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

Latest IRB Review: Continuing Review 6/2/04
Latest Amendment Approved: Amend H 7/14/04
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.

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. The cancers that we will treat in this study include non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, and acute lymphocytic leukemia. We will also treat pre-cancerous blood conditions including myelodysplasia, idiopathic myelofibrosis, polycythemia vera, and chronic myelomonocytic leukemia.

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 them 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. Large doses of chemotherapy drugs and/or radiation were traditionally 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 only 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.

However, transplants performed with such high doses of chemotherapy or radiation have a high complication rate because they can cause serious side effects, including sometimes death. Also, a transplant recipient's own stem cells can be so severely damaged that if the donor stem cells are rejected, the patient's bone marrow cannot produce blood cells, usually leading to death. This study will use a newer method of allogeneic SCT that includes smaller, less toxic doses of chemotherapy beforehand. Allogeneic SCT performed in this way does not completely eliminate the recipient's stem cells and immunity; instead, it reduces them enough to prevent the donor stem cells from being rejected. This kind of transplant is often called "reduced-intensity", or "nonmyeloablative".

Another serious complication of allogeneic SCT can occur if donor immune cells recognize and attack the patient's normal tissues, damaging the liver, intestinal tract, and skin. This type of immune attack is called "graft-versus-host disease", or GVHD. It is the leading cause of death in patients who receive an allogeneic SCT. Although reduced-intensity transplants are safer in some ways because they use lower doses of chemotherapy, GVHD has still been a major problem with this approach.

We have been studying ways to make allogeneic SCT safer for patients with hematologic (or blood-related) cancers and pre-cancerous conditions. In a previous study of allogeneic SCT, we gave patients 1 to 3 cycles of treatment, called "induction chemotherapy," designed to control their cancer and gradually reduce their immunity before transplantation. The reason for using induction chemotherapy that reduces one's immunity was to prevent patients from rejecting their donor's stem cells after transplantation. Patients next received reduced-intensity chemotherapy, called a "conditioning regimen," followed by transplantation from a matched sibling. All patients received standard treatment with a drug called cyclosporine that is used to prevent GVHD. In addition, some patients received experimental treatment with a form of donor immune cell (called a "Th2 cell") that is intended to reduce the chance of getting serious GVHD. The primary goal of that study was to see if Th2 cells could be given safely to patients after allogeneic SCT. In our next study with Th2 cells, we plan to examine how well they work by comparing them directly with standard treatments to prevent GVHD.

Our results so far have shown two major ways to improve the method we used for allogeneic SCT in the previous study. Some patients' cancers grew even though they were receiving induction chemotherapy, and some other patients may

have received more cycles of induction chemotherapy than they needed to prevent graft rejection. Also, the number of patients who developed significant GVHD without receiving Th2 cells was greater than we expected. When our previous study was designed, many people believed that GVHD would be less of a problem after reduced-intensity allogeneic SCT. Since then, the experience here and at other transplant centers has shown that GVHD can be as great a problem as it is with traditional transplant approaches.

The purpose of this study is to improve upon the results described above. Our first goal is to try to decrease GVHD, using standard treatments that are known to prevent it effectively. To accomplish this, we are adding a drug called methotrexate to the cyclosporine used in the earlier study. These drugs are widely used together to prevent GVHD after allogeneic SCT, and many people consider them to be the standard drug treatment for GVHD prevention. We hope to show that this drug combination offers better protection against GVHD after the kind of reduced-intensity transplants we perform. In addition, we want to learn if using cyclosporine and methotrexate changes the way that donor stem cells engraft after allogeneic SCT. Also, we have increased the induction chemotherapy in ways that we believe will control patients' cancers better, without causing excessive side effects or interfering with the transplant. This study will help us determine if the changes in the induction chemotherapy make it more effective at controlling cancers before patients undergo transplantation.

OVERVIEW OF THE TREATMENT PLAN

Treatment on this study will take place as follows (details are included in later sections):

- First, we must establish proof of a genetic match between you and your donor.
- Next, we will collect your donor's stem cells and immune cells by an apheresis procedure.
- You will receive one, two, or three cycles of induction chemotherapy to treat your disease and to suppress your immune system.
- After you have finished receiving induction chemotherapy, you will receive 4 days of chemotherapy called the "conditioning regimen" to prepare you for the transplant
- Three days after this chemotherapy, you will receive the transplant with your donor's stem cells and immune cells.
- When your condition is stable, you will be discharged from the hospital and be seen frequently as an outpatient.
- You will continue on medications to lower the risk of GVHD and infections.
- You may receive additional donor cells, called a "donor lymphocyte infusion", after the transplant.
- You will visit our clinic regularly for the first six months after the transplant, and then less often for at least five years.

Pre-Transplant Evaluation of You and Your Donor

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 transplant procedure. About 5 to 10 tablespoons of blood will be drawn to check how closely you and your donor 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 the parasite Toxoplasma. You will asked to collect 24 hours of your urine to measure your kidney function. In addition, you will have a special breathing test, a test for heart health, and several X-ray studies. If you have lymphoma, we will

obtain a nuclear medicine test called a positron emission tomography (PET) scan. You may also have a bone marrow aspiration and biopsy. This test is performed by numbing the iliac (hip) bone with a local anesthetic called lidocaine. A small cut will be made in the skin, a needle is inserted into the iliac bone, and about two tablespoons of liquid samples are removed from the bone marrow through the needle. A small fragment of the bone marrow may also be removed with the needle. You will also undergo a dental evaluation and meet with a social worker. You will be encouraged to name someone as your "durable power of attorney". This should be someone whom you trust to make medical decisions for you if you become physically or mentally unable to make your own treatment decisions. You should know that being in this study may keep you from being in other research studies that limit the number or types of treatments that you are allowed to have received previously.

The Central Venous Catheter

If you do not already have one before you enroll in this study, you will receive an intravenous line called a central venous catheter that can be used throughout your transplant procedure and follow-up treatment. This kind of catheter is sometimes called a "Hickman catheter". It will be used to give you chemotherapy, donor cell products, transfusions, and other medications such as antibiotics. It can also be used for drawing blood samples for tests. Since blood will be drawn often during your treatment (about 4 to 10 teaspoons of blood, at least once daily during your hospitalization for transplantation and about 2 to 3 times per week at other times), the catheter will make it easier and less painful. Most of the blood will be used to check on your health during and after your treatment. Some blood will be drawn for research.

Your catheter will be placed in the upper part of your chest and tunneled under the skin into a neck vein. If the catheter becomes infected or clogged, it can be replaced. It will be flushed once daily to prevent clogging. The nursing staff will teach you how to do this yourself.

Induction Chemotherapy

In this study you will receive one, two, or three cycles of "induction chemotherapy" to treat your disease and to suppress your immune system. This chemotherapy will include the following drugs: fludarabine, cyclophosphamide, etoposide, doxorubicin, vincristine, and prednisone. Some patients with lymphomas and certain forms of leukemia may receive an additional drug called rituximab. We will test a biopsy specimen from your cancer to determine if you should receive rituximab with your induction chemotherapy. To start, you will receive common doses of these drugs for five days followed by a 16-day rest period. The effect of the chemotherapy on your immune system and on your disease will determine how many cycles of induction chemotherapy you receive. If your immune system is very suppressed after one cycle, you will go directly to the transplant. If your immune system is not very suppressed and your disease is not growing after one cycle of induction chemotherapy, you will receive one or two more cycles (5 days of drugs followed by 16 days of rest per cycle). If your disease is grows in spite of the induction chemotherapy, or if your white blood cell count (neutrophil count) remains low for a prolonged period after induction chemotherapy, then the induction chemotherapy will be stopped, and you will go directly to the transplant. At most, you will receive 3 cycles of this chemotherapy.

Transplantation of the Blood Stem Cells From Your Donor

Rarely, we may be unable to collect enough stem cells to perform the transplant. If this occurs, your donor will be removed from the study; you will also be removed from the study before transplantation, unless you have another suitable donor.

If we have collected enough stem cells from your donor, you will be admitted approximately six days before transplantation to the Experimental Transplantation Unit of the NCI's Medical Oncology Clinical Research Unit at the NIH Clinical Center. You will receive 4 days of transplant chemotherapy called the "conditioning regimen," which will permit you to accept your donor's stem cells. This regimen uses fludarabine and cyclophosphamide at higher doses than were given as part of induction chemotherapy. With this chemotherapy, we also give a drug called "mesna" to protect the bladder from injury by cyclophosphamide (explained further on page 5, under "Risks or Discomforts of Participation").

Three days after completing this chemotherapy, you will receive the stem cell graft from your donor. Your donor's stem cells will be infused through one of your central venous catheters. This is referred to as day 0. You will be monitored very closely after transplantation for possible complications from your transplant (e.g., infections), which are described below. You will receive standard supportive care such as antibiotics, growth factors (G-CSF), transfusions, and intravenous nutrition to prevent or treat these problems. Blood will be drawn frequently during your treatment. Most of the blood draws will be to monitor your health during and after the chemotherapy and transplant procedure. 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 transplant chemotherapy, the stem cell transplant itself, and graft-versus-host disease (if it occurs). In general, 20 to 50 ml of blood (4 to 10 teaspoons) will be drawn an average of 2 to 3 times per week.

Once your stem cells have engrafted and you feel strong enough, you will be discharged from the hospital and followed closely as an outpatient. The average hospital stay is three to four weeks; however, this varies from person to person. You will be required to remain in the Washington, D.C. area for approximately three months after transplantation to monitor for complications. It is possible that you will require re-admission to the hospital for complications. You will be followed closely in the NCI clinic for the first six months after transplant, and then you will be followed less frequently for at least five years.

In most cases you and your donor are not completely the same genetically (i.e., identical twins). Because you are not identical, it is possible that your donor's stem cells will recognize certain body tissues as foreign (such as the skin, the gut, and the liver) and attack them. This attack by your new immune system is referred to as graft-versus-host disease (GVHD) and at times can be life-threatening. You will receive the drugs cyclosporine and methotrexate to help prevent GVHD. Methotrexate is given for four doses intravenously (through the vein), shortly after the transplant. Cyclosporine is given either intravenously or by mouth for approximately six months after transplant.

In allogeneic SCT, donor T lymphocytes are the main cells that contribute to engraftment of the transplanted cells and to the graft-versus-tumor effect. After the transplant, tests may show that your blood and immune cells have not fully converted to your donor's type. This is known as "mixed chimerism". If this occurs, then your cyclosporine will be tapered (lowered) to help the process of completely changing your blood and immunity to your donor's type. This is called "full donor chimerism". Sometimes, additional lymphocytes from your donor may be needed to reach a state of full donor chimerism. These may be given as an intravenous infusion; this is called a "donor lymphocyte infusion", or DLI. If your cancer is still present or grows after the transplant, cyclosporine may be tapered in an attempt to permit a stronger graft-versus-tumor effect. After this, if there are no signs of significant graft-versus-host disease (GVHD), then

you may receive one or more DLI at increasing doses. These DLI are intended to "boost" your new immune system and can enhance the graft-versus-tumor effect in some, but not all, patients. DLI can sometimes lead to the development of GVHD, so we will monitor you very closely for signs of GVHD after these infusions. If you experience significant GVHD after a DLI, we will give you treatment for GVHD, but you will not receive any further DLI. You may also be eligible to receive chemotherapy or other standard therapy after the transplant if your cancer requires further treatment. This therapy can be given alone or combined with DLI.

Frequent Follow-up at the NCI in the First Year After Transplant

If you are in good health after the three month post-transplant period, you will then be allowed to return home to the care of your primary physician. You will be required to return monthly until approximately six months after transplantation to monitor for late transplantation complications including GVHD and infection. Thereafter you will be seen here every three months until you are two years after transplant. During these visits you will be scheduled to have bone marrow aspirates and biopsies, blood draws, and other appropriate tests to monitor disease status. You will also have additional blood tests to study how your immune system recovers after the transplant.

This treatment is likely to result in sterility (the inability to produce children). Still, it is unknown what effects this treatment may have on an unborn child. For this reason you will be asked to practice an effective method of birth control while you are participating in this study.

Alternative Treatment

To be eligible for this study, you must have already received the standard or conventional treatment for your disease. You may consider other treatments such as other forms of chemotherapy, radiation, surgery, or immune therapies. In some cases, you may be eligible for an autologous bone marrow or stem cell transplant, in which your own stem cells are returned to your body following high dose treatment. Instead of participating in a research study such as this, you may also be eligible to receive a standard allogeneic transplant with high dose chemotherapy and/or radiation to completely wipe out your bone marrow before donor cells are transplanted. Another option is not to receive any further therapy at all. You should discuss with your referring doctor and your doctors at the NCI whether or not any of these other treatments might be a reasonable treatment choice for your disease.

Risks or Discomforts of Participation

Risk of Death from Allogeneic SCT: Patients undergoing allogeneic SCT are at risk of dying from the transplant procedure and its possible complications. In some studies of allogeneic SCT, as many as half of the patients have died as a direct result of the transplant or its complications. In transplant studies similar to this one, between 10 and 30 percent of patients have died from the transplant procedure. The risk of death or other complications can vary greatly, depending on the age of the patient, the way the transplant is performed, and other factors.

Bone Marrow Aspiration and Biopsy: This procedure usually causes only mild pain for a short time at the biopsy site. Very rarely, bleeding or an infection may occur at the biopsy site.

Central Venous Catheter: Side effects of placing a central venous line in your chest wall include bleeding, bruising, blood clot, or pain in the area of insertion. This line will be placed by physicians with experience in this procedure; these physicians will discuss the above risks at the time of the line insertion. Rarely, placement of a central venous

catheter can result in a collapsed lung. If a collapsed lung occurs, it may require hospitalization and temporary insertion of a plastic tube in your chest to re-expand the lung.

Induction Chemotherapy: The chemotherapy agents that will be administered on this protocol include fludarabine, cyclophosphamide, etoposide, doxorubicin, vincristine, and prednisone. Patients will receive all of these drugs as part of induction chemotherapy; in addition, induction chemotherapy will include rituximab for some patients, as discussed before. You will receive one to three cycles of this chemotherapy; each cycle will last 21 days, including five days of moderate doses of these drugs, followed by a 16-day rest period. It is important for you to know that this type of induction chemotherapy is likely to reduce your white blood cells for many days. This will place you at increased risk of infection. Such infections can be very serious and may result in death. For this reason, if you develop a fever higher than 101° F, you must see your doctor immediately. If necessary, you will be treated with antibiotics. Also, this chemotherapy will likely cause your platelet count to fall. This may place you at increased risk of bleeding. If your platelet count becomes dangerously low, you will receive platelet transfusions. Because chemotherapy and other medicines used in this study can pose a risk during pregnancy, birth control measures are required for patients on the active treatment portion of this study. Because the induction chemotherapy on this protocol is a new combination of drugs, there is a chance that unexpected toxic effects will occur. The following are known specific risks of each drug used:

Fludarabine can reduce your immune T cells, which can increase your risk of developing infection. Fludarabine can also cause nausea, vomiting, diarrhea, loss of appetite, swelling, skin rashes, internal bleeding, headache, fatigue, nervous system toxicity, and lung injury. These side effects are uncommon at the doses of fludarabine used in this study.

Etoposide may cause diarrhea, nausea and vomiting, loss of hair, decreased blood counts, decreased blood pressure, shortness of breath, mouth sores, and leukemia.

Prednisone may cause stomach or bowel ulcers, elevated blood pressure, diabetes, increased risk of infection, weight gain, mood change, thinning of bones with increased risk of fracture, and rounding of the face.

Vincristine may cause numbness and weakness of feet and hands, constipation, hoarseness and pain in the jaw, arms, and legs. In general, these side effects improve or resolve when the drug is stopped. Skin and muscle damage could occur that may require surgery if vincristine leaks out of the catheter into surrounding tissues.

Doxorubicin may cause decreased blood counts, hair loss, heart damage, and bleeding in the bowel or stomach. Skin and muscle damage could occur that may require surgery if doxorubicin leaks out of the catheter into surrounding tissues.

Cyclophosphamide can also result in nausea, vomiting, and hair loss. It can result in fluid and electrolyte abnormalities. It can also cause bleeding in your bladder (hemorrhagic cystitis). You will receive intravenous fluids and a drug called mesna to prevent bladder injury when you receive cyclophosphamide at high doses as part of the conditioning regimen. Cyclophosphamide can also cause damage to heart muscle, which can lead to heart failure.

Rituximab can cause serious, sometimes fatal allergic reactions in rare cases. Most reactions usually can be prevented or successfully treated with medications and slowing or stopping the rituximab infusion. Mild reactions are common during rituximab infusions, including fevers, chills, itching, and skin rash. Other common reactions are mild shortness of breath, low blood pressure, elevated blood pressure, nausea, vomiting, throat swelling, headache, muscle aches, and dizziness. Rarely, rituximab has caused kidney damage and serious chemical disturbances of the blood by killing a very

large number of tumor cells quickly. Sometimes this complication has required dialysis, and some cases have been fatal. Severe, sometimes fatal skin reactions have been reported after rituximab in a small number of patients.

Filgrastim (G-CSF) may cause bone and muscle pain, headache, fever and chills. There can be some pain, bruising and swelling at the injection site. In rare cases it can cause an allergic reaction with rash, itching, and difficulty breathing. Very rarely, filgrastim has been reported to cause swelling and rupture of the spleen, requiring surgery and resulting in some deaths.

Transplantation Chemotherapy: The main side effect of fludarabine and cyclophosphamide at these doses is severe bone marrow and immune system suppression, which decreases the production of red blood cells, white blood cells, and platelets. The doses that will be used could cause prolonged marrow suppression, if the transplanted stem cells were rejected. Until your new stem cells start to produce adequate numbers of blood cells, you will be at significant risk for infections, bleeding and severe fatigue. These will be treated with antibiotics and transfusions. Other potential side effects of fludarabine and cyclophosphamide are described above.

Mesna can cause nausea, vomiting, and diarrhea. A rare but sometimes fatal complication of mesna is the development of cough, shortness of breath, and fever with lung injury leading to scarring.

Cyclosporine: Cyclosporine can cause nausea, vomiting, tremor, high blood pressure, unsteady gait and headache. In some instances it can result in seizures, temporary blindness, and kidney failure. Cyclosporine levels will be carefully monitored to prevent these complications. In addition, cyclosporine suppresses the immune system in order to prevent GVHD. Immune suppressing drugs leave patients at increased risk for infection and in theory may reduce the chances for the allogeneic transplant to be effective.

Stem Cell Infusion: Because the donor cells are frozen in a drug called DMSO to protect them from the effects of freezing, patients receiving thawed cells often will develop toxicity from the DMSO. This toxicity is usually mild and temporary. DMSO toxicity may include fever and allergic reactions, such as skin rash, itching, difficulty breathing, and drop of blood pressure. If these reactions occur, they can be easily treated with IV fluids and medications.

Methotrexate: The major side effect associated with methotrexate primarily involves the gastrointestinal tract (mouth, esophagus, stomach, and intestines). Severe mouth sores can occur. Other gastrointestinal symptoms include nausea, vomiting, and diarrhea. Methotrexate can cause temporary inflammation of the liver. Methotrexate can delay the recovery of blood counts after the stem cells are infused. There is a small chance that methotrexate could prevent the donor cells from engrafting (see below).

Other Medications: Patients will routinely receive several other drugs to prevent or treat various infections and other transplant-related complications. These medications and their common side effects are listed as follows.

Diphenhydramine may cause tiredness, dizziness, upset stomach, disturbed coordination, dry mouth, flushing, or difficulty urinating.

Valacyclovir can cause nausea, vomiting, headache, dizziness, abdominal pain, bone pain, allergic reactions, mild liver inflammation, kidney injury, and abnormal nervous system function.

Fluconazole can cause nausea, vomiting, headache, skin rash, abdominal pain, and diarrhea. Rare but sometimes serious liver toxicity has also been reported. Fluconazole can increase the blood levels of other drugs, which can increase their effectiveness and/or their side effects.

Trimethoprim/sulfamethoxazole (Bactrim) may cause nausea, vomiting, loss of appetite, allergic skin rashes, and suppression of bone marrow function. Rare but severe reactions may affect the skin and bone marrow; these have sometimes been fatal.

Medroxyprogresterone acetate (Provera) can cause nausea, breast tenderness, lactation, allergic skin reactions, increased acne and body hair growth, scalp hair loss, fluid retention, depression, jaundice, vaginal spotting, changes in cervical secretions, and blood clots.

Immune Globulin Intravenous (IGIV, or IVIG) can rarely cause severe allergic infusion reactions, including anaphylaxis. More common reactions include flushing, chest tightness, chills, fever, dizziness, nausea, sweating, backache, leg cramps, skin rash, and decreased or elevated blood pressure. IGIV can also cause abnormal kidney function or kidney failure. Inflammation of the membranes that surround the brain and spinal cord (called "meninges") has been reported uncommonly. Because IGIV is produced from human plasma (blood), there is a low risk of transmitting viruses and other infectious agents. There is also evidence that IGIV may rarely contribute to the development of blood clots, sometimes leading to heart attacks or strokes.

Engraftment: There is the possibility that your donor's stem cells will be rejected or fail to engraft. We believe that the chance of this occurring is less than 1%. You will receive the growth factor filgrastim to help the cells engraft. In the event that your cells do not engraft, we will ask your donor to donate more cells. Filgrastim can cause the following side effects: bone pain, muscle aches, headache, fatigue, and insomnia. Other more rare side effects of filgrastim include allergic reactions, chest pain, and a decrease in blood pressure after the first injection; these reactions resolve once the filgrastim has been stopped.

Graft-Versus-Host Disease (GVHD): You will remain at risk for the development of GVHD for the remainder of your life after transplantation. GVHD occurring within the first 100 days after transplantation is referred to as acute GVHD. Roughly 2 out of 3 patients undergoing this form of transplantation develop acute GVHD when cyclosporine alone is used to prevent it. In other studies using cyclosporine and methotrexate together, acute GVHD usually affects about 1 of every 3 patients. Acute GVHD most commonly attacks the liver, intestines, and skin. Symptoms of skin GVHD may be as mild as a rash with itching or as severe as blistering and loss of the skin. Symptoms of intestinal GVHD may be as mild as heartburn and mild diarrhea and as severe as cramping abdominal pain and bloody diarrhea. Liver GVHD may be as mild as slight disturbances in liver function to severe as jaundice with liver failure. Mild GVHD (skin rash only) can be managed with topical steroid creams. Severe GVHD can be lethal and needs to be treated aggressively. Treatment of severe GVHD initially includes suppression of the immune system, usually with intravenous steroids. Suppression of the immune system increases the risk of infection.

A delayed form of GVHD, known as chronic GVHD, may occur after day 100 post-transplant. Some degree of chronic GVHD affects about half of patients after transplantation. It most commonly attacks the skin, the liver and the intestines, but it may also affect other organs such as the lungs, the eyes, the muscles, the joints, and the bone marrow. Symptoms of chronic GVHD may include dryness of the mouth and eyes, a loss of appetite, weakness, hair loss, weight loss, liver damage (including jaundice), and lung damage leading to shortness of breath and cough. Patients with severe chronic GVHD are also at increased risk of infection and dying. Chronic GVHD is also treated with drugs that suppress the immune system such as steroids. This again increases the risk of infection.

Late Transplant Complications: There are a number of potential complications that could occur long after transplantation. These complications could affect any organ in the body including the heart, lungs, kidneys, liver, muscles, and brain. Rarely, patients who receive an allogeneic SCT are at risk for developing a second cancer such as leukemia or lung cancer.

Potential Benefits of Participation

By being in this study, you will receive evaluation and treatment of your cancer. All of the evaluations, tests, and treatments that you receive at the NIH will be free of charge to you. The chemotherapy you receive may cause improvement in your cancer, although it will not result in a cure by itself. The allogeneic SCT may improve the chance that your disease will enter into a long remission and possibly be cured. However, you should understand that this cannot be guaranteed. In addition, your participation in this protocol may contribute to advances in the understanding and development of new approaches to the use of allogeneic SCT for the treatment of 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 JUNE 2, 2004 THROUGH DECEMBER 2, 2004.

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