AflacLL1901 (CHOA-AML): A Pilot Study for Newly Diagnosed Pediatric Patients with Acute Myeloid Leukemia (AML)

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You Are Being Asked to Be in a Research Study
Concise presentation of key concepts

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree to be in the study, you will be one of 30 people who are being studied at Emory and Children's Healthcare of Atlanta.

Why is this study being done?
This study is being done to answer the question: We want to study whether adjusting your treatment from 5 cycles to 4 cycles will provide you with the same treatment results. We hope that fewer cycles will decrease the amount of side effects that you may experience during your treatment. We also want to test whether or not the addition of a drug used to treat AML, Gemtuzumab Ozogamicin (GO, Mylotarg™), will reduce the chances of your type of AML from coming back after initial treatment.

Do you have to be in the study?
It is your decision to be part of this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. Before you make your decision, you should take time to learn about the study.

What do I have to do if I choose to participate in this study?
If you are eligible and want to be part of the study, you are expected to receive treatment for about 6 to 8 months. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health every year for about 10 years after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

How is this study going to help you?
If you are in the study, you will be helping the researchers answer the study question. There may be no direct benefit to you. This treatment may help prevent your AML from returning and reduce side effects. The researchers may learn things from your participation in this study that can help other transplant patients.

What are the risks or discomforts I should know about before making a decision?
The study will take time. The procedure that is being tested may not work any better than regular care and may even cause harm. All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious – for this study, these include infusion risks, risks associated with blood draws, loss of privacy, and breach of confidentiality. A full list of expected risks, their frequency and severity are in the "What are the possible risks and discomforts?" section of this document.

Alternatives to Joining This Study
You can choose not to be in this study. You should know about your treatment options before you decide whether you will be in this study. You could be treated using standard medications and treatment cycles for AML.

Costs
You will have to pay for some of the study procedures, in particular those that are not covered by your medical insurance.

The study team can help you work out how much you might have to pay. There is more information in the cost section below.

What Should I Do Next?
Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc.) Make sure you understand which parts of the study are research and which are standard care that you would have even if you did not join the study. Take time to consider this and talk about it with your family and friends.

EMORY UNIVERSITY | Institutional Review Board
Research Administration

Emory University and Children's Healthcare of Atlanta
Consent to be a Research Subject / HIPAA Authorization

Title: AflacLL1901 (CHOA-AML): A Pilot Study for Newly Diagnosed Pediatric Patients with Acute Myeloid Leukemia (AML)

IRB#: 111627

Principal Investigator: Himalee Sabnis, MD

Study-Supporter: Aflac Cancer and Blood Disorders Center

If you are the legal guardian of a child who is being asked to participate, the term "you" used in this consent refers to your child.

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form, you will not give up any legal rights.

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.

What is the purpose of this study?

You are being asked to take part in this research study because you have been newly diagnosed with Acute Myeloid Leukemia (AML). AML is a cancer of the bone marrow, the spongy tissue inside the large bones of the body where blood cells are made. In AML, the bone marrow makes large numbers of immature white blood cells called blasts. These blast cells crowd out the normal cells of the bone marrow. They may also invade body organs including the brain, testes, ovaries, or skin. These cancerous AML cells can sometimes form a solid tumor called a chloroma.

The current standard of care per cooperative pediatric oncology groups is to treat most patients with five cycles of chemotherapy. We have treated AML patients with four (similar but not exactly same) cycles of chemotherapy over the last five years and achieved similar cure rates like national studies. We now want to study prospectively in a larger group whether adjusting your treatment with 4 cycles of our treatment regimen will provide you with the same treatment results. We hope that fewer cycles will decrease the amount of side effects that you may experience during your treatment and especially reduce your risk of heart-related complications with therapy. With our 4-cycle regimen, we want to test whether or not the addition of a drug used to treat AML, Gemtuzumab Ozogamicin (GO, Mylotarg™), will reduce the chances of your type of AML from coming back after initial treatment. We will compare the results of this study with previous studies.

Another goal of the study is to understand the biology of AML better. Study doctors want to obtain and store blood or bone marrow for certain genetic changes (called *genetic markers*) in leukemia cells that will be studied in future. This would help them to learn more about AML and how to treat patients better.

What will I be asked to do?

This research study will be done at Children's Healthcare of Atlanta, in the Aflac Cancer Center & Blood Disorders Center. The people that you will interact with on this research study will include bone marrow transplant doctors and nurses, research nurses, and other specialists, as needed.

What is the Current Treatment for this Disease?

The standard treatment for this disease is to use a combination of cancer-fighting drugs called chemotherapy given in different phases (also called *courses*). Chemotherapy destroys the leukemia cells in the blood and bone marrow. In the first phase, called Induction I, we try to remove all visible signs of leukemia and allow normal blood cells to be restored. This is called remission. The next phase of treatment is called Induction II which is another round of chemotherapy to kill the few remaining leukemia cells that may have survived Induction I. In the next phase of treatment, called Intensification I, more chemotherapy is used to kill any remaining blast cells. Then we do a Stem Cell Transplantation (SCT) or give additional high doses of chemotherapy (in a last phase called Intensification II) to try to maintain the remission.

If you agree to participate in this study, you will undergo the following procedures:

Screening and Pre-treatment Assessments

No study procedures will be done until after you have agreed to participate by signing this Informed Consent.

Standard Medical Tests

Before treatment on this study begins, and while getting treatment, you will have a series of standard medical tests. These tests would be done even if you were not in this study:

- **Physical exam** – including asking you some questions about your medical history and recording your height, weight, blood pressure, pulse, blood oxygen, and organ function.
- **Blood tests** - we will take about a tablespoon of blood from your vein. We will look for infections, kidney function, liver function, and blood counts. Many blood samples will be taken during treatment to check blood counts and the balance of salts in the blood.

- **HLA typing** - we will take blood samples from you and your family for this genetic typing test. The results of this test will determine if any of your family members can be your bone marrow donor.
- **Urine tests** - we will take a small sample of your urine to check for damage, bleeding, or infection in the kidneys or bladder.
- **Pregnancy tests** – given to females of childbearing age prior to treatment
- **Magnetic Resonance Imaging (MRI)** – Only for patients who have a chloroma. MRI uses magnetic waves to look at soft tissues of the body. Sometimes MRI requires an injection of contrast to see other areas of the body. MRI contrast (gadolinium) is administered through a small needle placed into a vein. During the administration of MRI contrast (gadolinium), you may experience the sensation of the contrast being injected. MRIs will be done throughout your treatment on this study.
- **Computed Tomography (CT) Scan** – Only for patients who have a chloroma. CT scans use a computer to put multiple x-rays (pictures of the inside of your body taken with energy beams) together to create a complete picture of the inside of your body.
- **Biopsy** - Only for patients who have a chloroma. A surgical procedure will be done to take a piece of the chloroma for testing. You will be given other consents that cover the risks of the biopsy and the anesthesia.
- **Hearing test** - audiograms will be done throughout your therapy to monitor for changes in your hearing.
- **Spinal Tap** – we will use a needle to take a small sample of the fluid surrounding your spinal column. This sample will be used to see if the tumor has spread to the spinal fluid. You will get pain medication during this procedure. You will be presented with a separate consent that explains the risks of this procedure. This is a not a research test and is considered standard of care.
- **Eye exam** – an eye exam will be done at the time you are diagnosed to make sure your vision is okay.
- **Bone marrow tests** - we will take a small amount of the soft part (marrow) of the center of your hip bone. This sample will be used to determine if the tumor has spread to your bone marrow. You will get pain medication during this procedure. You will be presented with a separate consent that explains the risks of this procedure. Testing of bone marrow includes estimation of disease by a technique called flow cytometry. A special kind of flow cytometry is called Minimal Residual Disease (MRD) testing and will be done as standard of care at the end of each therapy cycle.
- **Chest x-rays** – we will use energy beams to take a picture of your chest to check for infection.
- **Tests of heart function**– you will have an EKG (electrocardiogram, a recording of the electrical activity of the heart) and echocardiogram (ultrasound of the heart) to test how the heart works.
- **Tests of lung function** – Only for transplant patients. We will check how your lungs are working by having you breathe into a machine. This is called a Pulmonary Function Test.
- **Tests of kidney function** – we will check how your kidneys are working by checking blood levels of creatinine or by doing a Glomerular Filtration Rate (GFR) or a Creatinine Clearance. To do a GFR, you are injected with a special dye and then have several imaging studies of your kidneys. The imaging studies will take about 20 minutes each and will be done 1 to 2 hours apart. You will get a separate consent from that covers the risks of a GFR scan. To do a Creatinine Clearance we will have to collect a 24-hour urine sample and then take one blood sample at the end of the 24-hour period.

Treatment Plan

The treatment plan involves cancer fighting medicine called chemotherapy. The treatment on this clinical trial takes about 6 to 8 months. It is divided into 4 stages: Induction I, Induction II, Intensification I, and Intensification II. Chemotherapy will also be given in the spinal fluid during Induction I, Induction II and

Intensification I. Depending on your disease risk group, you may receive a stem cell transplant instead of Intensification I and II.

Chemotherapy will be given in the following stages:

- Induction I: chemotherapy given for 10 days followed by 3 weeks of rest (28 days total).
- Induction II: chemotherapy is given for 6 days followed by 3 weeks of rest (28 days total).
- Intensification I: chemotherapy is given over 5 days followed by 3 weeks of rest (28 days total).
- Intensification II: chemotherapy is given over 9 days followed by 3 weeks of rest (28 days total).

During first course of chemotherapy (Induction I), genetic markers in your blood will be used to determine whether or not you receive gemtuzumab ozogamicin (GO). After completion of first course of chemotherapy (Induction I), patients will be classified into low or high-risk groups.

Both groups will receive the treatment described in Induction II.

The study doctor will then decide whether you get a stem cell transplant or more chemotherapy. This will be decided based on 2 factors: 1) whether your leukemia is considered high or low risk for relapse and 2) whether there is an appropriate stem cell donor for you. In all cases, the study doctor will discuss the pros and cons of each treatment option.

In this study, subjects who are considered to be Low risk for relapse will not have a stem cell transplant even if they have a matched family donor. Researchers want to know if this group of subjects can have the same or better cure rate without the risk of side effects from a stem cell transplant. Subjects who are High risk will have a stem cell transplant with either a matched family donor or an alternative donor (matched non-family donor).

If you are ***low risk***, you will be given more chemotherapy, then you will proceed to:

- Intensification I: chemotherapy is given over 5 days followed by 3 weeks of rest (28 days total) followed by
  Intensification II: chemotherapy is given over 9 days followed by 3 weeks of rest (28 days total).

If you are ***high risk*** and given a stem cell transplant, then you will proceed to:

- 5 days of treatment to kill all of your bone marrow cells. The stem cell transplant will then replace these cells with stem cells from a matched donor. The donor may be a family member, an unrelated person, or donated cord blood. A separate consent with additional information about SCT will be provided to subjects proceeding to SCT.

If you are high risk and there is a delay in receiving stem cell transplant, then you will proceed to:

- Intensification I: Your physician will decide the best chemotherapy option for you during this cycle After this, you will proceed to stem cell transplant

Patients who have a mutation in their leukemia called FLT3-ITD will be deemed **high-risk**. These subjects will take a FLT3-ITD inhibitor called sorafenib by mouth until Day 28 of each stage. Subjects will also be given a stem cell transplant if there is an appropriate donor following Induction II or Intensification I. As a final course,

these patients will receive 1 year of treatment with sorafenib alone, called Maintenance after stem cell transplant.

Bone marrow tests are done at the end of Induction I, Induction II, Intensification I and at the end of treatment. If you are not responding to treatment, your doctor will remove you from the study and recommend a different treatment.

Treatment Plan Tables

Treatment that is standard for AML is described in **Attachment #1.** This includes the commonly used chemotherapy that all subjects will receive during Induction I, Induction II, and Intensification I, and also the radiation therapy that you may receive on this study if you have a chloroma (a greenish solid tumor mass that some people with AML have. It is made up of abnormal white blood cells and occurs anywhere in the body).

The following tests will be done as standard of care.
The results of these tests will be used to identify what risk group subjects belong to and will be used to make treatment decisions on this study. For these samples, we will label them with your name and the results will be part of your medical record.

Cytogenetic Testing:

The study doctors want to know about changes in the genetic material in your leukemia cells. This will help study doctors to identify abnormalities in the genes that might affect the development of AML and its treatment. This information will be sent to a reference laboratory to define the risk classification for relapse. Although cytogenetic testing is usually part of standard care, this study recommends that cytogenetic testing be done by an approved laboratory. If your institution does not have an approved laboratory, then it is possible that your blood/bone marrow samples will be shipped to a laboratory outside of your institution for cytogenetic testing. For this study, samples will be sent to FoundationOne® Heme. Additionally, once the testing has been done, a copy of the cytogenetics information will be sent to a cytogenetics specialist who will make sure that the diagnosis is correct. Having a specialist check the diagnosis is not part of standard care. For this testing we will collect about ½ teaspoonful to ¾ teaspoonful of bone marrow. If we cannot collect enough bone marrow, we may also collect some blood (about 1 teaspoonful).

FLT3 Testing:

The study doctors also want to know if there are molecular changes in the FLT3 gene of your leukemia cells. This will allow study doctors to identify FLT3 mutations (molecular changes) that may affect your treatment. Samples will be sent to an approved laboratory for this testing. FLT3 test results will define the risk classification in this study. If you have certain mutations in your FLT3 gene which have been shown to predict a higher risk of relapse, you will be assigned a high-risk classification.

Minimal Residual Disease at Diagnosis and End of Induction I:

The study doctors want to look for minimal residual disease (MRD) in bone marrow and blood. MRD is a test to look for very small amounts of leukemia cells and is performed by a special test called flow cytometry. Flow cytometry is routinely done at the time of diagnosis to confirm the diagnosis of AML. MRD is a special kind of flow cytometry. MRD levels may be used to predict the risk of leukemia coming back. The results of the first MRD test at the end of Induction I (the first course of chemotherapy) will be used to evaluate how effective

treatment is for you and determine risk assignment and subsequent treatment. If you are MRD "positive" after Induction I, you will be assigned a high-risk classification. If you are MRD "negative" after Induction I, you will be assigned a low risk classification. Subjects that are classified as high risk will receive different treatment than subjects that are classified as low risk. Therefore, the MRD results may determine the type of treatment you receive. MRD testing is required for study participation and is not investigational. The amount of extra bone marrow taken at each time will be about ½ teaspoonful to 1 teaspoonful. If we cannot collect enough bone marrow, we may also collect some blood (about 1 teaspoonful). This study will provide more information about the use of MRD tests to determine the risk of leukemia relapse.

Research Study Tests and Procedures

Optional Research Tests

There are biology research tests. These tests are not part of standard care and will only be done if you agree to give extra blood or bone marrow samples. At the end of this consent, there are questions for you to indicate if you want to take part in these optional research tests.

Future Studies:

If you agree, as part of future genetic studies we would like to take about 1 teaspoonful of blood before the beginning of treatment on this study and again at the end of Induction Course 1 therapy. The extra blood for this optional test can usually be obtained through the same needle stick as the samples for the routine tests. However, sometimes a second needle stick may be required. There may be additional pain associated with obtaining the blood.

If you agree, we would like to keep any extra bone marrow or blood to bank for future studies. The research that may be done with the samples is not designed to help you during your present treatment. It might help people who have cancer and other diseases in the future.

You will receive no payment or money for taking part in this study. If you provide specimens to the researcher, there are no plans for you to profit from any new products developed from research done on your specimens.

Parts of your transplant care that will not be affected by being in this study

Other parts of your AML care are not affected by being in this study. Participating in this study does not prevent your doctor from starting or stopping any medicines or doing any tests that they think are needed.

How long will I be in the study?

Participants in this clinical trial are expected to receive treatment on this study for 6 to 8 months. After treatment, subjects will have follow-up examinations. We will continue to collect some medical information about how you are doing for 10 years after the last subject starts the study.

Your doctor or the study doctor may decide to take someone off this study under the following circumstances:

- if he/she believes that it is in the person's best interest
- if the subject's disease comes back during treatment
- if the subject experiences side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for the person

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. Your study doctor or regular doctor will be able to help you stop treatment in way that is safe for you.

Who owns my study information and samples?

If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study. If you withdraw and want your leftover samples destroyed, please write to Dr. Himalee Sabnis, 2015 Uppergate Drive, Atlanta, GA 30322.

What are the possible risks and discomforts?

There are risks involved in this study, and there may be side effects from the treatment. The side effects we know about are described below. They may vary from person to person. With any drug, there may be complications or side effects that we do not know about. Please talk with your doctor about this. If you want to read more about AML, please ask the doctor for more information.

Treatment Risks

All people who receive cancer treatment are at risks of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications.

Common side effects include nausea, vomiting, hair loss, and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. Some chemotherapy may lead to sterility. Sterility is the inability to have children. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy. The risks of the individual drugs given as standard treatment and risks of radiation therapy are listed on the tables in **Attachment #2.** Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency.

There is a risk that the treatment will not cure the cancer or that the cancer can go away after the treatment and then come back at a later date.

For Women:

The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. Since chemotherapy may alter/disrupt normal menstrual cycles, resulting in missed or absent periods, natural methods of family planning should not be used. If you

have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your doctor immediately.

If you are nursing a baby, the drugs used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctor about the length of time you need to avoid nursing.

For Men:

The treatment on this study can damage sperm. You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use an effective method to avoid pregnancy that works well, or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your doctor immediately.

The most serious side effect from cancer treatment is the depression of the number of blood cells. This can result in anemia, increased chance of infection and bleeding tendency. These complications can sometimes be fatal. Bone marrow tests, blood work, scans, spinal taps and laboratory tests will be done to monitor your progress. Blood transfusions may be necessary if the number of blood cells becomes too low. Transfusions of platelets (clotting cells) may also be necessary.

Side effects can be increased with chemotherapy drugs are combined. Side effects are usually reversible when the medication is stopped, but occasionally can persist and cause serious complications.

Risks of Study

If you are being treated with gemtuzumab:

The use of gemtuzumab may cause more complications when combined with the use of standard chemotherapy treatment for AML. The combination of standard therapy with gemtuzumab may result in possible side effects, including a serious liver ailment called Veno-occlusive Disease (VOD). VOD is characterized by an increased bilirubin in the blood and possible jaundice (temporary yellowing of the skin), an enlarged and painful liver, and fluid retention with associated weight gain. In severe cases, VOD can be fatal. The risk of VOD may be greater if you get gemtuzumab and a stem cell transplant.

The risks and side effects related to gemtuzumab are listed in the table below. In addition to the risks described here, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Risks and side effects related to gemtuzumab

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• Headache
• Mouth Sores
• Loss of desire to eat
• Constipation
• Fever and chills including shaking chills. These reactions are more common with the first dose.
• Feeling short of breath
• Pain in the abdomen
• A feeling of tiredness or weakness
• Fewer white blood cells, red blood cells and platelets in the blood
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of platelets causes you to bruise and bleed more easily
• Low levels of potassium in the blood which may make you feel weak or your heartbeat irregularly
• Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage
	• A decrease or an increase in blood pressure
	• Rash, hives or itchiness during the infusion
	• Irregular heartbeat during the infusion
	• Pain in the back
	• Upset stomach
	• Diarrhea
	• Dizziness or fainting
	• Cough
	• Abnormally low levels of certain salts in the body like magnesium, calcium, and phosphate which may require that you take replacement doses
	• Increase in the sugar in the blood
	• Anxiety or depression
	• Difficulty sleeping
		• Allergic reactions during the infusion that can be severe and life-threatening and may lead to difficulty in breathing, a drop-in blood pressure, irregular heartbeat, fluid in the lungs or damage to the lungs and shock.
		• The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heartbeat or damage to the kidneys.
		• Damage to the lungs that can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood.
		• Bleeding which can occur in the head, the stools, the nose, and urine and other places in the body.
		• Infections including those caused by bacteria, virus and fungus
		• Damage to the liver which can be severe and life-threatening and is more common if you have had a bone marrow transplant or plan to have one in the future.

We will be checking you closely to see if any side effects are happening. Side effects of drugs like gemtuzumab usually get better if the treatment is stopped, but in some cases the side effects can be serious or long lasting. If you do have side effects, we may recommend medicine or treatments to try to control them and make you more comfortable.

A risk for subjects randomized to standard Arm A is that you will not receive a new treatment for AML that may have some benefits.

Surgery Risks
Risks associated with any surgery will be presented in a separate consent form by the surgical staff.

Sedation Risks
If you require anesthesia for any procedure, you will be presented with a separate consent from that explains the risks associated with anesthesia.

Blood Transfusion Risks

This treatment and/or your disease may cause low blood counts. If your blood count gets low enough, you may need to have a blood transfusion. Blood products come from voluntary donors who are carefully selected and tested. However, there are still some risks to blood transfusion. Occasional risks include fever; allergic reactions and formation of antibodies. Less frequent risks include infections with viruses such as hepatitis (risk is 1 in 2,000,000 transfusions) and fluid overload. These complications are uncommon and are usually mild but may be severe or life threatening. Very rare risks are serious incompatibility reactions and infections other than hepatitis. This could include the virus that causes AIDS (risk is 1 in 2,000,000 transfusions). The alternative to volunteer donor blood is directed donor blood, if appropriate for your disease.

Bone Marrow Aspirate/Biopsy Risks
The test is painful and has some small risk of infection or bleeding. The pain normally lessens within seconds to hours. Many patients may get some form of sedation or anesthesia during this procedure. A small area over the hipbone on the back will be cleaned and numbed with lidocaine and/or with an anesthetic cream. You will be given another consent form that covers the risks associated with this procedure.

Spinal Taps Risks (Lumbar Punctures, "LPs")
Spinal taps are painful and may cause headaches. The skin at the site of needle insertion is usually numbed with an anesthetic cream or lidocaine. You will be given another consent form that covers the risks associated with this procedure.

Blood Draw Risks
Risks associated with needle sticks for drawing blood are slight, but some possible risks include excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Echocardiogram/EKG Risks
The echocardiogram and EKG tests are non-invasive. They do not require needles, blood samples, or tissue samples.

Scan Risks
Some scans require injections of substances (contrast) to make body parts more visible. There is a slight risk of an allergic reaction from the MRI contrast (gadolinium). You could also have pain or bruising at the injection site. Some types of scans (i.e., CT scans, x-rays, nuclear medicine scans), expose the patient to small doses of radiation. The principal risk associated with this radiation dose is the possibility of developing a radiation-induced cancer sometime later in life. The risk for radiation-induced cancer from this study is minimal. Everyone in the world is exposed to some level of "background radiation" or naturally occurring radiation from sources such as cosmic rays, buildings and soil. The level of background radiation everyone gets each year is about 300

millirems. In comparison, the exposure allowed to radiation workers is 5000 millirems per year. By participating in this study, you will be exposed to approximately 1865 millirems of radiation. However, all the scans done for this study are standard care and would be done even if you were not in this study.

Transplant Risks

Severe nausea and vomiting can be expected during the stage of BMT therapy when high dose Cyclophosphamide is given. Bladder soreness and bleeding may also occur during this period, producing blood in the urine. A condition called SIADH may also occur. This is characterized by a fluid imbalance that causes the body to retain water and not be able to excrete urine. The water retention may result in a fluid build-up in the body resulting in weight gain. We will take measures to less the side effects during Cyclophosphamide administration.

Bone Marrow Infusion

The donor cells are given through the central line, like a blood transfusion. Most patients do not have any side effects during the infusion. Rarely, patients can have blockage of blood vessels causing damage to organs (lungs, kidneys, brain). Occasionally, patients have nausea and temporary trouble breathing. Just like any blood transfusion, in rare cases patients have allergic reactions (may be life-threatening) or fever and infections from the infusion.

Graft Failure

It is possible that the donor cells will not grow in your bone marrow. You would either grow your own cells in the marrow again, or you would be without working bone marrow cells. We think that this problem, called graft failure, may happen in less than about 1 of every 20 patients treated on this research study. If you are not able to make new bone marrow cells, you could die. If you have graft failure, it may be necessary for you to receive additional medications and another collection of marrow cells from the same or another donor.

Graft Versus Host Disease

A transplant can cause a side effect called graft-versus-host disease or GVHD. This happens when certain white blood cells, called T-cells, in the donor cells (the graft) attack the patient's body. GVHD commonly causes skin, liver, stomach and intestinal problems, and may damage other parts of the body as well (including lungs, mouth and eyes). However, GVHD can be severe (blistering skin rash, severe or bloody diarrhea and severe jaundice) or even fatal. GVHD can happen any time after new cells start to grow and it can happen weeks or months later. It may go away but then come back again.

When GVHD happens in the first 3 months after transplant, it is called acute GVHD. When it does not go away, or starts after the 3 months after transplant, it is called chronic GVHD. Chronic GVHD can make you very sick and can even cause death. It causes a discolored skin rash that can become tight and make it hard to move. It can also cause dry mouth, dry eyes, chronic nausea and diarrhea, weight loss, and liver problems, and can increase the risk of severe or fatal infections.

We will try and prevent GVHD by giving Cyclosporine and Methotrexate. These drugs do not always work. If GVHD occurs, other medicines may be needed to suppress the immune system. GVHD is a main reason that you must take all medicines as instructed and must come to all clinic visits so that we can look for signs of GVHD.

Veno-Occlusive Disease (VOD) of the Liver
Some bone marrow transplant patients develop veno-occlusive disease of the liver or VOD, which can be fatal. This happens when the normal blood flow through the liver is blocked, causing jaundice and swelling in the body. In some studies, VOD happens in 1 to 6 of every 10 patients transplanted. VOD can range from mild, which causes mild jaundice and swelling, to severe, which may cause death. Your risk for VOD following transplant may be increased due to the use of gemtuzumab earlier in therapy.

Infections

Transplant patients can develop serious infections when numbers of infection-fighting cells are low around the time of the transplant. This can also happen later when infection-fighting cells from the donor are not yet present. Infections can come from any kind of germ, including bacteria, funguses and viruses. Most of these infections can be treated with medicines such as antibiotics. Sometimes an infection cannot be treated, and patients can die of infection.

Relapse
It is possible that your original disease may come back even if the transplant is successful.

Interstitial Pneumonitis
Some patients suffer severe lung problems from either a viral infection (CMV) or a reaction to the chemotherapy and/or radiation given in the preparative regimen. Treatments are available, but this complication can be fatal.

Immunodeficiency
Full and complete recovery of your immune system may take several months following successful marrow engraftment. During this time, there is an increased susceptibility to infections. You will be prescribed certain medications to reduce the chance of those infections, and you will be told how to take safety measures to reduce your risk. Preventive treatment is not always effective. If you have signs of an infection, you may have to be re-hospitalized after transplant. Some of these infections may be fatal (cause death).

Late Effects
Some side effects from the BMT preparative regimen and complications may not happen right away. In fact, they can happen many years after transplant. These include sterility, hormone problems, growth problems and body appearance changes, and organ damage (especially heart, lung and kidney). A second malignancy (cancer) different from the original disease may happen following chemotherapy and irradiation. This is a rare complication.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

<u>What Will Be Done to Minimize the Risks?</u>
The study doctor and/or staff will be checking you closely for side effects during the study. You will be checked with complete blood counts (CBC) including differential and studies of liver and kidney functions. You will also have scans (x-rays, CT scans, ultrasounds, etc.) to make sure the tumor is not growing back.

Most side effects disappear after the treatment is stopped. In the meantime, the study doctor may prescribe drugs to keep side effects under control. Your treatment will be changed, whenever needed, to prevent permanent damage. The study doctor will do everything possible to prevent any serious complications. If serious complications do occur, the study doctor will provide appropriate measures (blood transfusions, antibiotics, anti-vomiting medications, etc.).

Although you will be treated according to a specific plan (protocol), individual circumstances may arise. In such cases, your health will always be considered more important than strictly following the protocol. Changes will be discussed before they are made whenever possible.

Will I benefit directly from the study?

There may be no direct benefit to you from taking part in this study. We hope (but are not certain) that adding gemtuzumab will improve the effectiveness of this treatment. In addition, we hope that information learned from this study will benefit other patients with AML the future.

What are my other options?

If you choose not to be on this study, you may choose one of the following options:

- Another experimental treatment (if available)
- The standard therapy used for AML - the therapy as given on this study without gemtuzumab
- You may choose no therapy at this time. However, if you choose not to receive specific therapy for the disease, the cancer is extremely likely to progress and cause death. You will receive supportive therapy (such as narcotics for pain or transfusions for anemia).

The study doctor can give you detailed information about the disease and the benefits of the various treatments available. Please feel free to discuss the disease and future outlook with the study doctor. You can still be treated at our centers, even if you do not take part in this study.

Please talk to your regular doctor about these and other options.

Compensation

You will not receive any money or other gifts or rewards for being in this study. You will not get anything for free (for example, medications) because you are in this study.

How will you protect my private information that you collect in this study?

Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

Medical Record

If you have been an Emory and Children's Healthcare of Atlanta patient before, then you already have an Emory and Children's Healthcare of Atlanta medical record. If you have never been an Emory and Children's Healthcare of Atlanta patient, you do not have one. An Emory and Children's Healthcare of Atlanta medical

record will be made for you if an Emory and Children's Healthcare of Atlanta provider or facility gives you any services or procedures for this study. Copies of the consent form/HIPAA authorization that you sign will be put in any Emory and Children's Healthcare of Atlanta medical record you have now or any time during the study.

Emory and Children's Healthcare of Atlanta may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory and Children's Healthcare of Atlanta medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

Emory and Children's Healthcare do not control results from tests and procedures done at other places, so these results will not be placed in your Emory or Children's Healthcare medical record. They will likely not be available to Emory or Children's Healthcare to help take care of you. Emory and Children's do not have control over any other medical records that you may have with other healthcare providers. Emory and Children's Healthcare will not send any test or procedure results from the study to these providers. If you decide to be in this study, it is up to you to let your health providers know.

The researchers will review the results of certain study tests and procedures only for the research. The researchers will not be looking at the results of these tests and procedures to make decisions about your personal health or treatment. For this study, those things include research blood tests.

In Case of Injury

If you get ill or injured from being in the study, Emory and Children's Healthcare of Atlanta will help you get medical treatment. Emory and Children's Healthcare of Atlanta have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory and Children's Healthcare of Atlanta employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact Dr. Himalee Sabnis at [redacted] You should also let any health care provider who treats you know that you are in a research study.

Costs

Most of the costs on this study are from tests and treatments that are part of regular medical care for a patient with AML. We will not bill you for any tests that are only for research, or for any testing required before the infusion that is not considered standard of care.

You will have to pay for the items or services that are not paid for by the study. We will not pay for your regular medical care. If you have insurance, Emory and Children's Healthcare of Atlanta will submit claims to your insurance for items and services that are part of this study. Emory and Children's Healthcare of Atlanta will send in only those claims for items and services that it reasonably believes your insurance will pay and that the study has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Emory and Children's Healthcare of Atlanta will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

If you do not have insurance, Emory and Children's Healthcare of Atlanta will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Withdrawal from the Study

You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

Taking part in this study is your choice. You have the right to refuse to be in this study. You can still be treated here, even if you decide not to be in the study. You can stop being in the research at any time after giving your consent, by telling your transplant doctor. This decision will not affect your current or future medical care or any other benefits that you are otherwise entitled to. It will not affect your relationship with this institution and your doctors**.** Once you have had the transplant, you will continue to get the special medical care needed for any transplant patient, even if you decide to leave the study.

Study doctors have the right to end your participation in this study without your consent for any of these reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- The investigator decides that continuing in the study would be harmful to you
- The study treatments have a bad effect on you
- You become pregnant
- You were to object to any future changes that may be made in the study plan
- For any other reason

If you stop being in the study or your doctor takes you out of the study, all study information about you that has already been collected will be part of the study. We would like to continue to learn about your progress from your doctor. You may, of course, say "no" to having your doctor give us your follow-up information

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the main study and for any optional studies in which you may choose to participate.

Main Study

PHI that Will be Used/Disclosed:

The PHI that we will use or share for the research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:

We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Use and Disclosure of Your Information That is Required by Law:

We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:

By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:

The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory and Children's Healthcare of Atlanta may use and disclose your PHI to get payment for study related treatment and to run normal business operations.

- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory and Children's Healthcare of Atlanta offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory and Children's Healthcare of Atlanta IRBs, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including the Food and Drug Administration. (The Food and Drug Administration will be involved in overseeing this research.)
    - Public health agencies.
    - Research monitors and reviewers
    - Accreditation agencies
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Optional Study: Biology research tests (blood and bone marrow banking)

> **Authorization for This Use of PHI is Required to Participate in Optional Study, but Not in Main Study**:
> You do not have to authorize the use and disclosure of your PHI for the optional study(ies). If you do not authorize the use and disclosure of your PHI for the optional study(ies), then you may not participate in the optional research study, but you can still be in the main research study.

Expiration of Your Authorization
This authorization will not expire because it is a research study.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must write to Dr. Himalee Sabnis, 2015 Uppergate Dr., Atlanta, GA 30322.

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly, and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information

Contact Dr. Himalee Sabnis at [redacted]:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at [redacted]:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at [redacted]

If you are a patient receiving care at Children's Healthcare of Atlanta of Atlanta and have a question about your rights, please contact Sarah Marie Huban, Director of Research Administration at [redacted].

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in the study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

Name of Subject

Signature of Subject (18 or older and able to consent) **Date** **Time**

Signature of Legally Authorized Representative with authority for research decisions **Date** **Time**

Authority of Legally Authorized Representative or Relationship to Subject

TO BE FILLED OUT BY STUDY TEAM ONLY

Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion **Date** **Time**

ADDITIONAL CONSENT POSSIBILITIES

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No" then add your initials and date after your answer.

1. My bone marrow and/or blood may be kept (banked) for future use in research to learn about, prevent, or treat cancer or to learn why some people have complications from therapy and others do not (including genetic studies on leukemia cells).

#1: Yes_____ No_____ _/ _____ Initials
Date

2. My bone marrow and/or blood may be kept (banked) for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

#2: Yes_____ No_____ _____/ _____

Initials Date

Attachment #1

Treatment and Procedures Common to all Subjects with *de novo* AML

Methods for Giving Drugs

Various methods will be used to give drugs.

- **IV** – Drug is given using a needle or tubing inserted into a vein. It can be given over a few minutes ("push ") or slowly over minutes or hours ("infusion").
- **IT** – Drug used to treat the brain and spinal cord is given using a needle inserted into the spinal fluid (intrathecally, IT).
- **IM** – Drug is given by inserting a needle injected into the muscle (IM shot).

Central Line

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your chest that can stay in for a long time. The risks connected with central lines will be explained to you and all your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure.

Standard Treatment Tables

The treatment described below is standard treatment for patients with *de novo* AML.

The chemotherapy treatment plan described below for low risk subjects has been used in past COG AML studies.

Induction I - Standard therapy (28 Days)

Chemotherapy is given for 10 days followed by 3 weeks of rest (28 days total).

Drug	How the drug will be given	Day(s)
Intrathecal Cytarabine (IT ARAC)	Intrathecal (IT)	given at diagnostic lumbar puncture or Day 1
Cytarabine	IV over 1-2 minutes given every 12 hours	1-10
Daunorubicin	IV over 15 minutes	1, 3, and 5
Etoposide	IV over 60-120 minutes	1-5

If you have a chloroma at the time you begin this study, your doctor may treat it with radiation therapy at the beginning of Induction. The risks of radiation therapy for chloroma are found in **Attachment #2.**

Induction II – Standard Therapy (28 Days)

Chemotherapy is given for 6 days followed by 3 weeks of rest (28 days total)

Drug	How the drug will be given	Day(s)
Intrathecal Cytarabine (IT ARAC)	Intrathecal (IT)	given on Day 1 of Induction II or with bone marrow evaluation

		diagnostic lumbar puncture or Day 1
Cytarabine	IV over 1-3 hours given every 12 hours	1-4
Mitoxantrone	IV over 15-30 minutes	3-6

Intensification I – Standard Therapy (28 Days)
Chemotherapy is given over 5 days followed by 3 weeks of rest (28 days total)

Drug	How the drug will be given	Days
Cytarabine	IV over 1-3 hours given every 12 hours	1-5
Etoposide	IV over 60-120 minutes	1-5

You will receive eye drops during and for 24 hours after you receive this drug to help with the side effects of the drug.

Intensification II – Standard Therapy (28 Days)
Chemotherapy is given over 9 days followed by 3 weeks of rest (28 days total).

Drug	How the drug will be given	Days
Cytarabine	IV over 3 hours, every 12 hours	1, 2 and 8, 9
Erwinia L-Asparaginase	IM (may be given IV over 1 hour	2, 9

You will receive eye drops during and for 24 hours after you receive this drug to help with the side effects of the drug.

If after Induction I, your AML has been classified as **high risk**, you may receive a Stem Cell Transplant. More information will be given to you with a separate consent.

- If there is no stem cell donor available, you will receive treatment with more chemotherapy similar to low risk patients, during Induction II, Intensification I and Intensification II.
- If you have high amounts of FLT3-ITD gene mutations you are classified as high risk and will receive therapy with a drug called sorafenib and you may receive a stem cell transplant. If you do not have an appropriate donor, you will receive treatment with more chemotherapy similar to low risk patients, during Induction II, Intensification I and Intensification II and in addition you will receive sorafenib in each chemotherapy cycle.

Standard Tests and Procedures
The following tests and procedures are part of regular cancer care and may be done even if you do not join the study:

- Frequent labs to monitor your blood counts and blood chemistries
- Urine tests to measure how your kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins
- X-rays and scans to monitor your response to treatment
- Tests to monitor your heart and lung functioning
- Bone Marrow Aspirations to see if the leukemia is responding to treatment.
- Spinal Taps to check for leukemia cells in the spinal fluid and to give chemotherapy into the spinal fluid.

Attachment #2
Risks of Chemotherapy Drugs and X-Ray Therapy Used to Treat *de novo* AML

Possible Side Effects of Erwinia Asparaginase

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Erwinia Asparaginase, more than 20 and up to 100 may have:**
• None
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Erwinia Asparaginase, from 4 to 20 may have:**
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
RARE, AND SERIOUS **In 100 people receiving Erwinia Asparaginase, 3 or fewer may have:**
• Blood clot • Nausea • Diabetes • Pain in belly • Vomiting • Mini stroke • Bleeding • Increased blood level of liver tests which may mean there has been damage to the liver • Increased blood sugar levels which could lead to diabetes

Possible Side Effects of Cytarabine (Ara-C) IV

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Cytarabine (Ara-C), more than 20 may have:**
• Blood clot • Rash • Swelling in the rectum which may cause rectal pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Anemia which may cause tiredness, or may require blood transfusions • Fever
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Cytarabine (Ara-C), from 4 to 20 may have:**
• Infection, especially when white blood cell count is low • Bruising, bleeding • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Numbness and tingling of the arms and legs • Severe blood infection • Kidney damage which may cause swelling, may require dialysis • Headache • Chest pain • Hair loss • Liver damage which may cause yellowing of skin or eyes • Swelling and redness of the eye
RARE, AND SERIOUS **In 100 people receiving Cytarabine (Ara-C), 3 or fewer may have:**
• None

Some drugs, food, and supplements may interact with cytarabine. Examples include:

Drugs that may interact with cytarabine*
• Clozapine • Digoxin • Flucytosine • Leflunomide

Food and supplements that may interact with cytarabine**
• Echinacea

**Sometimes these drugs are used with cytarabine on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided. Talk to your doctor before starting any new medications or herbal supplements and before making a significant change in your diet.*

Possible Side Effects of Daunorubicin

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Daunorubicin, more than 20 and up to 100 may have:**
• Hair loss • Nausea, vomiting • Pink or red colored urine, sweat, or saliva
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Daunorubicin, from 4 to 20 may have:**
• Damage to the heart which may cause shortness of breath, tiredness • Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Pain and sores in mouth and throat • Dark discoloration of the nail, skin • Loss of nails • Redness and pain at the site of previous radiation • Swelling and redness at the site of injection • Diarrhea
RARE, AND SERIOUS **In 100 people receiving Daunorubicin, 3 or fewer may have:**
• Cancer of the bone marrow (leukemia) cause by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Some drugs, food, and supplements may interact with daunorubicin. Examples include:

Drugs that may interact with daunorubicin*
• Some antibiotics and antifungals (clarithromycin, erythromycin, itraconazole, ketoconazole) • Some antiepileptics (carbamazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (darunavir, lopinavir; nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir) • Some heart medications (amiodarone, carvedilol, digoxin, dronedarone, nicardipine, propranolol, verapamil) • Other agents, such as atorvastatin, clozapine, cyclosporine, dexamethasone, ivacaftor, leflunomide, natalizumab, nefazodone, progesterone, rifampin, tacrolimus, tofacitinib, and trazodone

Food and supplements that may interact with daunorubicin**
• Echinacea • Grapefruit, grapefruit juice, Seville oranges, star fruit • St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Sometimes these drugs are used with daunorubicin on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided. Talk to your doctor before starting any new medications or herbal supplements and before making a significant change in your diet.*

Possible Side Effects of <u>Etoposide</u>

COMMON, SOME MAY BE SERIOUS In 100 people receiving Etoposide, more than 20 may have:
• Hair loss • Chills • Sores in mouth which may cause difficulty swallowing • Diarrhea, loss of appetite, nausea, vomiting • Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Tiredness • Fever
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Etoposide, from 4 to 20 may have:**
• Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness • Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body • Liver damage which may cause yellowing of eyes and skin, swelling
RARE, AND SERIOUS **In 100 people receiving Etoposide, 3 or fewer may have:**
• Cancer of bone marrow caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Some drugs, food, and supplements may interact with etoposide. Examples include:

Drugs that may interact with etoposide*

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Aripiprazole, clozapine, nefazodone
• Antifungals
  • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tofacitinib
• Anti-rejection medications
  • Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Atovaquone, bosentan, sitaxentan, aprepitant, dexamethasone, mifepristone, natalizumab, pimozide, ivacaftor, deferasirox, lomitapide

Food and supplements that may interact with etoposide**
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Sometimes these drugs are used with etoposide on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided. Talk to your doctor before starting any new medications or herbal supplements and before making a significant change in your diet.*

Possible Side Effects of Mitoxantrone Hydrochloride

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Mitoxantrone hydrochloride, more than 20 and up to 100 may have:**
• Diarrhea, nausea, vomiting • Infection, especially when white blood cell count is low • Headache • Hair loss • Sores in mouth and throat which may cause difficulty swallowing • Pain • Hives, rash • Abnormal or absence of menstrual period
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Mitoxantrone hydrochloride, from 4 to 20 may have:**
• Damage to the heart or heart failure which may cause shortness of breath, tiredness and swelling • Anemia which may cause tiredness, or may require transfusion • Bruising, bleeding • Darkening of the skin and nails • Loss of nails • Swelling and redness at the site of the injection • Liver damage which may cause yellowing of the eyes and skin • Bluish/greenish discoloration of the urine, skin, eyes and saliva

RARE, AND SERIOUS **In 100 people receiving Mitoxantrone hydrochloride, 3 or fewer may have:**
• Cancer of the bone marrow (leukemia) caused by chemotherapy

Some drugs, food, and supplements may interact with mitoxantrone. Examples include:

Drugs that may interact with mitoxantrone*
• Aripiprazole • Clozapine • Cyclosporine • Dofetilide • Leflunomide • Natalizumab • Pimozide • Tofacitinib

Food and supplements that may interact with mitoxantrone**
• Echinacea

**Sometimes these drugs are used with mitoxantrone on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided. Talk to your doctor before starting any new medications or herbal supplements and before making a significant change in your diet.*

Radiation Risks from X-Ray Therapy for Chloroma

X-ray therapy for chloromas may cause temporary or permanent side effects from the radiation. Subjects may experience changes in normal tissues in the area of the chloroma(s) being treated. The skin overlying the chloroma may become temporarily darkened, dry, and itchy. Additionally, a bone close to the chloroma being treated may not grow to a normal size. If subjects are receiving X-ray therapy near the brain, permanent losses may develop in thinking abilities and hormone production. Radiation may also increase the risk of having a second cancer. The risk, severity, and type of side effects will vary based upon your age, other treatment, and the normal tissues that are in or near the area that gets radiation.