INSTITUTE: National Cancer Institute

STUDY NUMBER: 03-C-0077 PRINCIPAL INVESTIGATOR: Michael R. Bishop, M.D.

STUDY TITLE: A Pilot Study of EPOCH-F/R Induction Chemotherapy and Reduced-Intensity, HLA-Matched, Related Allogeneic Hematopoietic Stem Cell Transplantation, with Cyclosporine & Methotrexate GVHD Prophylaxis for Refractory or Relapsed Hematologic Malignancies

Continuing Review Approved by IRB on 9/11/06
Amendment Approved by IRB on 6/22/07 (I)
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.

Description of Research Study

We are conducting a study of allogeneic stem cell transplantation for cancers (and certain pre-cancerous conditions) of the blood and immune system. In the past, stem cell transplantation was more commonly called "bone marrow transplantation." When "stem cells" for the blood and immune system are taken from one person (called the "donor") and given to another person (called the "recipient"), it is known as "allogeneic" stem cell transplantation. Stem cells are immature blood cells, like seeds; they can grow in the bone marrow and produce all of the cells needed for normal blood and immunity. Originally, stem cells were collected for transplantation by taking samples of bone marrow from the donor. Now, though, most allogeneic transplants are performed with stem cells collected from the donor's blood; this is often called "peripheral blood stem cell transplantation."

Allogeneic stem cell transplantation (SCT) has been used successfully to treat, and sometimes cure, many kinds of cancer or pre-cancerous conditions that originate in the blood or immune system cells. Chemotherapy drugs and/or radiation are used to eliminate most of the cancerous or abnormal cells from the recipient's system, along with many of his or her own stem cells and immune cells. Donor stem cells can then replace the recipient's stem cells in the bone marrow, restoring normal blood production and immunity; this process is called "engraftment". In this way, the recipient of an allogeneic SCT receives not just new blood cells but an entire new immune system. Immune cells from the donor are important not only to protect the transplant recipient from infections; these transplanted cells can also attack and eliminate the abnormal cells that caused the patient's disease. This type of immune attack is called the "graft-versus-tumor" (GVT) effect, and it is thought to be the main reason that allogeneic SCT can sometimes cure patients of these conditions.

Your relative has a disease for which allogeneic SCT may be an effective treatment. That is why we are inviting you to donate stem cells for transplantation into your relative. If accepted by your relative's body, your stem cells will help his or her body to grow normal blood and immune cells.

Your Evaluation for Stem Cell Donation

On your first visit to the NIH Clinical Center, you will have a complete medical history and physical examination in the NCI Medical Oncology Clinical Research Unit clinic. You will meet with members of the transplant team, who will review your medical history and explain the procedure for stem cell donation. About 5 to 10 teaspoons of blood will be drawn to check how closely you and your relative are genetically matched; you must match on all 6 of 6 genetic markers to enroll in the study. This blood sample will also be used to check the health of your kidneys and liver. We will also test for exposure to a variety of infections, including hepatitis B and C, human immunodeficiency virus (HIV, the virus that causes acquired immunodeficiency syndrome, or AIDS), syphilis, and a virus called cytomegalovirus (CMV). You will also be tested for the viruses for hepatitis A, HTLV-1 and -2, adenovirus, Epstein-Barr virus, herpes simplex virus, and a parasite called Toxoplasma. Staff from the NIH Department of Transfusion Medicine will also examine your arms to see if your veins are suitable for the apheresis procedure.

To donate cells, you must be in good health without evidence of any active or chronic infection. You must not have a medical history of stroke, myocardial infarction (heart attack), severe heart disease, or autoimmune disease such as rheumatoid arthritis. 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. Your blood will be tested for diseases that are spread through the blood. These diseases include HIV (the virus that causes AIDS) and hepatitis B and C. If you have a positive test for any of these diseases, we will inform you, and you will not be allowed to be a donor. If you are a woman, you will need to take a urine pregnancy test. Because of health risks to the fetus, pregnant women cannot be donors. Breastfeeding women can be donors only if they are willing and able to stop breast feeding while receiving filgrastim injections and having stem cells collected. Women can resume breast feeding after the stem cell collection is finished.

The Donation

Once it is decided that you can be a donor, we will schedule the procedure for stem cell collection. In order to collect your stem cells, we will give you injections (with needles) of a drug called filgrastim, also called "G-CSF" and "Neupogen". Filgrastim is a growth factor that our bodies normally produce in small amounts; it works like a hormone to stimulate the growth of our white blood cells, and it causes stem cells to be released from the bone marrow into the

blood. We use a highly purified filgrastim product that is produced in laboratories by genetically engineered bacteria. The U.S. Food and Drug Administration and the National Marrow Donor Program have both approved filgrastim for use in stem cell collection.

Four days before the scheduled stem cell collection, you will begin to receive filgrastim injections under the skin of your arm or thigh. We will teach you or a family member how to give these injections at home. They will be given for a period of 5, 6, or 7 days. Usually, you will be ready for stem cell collection on the fifth day of filgrastim injections. A blood test, requiring only a small amount of blood (two teaspoons), will help us decide that. Once the stem cells are in your blood, they can be collected from your veins using a process called "apheresis."

Apheresis is a standard procedure performed by trained personnel in the NIH Department of Transfusion Medicine. During apheresis, an intravenous catheter (IV) is placed into a vein in each of your arms. Your blood will circulate from one arm into a machine that collects and saves your white blood cells and stem cells. The rest of your blood will go back into your body through the other arm. The collection usually takes 4 to 6 hours, after which the stem cells are frozen and stored until the day of the transplant. The IV's will be removed after the cells are collected. If your arm veins are not large enough for apheresis, an experienced physician will temporarily insert a special IV into the femoral vein (in your groin) for the procedure. This IV would be removed after your stem cells are collected. If you require a femoral IV catheter for apheresis and more than one stem cell collection is needed (see below), you will be admitted to the NIH Clinical Center overnight for care of the catheter until the collection is completed (usually the next day). Apheresis avoids the need for an operation under anesthesia to take stem cells directly from the bone marrow in your hip bones.

We usually gather enough stem cells in a single collection to be able to perform a transplant to your relative. Sometimes it is necessary to continue the filgrastim shots and repeat the apheresis on the next day (day 6). Rarely, a third apheresis on day 7 could be required. If we still did not have enough cells to perform the transplant, we would ask that you rest for two weeks before repeating the filgrastim shots and apheresis. Within one week after the apheresis procedure(s), you will be checked for any side effects at the Outpatient NCI Clinic.

In rare cases, we are unable to collect enough stem cells to perform a transplant. If this occurs, you will be removed from the study; your relative will also be removed from the study before transplantation unless he or she has another suitable donor.

Sometimes we ask donors to donate additional cells. The additional cells can be used to help the transplant take over full production of blood and immune cells in your relative. These cells can also be used to "boost" your relative's new immune system and can sometimes enhance the graft-versus-tumor effect. Immune cells called "lymphocytes" are most commonly used in these situations. Donor lymphocytes are usually collected by apheresis without treating the donor with filgrastim before the cells are collected. However, in some situations you may be asked to undergo a course of filgrastim before lymphocyte collection.

Alternative Approaches or Treatments

Usually, enough of your stem cells can be collected by apheresis. Most donors prefer this method of collecting stem cells to having an operation on their hipbone to collect bone marrow cells. Also, stem cell collection by apheresis avoids the risks of general anesthesia ("putting you under") that come with an operation.

Risks or Discomforts of Participation

Filgrastim (G-CSF) may cause bone and muscle pain, headache, fever and chills, tiredness, and difficulty sleeping. There can be some pain, bruising and swelling at the injection site. Some people who receive filgrastim shots and apheresis have a temporary decrease in blood platelets (cells that help your blood to clot); however, this side effect has not led to an increased amount of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure. Rare side effects of filgrastim include allergic reactions with rash, itching, difficulty breathing, chest pain, and a lowering of the blood pressure. These reactions resolve once filgrastim has been stopped. Very rarely, filgrastim has been reported to cause swelling and rupture of the spleen, usually requiring surgery to remove the spleen, and resulting in some deaths. Filgrastim should not be used in patients with a history of having a heart attack, stroke, severe rheumatoid arthritis, or other serious autoimmune diseases. If you think that you may have any of these conditions, and you have not discussed them with your physician or any of the other NCI staff, be sure to notify them about these medical problems immediately.

Side effects of blood being drawn include pain and bruising in the area where the needle was placed, 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).

The apheresis procedure may cause low blood pressure. Other side effects include tingling in the mouth, fingers and toes, and mild muscle cramps; these side effects are due to the anticoagulant (blood thinner) used to prevent your blood from clotting while it passes through the apheresis machine. Adjusting or stopping the apheresis machine or administering calcium can correct these problems.

Possible side effects of a temporary IV in the femoral vein of your groin (if required) include bleeding, bruising, blood clot, or pain where the IV was placed. Only physicians with experience in this procedure will place a femoral IV catheter. They will discuss the risks with you before the procedure.

Potential Benefits of Participation

By participating in this investigational transplant protocol, you will provide a source of stem cells and immune cells for your relative. However, there are no direct benefits to your health from participating in this study. Hopefully, your donation of cells will help to improve your relative's cancer. Your participation may also help increase our knowledge of stem cell transplants and improve the way that we treat 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. You will be given a copy of the consent for your records. We encourage you to ask our staff any questions that you have.

## 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 people.

**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.

**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, Michael R. Bishop, M.D.; Building 10, Room 12N226, Telephone: (301) 435-2764. Other researchers you may call are: Robert Dean, M.D., (301) 435-5807; Daniel Fowler, M.D., (301) 435-8641; Claude Kasten-Sportes, M.D., (301) 435-5280; Kate Castro, R.N., M.S.N., (301) 435-5942.

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 _____

**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 _____

**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 _____

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM SEPTEMBER 11, 2006 THROUGH SEPTEMBER 10, 2007.**

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____