H-25064- UMBILICAL CORD BLOOD TRANSPLANT FOR CONGENITAL PEDIATRIC DISORDERS (UCB)

Background

When reading this form, please note that the words “you” and “your” refer to the person in the study, rather than to a parent or guardian, or legal representative who might sign this form on behalf of the person in the study.

You were born with a disease that affects your body's metabolism (the system that helps eliminate toxins from your cells) or immune system (which is responsible for helping you fight infections). Your doctor plans to treat you for this illness with a stem cell transplant. While improved medical care has allowed many people with these diseases to live longer, the only way to truly cure these diseases is by means of a stem cell transplant from a donor who does not have the disease. A stem cell transplant will replace sick cells with new healthy donor cells. Stem cells grow into different types of blood cells that you need, including red blood cells, white blood cells, and platelets. In a stem cell transplant, your own stem cells will be killed by a chemotherapy drug, and then replaced by stem cells from the donor. Stem cells can be collected from the bone marrow, peripheral blood or umbilical cords. In this study, umbilical cords will be the source of the stem cells.

Currently, large inventories of umbilical cord blood units are available in public banks for transplantation in those lacking bone marrow donors. UCB transplants (UCBT) offer several advantages over adult bone marrow or peripheral blood stem cell transplants, including:

1) Rapid availability.
2) Absence of donor risk.
3) Low risk of transmissible infectious diseases.
4) Low risk of acute graft-versus-host disease (GVHD), as compared to recipients of unrelated donor marrow and peripheral blood cells. GVHD will be discussed in more detail later in this consent.

The two main causes of death after umbilical cord blood transplantation for disorders like yours are graft failure (this is when the donor cells do not replace your cells permanently), and infection. In this study, we are trying to address these two problems by using different drugs to prepare you for the transplant.

To help improve engraftment (when the transplanted cells begin to grow), we will add the drug fludarabine to the usually used busulfan and cytoxan that you will receive before your transplant. We will try to decrease the chance for infections by using mycophenolate mofetil (MMF) instead of anti-thymocyte globulin (ATG), which is normally used.

Please read the information in this consent form carefully to decide whether you want to participate. Your participation in this study will last for about 3 years.

This research study is sponsored by Baylor College of Medicine.

Purpose

To determine the safety and effectiveness of umbilical cord blood transplant (UCBT) to treat your disease, and to see whether this treatment can decrease the incidence of GVHD.

Procedures
The research will be conducted at the following location(s):
Baylor College of Medicine and TCH: Texas Children's Hospital.

Up to 60 patients will take part in this study.

You will be examined to make sure that you meet the requirements of this study. There will be tests of your heart (echocardiogram, an ultrasound of the heart) and of your lungs (pulmonary function studies to see how well your lungs are functioning). X-rays will be taken of your lungs and other organs, depending on your disease. An MRI and consultations with different specialists (such as genetics, vision, hearing, liver, lung, brain, and heart) will also be conducted.

You must have a negative pregnancy test before entering this study if you are a woman of childbearing potential. Your blood will be tested for viruses, and to look at the functioning of your liver and kidneys. The examination also includes HIV testing. HIV is the virus that causes Acquired Immune Deficiency Syndrome (AIDS). If you have HIV, you will not be able to be treated on this protocol.

After we have determined that you are eligible for treatment on this study, and a suitable UCB stem donor has been found, you will have a central line placed. A central line involves the placement of a large tube (called a double lumen catheter) into a large vein in your body. The large vein will be either in the groin or in the chest. The catheter will be placed by a surgeon. The risks of having a central line placed are primarily related to this surgical procedure. They will be discussed further in the RISKS section of this consent form. The risks of having a central line placed will also be discussed with you separately, and you will sign a separate consent form for the placement procedure.

RESEARCH THERAPY:

After placement of the central line, the following chemotherapy will be given to you after admission to the hospital:

- 9 days before the infusion through 6 days before the infusion: busulfan every 6 hours for 16 total doses.

- 5 days before the infusion through 2 days before the infusion: cytoxan given daily for 4 days over 2 hours (can be given over 1 to 4 hours as decided by the physician). MESNA will be given per standards.

- 4 days before the infusion through 1 day before the infusion: fludarabine given daily for 4 days over 1 hour.

Stem cell transplant (infusion of the UCB stem cells) is defined as Day 0 of the treatment. All other "numbered" days relate to this infusion date. For example, Day 1 is the first day after the stem cell transplant.

STANDARD THERAPY:

Phenytoin will be given according to institutional standards.

Cyclosporin A (CSA) will be given starting 2 days prior to the stem cell infusion. It will be given daily over 2 hours every 12 hours, and then tapered if no GVHD is present.

Administration of mycophenolate mofetil (MMF) will start on the day the stem cell infusion is completed, and will continue daily for 45 days, unless you develop GVHD.

Intravenous immunoglobulin (IVIG) and Granulocyte-Colony Stimulating Factor (G-CSF) will be given as per institutional standard.

STUDY EVALUATIONS:

The following evaluations will be collected before transplant:

- Pregnancy test
- Chest X-ray
- ECG/ECHO
- Pulmonary Function Tests, as applicable
- DXA Scan, as applicable
- BRAIN MRI
- Low dose ACTH
- Endocrine testing
- Urinalysis
- Immunoglobulin Levels
- Genetic counseling
- Audiology consultation*
- Ophthalmology consultation*
- Endocrinology evaluation*
- Cardiology consultation*
- Pulmonary consultation*
- Neurology evaluation*
- Neuropsychometric testing will occur at Months 12, 24, 36 and 60.

*Multidisciplinary team evaluation also performed at Day 180 and Month 12, 24, 36 and 60 if applicable.

The following evaluations will be collected before transplant; at Days 0, 21, 42, 60, and 100; and at Months 6, 9, 12, 24, 36 and 60:

- Physical exam, weight, height, vital signs, performance status.
- CBC with differential and platelets

- Electrolytes, BUN, Creatinine
- AST, ALT, Bilirubin, Albumin and LDH
- ECHO*

* Months 12, 24,36 and 60 only.

Enzyme analysis will be collected as clinically indicated.

PB STRs / FISH will be collected on Days 21, 60, and 100; and as clinically necessary.

Lymphocytes subset / PHA assay will be collected between Days 21-42; Days 60-100; and at Months 6, 9, 12, 24, 36 and 60. Immunoglobulin levels will be collected pre-study, at Day 100, and at 6, 9, 12, 24, 36 and 60 months.

BLOOD SAMPLES:

To study how these cells are working in your system, blood samples will be taken on Days 21, 42, 60, and 100; at Months 6, 9 and 12; and at Year 2 and Year 3 following transplant. Approximately 6-8 teaspoons of blood will be collected each time. The total blood drawn for this study over three years should not exceed 1 and 3/4 cups. This amount is considered safe in adults. The amount of blood collected will be decreased in children and/or in patients where this amount of blood collection would not be appropriate.

If you have a central line, the blood will be taken from it, so that extra needlesticks should not be needed. If you do not have a central line, you will need to have one placed. This will be a separate procedure for which you will sign a separate consent form. You will need to come to the clinic on the days of blood drawing and to be seen at Texas Children's Hospital. This blood is not for research purposes, but rather for treatment response monitoring.

FOLLOW-UP:

After year 1, you will be asked to return to the clinic once a year for consultations. These consultations with specialists will be similar to the ones you had before your transplant.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine and TCH: Texas Children's Hospital to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records
- Photographs, videotapes, and/or audiotapes of you

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, and TCH: Texas Children's Hospital.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and TCH: Texas Children's Hospital are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and TCH: Texas Children's Hospital to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine and TCH: Texas Children's Hospital maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine and TCH: Texas Children's Hospital to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to

you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine and TCH: Texas Children's Hospital.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, Data and Safety Monitoring Board, and TCH: Texas Children's Hospital may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Caridad Martinez, MD
BCM Center for Cell and Gene Therapy, Suite 1640
Feigin Center, 1102 Bates Avenue
Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

RISK OF CENTRAL LINE PLACEMENT:

The risks of central line placement include the risk of the surgical procedures to insert the catheter. These risks include a pneumothorax (air inside the chest), bleeding, infection, and the risk of anesthesia. These risks will be explained in greater detail by your surgeon prior to placement of the central line. After placement, the central line may become infected, necessitating hospitalization, treatment with intravenous antibiotics, and possibly removal of the line and placement of a new line. In addition, a blood clot may develop in the line. If the clot cannot be dissolved, the line will need to be replaced and a new line inserted.

RISKS OF BUSULFAN:

The side-effects of this agent include the suppression of bone marrow activity, resulting in reduction in the number of platelets, red cells, and white cells found in the circulation. It can also cause nerve damage, which could result in seizures. Other side-effects include rapid heart rate, darkening of the skin, and sterility. Rarely, it can cause serious liver and lung problems.

RISKS OF CYTOXAN:

Common side-effects may include upset stomach and vomiting, mouth sores and stomach ulcers, fluid retention with seizures, diarrhea, bladder problems that cause pain when urinating or cause blood in the urine (this may be prevented by giving extra amounts of fluids by vein or by a drug called MESNA), hair loss, skin rashes, low blood counts with higher risk for infection, bleeding and/or anemia, and sterility

(inability to have children). Rare side-effects may include heart damage, second cancers (very rare), lung damage, and blurred vision.

RISKS OF FLUDARABINE:
Likely (may happen in more than 20% of patients):
Low number of red blood cells (anemia); Low number of white blood cells; Low number of blood platelets; Feeling tired; Nausea (feeling sick to your stomach); Throwing up (vomiting); Weak immune system; Pneumonia; Infection; Bleeding; Pain; Electrolyte imbalance.

Less likely (may happen in fewer than 20% of patients):
Diarrhea; Mouth sores; Skin rash; Fever; Swelling of hands and feet; Numbness and tingling in hands and/or feet; Loss of appetite.

Rare but serious (may happen in fewer than 2% of patients):
Changes in vision; Feeling nervous or anxious; Confusion; Cough; Difficulty breathing; Feeling weak; Severe brain injury which can lead to death; Kidney damage that could require dialysis; Coma; New (secondary) cancers.

RISKS OF MESNA (SODIUM 2-MERCAPTOETHANE SULFONATE MESNEX):
May cause nausea and vomiting, and a bitter taste in your mouth during IV administration. Rare side-effects have included abdominal discomfort, headache, limb and joint pain, tiredness, and diarrhea.

RISKS OF MYCOPHENOLATE MOFETIL (MMF):
Risks may include upset stomach, including diarrhea and vomiting; risk of serious infections; bleeding and easy bruising; risk of certain cancers with long-term treatment; risks to an unborn baby during pregnancy.

These drugs are standard in the treatment of your disease:

CYCLOSPORIN A (CSA): Risks may include acne; dizziness; headache; increased hair growth; nausea; runny nose; sleeplessness; stomach discomfort; vomiting.

PHENYTOIN: Risks may include constipation; dizziness; headache; mild nervousness; nausea; trouble sleeping; vomiting.

IVIG: Risks include headache, myalgia, fever, chills, backache, chest pain, nausea and/or vomiting.

G-CSF: Risks may include aching or pain in the bones; local irritation at the site of the Injection; headache; higher than normal levels of liver enzymes in the blood which may indicate liver irritation or damage; increase of uric acid in the blood; a low number of platelets in the blood which may cause you to bruise and bleed more easily; low fever; enlargement of the spleen (an organ in the abdomen/belly which stores blood cells) which may cause pain in the abdomen or left shoulder; rash or worsening of

skin rashes; inflammation of blood vessels in theskin leading to a raised purple rash and bruising that has been seen mainly in patients who are treated for a long time; higher than normal white blood coun; skin condition marked by fever and painful skin lesions that appear mainly on the face, neck, back and arms.

Rarely it may cause:

- Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling. This reaction is very rare and has been associated mainly with intravenous administration If you are known to have sickle cell disease, filgrastim may cause a sickle cell crisis;

- Severe damage to the spleen (an organ in the abdomen/belly which stores blood cells) which could lead to pain and loss of blood into the abdomen (belly) and maybe life threatening;

- Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected;

- A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time.

RISK OF GRAFT FAILURE:
Graft failure occurs when the stem cells from the donor do not begin to grow and produce healthy blood cells. This means that you would have low blood counts for a long time. This increases your chances of bleeding or getting an infection, which can be fatal. If no further treatment is received, or despite treatment, it is still possible that you may die from your disease or from complications caused by having too few stem cells.

RISK OF GRAFT VERSUS HOST DISEASE (GVHD):
Another significant risk of this research study is that GVHD may develop. GVHD occurs when the new stem cells (known as the graft) recognize that the body tissues of the patient (host) are different from those of the donor. When that happens, the graft attacks host and can cause significant health problems, specifically in the lungs, eyes, mouth, liver, skin, joints, and muscles. The risks of GVHD are higher with unrelated donor transplants. Signs of GVHD include diarrhea, skin rashes and blisters, and liver problems. Severe GVHD disease can be life-threatening and requires drug treatment. Occasionally, it may be fatal despite the best available treatment.

RISKS OF BLOOD DRAWS:
The risks of having blood drawn include pain during the procedure, and a rare chance of bleeding and/or infection at the site of the needlestick, as well as a bruised feeling following the procedure. The amount of blood taken will not exceed the amount that is considered safe by institutional guidelines.

ADDITIONAL RISKS:

The degree of immune suppression in stem cell transplant patients leads to an increased risk of infections, especially those due to cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), pneumonia, and other viruses. Preventative medicines are given when possible (Acyclovir, Bactrim, antifungal and antibacterial mouth rinses, etc.), and treatment is started very promptly, usually before the infection is confirmed. The hematologic malignancy may recur. The administration of blood products carries the risk of blood born infections such as hepatitis,
CMV, and HIV. Blood products are carefully screened for these agents.

Other complications of an unexpected nature may occur. In fact, almost every patient develops some new or very rare complication during his/her transplant. In addition, there is a chance that you could die from this treatment or from side-effects of the treatment, such as bleeding or infection.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: improved potential for cure or improved survival. Improved survival means you may live longer before the disease comes back (in remission) than you would do without the transplant. You may also experience decreased risk of toxicities from the UCB stem cell transplant. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: other chemotherapy, other drugs being studied, the standard preparative regimen for an allogeneic stem cell transplant, or no treatment at all.

Subject Withdrawal from a Study

Withdrawing from this protocol during the conditioning regimen (and before infusion of the stem cells) may lead to serious consequences, including death. Please contact your study doctor if you decide to withdraw from the study. She will help you stop safely.

Subject Costs and Payments

All medical expenses related to this treatment protocol will be the responsibility of the patient. You will have an opportunity to discuss the expenses or costs associated with participation in this study. All costs related to your medical care will be charged to you or your insurance carrier.

You or your insurance company will be responsible for all treatments, medicines (including Busulfan, Cytoxan, Fludarabine, Mesna, MMF, Cyclosporin A, IVIG and Phenytoin), and/or procedures in this study.

You will not be charged for studies or procedures that are performed solely for research purposes, such as the blood collected to learn more about the way the new cells are growing (mentioned above in the procedures section). The cost of this treatment and your insurance coverage will be discussed with the patient's insurance carrier, or other agencies as needed. Financial counseling is available upon request to discuss the cost of this treatment and your insurance coverage, or coverage as provided by other agencies.

You will not be paid for taking part in this study.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

Research Related Injury

If you are injured as part of your participation in this study, there are no plans to pay you. Please contact your study doctor, Dr. Caridad Martinez, if you feel you have been injured as a result of taking part in this study.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex and for (3) months afterwards:

* oral contraceptives ("the pill"),
* intrauterine devices (IUDs),
* contraceptive implants under the skin, or contraceptive injections,
* condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, CARIDAD A. MARTINEZ, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: DR. CARIDAD MARTINEZ at 832-824-4692 during the day, and 832-826-0860 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Legally Authorized Representative Parent or Guardian	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date