H-26558- UMBILICAL CORD BLOOD TRANSPLANT FOR CHILDREN WITH MYELOID HEMATOLOGICAL MALIGNANCIES (UCAML)

Background

You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study.

You have a type of blood cell disorder that is very hard to cure. We are suggesting a treatment that might help you live longer without the disease. This treatment is known as a stem cell transplant. It uses much stronger doses of drugs and radiation to kill the diseased cells than could be given without the transplant. We also think that the healthy cells from the donor may help fight any diseased cells left after the transplant.

For the transplant to take place, we will administer stem cells from a 'donor' whose cells best 'match' yours and give them to you. Stem cells are special 'mother' cells that are found in the bone marrow (the spongy tissue inside the bones), blood, and umbilical cord blood of newborn babies. As stem cells grow, they give rise to white blood cells which fight infection, red blood cells which carry oxygen and remove waste products from the organs and tissues or platelets, which enable the blood to clot. In this study umbilical cords will be the source of the stem cells.

Before the transplant, two very strong drugs will be given to you (pre-conditioning). This treatment will kill most of your blood-forming cells in the bone marrow. We will then give you the healthy stem cells. Once these healthy stem cells are in your bloodstream they will move to the bone marrow (graft) and begin producing blood cells that will eventually mature into healthy red blood cells, white blood cells and platelets.

If you have CNS relapse or primary CNS disease, you will receive irradiation to the cranio-spinal axis before starting the conditioning, in an attempt to achieve CNS disease control. Irradiation will not be given for children under 2 years old.

Currently, many umbilical cord blood units are available in public banks for transplantation in patients lacking bone marrow donors. UCB transplants (UCBT) may 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 GvHD (graft-versus-host disease) as compared to recipients of unrelated donor marrow and peripheral blood cells. GvHD will be discussed in more detail later in this consent.

The three main causes of death after umbilical cord blood transplantation for disorders like yours are graft failure (this is when the donor cells do not grow), infection, and disease relapse.

In this study we are trying to address these three problems. To help improve engraftment (cells begin to grow) we will add the drug Fludarabine to Cytoxan and Busulfan. Fludarabine is a very strong medicine. We will try to decrease infections and reduce leukemia relapse (return of cancer cells) by using

fludarabine instead of anti-thymocyte globulin (ATG).

Please read the information in this consent form carefully to decide if 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 UCBT to treat your disease, and to see if this treatment can decrease the incidence of leukemia relapse, GvHD, and infections.

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

A total of 20 subjects will be enrolled to 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 and electrocardiogram (ECG), an ultrasound of the heart), liver, and kidneys. You will have tests to check how well your lungs work if you are old enough.

You also 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 including HIV testing. HIV is the virus that causes Acquired Immune Deficiency Syndrome or 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 tube (called a double lumen catheter) into a large vein in your body. If the patient is too small for a central line in the arm, the central double lumen line will be placed in the chest. The large vein may also be in the groin. The catheter will be placed by a surgeon. They will be discussed further in the RISKS section of this consent form. The risks of a central line 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 and before the infusion of UCB stem cells:

9 days before the infusion through 6 days before the infusion: Busulfan every 6 hours as an intravenous infusion for a total of 16 doses.

5 days before the infusion through 2 days before the infusion: Cytoxan given daily for 4 days over 1 hour

as an intravenous infusion. Mesna will be given per standards. Mesna is a drug given to decrease the side-effects of Cytoxan. It will be given daily while you receive Cytoxan.

3 days before the infusion through 1 day before the infusion: Fludarabine given daily for 3 days over 1 hour as an intravenous infusion.

Stem cell transplant (infusion of the UCB stem cells) - 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.

The following medications will be given to help decrease side-effects from the chemotherapy and UCB infusion:

Cyclosporine 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 after the infusion, and then tapered if no GvHD is present.

Administration of 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) will be given monthly until GvHD therapy is stopped and there is evidence that your body is producing antibodies.

STUDY EVALUATIONS:

The following evaluations will be collected before transplant:

- Physical examination by a Pediatric Bone Marrow Transplant physician (includes History, Physical Examination, Weight, Vital Signs, Pulse Oximetry, and Performance Status)
- Pregnancy test
- Complete blood count with differential, C-reactive protein
- Serum chemistries
- Liver function tests
- An electrocardiogram: a test that shows the electrical activity of the heart
- An echocardiograph: picture of the heart in motion
- Tests to see how well blood clots
- Viral tests
- Bone marrow aspirate and biopsy/lumbar puncture within 2-3 weeks of starting conditioning, as clinically indicated
- Renal function
- Lumbar puncture will be performed to evaluate any evidence of disease recurrence (if previously positive and/or clinically indicated)
- Pulmonary function test, if applicable

The following evaluations will be collected on Days 0, 21, 42, 60, and 100:

- Infusion of cells on Day 0
- Physical examination by a Pediatric Bone Marrow Transplant physician (includes History, Physical Examination, Weight, Vital Signs, Pulse Oximetry (on Day 0 only), and Performance Status)
- Complete blood count with leukocyte differential, C-reactive protein
- Serum chemistries
- Liver function tests
- Evaluations of the graft between Days 21-42, 60 and 100
- White blood cell recovery will be performed between Day 21-42 and 60-100
- Bone marrow aspirate and biopsy for assessment of leukemia status and UCB engraftment between Days 21-42, and will be repeated between Days 90-100 as clinically indicated
- Lumbar puncture will be performed between Day 21-42 and between Day 90-100 to evaluate any evidence of disease recurrence (if previously positive and/or clinically indicated)
- Immunoglobulin (IgG, IgA, IgM) will be taken prior to administration of IVIG between Day 60-100

The following evaluations will be collected after Day 100 around 6, 9, 12, 24 and 36 months:

- Physical examination by a Pediatric Bone Marrow Transplant physician (includes History, Physical Examination, Weight, Vital Signs, and Performance Status)
- Complete blood count with differential, C-reactive protein
- Serum chemistries
- Liver function tests
- Evaluations of the graft around 6, 12, and 24 months or more frequently as clinically indicated
- Echocardiograph (how well your heart pumps out blood to the rest of your body) at month 12
- Bone marrow aspirate and biopsy assessment of leukemia status and UCB engraftment around 6, 9, 12 and 24 months, as clinically indicated.
- White blood cell recovery will be performed around 6, 9, 12 and 24 months after transplant
- Immunoglobulin (IgG, IgA, IgM) will be taken at month 6, 9, 12 and 24 months

BLOOD SAMPLES:
To study how these cells are working in your system, blood samples will be taken at about 1, 2, 3, 6, 9, 12, 15, 18 and 24 months after the transplant. Approximately 3-4 teaspoons of blood will be collected each time. The total blood drawn for this study over three years should not exceed 3/4 cups. This amount is considered safe in adults. The amount of blood collected will be less for 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. You will need to come to the clinic on the days of blood drawing and to be seen at Texas Children's Hospital.

FOLLOW-UP:
After year 1, you will be asked to return to the clinic once a year for consultations and bone marrow tests. A follow-up bone marrow biopsy and aspirate will be done 1 and 2 years after transplant. 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

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
BCM Center for Cell and Gene Therapy
Feigin Center, Suite 1630
1102 Bates Street
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
BUSULFAN: The side-effects of this agent include low blood counts, 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, nausea, vomiting, and sterility. Rarely, it can cause serious liver and lung problems.

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.

FLUDARABINE: The side-effects of this agent include low blood counts, resulting in reduction in the number of platelets, red cells, and white cells found in the circulation. It can also make certain kinds of anemia, a reduction of the red cells in the blood, worse. Rarely, it can cause your immune system to be suppressed for a long period of time, which could make you vulnerable to infections. Another rare side-effect is nerve damage, fever and central nervous system changes.

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 been abdominal discomfort, headache, limb and joint pain, tiredness, and diarrhea.

MYCOPHENOLATE MOFETIL (MMF): Risks may include upset stomach, including diarrhea and vomiting; risk of serious infections; bleeding and easy bruising; risk of some cancers with long term treatment; risk to baby in pregnancy. It will also cause decrease function on your lymphocytes (immunosuppression).

CYCLOSPORIN A (CSA): Risks may include acne, dizziness, headache, increased hair growth, nausea, runny nose, sleeplessness, stomach discomfort, vomiting and seizures. It will also cause decrease function on your lymphocytes (immunosuppression).

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

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.

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) as different from those of the donor. When that happens, the graft attacks the 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.

BLOOD DRAWING: 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, anti-fungal and anti-bacterial mouth rinses, etc), and treatment may be started before an 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. 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: The benefits of participating in this study may be: improve the 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.

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 radiation, Cytoxan, Fludarabine, Mesna, MMF, Cyclosporine 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. 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.

You will not be paid for taking part in 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 at 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.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

The National Institutes of Health and the National Cancer Institute may have access to your records for research purposes. Coded information may be provided to the NIH/NCI such as Patient ID, Patient Zip code, Patient country code, and Patient Birth date (month/year). However, in the event of an audit NIH/NCI might have access to more information that is part of your research record.

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