INSTITUTE: National Cancer Institute

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

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

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Recipient

INTRODUCTION

We are asking 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.

If you are signing this consent for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

We are conducting an experimental research study of allogeneic stem cell transplantation (SCT) from HLA-matched related or unrelated donors for patients with mutations in GATA2. 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. Another purpose of this study is to test if the treatment with allogeneic SCT is safe.

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

Because you have this disease (GATA2 deficiency), we are inviting you 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 has a relative donor, unrelated donor, or umbilical cord blood 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 be 12-60 years of age and must match on 10 out of 10 or 5 out of 10 HLA markers with your potential related donor, match 10/10 or 9/10 HLA markers with your potential unrelated donor, or match 4 out of /6 HLA markers with your umbilical cord blood donor. Human Leukocyte Antigen (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. The better the match between the donor's HLA markers and your HLA markers, there may be less risk of some types of side effects. This is explained in more detail below. In this study, we will accept patients 12 to 60 years of age, however, individuals that are 12-17 years of age must have myelodysplastic or pre-leukemic changes to the bone marrow along with changes in the chromosomes of the bone marrow cells.

How many people will take part in this study?

Up to 15 patients and their donors will take part in this research study.

Description of Research Study

"Stem cells" are immature blood cells, like seeds; they grow in the bone marrow and produce all of the cells needed for normal blood and immunity. When these stem cells are taken from one person (called the "donor") and given to another person (called the "recipient"), it is known as "allogeneic" stem cell transplantation. Originally, stem cells were collected for transplantation by taking samples of bone marrow from the donor. This was commonly called "bone marrow transplantation." Now, most allogeneic transplants use 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 immune diseases, cancer, or pre-cancerous conditions that develop in 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 most 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 the normal jobs of the bone marrow – growing blood cells and immune cells; this process is called "engraftment". In this way, an allogeneic SCT provides not only new blood cells but an entirely new immune system. Immune cells from the donor are important not only to protect the transplant recipient from infections; these transplanted cells can sometimes destroy 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 cures some patients of these conditions.

If the recipient's immune system remains strong enough after large doses of chemotherapy or radiation, it may attack and destroy the donor's cells after the transplant. This is called "graft rejection." When this happens, the transplant recipient's own stem cells may be so severely damaged after chemotherapy or radiation that they cannot produce blood cells, usually leading to death. Another serious complication can occur if donor immune cells recognize and attack the recipient's normal tissues, damaging the liver, intestinal tract, and skin. This type of immune attack is called "graft-versus-host disease", or GVHD.

Graft rejection or GVHD after allogeneic SCT are less likely when the transplant recipient and donor are very similar genetically. To measure how genetically similar a recipient and donor are, both persons are tested to identify protein markers on the surface of their blood cells and other body tissues. As described previously, these markers are called "human leukocyte antigens", or HLA. A person inherits half of his or her HLA markers from each parent. Your immune system uses HLA proteins on your body's cells to tell the difference between normal, healthy tissues and foreign organisms like bacteria or viruses. Differences in HLA proteins between a donor and recipient make it more likely that one person's immune system will recognize the other person's cells as foreign, causing graft rejection or GVHD. A donor and recipient who share all 10 of their HLA markers are called "HLA-identical". A transplant from an HLA-identical sibling (brother or sister) has a lower chance of graft rejection or GVHD, compared with other donors for allogeneic SCT. Many people have diseases that could be treated with allogeneic SCT, but only 20-30% of people have HLA-identical sibling donors. For some people without HLA-identical sibling donors, a partially matched related donor or a HLA-matched unrelated donor can be used, but the risk of graft rejection and GVHD is higher. If a 10/10 matched related donor, a 5/10 matched related donor, or a 10/10 matched unrelated donor cannot be identified, a 9/10 matched unrelated donor or a closely compatible umbilical cord blood donor may be used. The risk of graft rejection using a 9/10-matched unrelated donor, a partially matched related donor or umbilical cord blood donors is higher. The risk of GVHD is higher with a 9/10 matched unrelated donor or a partially matched related donor, but the risk of GVHD is lower with umbilical cord blood when compared to a matched unrelated donor. In this research study, we will use the best match to perform an allogeneic SCT to help treat your disease.

Reduced-Intensity Allogeneic Stem Cell Transplantation (RIST)

In the past, allogeneic SCT was done after giving very high doses of chemotherapy and/or radiation. This intensive treatment was used to destroy as much of the recipient's disease as possible, and it also helped to prevent graft rejection by weakening the recipient's immune system. However, such intensive chemotherapy or radiation can cause serious or even fatal side effects. Because of these risks, only relatively young and healthy patients were considered for this form of treatment. A newer method uses smaller, less toxic doses of chemotherapy and/or radiation before allogeneic SCT. This method is often called "reduced-intensity", or "nonmyeloablative". It was first studied in patients who could not receive high-intensity ("myeloablative") allogeneic SCT because of their age or other medical conditions. In reduced-intensity stem cell transplants (RIST), the recipient's stem cells and immunity are not completely

eliminated, but they are weakened enough to prevent the donor's cells from being rejected. In most studies of RIST, serious complications are less common than for myeloablative allogeneic SCT. However, GVHD can still be a significant problem with RIST. Also, graft rejection and relapses of disease have happened more often in some studies of RIST than with myeloablative transplants. These problems may have occurred because the lower doses of treatment in RIST can leave the recipient's immune system strong enough to resist being replaced completely by the donor's cells, and the disease may survive after reduced-intensity chemotherapy or radiation than after myeloablative treatment.

We have been studying RIST to try to improve the results of allogeneic SCT for patients with hematologic (blood-related) cancers and pre-cancerous conditions. In animal models we have used a low dose of radiation therapy before transplantation to help the donor cells to engraft.

This experimental research study will use chemotherapy and low dose radiation therapy to decrease the chance of graft rejection after RIST from a matched related or unrelated donor and to try to decrease the overall side effects of the transplant.

Prevention of Graft-Versus-Host Disease

A clearly superior combination of drugs to prevent GVHD regimen has not been established in patients who have received SCT from HLA-matched related or unrelated donors. Preliminary studies indicate that a drug called sirolimus is beneficial in matched related donors. The best results for matched unrelated donors that have been reported in the medical literature are with the combination of drugs called tacrolimus, methotrexate, and sirolimus. In this study, we will use the combination of tacrolimus and sirolimus to try to prevent GVHD. Partially matched related donor recipients will also receive a Chemotherapy drug called cyclophosphamide post-transplant.

What will happen if you take part in this research study?

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

- First, we must establish proof of a genetic match (at least 10 out of 10 HLA genes for matched related donors; at least 9/10 HLA genes for matched unrelated donors; at least 5/10 HLA genes for a partially matched related donor; at least a 4/6 match for umbilical cord blood units) between you and your potential related donor or unrelated donor. Approximately 5-10 tablespoons of blood will be drawn, often this has already been performed at your home medical office, prior to a visit to the NIH, or it will be performed at the NIH Clinical Center.
- If you are going to receive matched related donor stem cells, we will arrange for the collection of the stem cells from your donor. Because pediatric donors will not be eligible to participate in this study, pediatric subjects will not receive their transplant from a pediatric sibling. This may result in a small increase in the incidence of GVHD.
- If you are going to receive matched unrelated donor stem cells, we will arrange to have your donor's stem cells collected at a center in cooperation with the National Marrow Donor Program, and shipped to the NIH.

- If you are going to receive umbilical cord blood cells, we will arrange to have the umbilical cord blood donor stem cells shipped to the NIH.
- Depending on the source of your donor cells, you will receive several doses of pre-transplant chemotherapy and radiation therapy. This combination is called "conditioning regimen" and it is given to prepare you for the transplant. The various "conditioning regimens" are described below:
    - If you are going to receive umbilical cord blood cells, you will receive one infusion into your vein (IV) of a chemotherapy drug called cyclophosphamide 6 days before the transplant. You will receive infusions of another chemotherapy drug called Fludarabine on days -6, -5, -4, -3, and -2 before the transplant.
    - If you are receiving a matched related or unrelated donor cells, you will receive infusions through the vein of a chemotherapy drug named Fludarabine on days -4, -3, and -2 before transplant.
    - If you are receiving a partially matched related donor cells, you will receive infusions through the vein of a chemotherapy drug named Fludarabine on days -6, -5, -4, -3, and -2 before transplant. You will also receive two infusions into your vein (IV) of a chemotherapy drug called cyclophosphamide on days -6 and -5 before the transplant.
    - All patients will receive a single dose of radiation therapy one day before the transplant.
- One day later, you will receive the transplant with your donor stem cells.
- Starting a few days before transplant, and continuing for 3 months after transplant, you will receive two drugs, tacrolimus and sirolimus, to help prevent GVHD.
- Patients receiving a partially matched related donor transplant will also receive a chemotherapy called cyclophosphamide on day +3 and +4 following the transplant.
- 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 immune cells, called a "donor lymphocyte infusion", after the transplant to treat your disease.
- You will visit the NCI clinic regularly for the first six months after the transplant, and then less often for at least five years.

Pre-Transplant Evaluation

Once it is determined that you have a potential donor, you will be seen at the NIH Clinical Center, at which time you will have a complete medical history and physical examination in the NCI Oncology Clinic. Members of the transplant team will review your medical history and explain the transplant procedure. A 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, T. Cruzi (Chagas agent), and a virus called cytomegalovirus (CMV). 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. 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. If you are a woman, you will have a urine pregnancy test. You will be 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, several X-ray studies, and/or an MRI. You may have a PPD skin test if you are considered high risk by the study doctor. You may also have a bone marrow aspiration and biopsy. This test is performed by numbing the hip bone with a local anesthetic called lidocaine. A small cut will be made in the skin, a needle is inserted into the hip 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.

Birth Control

If you are a woman of child-bearing potential, you will be placed on an oral contraceptive (birth control pill) when you enroll in this study and continue taking the pills until your blood counts recover after the transplant. 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 and for 1 year after transplant. If you think you or your partner is pregnant, you should tell your study doctor or nurse immediately.

The Central Venous Catheter

If you do not already have one before you enroll in this study, you will receive an intravenous (I.V.) 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, DLI (if needed), transfusions (if needed), 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. In general, 3 to 4 tablespoons of blood will be drawn for research on average of once per week.

The maximum amount of blood taken from you is based on your age and will not be more than the strict blood volume limit set for research by the NIH. In adults that limit is 37 tablespoons in an 8 week period. If you are under age 18, we will not draw more than 2 teaspoons of blood for every kilogram (2.2 pounds) of your body weight in an 8 week period. For example, if you weigh 85 pounds (weight of some 12 year olds), your weight in kilograms is about 38 kg;

therefore, we would not draw more than 76 teaspoons (or 25 tablespoons) of blood in an 8 week period.

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.

Transplantation of the Blood Stem Cells from Your Donor

Matched related donor transplant
If you are undergoing a matched related donor transplant, prior to transplant your related donor will have a medical examination by a physician in the Experimental Transplantation and Immunology Branch at the National Cancer Institute. This includes testing for evidence of infection with HIV, Hepatitis B, Hepatitis C, and possible infectious diseases that may be transmitted by stem cell donation. The donor's exam will also ensure that they remain available and are physically well enough to undergo the donation procedure. The donor's medical clearance will be verified before you receive any pre-transplant chemotherapy or radiation therapy.

Partially matched related donor (Haploidentical) transplant
If you are undergoing a partially matched related donor transplant, prior to transplant your related donor will have a medical examination by a physician in the Experimental Transplantation and Immunology Branch at the National Cancer Institute. This includes testing for evidence of infection with HIV, Hepatitis B, Hepatitis C, and possible infectious diseases that may be transmitted by stem cell donation. The donor's exam will also ensure that they remain available and are physically well enough to undergo the donation procedure. The donor's medical clearance will be verified before you receive any pre-transplant chemotherapy or radiation therapy.

Matched unrelated donor transplant
If you are undergoing a matched unrelated donor transplant because you do not have a matched related donor, before you begin the pre-transplant chemotherapy and radiation therapy, your unrelated donor will have a medical examination by a physician in the National Marrow Donor Program (NMDP) network that includes extensive testing for evidence of infection with HIV, Hepatitis B, Hepatitis C, and possible infectious diseases that may be transmitted by stem cell donation. The donor's exam will also ensure that they remain available and are physically well enough to undergo the donation procedure. If you receive unrelated donor stem cells, the NMDP will notify NIH if there are any abnormalities that increase the risk of transmitting infectious diseases to you. These findings will be discussed with you. The donor's medical clearance will be verified before you receive any chemotherapy.

Unrelated donors are confidential, and the identity of the donor will be anonymous. This means that you will not know who your donor is or where they are located. You will know the age and gender of the donor and any history or medical exam findings that could possibly change the risk of your transplant. Likewise, the donor will not know who you are or where you are located.

He/she will know your age, gender, and the type of disease that you have. The donor will be given basic updates about your condition 30 days, 6 months, and 1 year after your transplant. The only information they will receive is whether or not the stem cells engrafted and if you have been discharged from the hospital. The donor will also be notified in the event of your death.

Depending on the policy of the particular donor center, you may be able to communicate without revealing your identities in an anonymous manner with your donor beginning at the time of your transplant. In some cases, if both you and the donor agree, you may be able to learn who your donor is after one year. There are some cases when a donor and patient may never communicate or meet. Your transplant coordinator will tell you the details of if and how you may contact the donor once the donor has completed his or her medical exam.

Your matched related or unrelated donor will receive daily injections of a medication that stimulates the stem cells to be released from the bone marrow and into the bloodstream. The donor will have these cells removed through a process called apheresis. To perform apheresis, the donor's blood is removed through an intravenous catheter and circulated through a machine which separates the peripheral blood stem cells. These cells are removed, and the rest of the blood is returned through the catheter. This collection occurs at the NIH Clinical Center or at the NMDP apheresis center closest to the donor. The cells are hand-carried by a trained courier to NIH. Once they arrive at NIH, the cells will be given via I.V. through your central line within 24 hours.

Umbilical cord blood transplant
If a matched related donor or matched unrelated donor cannot be identified, you may receive a partially matched umbilical cord blood transplant. You will begin two pre-transplant chemotherapy drugs along with radiation therapy. Umbilical cord blood units are collected and stored in a national cord blood registry. The partially matched units of cord blood are sent to NIH prior to the transplant. On the day of the transplant, the units are thawed and given to you via I.V. through your central line within a few hours of thawing.

Rarely, your matched related donor or matched unrelated donor may become unavailable, or the donor apheresis center is unable to collect enough stem cells to perform the transplant. If this happens, you will be removed from the study before transplantation unless we are able to identify another suitable unrelated donor or partially matched umbilical cord blood units.

Transplant Procedure:

You will be admitted approximately seven days before transplantation to the NCI's Patient Care Unit at the NIH Clinical Center. If you are receiving matched related or unrelated cells from a donor, you will receive 3 days of pre-transplant chemotherapy with Fludarabine and one day of radiation therapy. If you are receiving umbilical cord blood cells, you will receive 5 days of pre-transplant chemotherapy with Fludarabine, one day of pre-transplant chemotherapy with Cyclophosphamide, three days of horse antithymocyte globulin and one day of radiation therapy. If you are receiving a partially matched related donor transplant, you will receive 6 days of pre-transplant chemotherapy with Fludarabine, two days of pre-transplant chemotherapy with

Cyclophosphamide, and one day of radiation therapy. This is called the "conditioning regimen," which will prepare your body to accept your donor's stem cells because it lowers your immune system. One day after completing the radiation, you will receive the stem cell transplant. Your donor's stem cells will be given to you through an I.V. (central venous catheter). This is referred to as "day 0".

While you are in the hospital for your transplant, you will be watched very closely for possible complications, which are described below. You will receive standard supportive care such as antibiotics, growth factors (a drug called G-CSF), transfusions, and I.V. nutrition to prevent or treat any problems. Blood will be drawn frequently during your treatment. Most of the blood drawn will be to watch 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, 4 to 10 teaspoons of blood will be drawn an average of 2 to 3 times per week. The average time in the hospital is three to four weeks, but it could be longer if there any complications.

Beginning three days before you receive the stem cell transplant, you will receive the drugs tacrolimus and sirolimus to help prevent GVHD. Sirolimus is given by mouth one time a day between lunch and dinner for approximately six months after transplant. Tacrolimus is given either in your I.V. or by mouth (taken twice a day) for approximately six months after transplant. Partially matched related donor recipients will receive cyclophosphamide on days +3 and +4 following transplant, as well as Sirolimus and tacrolimus starting 5 days after transplant. If you develop GVHD, you may be given additional medications to treat GVHD. The study doctor will discuss these medications with you, if they become needed. Before the transplant and continuing until day +100 after the transplant, you will also take a drug by mouth twice a day called ursodiol to help protect your liver. After the transplant you may receive injections (shots) of a drug called G-CSF to raise your white blood cell count which will help your body fight infections. The study team will show you or a family member how to give these shots at home.

Once the stem cells have engrafted (become part of your body) and you are strong enough, you will be discharged from the hospital and followed closely as an outpatient. The average hospital stay is three to four weeks, but 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 watch for complications. You may require re-admission to the hospital if you have complications. You will be seen frequently in the NCI clinic for the first six months after transplant, and then you will be seen less frequently for at least five years.

After the transplant, if tests show that your blood and immune cells have not fully converted to your donor's type (called "mixed chimerism"), then your sirolimus and/or tacrolimus dose will be lowered to help change your blood and immunity to help convert your blood and immune cells to that of your donor's, this is called "full donor chimerism." Sometimes a donor lymphocyte infusion (DLI) may be given IV to reach a state of full donor chimerism. A DLI takes the immune cells collected from your donor and gives them to you to help convert your

blood and immune system to full donor chimerism. If your disease is still present after the transplant, tacrolimus or sirolimus may be reduced in an attempt to permit a stronger graft-versus-tumor effect. After this, if there are no signs of significant 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 watch you very closely for signs of GVHD after these infusions. If you develop severe 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 disease 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 to the NCI clinic monthly until approximately six months after transplantation to monitor for late transplant complications including GVHD and infection. Thereafter you will be seen here every three months until two years after your transplant. During some visits you will have bone marrow aspirates and biopsies, blood draws, and other appropriate tests to check your disease status. You will also have blood drawn for research to test how your immune system recovers after the transplant.

Alternative Treatment

There are options you may consider other than participating on this trial, including:

- Continuing to receive medications for your current infections as they arise.
- Instead of participating in a research study such as this, you may also be eligible to receive an allogeneic transplant with high dose chemotherapy and/or radiation to completely wipe out your bone marrow before donor cells are transplanted.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by your disease. It does not treat the disease directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.
- Another option is not to receive any further treatment 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 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. There is about a 20 percent chance of death from complications of conventional allogeneic bone marrow transplants. Based upon our previous results, we hope that the risk of death related to the transplant will be less than 20% in this study. 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. Deterioration of pulmonary function is a risk of allogeneic stem cell transplantation, including transplants from umbilical cord blood donors. Because patients with GATA2 deficiency often have reduced lung function as part of their underlying disease, they may be at greater risk of this complication. There is also the risk of complications that cannot be predicted.

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.

Blood Draws: Blood will be drawn frequently during your treatment. Most of the blood draws will be to check 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 GVHD (if it occurs).

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, putting in a central venous catheter can result in a collapsed lung. If a collapsed lung occurs, it may require hospitalization and putting a plastic tube in your chest temporarily to re-expand the lung.

Reproductive Risks: This treatment is likely to result in sterility (the inability to have children). However, we cannot predict for certain that you will become sterile during this treatment. It is unknown what effects the pre-transplant chemotherapy, radiation therapy, and other drugs included in this treatment may have on an unborn child, but they would most likely be harmful. Women should not breastfeed a baby while participating in this study.

Treatment with Fludarabine, Cyclophosphamide and Radiation therapy: The drugs and radiation that you will receive on this protocol are likely to lower the number of white blood cells in your blood for many days. This will increase your risk of infection. If you develop an infection, it 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, these drugs and radiation are likely to cause your platelet count to fall. This will increase your risk of bleeding. If your platelet count becomes dangerously low, you will receive platelet transfusions. These chemotherapies may also cause you to develop a low red blood cell count, called anemia. Anemia can cause a lack of energy and other symptoms. Transfusions of red blood cells are sometimes needed to treat anemia. The following are known specific risks of each drug used within the specific regimen that you will receive:

Fludarabine:

Likely:	Less likely:	Rare:
• low blood counts, • lowered level of	• nausea and vomiting; • diarrhea,	• GI bleeding, • lung damage,

immune cells and increased risk of infection	• fever, • mouth sores, • loss of appetite, • swelling (edema), • skin rash, • muscle aches, • headache, • agitation, • hearing loss, • fatigue, • weakness, • numbness / tingling ("pins and needles")	• kidney damage, • severe neurologic (brain and/or spinal cord) toxicity has occurred after very high doses including blindness, deterioration of mental status, and death.

Cyclophosphamide:

If you receive partially matched related donor cells or umbilical cord blood donor cells, you will also receive a drug called cyclophosphamide. The potential side-effects of cyclophosphamide are listed below:

Likely:	Less Likely:	Rare:
• low blood counts, • hair loss	• nausea and vomiting, • painful and bloody urination, • sterility, • water retention	• heart damage, • secondary leukemia (a different type of cancer), • skin rash • retention of too much water in the body • pulmonary fibrosis

Radiation

Radiation therapy can reduce your immune T cells and increase your risk of developing infection. The radiation 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 dose of radiation used in this study.

Filgrastim (called G-CSF):

Likely:	Less likely:	Rare:
• bone pain, • reversible lab changes in your blood test results	• headache; • pain at the needle site, • fevers, • tiredness	• G-CSF can cause rupture of the spleen, which can cause death

Ursodeoxycholic acid, also known as ursodiol:

Likely:	Less likely:	Rare:
• nausea, • vomiting, • heartburn, • a metallic taste, • abdominal pain, • an inflamed gallbladder, • constipation, • mouth pain, • flatulence, • diarrhea, • itching, • rash, • dry skin, • hives, • headache, • fatigue, • anxiety, • depression, and • sleep disorders.	• sweating, • thinning of hair, • back pain, • muscle and joint pains, • runny nose, and • cough.	• None

Graft-versus-Host Disease Prevention: As described above, you will receive two drugs to prevent GVHD. They are called: tacrolimus and sirolimus.

Tacrolimus:

Likely:	Less likely:	Rare:
• headache, • tremor, • changes in mental status,	• increase in blood tests of liver function, • diabetes, • anemia,	• Seizure • Coma

• high blood pressure, • abnormal kidney function, • constipation, • diarrhea, • abdominal pain and • difficulty sleeping (insomnia) • Mild to severe increase in a blood electrolyte called potassium, which will be carefully monitored, had been observed following tacrolimus administration.	• an allergic reaction, and • sensitivity reaction to light.	

Sirolimus:

Likely:	Less likely:	Rare:
• Because sirolimus is an immune suppression drug, it is likely that the risk for some infections may be increased. • very high levels of fats (triglycerides) and increase in cholesterol (increased lipid blood levels),	• diarrhea, • nausea, • damage to the liver, • low blood counts, • mouth ulcers, • headache; • increased risk of infection, • red blood cell breakdown with abnormal kidney function.	• severe swelling of the pancreas, • secondary cancers (a different type of cancer)

Equine ATG

Likely:	Less likely:	Rare:
• fevers and chills • allergic reactions • skin rash • aching in muscles • aching in joints • reactivation of viruses that have been dormant in the patient	• serum sickness with skin rashes, itching, fever, aching the muscles and joints, chest pain, difficulty breathing, enlargement of lymph nodes • infection with viruses	• bleeding • lung injury

prior to ATG	• new cancers •	

Stem Cell Infusion: The donor cells are frozen with a chemical called DMSO to protect them from the effects of freezing. Patients receiving thawed cells often develop side effects from the DMSO. DMSO side effects may include headache, upset stomach, fever and allergic reactions, such as skin rash, itching, difficulty breathing, and low blood pressure. These reactions are usually mild and temporary, and they can be easily treated with IV fluids and medications. DSMO frequently causes a 'garlic-like' breath and body odor.
Veno-Occlusive Disease (VOD): A severe liver complication known as VOD occurs in less than 5 percent of allogeneic transplants. VOD is a chemotherapy side effect that causes blood vessels in the liver to be blocked. Severe VOD can lead to liver failure and death.

Graft Rejection: There is a chance that you may reject your donor's stem cells. If that were to happen, you would most likely recover your own blood cells. However, there is the rare possibility that your own cells may not recover. This may result in prolonged low blood counts, which may result in infection or bleeding and may lead to death. In this event, we would attempt to support you with transfusions, growth factors and antibiotics until your own blood counts recover. A blood test will be performed at 30, 60, 100 days and 6, 12, and 24 months after your transplant to find out if your body has accepted the donor cells. If no donor cells can be found, then we will conclude that you rejected them. In that case, your blood counts will probably return to the same levels as before the transplant in about 2 to 3 weeks. You will receive a drug called G-CSF to help the cells engraft (help your body accept the donor cells). In the event that your cells do not engraft, we may ask your donor to donate more cells.

We have specifically added ATG for recipients of umbilical cord blood to prevent graft rejection. One patient who received an umbilical cord blood transplant without receiving ATG rejected the umbilical cord blood units and required a second transplant.

Immune reactivation: In two cases we have observed an immune reactivation syndrome in which the new immune system from the transplant reacted with the residual recipient cells in the blood system and kidney resulting in both blood and kidney problems requiring treatment with high doses of steroids.

Graft-Versus-Host Disease (GVHD): You will be at risk for the development of GVHD for the rest of your life after transplantation. GVHD occurring within the first 100 days after transplantation is referred to as acute GVHD. 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, or as severe as cramping abdominal pain and bloody diarrhea. Liver GVHD may be as mild as slight disturbances in liver function, or severe as yellowing of the skin with liver failure. Mild acute GVHD (skin rash only) can be managed with topical steroid creams. Severe acute GVHD can be lethal and needs to be treated aggressively.

Treatment of severe GVHD initially includes slowing down the immune system, usually with I.V. steroids/medications. Slowing down 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, eyes, muscles, 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 yellowing of the skin), 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 slow down the immune system such as steroids. This again increases the risk of infection.

Because of the risk of infections, and the possibility of adverse effects such as return your own blood cells due to continuing immune suppression, both Sirolimus and Tacrolimus will be tapered starting 6 months post-transplant providing that there is no evidence of GVHD. The goal will be to completely stop both drugs by one year post-transplant.

Late Transplant Complications: There are other potential complications that can 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 type of cancer such as leukemia or lung cancer.

Other complications are also possible following your transplant. The most common complication is infections. Because you will be receiving drugs (e.g. fludarabine and cyclophosphamide) that slow down the immune system, you are at greater risk to develop infections from uncommon organisms. These infections can be life-threatening, and may cause death. Less common complications after transplant include organ damage in the heart, liver, kidney, lungs, and brain.
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.

Potential Benefits of Participation

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 experimental study may contribute to understanding and developing new ways of using allogeneic SCT for the treatment of blood diseases. Knowledge gained from this study may help others in the future who have this disease.

Interim Results from First 10 Patients Enrolled in Study

Ten patients have been enrolled on this study to date. In brief, three patients received a matched related donor hematopoietic stem cell transplant (HSCT), three patients received matched unrelated donor HSCT, and four patients received umbilical cord transplants:

Patient # 1: Received his peripheral blood stem cell (PBSC) transplant and is now more than two and a half years from transplant with a normal blood cell counts. He had one episode of late GVHD and has chronic GVHD.

Patient #2: Received PBSC from an unrelated donor and is now two and a half years after transplant with normal blood cell counts. He is not taking any immunosuppressive medications. He has no GVHD.

Patient #3: Underwent a single umbilical cord hematopoietic stem cell transplant and is now two years post-transplant and living at home. She is not taking any immunosuppressive medications. She has no GVHD.

Patient #4: Received a 10/10 matched unrelated donor transplant and is now one and a half years after transplant with normal blood cell counts. She takes immunosuppressive medication for GVHD.

Patient #5: Transplanted with a double umbilical cord blood units and is now one and a half years post-transplant. He does not require blood or platelet transfusions and has no GVHD.

Patient #6: Transplanted with a matched related donor is now 14 months post-transplant tapering off immunosuppression. She has no GVHD although she had recurrence of her pre-transplant abnormal cytogenetics.

Patient #7: Transplanted with a double umbilical cord blood unit and died 5 days after transplant of massive infection.

Patient #8: Transplanted with a double umbilical cord blood and had graft rejection. She was re-transplanted with her father's stem cells and subsequently died from a serious infection.

Patient #9: Transplanted with a matched related donor and is now 120 days post-transplant with no medical issues.

Patient #10: Transplanted with a matched unrelated donor and is now 10 days post-transplant with no medical issues.

Stopping Therapy

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

In this case, you will be informed of the reason therapy is being stopped.

Participation in this research study is voluntary. You may stop your participation 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 and your regular doctor first. There are no penalties for withdrawing from the study. However, if you withdraw after the transplant chemotherapy ("conditioning regimen") without receiving the infusion of donor stem cells, you would be at high risk for serious complications, including death.

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.

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, transplant, 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.

Additional Therapies

Treatments covered under this protocol that are standard therapies given for disease control may include a single medication or a combination of medications, surgery or radiation. The treatment to be used will be determined by your NIH doctors based on your diagnosis, the type and extent of your illness, your prior treatments, and your ability to tolerate additional treatment. These treatments will not be experimental. Your doctors will describe their treatment plan to you in detail including the name of the treatment(s), the schedule, the possible harmful effects, the potential benefit, and possible alternatives to you before having you sign this consent form. If surgery or radiation therapy is required to treat your illness, you may be asked to sign a separate consent form by the surgeon or radiation therapist.

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.

<u>Use of Specimens and Data for Future Research:</u>

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of

these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

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., Building 10/Clinical Research Center, Room 3-3142; Telephone: (301) 594-1718; Blackberry: 301-795-8778. Other researchers you may call are: Dr. Mark Parta 240-409-4120. For questions about the use of your specimens, or data for future research studies, you may contact the Clinical Director, NCI at 301-496-4251.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

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 — Signature of Witness — Date

_____ _____

Print Name — Print Name