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 5/13/13
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Donor

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?

Your relative has had an allogeneic hematopoietic stem cell transplantation (allotransplant) for his/her blood system cancer. While he/she may have had some response as a result of the new immune system, at this time he/she has tumor that is not being controlled by the transplant. Your relative has been offered an experimental therapy for the cancer. In this study, a single dose of radiation will be given to boost the donor immune response. 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. There are other treatment options that may be available to your relative, including chemotherapy (standard or experimental), other forms of immunotherapy, other kinds of radiation treatments, or therapy directed toward keeping your relative comfortable rather than trying to control the tumor.

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.

Why are you being asked to take part in this study?
Your relative will be among the first patients with blood system cancers (such as: Hodgkin's or non-Hodgkin's lymphomas, leukemias, and multiple myeloma) treated with this form of therapy. You have donated stem cells, the "seeds" of the bone marrow, to your relative. You may have also donated lymphocytes (DLI) as part of that treatment program. You would be donating lymphocytes to be given to your relative as part of this study, and also donating part of what is collected for research. Some patients with blood system cancers respond to DLI, which we believe is the result of the donor T cells traveling to the tumor and attacking it. Although the immune cells in your relative's blood and in the tumor come from you, they have likely gone through extensive changes in response to being in another person's body. Comparing the immune cells we find in your relative's blood and tumor to the immune cells that remain in your blood, which have not yet seen your relative's body or the tumor, may help us understand how these cells change and how to improve their tumor-fighting ability.

What will happen if you take part in this research study?
Your immune cells will be collected by a process known as apheresis. It is the same process that was used to collect your lymphocytes for DLI. Apheresis is the process where 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 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 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 relative.

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 as a donor.

Following apheresis, two tubes of your whole blood will also be collected for research.

On your next visit to the NIH Clinical Center, you will be seen by a physician and other members of the 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. Your blood will also be tested to see whether you have the following viruses: Hepatitis A, B, and C; T. Cruzi (Chagas agent), HTLV I-II, CMV (cytomegalovirus), adenovirus, EBV (Epstein-Barr Virus), HSV (Herpes Simplex Virus), toxoplasma and syphilis. Approximately 20 teaspoons of blood will be collected. 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 newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

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, your relative may still receive the radiation portion of this treatment. S/he may be able to receive donor lymphocytes as well, if there are additional donor lymphocytes available in our department of transfusion medicine. If not, your relative would not receive a DLI. Additionally, we would not be able to compare the immune cells from your relative's blood or tumor with the immune cells in your blood.

Risks or Discomforts of Participation

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.

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 reversed by administering 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, it is highly unlikely your platelet count would drop low enough from this procedure to be harmful.

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. These blood 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 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, the donor. Hopefully, your donation of cells will contribute to our understanding of how the 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 potential diagnosis of a previously unknown illness (such as viral hepatitis) 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 M. Hardy, M.D., telephone: 301-451-1406. You may also call 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 _____