Masonic Cancer Center, University of Minnesota
Blood and Marrow Transplantation Program

PARENTAL CONSENT TO PARTICIPATE IN RESEARCH
(for children < 18 years of age)

Hematopoietic Cell Transplantation In Children With Juvenile Myelomonocytic Leukemia

Your child is invited to participate in a research study because she/he has juvenile myelomonocytic leukemia. This study uses chemotherapy to destroy the diseased marrow followed by the infusion (transplantation) of umbilical cord blood (UCB) cells donated at the time of the baby's birth and stored frozen in a cord blood bank until needed. Because the chemotherapy destroys both the cancer cells and the bone marrow, the infusion of the healthy donor cells is needed to replace the diseased marrow.

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 permit 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.

Research studies only include people who want to take part in the study. Please take time to make your decision. We encourage you to discuss your decision with your child's doctors, family, and friends.

This study is being conducted by the Masonic Cancer Center of the University of Minnesota. Dr. Margaret L. MacMillan of the Department of Pediatrics at the University of Minnesota is the lead (principal) investigator for the study.

Contact information for emergencies after hours or on weekends or holidays:
Call (612) 273-3000, the University of Minnesota Medical Center Switchboard operator. Ask to have the BMT Physician On Call paged.

Introduction

Juvenile Myelomonocytic Leukemia (JMML) is a very rare cancer of the bone marrow usually occurring in children 4 years of age or younger. Intensive chemotherapy (anti-cancer drugs) may prolong survival, but it is not a cure. Long term survival has only been achieved using bone marrow transplantation.

The transplant procedure consists of three major components: 1) a short course of chemotherapy drugs to clear the bone marrow of leukemia cells and make room for the donor cells to take hold (engraft), 2) the transplant which is simply an infusion of the donor cells (UCB cells in this case) similar to a blood transfusion, and 3) a recovery period of low blood counts while waiting for the donor cells to engraft and blood counts returning to normal. The entire transplant from the start of the preparative regimen to blood count recovery typically takes 4 to 6 weeks, but may be shorter or longer depending on the recovery course.

Study Purpose

Different transplant centers have used various combinations of chemotherapy and/or radiation to as a preparative regimen. The purpose of this study is to provide a preparative regimen that does not include radiation for this very young group of patients with juvenile myelomonocytic leukemia.

This study plans to enroll 20 patients over approximately 25 years.

Procedures

Pre-transplant evaluation:

If you agree for your child to take part in this study, the following tests and evaluations will be performed to determine if he/she can safely participate:

- Medical history including date of diagnosis, symptoms that lead to the diagnosis, and prior treatment, if any
- Physical examination, including height and weight.
- Routine blood tests (approximately 4 – 5 tablespoons) to determine your child's general health, including liver and kidney function.
- Blood tests (requiring 2 tablespoons of blood will be drawn to test to check for exposure to hepatitis and other viruses. If the results are positive, you will be notified and it will be recommended that a Blood Bank physician contact your child's personal physician regarding possible further testing. By law the Minnesota Department of Health must be notified if your child test positive for hepatitis. Because of the sensitive nature of these tests, you have the right to review the results. If your child has hepatitis he/she will not be eligible to take part in this study. You child will be referred to the appropriate physicians and counselors.
- Routine urine tests
- Bone marrow biopsy
- Tests to evaluate heart and lung function
- Chest x-ray and other x-rays or scans as needed to look for infections

Before treatment is started a central line will be placed to allow easier administration of intravenous (IV) therapies. A central venous catheter is a flexible sterile tube that will be placed into a large vein that runs under your child's collarbone so that blood can be

withdrawn and medications given to your child more easily and with less discomfort. This tube is placed under either local or general anesthesia.

Some additional tests may be done to evaluate your child's disease. These tests will help your child's doctor determine the amount of disease she/he has at the start of treatment and to follow the status of your child's disease throughout treatment.

Pre-Transplant Chemotherapy (Preparative Regimen)
Beginning 6 days (on day -6) before the planned transplant day, your child will receive a course of chemotherapy drugs to clear the bone marrow cells and to lower the immune system in preparation for the donor cells.

Note about treatment day numbering with transplants: The day of the transplant is called day 0. Days before the transplant are indicated by a negative number and days after the transplant are indicated by a positive number (or no sign). This study begins on day -8 or 8 days before the day of the planned transplant.

Busulfan will be given through the central venous line (days -7, -6, -5, and -4) . After the first dose, your child's blood will be checked. The hospital pharmacists will calculate the rest of the busulfan doses based on results of the blood testing.

Cyclophosphamide will be given once a day through the central venous line for two days (days -3 and -2)

ATG will be given once a day through the central venous line for three days (days -3, -2, and -1), and

Melphalan will be given once through the central venous line on day -1.

The Transplant (day 0)
On the day of the transplant (Day 0), the umbilical cord blood cells will be infused through your child's central venous line similar to a blood transfusion.

After the transplant your child's blood counts will be checked daily until about a week after the counts show sign of recovery. This is expected to take approximately 4 weeks. Once your child's blood counts recover, they will be checked at least once a week for the 1st 3 months after the transplant.

Retinoic Acid will be started 60 days after the transplantation, once a day by mouth and will continue for 1 year. The purpose of this medication is to help prevent the leukemia from recurring.

Follow-Up After the Transplant

Your child will be seen at 2, 3, 6, 12 months, and 2 years after the transplant for follow-up. At these visits a physical exam will be done, blood and bone marrow tests performed and a disease reassessment made. Additional visits may be required based on your child's individual needs.

After 2 years your child will continue to be followed at least once a year as is standard for all transplants at the University of Minnesota. This may be in person or by letter.

Risks/Discomforts

While on treatment, your child will have side effects from the study drugs. Your child is at 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. Also, there is always the chance of a side effect that is not yet known.

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

Risks Associated with the Preparative Regimen:

Busulfan		
Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
• 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 • serious infection due to low white blood cell count	• 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 • leukemia (several years after treatment) • darkened skin • heart problems with high-dose treatment, most often in people with thalassemia (a type of genetic anemia that is present at birth) • problems with the hormone system that cause weakness, tiredness, poor appetite, weight loss, and darker skin

Busulfan		
Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
		• 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). Many anti-seizure drugs, including Keppra, have been shown to increase the risk of depression and suicidal thoughts. Report any new or worsening symptoms of depressed mood to your child's doctor. This might include mood or behavior changes, depression, anxiety, or if your child is more agitated, hostile, irritable, hyperactive (mentally or physically), or is having thoughts about suicide or self-harm. Less serious side effects include dizziness, spinning sensation; drowsiness; feeling irritable; headache; runny nose, sore throat; or neck pain.

Cyclophosphamide:		
Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
• low white blood cell count with increased risk of infection • diarrhea • vomiting • liver damage • lower sperm production in men • hair loss • nausea • loss of appetite • missing or stopping menstrual cycle in women	• sores in mouth or on lips • blood in urine • fatigue • low platelet count (mild) with increased risk of bleeding • darkening of nail beds • fetal damage if pregnancy occurs while taking the drug	• lung scarring with cough and shortness of breath • heart failure with high doses • decrease in sodium level in the blood with high doses • risk of developing other cancers in the future

Cyclophosphamide can cause bleeding in the bladder. Giving more fluid through your child's central line and drinking extra liquids may prevent this. A drug called Mesna is given to prevent damage to the bladder and kidneys. Rarely an allergic reaction occurs usually in the form of skin rash and/or itchiness.

Melphalan		
Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
• nausea (at higher doses) • vomiting (at higher doses) • low white blood cell count with increased risk of infection • low platelet count with	• 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

Melphalan		
Likely Side Effects	**Less Likely Side Effects**	**Rare Side Effects**
increased risk of bleeding • anemia (low red blood cell count) with symptoms like tiredness, paleness, or trouble catching breath		• rash • itching • second type of cancer (may happen years after treatment) • death from lung damage or other causes

Thymoglobulin (ATG)		
Common	**Less Frequent**	**Uncommon**
• fever • chills • lowered white blood cell count • pain • headache • abdominal pain • diarrhea • hypertension • nausea • lowered platelet count • swelling of your hands and/or feet • shortness of breath (dyspnea) • lack or loss of strength and energy (asthenia) • abnormally high levels of potassium (hyperkalemia) with symptoms of nausea and weakness • faster than normal heart rate (tachycardia)	• malaise (feeling poorly) • dizziness	• severe allergic reaction (anaphylaxis)

Risks Associated with Transplant (regardless of donor cell source):

Stem Cell Infusion Reaction: The donor stem cells are given in a manner similar to a blood transfusion, and as with a blood infusion there is a small risk of an allergic reaction to the cells as they are given. This may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, and headache. Medications are given before the cell infusion to reduce the risk of an allergic reaction. If during the infusion symptoms develop, the rate of the infusion may be slowed or stopped and/or additional medications given to reduce the intensity of any reactions.

Graft versus Host Disease: (also called GVHD) is caused by donor (or graft) cells attacking the patient's (recipient 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). Two drugs (tacrolimus and MMF) are given beginning on day -3 to suppress the immune system reducing the risk of 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 steroids (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 like steroids, or it could be very severe; it may also last for several years.

Risks associated with the drugs given to reduce the risk of GVHD:

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**.** 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	• diarrhea • swelling of the hands, arms, feet, ankles, or lower legs • difficulty breathing • chest pain • fast heartbeat

Mycophenolate Mofetile (MMF)	
Common	**Rare, but may be serious**
joints • uncontrollable shaking of a part of the body • headache • rash	• 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

Marrow Aplasia (Suppression of the 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 (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 stem cell transplant; however not all patients are able to have a transplant.

Damage to the Vital Organs: Some patients will experience severe lung problems due to infections such as cyomegalovirus (CMV) and/or 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 high doses of chemotherapy and/or radiation. Patients who have VOD become jaundiced (yellowish skin), have liver function abnormalities, abdominal swelling, and abdominal pain. Although many patients recover, these complications may result in organ failure and permanent damage, or even death.

Serious Infections: Complete recovery of the immune system may take many months following the initial recovery of the white cell count. 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.

Sterility and Future Childbearing Potential for Men and Women: 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. These risks and options will be discussed in detail with the medical staff before beginning treatment.

Risks Associated with Umbilical Cord Blood (UCB) as a Stem Cell Source
Genetic disease within the cord blood cells: It is possible that certain genetic diseases (for example thalassemia or Gaucher's disease) may be passed through the transplanted umbilical cord blood cells. While these diseases are very rare, each umbilical cord blood unit can only be tested for a few of the many possible genetic diseases. 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.

Retinoic Acid	
Common	**Rare, but may be serious**
• typical retinoid toxicity: (symptoms that are similar to those found in patients taking high doses of vitamin a) headache, fever, dry skin, dry mucous membranes (mouth, nose), bone pain, nausea and vomiting, rash, mouth sores, itching, sweating, eyesight changes. • flu-like symptoms: malaise, chills • bleeding problems • infections • swelling of feet or ankles • pain (bone and joint pain, chest discomfort) • abdominal pain	• weight increase • heart rate irregularities (arrhythmias) • flushing • poor appetite • weight loss • earache or feeling of fullness in the ears • diarrhea • dizziness • constipation • numbness and tingling in hands and feet • anxiety • heartburn • low blood pressure • insomnia • depression • high blood pressure • confusion

Retinoic acid causes birth defects and must never be taken by a pregnant woman.

Benefits of Study Participation

Hematopoietic cell transplantation may prolong your child's survival or possibly permanently eliminate the leukemia; however this is not guaranteed. It is hoped that

this study will be of benefit of other children with juvenile myelomonocytic leukemia in the future.

Alternatives to Participation
Instead of being on this study you may consider the following alternatives for your child:

- Additional chemotherapy
- To be enrolled in other investigational research studies at another medical center
- To receive no further treatment, other than that which is required for comfort, could also be given. However, this almost always results in death within months.

Costs
You are responsible for the costs of treatment for your child's treatment on this study, including the cost of the umbilical cord blood (UCB) unit. Costs associated with the pre-transplant work-up, the preparative chemotherapy, the collection and processing of the cells for the infusion on day 0, routine tests and procedures, medications to reduce or prevent side effects, and hospital/clinic costs are all considered standard of care, and will therefore be billed to you or your insurance company. Your insurance provider may not cover all or part of these costs. If you have concerns or questions regarding coverage or potential charges, you should contact the BMT Patient Financial Representative at (612) 273-2800 to review the situation.

Research Related Injury
In the event that this research activity results in an injury to your child, 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)
Your child's PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Confidentiality
The records of this study will be kept private. Information will be kept in your child's medical record and in study case report forms. Information gained from this study will be used for research and educational purposes. If information from this study is published or presented at scientific meetings, your child's name and other personal information will not be used.

If you decide to allow your child to participate in this study, some private health information about him/her will be stored in a computer database at the Masonic Cancer Center at the University of Minnesota. This information will include your child's name and medical record number, date of birth, diagnosis, race/ethnicity, and information about his/her participation in this study. The purpose of storing this information is to assist the Cancer Center in creating reports about research and in making sure that research studies are being done correctly. Your child's information will not be used for any other purpose. There are no plans to erase information from the database. It will be stored indefinitely at the Masonic Cancer Center.

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

- Departments at the University with appropriate regulatory oversight;
- Government agencies including the Food and Drug Administration (FDA), the Office for Human Research Protections, (OHRP), the National Cancer Institute (NCI). These agencies may review the research to see that it is being done safely and correctly.

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

Voluntary Nature of the Study
You are free to withdraw your child from participation in this study at any time, for any reason. However, withdrawal after initiation of treatment could be life-threatening or even fatal, and may not be reasonable. A decision not to participate or withdraw at a later time will not jeopardize your child's ability to receive medical care at present or in the future. Your decision allowing your child to participate in this research is voluntary.

New Information
If during the course of this research study, significant new findings are discovered which might influence your willingness to continue, the researchers will inform you of those developments.

Questions
If you have any questions concerning this particular study, you may contact Dr. Margaret MacMillan at (612) 626-2778.

This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protection 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.

YOU WILL BE GIVEN A SIGNED COPY OF THIS CONSENT FORM

Statement of Consent

I have read the above information and have had an opportunity to discuss my questions. I consent to allow my child to participate in this study.

_____ _____

Parent's signature Date

_____

Parent's Name (printed)

I have explained fully to the parent the above objective of this study, what is to be expected, and the possible complications.

_____ _____

Counseling Physician's signature Date

_____ _____

Counseling Physician's Name (printed)

Signature Block for Witness:

WITNESS STATEMENT:

The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is unable to read the information
☐ The participant is visually impaired
☐ The participant is non-English speaking
☐ The participant 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:

A**s** someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject 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 subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

_____ _____
Signature of Individual Date

_____
Printed Name of Individual