INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0096 PRINCIPAL INVESTIGATOR: Dennis Hickstein, M.D.

STUDY TITLE: Pilot and Feasibility Study of Reduced-Intensity Hematopoietic Stem Cell Transplant for Patients with GATA2 Mutations

Continuing Review Approval by the IRB on 06/30/15
Amendment Approved by the IRB on 06/10/16 (T) Date Posted to Web: 06/11/16
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?

The purpose of this study is to test if stem cells from related or unrelated donors will be able to survive (engraft) after allogeneic stem cell transplantation (alloSCT) in patients with mutations the gene GATA2.

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

Because your relative has this disease (GATA2 deficiency), we are inviting him/her to participate in this research study, called: "Pilot and Feasibility Study of Reduced-Intensity Hematopoietic Stem Cell Transplant for Patients with GATA2 Mutations." This research study is for patients with this newly described disease that have a potential HLA-matched related donor, or unrelated donor identified through one of the bone marrow donor registries such as the National Marrow Donor Program. To be eligible to participate on this study you must match on at 5 out of 10 or 10 out of 10 Human Leukocyte Antigen (HLA) markers with your relative. HLA are proteins (or markers), found on most cells in your body. Your immune system uses these markers to recognize which cells belong in your body and which do not. To be a donor on this study, you must be 15-60 years of age.

How many people will take part in this study?

Up to 15 patients and their donors will participate in this study.

Description of Research Study

Your Evaluation for Donation of Cells

On your first visit to the NIH Clinical Center, you will see a physician and other members of the transplant team. The doctor will take your medical history, perform a physical exam, and explain the procedure. Approximately 4 to 10 teaspoons of your blood will be drawn to see if you and your relative are a good match. You and your relative must be a match on ten of ten genetic (hereditary) HLA tests.

To donate cells, you must be in good health. In particular, your blood will be analyzed to determine that you have no evidence in your blood for mutations in GATA2 for which your relative is receiving the transplant. This testing will be done in the laboratory of Dr. Steven Holland at the NIH, and you will be informed of the results and counseled as to the significance of the testing by Dr. Holland and his associates. Your lungs and your heart will also be tested. If you have symptoms of heart disease, you cannot be a donor. If you have had any heart operations such as a bypass graft or angioplasty, a cardiologist must evaluate you and state that you are not putting yourself at risk by donating cells. If you have had cancer you may not be eligible to donate your stem cells. You must not have any infection in order to be a donor. If you have history of rheumatic diseases or immune thyroid disorders, or a history of blood clots in the legs or lungs, you are ineligible to serve as a donor. Donors receiving experimental therapy or investigational agents are not eligible to serve as donors. If you have psychiatric disorder that prevents you from providing appropriate informed consent, this may prevent you from being a donor.

We will also test your kidneys and liver. As mentioned above, your blood will also be tested for Hepatitis B and C, T. Cruzi (Chagas agent), a virus called cytomegalovirus (CMV), adenovirus,

Epstein-Barr virus, herpes simplex virus, toxoplasmosis, and syphillis. As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection. Approximately 6-10 teaspoons of blood will be collected to perform these tests. If you have a positive Hepatitis B or C test the study doctor will determine if you are allowed to be a donor.

If you are female able to have children, you will have a urine pregnancy test. Because of health risks to the fetus or newborns, pregnant women cannot be donors. A donor who is breastfeeding must be willing and able to interrupt breastfeeding or substitute formula feeding for her infant during the period of G-SCF stimulation and for two days following the final dose of G-CSF if you are donating peripheral blood stem cells.

We will also look at your arms to make sure that the veins are suitable for the apheresis procedure (the procedure that collects your stem cells). If it is decided that your veins cannot be used for apheresis, it will be necessary to insert the I.V. into a large vein in your groin or neck. If you are donating bone marrow, you will be evaluated by the anesthesia service to determine your eligibility.

How Stem Cells Are Collected:

Your relative can receive the bone marrow of others to help them fight their cancer. That is why we are inviting you to donate cells from your bone marrow (called stem cells). If accepted by your relative's body, your stem cells will help their body begin to grow normal bone marrow cells.

If you are donating peripheral blood stem cells, before you donate your stem cells, you will have had several injections (shots) of a drug called filgrastim or G-CSF for short. G-CSF is a protein normally produced by your body in small amounts. The U.S. Food and Drug Administration and the National Marrow Donor Program have both approved G-CSF for use in stem cell collection. It causes your stem cells to travel from your bone marrow into your blood. Once the stem cells are in your blood, they can be taken from your veins using a process called apheresis. An I.V. (intravenous catheter) is placed into a vein in each of your arms. This will mean two needlesticks. Your blood will circulate through a machine that will collect and save your white blood cells and stem cells. The rest of your blood will go back into your body. The I.V. will be removed after the cells are collected. The whole procedure usually takes 4 to 6 hours. Apheresis avoids the need for an operation that would take the stem cells from your hipbone. It will be performed by trained personnel from the NIH Department of Transfusion Medicine.

If you are donating bone marrow cells, you will receive a general or a spinal anesthesia, and the bone marrow cells will be harvested from the back of your hips while you are under anesthesia.

The Donation:

Once it is decided that you can be a peripheral blood stem cell donor, you will then be started on G-CSF shots. You will receive them in the arm or thigh. We will teach you or a family member how to give you these shots at home. They will be given for a period of 5, 6, or 7 days. Usually, you will be ready for the apheresis procedure for stem cell collection on day 5. We usually collect enough stem cells at this time to be able to perform a transplant to your relative. Sometimes, it is necessary to continue the G-CSF shots and repeat the apheresis on the next day (day 6). In the unusual case that we still do not have enough cells to perform the transplant, we will ask that you rest for two weeks before repeating the G-CSF shots and apheresis. Within one week after the apheresis procedure(s), you will be checked for any side effects at the Outpatient NCI Clinic. If your stem cells are accepted (not rejected) by your relative's body but their disease is still not under control, you may be asked also to donate immune cells.

Birth control:

Men and women who are sexually active on this study must agree to use an effective form of contraception (examples include: intrauterine device (IUD), hormonal (birth control pills, injections, or implants), tubal ligation/hysterectomy, partner's vasectomy, barrier methods (condom, diaphragm, or cervical cap), or abstinence while participating in this study.

Collection of Stem Cells by Bone Marrow Harvest

If you are a haploidentical donor, you will donate bone marrow. If you are a 10 out of 10 matched related donor, you will donate peripheral blood stem cells. In the unusual event that you are unable to donate peripheral blood stem cells, bone marrow will be used as the source of stem cells. Such cases where peripheral blood stem cell cannot be obtained may involve donors who are medically not eligible to receive G-CSF, donors for whom the G-CSF results in a sub-optimal collection of stem cells, or donors who prefer the marrow procedure relative to the apheresis procedure. The stem cells will be collected from the bone marrow in the operating room using anesthesia. Bone marrow will be obtained from the hipbones in the same way that a standard bone marrow test is performed. Needles will be inserted into the hip bones and liquid bone marrow will be drawn into syringes. The amount that will be collected will be based on the size of the transplant recipient and the white blood cell count performed on the bone marrow during collection. Approximately 1-2 teaspoons of marrow is required for every pound of recipient body weight. As much as 3 pints may be needed. The anesthesia options (general anesthesia versus spinal anesthesia), risks, and procedures will be discussed with you prior to the bone marrow collection and you will sign a separate informed consent form at that time. You may be admitted to the hospital the night before the bone marrow harvest depending on the scheduled time of the collection. You will remain in the hospital for 1 night after the harvest.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?
Instead of being in this study, you have these options:

- As discussed above, there is an alternative approach to apheresis where you would have an operation on your hipbone to collect bone marrow cells, but most donors prefer collection of stem cells by apheresis. Also, stem cell collection by apheresis avoids the risks of general anesthesia ("putting you under") that is required with an operation. Usually, enough of your stem cells can be collected by apheresis. However, for haploidentical donors, bone marrow is the preferred source of stem cells.

Risks or Discomforts of Participation

The risks and discomforts of participating as a donor include the shots of G-CSF, blood drawing, and the apheresis procedure.

G-CSF can cause the following side effects (these side effects stop once G-CSF has been stopped):

Likely:	Less likely:	Rare:
• bone pain, • muscle aches, and • headache	• Some people who receive G-CSF shots and apheresis have a low number of blood platelets for a short period of time. Platelets help your blood to clot. However, low platelet count from G-CSF has not caused an increased amount of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure. • Other common lab abnormalities have been seen but are reversible once G-CSF is stopped.	• allergic reactions, • chest pain, and a lowering of the blood pressure. • There is a very rare side effect (1 in 486,000 people) of one's spleen rupturing due to G-CSF.

Side effects of blood being drawn include pain and bruising in the area where the needle was put in, lightheadedness, or rarely, fainting. When too much blood is taken, one's red blood cell count may drop causing anemia. However, the amount of blood that you will donate in this study (a total of 20 teaspoons) should not cause anemia. To be safe, we will check your red blood cell level. If we find that you have anemia, we will give you treatment for this condition (in the form of iron tablets).

Side effects of the apheresis procedure may include low blood pressure. If this happens, we will adjust the apheresis machine to correct this problem. Other side effects include tingling in the mouth, fingers and toes, and mild muscle cramps. These discomforts can be stopped by adjusting or stopping the procedure.

Side effects of a temporary I.V. in the groin or neck vein (if required) include bleeding, bruising, blood clot, or pain where the I.V. was placed. The I.V. will be put in only by physicians with experience in this procedure. They will discuss the risks with you before the procedure.

For donors who elect to donate stem cells by bone marrow harvest, other specific risks should be considered. These risks are the same for donors of any age. The main risk of marrow harvest relates to the need for anesthesia, which will involve either general anesthesia or spinal anesthesia. The specific risks of these procedures will be discussed in a separate consent procedure performed by the anesthesiology department. Bone marrow donation is very safe. The procedure commonly causes temporary pain and bruising over the sites where the marrow was collected. This usually can be managed with pain medicine (e.g., Tylenol) alone. Occasionally, stronger pain medicines like codeine are required. Rarely, infection or bleeding at the needle sites may occur. Anemia due to removal of large amounts of bone marrow may require treatment with iron or a blood transfusion. Serious side effects of bone marrow harvest are extremely rare and include fat embolism (like blood clots in the lungs) and risks of anesthesia.

Potential Benefits of Participation

By being a donor, you will provide a source of stem cells and immune cells for your relative. Hopefully, your donation of cells will help his or her cancer treatment. Your participation may also help advance our understanding of stem cell transplants and improve the way that we treat cancer. Knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

Participation in this research study is voluntary. You may stop your participation in the study at any time. There are no penalties for withdrawing from the study. The study doctor may remove you from this study if he/she feels it is in your best interest.

You will be given a copy of the consent for your records. We encourage you to ask our staff any questions that you have.
You will be told about new findings that pertain to this research study. If we are required to stop this study because of serious side effects, we will continue to provide care for you according to the study protocol.

What are the costs of taking part in this study?

There will be no cost to you to donate your stem cells and immune cells for your relative. You will not be paid for your donation; however, you may be eligible for partial travel and housing reimbursement while participating 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 your history and physical exam at no charge to you. This may include laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH). 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 Participation

Your doctor may decide to stop your participation for the following reasons:
- if he/she believes that it is in your best interest
- if you have side effects from the donation that your doctor thinks are too severe
- if new information shows that another treatment would be better for your relative.

In this case, you will be informed of the reason your participation 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 first.

Conflict of Interest

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

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

Your records will be reviewed by representatives of the National Cancer Institute.

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 other 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, Dennis D. Hickstein, M.D. Telephone: 301-594-1718; Blackberry: 301-795-8778 or Dr. Mark Parta240-409-4120.

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 JUNE 30, 2015 THROUGH JUNE 29, 2016.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name