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Blood and Marrow Transplantation Program
Masonic Cancer Center
University of Minnesota

Parental Consent – For Minors Receiving Cord Blood

Hematopoietic Cell Transplantation in the Treatment of Infant Leukemia and Myelodysplastic Syndrome

Principal Investigator: Christen Ebens, MD

Your child is eligible to take part in a clinical research study because he/she has leukemia or myelodysplastic syndrome (both diseases of the blood).

Taking part in any clinical research involves risks and may provide some benefits. You need to understand these risks and benefits to make an informed decision about whether or not to allow your child to be in this study.

This form is called a consent form. The intent of this form is to let you know the purpose of this study, the treatment plan, and the possible risks and benefits of participation. If you wish for your child to take part in this study, you will be asked to sign this consent form.

This research study is being conducted at the Masonic Cancer Center of the University of Minnesota. Christen Ebens, MD of the Department of Pediatrics is the principal investigator (the physician in charge) of this research study.

Introduction

This study uses umbilical cord blood as the source of stem cells for transplantation after standard treatment with three chemotherapy drugs, busulfan, melphalan and fludarabine. After high doses of chemotherapy, it is necessary to transplant new stem cells since the patient's own stem cells have been killed. Stem cells are the "parent cells" of the blood and bone marrow. The source of these stem cells are from an umbilical cord that were collected at the time of a baby's birth (with permission from the mother) and stored frozen until needed. These "parent cells" make new bone marrow which in turn makes new blood cells.

In a standard transplant, the stem cells used are selected based on their "match" to the patient: typically the better the match, the better the transplant outcomes. Recent research however indicates that a less than perfect match or a "mismatch" between the donor stem cells and the patient may lessen the chance of the leukemia or MDS returning (relapsing). The research element of this study is the intentional use of a mismatched cord blood unit as the stem cell source.

Since your child's disease is at a high risk of relapsing after transplant, your child is being offered this research study using a mismatched umbilical cord blood unit to improve the chance of long-term disease control.

Study Purpose

The main purpose of this study is to determine how often blood count recovery occurs within 6 weeks in young children with leukemia or myelodysplastic syndrome after a standard umbilical cord blood transplant (UCBT) using a unit that is a "mismatch."

Three to four transplants are done each year under this study.

Study Procedures

The only research element in this trial is use of a mismatched cord blood unit. For a description of all the standard (routine) procedures that your child will undergo, please see Appendix I of this document.

Possible Risks and Side Effects of the Research

The risks associated with the transplant procedure are listed in Appendix II. There is a risk of having all, some, or none of these side effects and the side effects may vary in severity. The use of a mismatched cord blood unit may increase the likelihood of these risks. The severity may be mild, moderate or severe, including death. Any symptoms or conditions that are present before treatment starts may get worse. Also, there is always the chance of a side effect that is not yet known.

Medications are given to prevent or lessen the side effects. Many side effects are reversible and go away shortly after the treatment is completed, but in some cases side effects can be serious, long-lasting, or even fatal.

The biggest risk specific to using a mismatched cord blood unit is an increased risk of Graft versus Host Disease (GVHD).

GVHD is caused by donor (or graft) cells attacking the patient's (or host) body. GVHD can occur either within the first 3 months after the transplant (acute GVHD) or later, usually around 6 to 8 months after the transplant (chronic GVHD). Drugs that suppress the immune system are routinely given after a transplant to reduce the risk and/or severity of GVHD. If GVHD occurs, standard GVHD therapy is given.

Acute GVHD commonly involves the skin, liver, and the intestines with symptoms such as a skin rash, jaundice (yellowing of the skin), nausea, vomiting and diarrhea. The treatment of acute GVHD may require high doses of cortisone-like drugs (methylprednisolone or prednisone).

Chronic GVHD usually involves the skin, liver, eyes, glands and joints with symptoms such as skin rash, jaundice (yellowing of the skin), dry mouth or/eyes, weakness or a pain and tightening

around the joints. Chronic GVHD may be mild and respond to drugs which suppress the immune system, or it could be very severe; it may also last for several years.

Alternatives to Study Participation

You may decide to not have your child participate in this transplant study. Alternatives include:

- supportive care with no treatment for your child's disease
- investigational therapy at this hospital or at another institution
- a standard stem cell transplant with this conditioning regimen using a matched donor source

Your child's doctors can tell you more about the possible benefits of a transplant and of other options.

Potential Benefits

Your child may benefit from the transplant by curing the disease under treatment, but this cannot be guaranteed. When compared to related and unrelated bone marrow transplants, umbilical cord blood transplants have some known benefits. These include immediate availability and reduced risk of viral contamination. Overall umbilical cord blood is associated with significantly less acute GVHD as compared to bone marrow from a HLA matched unrelated donor.

Study Costs

You and your child's insurance provider will be responsible for all costs associated with the transplant, including the costs of the umbilical cord blood unit, routine diagnostic tests, the preparative regimen, hospitalizations and follow-up clinic visits. You will be responsible for payment of all fees and charges related to medical services not covered and of any deductibles and co-payments.

You will receive no monetary compensation for your child's participation in this study.

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that your child has suffered a research related injury let the study physicians know right away.

Protected Health Information (PHI)

We are committed to respect your privacy and to keep your child's personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you or your child. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

How will my child's information be used in publications and presentations?
We may publish the results of this research in scientific, medical, academic or other journals or reports, or present the results at conferences. Information that makes it easy to identify you or your child (such as your name and contact information, SSN and medical records number) will not be part of any publication or presentation. If your child has an extremely unique or rare condition that is not shared by many others, it is possible that some people may be able to determine your or your child's identity even without these identifiers.

Confidentiality

Efforts will be made to limit the use and disclosure of your child's personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your child's information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance (such as the Quality Assurance Program of the Human Research Protection Program (HRPP))..

Organizations that may look at and/or copy your child's medical records for research, quality assurance, and data analysis include:

- The University of Minnesota research team and any institutions or individuals collaborating on the research with us;
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- Others at the University of Minnesota and M Health/Fairview who provide support for the research or who oversee research (such as the Institutional Review Board or IRB which is the committee that provides ethical and regulatory oversight of research at the University, systems administrators and other technical and/or administrative support personnel, compliance and audit professionals (Such as the Quality Assurance Program of the Human Research Protection Program (HRPP)) , individuals involved in processing any compensation you may receive for your participation, and others);
- The Masonic Cancer Center at the University of Minnesota and/or their designee
- National and international transplant registries including the Center for International Blood and Marrow Transplant Research (CIBMTR) and National Marrow Donor Program (NMDP)
- The Cord Blood Bank (that provided the umbilical cord blood),
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

To this extent, confidentiality is not absolute.

A description of this clinical trial is available on www.ClinicalTrials.gov as required by U.S. law. This web site will not include information that can identify your child. At most, the web site will include a summary of the results. You can search this web site at any time.

If we learn about any of the following, we may be required or permitted by law or policy to report this information to authorities:

- Current or ongoing child or vulnerable adult abuse or neglect;
- Communicable, infectious or other diseases required to be reported under Minnesota's Reportable Disease Rule;
- Certain wounds or conditions required to be reported under other state or federal law; or
- Excessive use of alcohol or use of controlled substances for non-medical reasons during pregnancy.

Voluntary Participation

Your child taking part in this study is your choice. You may choose either for him/her to take part or not to take part in the study.

If you decide for your child to take part in this study, he/she may leave the study at any time. Once the preparative regimen is started, you may withdraw from continued data collection, however not giving the donor cells could result in your child's death. Please let your child's doctors know if you are thinking about stopping the study so they can discontinue collecting study data. The doctors will discuss with you the available standard options for restoring your child's bone marrow. The data collected on your child prior to withdrawal will remain part of the study database and will not be removed.

The study doctor may stop your child from taking part in this study if he/she believes it is in your child's best interest.

No matter what decision you make, there will be no penalty to your child and your child will not lose any of his/her regular benefits. Leaving the study will not affect your child's medical care. He/she can still get your medical care from our institution.

Will anyone besides the study team be at my child's consent meeting?

You may be asked by the study team for your permission for an auditor to observe your consent meeting. Observing the consent meeting is one way that the University of Minnesota makes sure that your rights as a research participant are protected. The auditor is there to observe the consent meeting, which will be carried out by the people on the study team. The auditor will not document any personal (e.g. name, date of birth) or confidential information about you or your child. The auditor will not observe your consent meeting without your permission ahead of time.

New Information

You will be told about new information or changes in the study that may affect your child's health or your willingness for him/her to continue in the study.

Contacts and Questions

The physicians involved in your child's care are available to answer any questions you may have concerning this study. In addition, you are encouraged to ask questions concerning this study that you may have in the future. If you have any questions concerning this particular study, you may contact the principal investigator of the study, Dr. Ebens at (612) 626-8094.

Whom do I contact if I have questions, concerns or feedback about my experience?

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants..

You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

The HRPP may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous. If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for study team contact information and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

If you choose for your child to participate, you will be given a signed copy of this form to keep for your records.

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Signatures

I have read it or it has been read to me. I have had my questions answered. I agree for my child to take part in this transplant study.

_____
Printed name of child

_____ _____
Signature of parent/guardian #1 Date

_____
Printed name of parent/guardian #1

_____ _____
Signature of parent/guardian #2 (optional) Date

_____
Printed name of parent/guardian #2 (optional)

_____ _____
Signature of the researcher obtaining consent Date

_____
Printed name of the researcher obtaining consent

Witness Signature (if applicable)
The parent/guardian was unable to read or sign this consent form because of the following reason:

☐ The parent/guardian is unable to read the information
☐ The parent/guardian is visually impaired
☐ The parent/guardian is non-English speaking
☐ The parent/guardian is physically unable to sign the consent form. Please describe:

_____

☐ Other (please specify):

_____

For the Consent of Non-English Speaking Participants when an Interpreter is Used:
As someone who understands both English and the language spoken by the parent/guardian, I represent that the English version of the consent form was presented orally to the parent/guardian in the parent/guardian's own language, and that the parent/guardian was given the opportunity to ask questions.

_____ _____
Signature of Interpreter Date

_____
Printed Name of Interpreter

OR:

Statement from a Non-Interpreter:
As someone who understands both English and the language spoken by the parent/guardian, I represent that the English version of the consent form was presented orally to the parent/guardian in the parent/guardian's own language, and that the parent/guardian was given the opportunity to ask questions.

_____ _____
Signature of Individual Date

_____
Printed Name of Individual

Appendix I: Procedures in a Standard of Care Transplant

Screening

The following routine tests and evaluations will be done to determine eligibility for a transplant:

- medical history, including review of disease symptoms
- physical exam including vital signs, height and weight
- routine blood tests (requiring approximately 2-3 tablespoons of blood) to evaluate bone marrow, liver, and kidney function and other disease related testing
- a pre-transplant viral panel (requiring 1 tablespoon of blood) to check for exposure to viruses, including hepatitis and HIV. Persons who test positive for HIV will not be eligible for a transplant. It will be recommended that a Blood Bank physician contact your child's personal physician regarding further testing. By law, the Minnesota Department of Health must be notified of persons testing positive for hepatitis or HIV.
- an electrocardiogram (ECG) - a test that shows the electrical activity of the heart
- an echocardiogram to determine the pumping ability of the heart
- a bone marrow biopsy
- a spinal tap (lumbar puncture)
- an evaluation by neuropsychology to assess your child's developmental level before the transplant
- any other tests or evaluations as felt medically appropriate

A central venous catheter will be placed in a large vein in the chest area to allow easier administration of intravenous (IV) medications including the chemotherapy drugs and for collecting blood without additional needle sticks. The catheter will also be used for blood transfusions (if needed) and for infusion of the stem cells (transplant).

Treatment Plan

Treatment can be thought of in 3 components – 1) preparative therapy given over several days using the standard drugs fludarabine, busulfan, and melphalan, followed by 2) the infusion of the umbilical cord blood cells through the catheter (transplant), and 3) the recovery phase, both in and out of the hospital.

1) Preparative Therapy

Your child will be admitted to the hospital approximately 9 days before the transplant to give the preparative chemotherapy. Busulfan will be given one time a day for 4 days followed by melphalan and fludarabine each given once a day, on the same day, for 3 days. All of the treatment will be given through your child's central line. After the 3rd day of melphalan and fludarabine, there will be one day of no treatment.

2) Transplant

On the day of the transplant, the UCB cells will be thawed out and given as a short infusion similar to a blood transfusion through your child's central line.

3) Blood Count Recovery

Recovery of your child's blood counts will take several days to several weeks to fully recover. Once your child's blood counts are at a safe level, he or she will be discharged from the hospital to begin follow-up.

Follow-up and Care After the Transplant

Frequent physical exams and blood tests will be done to check for blood count recovery and to look for side effects. During the first 2-3 weeks after the transplant, blood will be drawn daily to check for blood count recovery. Appropriate supportive care is given to all patients after a transplant. This may include transfusions of red blood cells or platelets, medicines to prevent or treat infections and drugs to encourage bone marrow recovery.

Blood will be drawn less frequently as blood counts improve. After blood count recovery and discharge from the hospital, at least weekly follow-up visits in the outpatient clinic will occur for the 1st 3 months after the transplant. Routine clinic follow-up is required at 6, 12 and 24 months after the transplant with yearly contact (in person, by phone or mail). To track the effect a transplant has on development, the neuropsychology assessment will be done a 12 and 24 months and again at 5 years after the transplant.

Appendix II: Risks of Preparative Regimen and Transplant

Possible Risks and Side Effects of the Treatment

There are risks associated with the transplant procedure. There is a risk of having all, some, or none of these side effects and the side effects may vary in severity. The severity may be mild, moderate or severe, including death. Any symptoms or conditions that are present before treatment starts may get worse. Also, there is always the chance of a side effect that is not yet known.

Medications are given to prevent or lessen the side effects. Many side effects are reversible and go away shortly after the treatment is completed, but in some cases side effects can be serious, long-lasting, or even fatal.

Risks of the Preparative Regimen

Busulfan		
Common	**Less Common**	**Rare**
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) which may cause tiredness, headache, dizziness • hair loss or thinning, including face and body hair (usually grows back after treatment) • long-term or short-term infertility (inability to have children) in men and women	• tiredness (fatigue) • sores in mouth or on lips • fever • nausea • vomiting • rash • loss of appetite • diarrhea	• abnormal blood tests results which suggest that the drug is affecting the liver • allergic reaction with hives, itching, headache, coughing, shortness of breath, or swelling of the face, tongue, or throat • scarring of lung tissue, with cough, difficulty breathing, and shortness of breath that may occur after prolonged use, or even months or years after stopping the drug • seizure • leukemia (several years after treatment) • darkened skin • heart problems with high-dose treatment, most often in people with thalassemia • problems with the hormone system that cause weakness, tiredness, poor appetite, weight loss, and darker skin • death due lung damage, bone marrow shutdown, or other causes

Seizures are a potential risk associated with busulfan; however the anti-seizure drug **levetiracetam (Keppra)** is effective at preventing them. Keppra will be given beginning before the 1st dose of busulfan and continuing through the last dose. Risks of Keppra include hallucinations; fever, chills, body aches, flu symptoms; weakness, lack of coordination; increasing or worsening seizures; and nausea, stomach pain, loss of appetite, itching, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes). Less serious side effects include dizziness, spinning sensation; drowsiness; feeling irritable; headache; runny nose, sore throat; or neck pain.

Fludarabine		
Common	**Less Common**	**Rare**
• low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness • tiredness (fatigue) • nausea • vomiting • fever and chills • infection	• pneumonia • diarrhea • loss of appetite • weakness • pain	• numbness and tingling in hands and/or feet related to irritation of nerves • changes in vision • agitation • confusion • clumsiness • seizures • coma • cough • trouble breathing • intestinal bleeding • weakness • death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes

Melphalan		
Common	**Less Common**	**Rare**
• nausea • vomiting • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness	• short-term or long-term infertility (inability to have children) • weakness	• severe allergic reaction • loss of appetite • scarring (fibrosis) or inflammation of lungs • hair loss, including face and body hair • rash • itching • second type of cancer (may happen years after treatment) • death from lung damage or other causes

Risks of the Transplant
With infusion of the stem cell (medications will be given before, during and after the infusion to less or prevent these side effects):

- nausea and vomiting
- possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)

Risks of a transplant regardless of where the stem cells come from include:

Marrow Aplasia (Empty Bone Marrow): All patients will have low blood counts from the chemotherapy, but are expected to normalize within a few weeks after the transplant. Marrow aplasia and failure to engraft are names used to describe when blood counts do not recover as expected.
Symptoms of marrow aplasia include increased risk of bleeding and/or bruising due to low platelets, increased risk of infection due to low white blood cell count, and shortness of breath and tiredness as a result of anemia due to low red blood cell count. Marrow aplasia is treated with blood transfusions and growth factor (G-CSF - which stimulates bone marrow cells), and other precautions. Severe or prolonged aplasia (lasting more than 1 month) can lead to death, usually from infection. If the bone marrow does not recover, sometimes it can be corrected by another transplant; however not all patients are able to have a transplant.

G-CSF will be given as a once a day infusion beginning on day +1 and continuing for 3 days after blood count recovery.

Graft versus Host Disease (GVHD): is caused by donor (or graft) cells attacking the patient's (or host) body. GVHD can occur either within the first 3 months after the transplant (acute GVHD) or later, usually around 6 to 8 months after the transplant (chronic GVHD). Drugs that suppress the immune system are routinely given after a transplant to reduce the risk and/or severity of GVHD. If GVHD occurs, standard GVHD therapy is given.
Acute GVHD commonly involves the skin, liver, and the intestines with symptoms such as a skin rash, jaundice (yellowing of the skin), nausea, vomiting and diarrhea. The treatment of acute GVHD may require high doses of cortisone-like drugs (methylprednisolone or prednisone).

Chronic GVHD usually involves the skin, liver, eyes, glands and joints with symptoms such as skin rash, jaundice (yellowing of the skin), dry mouth or/eyes, weakness or a pain and tightening around the joints. Chronic GVHD may be mild and respond to drugs which suppress the immune system, or it could be very severe; it may also last for several years.

As part of standard transplant care, Tacrolimus and Mycophenolate Mofetile (MMF) will be started 3 days before the transplant to prevent or reduce the severity of GVHD. MMF will be given for about 1 month after the transplant and Tacrolimus will continue in an oral (by mouth) form for approximately 6 months.

Tacrolimus		
Common	**Less Common**	**Rare, but may be serious**

Tacrolimus		
Common	**Less Common**	**Rare, but may be serious**
▪ kidney problems ▪ loss of magnesium, calcium, potassium ▪ high blood pressure ▪ tremors ▪ increases in cholesterol and triglyceride	▪ nausea ▪ vomiting ▪ liver problems ▪ changes in how clearly one can think ▪ insomnia ▪ unwanted hair growth ▪ confusion	▪ seizures ▪ changes in vision ▪ dizziness ▪ red blood cell destruction

It is very important that grapefruit or drinks with grapefruit juice are not consumed while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study**.** Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

Mycophenolate Mofetile (MMF)	
Common	**Rare, but may be serious**
• constipation • stomach pain or swelling • nausea • vomiting • difficulty falling asleep or staying asleep • pain, especially in the back, muscles, or joints • uncontrollable shaking of a part of the body • headache • rash	• diarrhea • swelling of the hands, arms, feet, ankles, or lower legs • difficulty breathing • chest pain • fast heartbeat • dizziness • fainting • lack of energy • pale skin • black and tarry stools • red blood in stools • bloody vomit • vomit that looks like coffee grounds • yellowing of the skin or eyes

Damage to the Vital Organs: Some patients will experience severe lung problems due to a reaction of the lungs to the chemotherapy. Although treatments are available for this type of pneumonia, interstitial pneumonia can be fatal.

Some patients will suffer veno-occlusive disease of the liver (VOD), a complication that may result from the chemotherapy. Patients who have VOD may become jaundiced (yellowish skin), develop liver function abnormalities, abdominal pain and weight gain. Although many patients recover, these complications may result in organ failure and permanent damage, or even death.

In order to help the liver and gall bladder the drug ursodiol will be given for at least 30 days after the transplant. It can only be given orally, and potential side effects of ursodiol are generally

gastrointestinal (diarrhea, constipation, upset stomach, indigestion, vomiting). Rarely flu-like symptoms can occur.

Serious Infections: Complete recovery of the immune system may take many months. During this time, there is an increased risk of infections. Medications to reduce the risk of developing an infection are prescribed during this time; however, preventative treatments are not always effective. If an infection develops, discharge from the hospital may be delayed or re-hospitalization required. Infections can be fatal.

lncomplete Donor Engraftment: This occurs when an insufficient number of the donor cells are present in the blood of the patient. Rarely a second transplant may be done.

Sterility and Future Childbearing Potential for Males and Females: Chemotherapy may affect fertility. Male patients may become sterile (unable to produce sperm). Female patients may find that their menstrual cycle becomes irregular or stops permanently. Damage to reproductive tissue may result in birth defects or permanent inability to father a child or become pregnant.

Additional Risks Associated with Umbilical Cord Blood (UCB) as a Cell Source:
Genetic disease within the cord blood cells: It is possible that certain genetic diseases of the blood or immune system may be passed through the transplanted umbilical cord blood cells. While these diseases are very rare, each umbilical cord blood unit cannot be tested for every possible genetic disease. To reduce this possibility further, cord blood is not collected from babies with a known history of genetic diseases.

Incorrect labeling of the UCB units: Though extremely unlikely, it is possible that incorrect labeling of an umbilical cord blood unit could occur. In this event, the transplant may be delayed for several hours while the UCB unit is typed (check to see if it is a correct match). Should the typing be incorrect, the transplant will be delayed until an alternative source of cells is located.