THROUGH MAY 12, 2014.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____