DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

Study title:	Adoptive Transfer of Haplo-identical DLI for AML and MDS
Principle Investigator:	Anthony Sung, MD
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DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study:
A Phase 1/2 Study of the Safety and Efficacy of Chemotherapy Combined with Adoptive Transfer of HLA-Haploidentical Donor Lymphocyte Infusion in Older Patients with High-Risk Acute Myeloid Leukemia and Myelodysplastic Syndrome

Recipient Consent

You are being asked to take part in this research study because you have been diagnosed with high risk acute myeloid leukemia (AML), a cancer of the blood and bone marrow (the spongy tissue inside bones where blood cells are made) or myelodysplastic disease (MDS), also called pre-leukemia or smoldering leukemia, a group of diseases in which the bone marrow does not make enough healthy blood cells.

Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Anthony Sung, MD and his study team will conduct the study.

WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, Dr. Anthony Sung or one of his associates will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine how safe, tolerable, and effective it is to combine donor lymphocyte infusions (DLIs) with the standard chemotherapy treatment for AML, which includes cytarabine and idarubicin. In DLI, blood cells (lymphocytes) from a donor (for example, parent, child) are infused into a patient, with the goal of helping the immune system attack and kill cancer cells. This has been suggested by some studies in the medical literature and is the reason we are doing this study. However, it has not been proven that outcomes are improved with DLI and the procedure is considered investigational.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 30 donors and 30 recipients, or up to 60 people total, will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?

Screening

If you agree to be in this study, you will be asked to sign and date this consent form.

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You will need to undergo the following exams, tests, or procedures to find out if you can be in the study. Some are part of regular leukemia-related care and may be performed even if you do not participate in the study.

- Complete medical history, complete physical examination, vital signs, height, and weight
- Comprehensive Geriatiric Assessment (CGA): An assessment of your ability to do daily tasks and mental processing. This questionnaire asks you about your daily activities, your health, your mood, your social activities and support.
- Bone marrow sampling and analysis.
- Blood Draw to perform the following tests:
  - Routine blood tests.
  - Serum pregnancy testing if you are a female of child bearing potential.
- If the study doctor thinks it is necessary, you may have a pulmonary function test (PFT) to test how your lungs are functioning

There may be reasons why you cannot be in the study. The study doctor or study staff will discuss these reasons with you.

Study Drugs
In this study, you will first receive standard chemotherapy for your AML or high risk MDS. The first cycle is called an "induction." During induction, you will receive cytarabine + idarubicin: cytarabine is given for 7 days of continuous infusion in the vein and idarubicin is given in the vein as a short infusion on days 1, 2 and 3. This part is standard therapy. This will be followed by a DLI or donor lymphocyte infusion. The DLI procedure is the collection of white blood cells from a donor through a collection process known as leukapheresis. This part is new. Cells for DLI will be collected from a related donor and then infused into you either directly after being collected or frozen and then thawed to be infused into you at a later date. The purpose of our study is to see if adding a DLI will help improve responses as well as the safety and tolerability of adding DLI.

If you are over 80 years of age, you will receive cytarabine for only 5 days of continuous infusion in the vein and idarubicin in the vein as a short infusion on days 1 and 2 followed by a DLI.

If after 6 to 12 weeks after beginning induction your disease has been not been successfully treated, you will receive a second induction with the exact chemotherapy regimen given to you with your 1st induction followed by a DLI. There is a possibility that you may receive a second induction of the exact chemotherapy regimen without a DLI. Your study doctor will discuss this with you further at that time

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If your disease still has not been successfully treated, you will come off study and be treated at the discretion of your physician.

If after your first or second induction your doctors cannot find any evidence of disease, known as being "in remission," you will move onto post-remission chemotherapy or "consolidation". Consolidation is standard for the treatment of AML or high risk MDS and helps prevent the disease from returning (relapse). For consolidation, you will receive 2 courses of cytarabine, given twice daily at 12 hour intervals administered over about a week, followed by a DLI after the second course, assuming there are enough cells collected from your donor. Again, cytarabine is standard chemotherapy, while the DLI is new.

The goal of giving DLI with induction is to help induce remission. However, in some cases, induction has to be given on an urgent basis to treat disease, and there may not be time to identify and evaluate a donor and collect cells for DLI before induction. In these cases, induction will be given as per clinical need, and DLI will be given with each course of consolidation. While giving DLI with consolidation would not carry the potential benefit of improving response rates and inducing remission, DLI with consolidations potentially may still improve disease-free and overall survival. There is no anticipated difference in the risks of giving DLI with induction + second consolidation vs. DLI with first and second consolidation.

Study Procedures and tests
The following procedures and tests will be performed:

- Complete medical history, complete physical examination, vital signs, height, weight, and blood counts daily during therapy and recovery, 8 weeks after last therapy and every 3 months for 2 years (this is part of standard therapy).
- Comprehensive Geriatiric Assessment (CGA): An assessment of your ability to do daily tasks and mental processing. A questionnaire about your daily activities, your health, your mood, your social activities and support (8 weeks after last therapy).
- Bone marrow sampling and analysis approximately two weeks after the induction(s) and at hematologic recovery approximately 4 to 6 weeks after the induction(s) (this is part of standard therapy).
- "Blood tests will be taken on selected days around the donor cell infusion to evaluate for cytokine release syndrome with DLI. We will use about 4-8 teaspoons of blood drawn from a vein by a needle-stick or through a central line each time you have these blood tests.

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- Special immune reconstitution blood tests, which evaluate how well your immune system is functioning at baseline and after chemotherapy (prior to beginning each next therapy, 8 weeks after last therapy and every 3 months for 2 years). We will use about 4-8 teaspoons of blood drawn from a vein by needle-stick or through a central line each time you have these blood tests.

HOW LONG WILL I BE IN THIS STUDY?

Your total time in the study will be approximately 3 years.

WHAT ARE THE RISKS OF THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all of the side effects that may happen. Side effects may be mild to very serious. Your health care team may give you medicines to help lessen side effects. Many side effects may go away soon after you stop taking cytarabine and idarubicin drug regimen. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor right away about any side effects that you have while taking part in the study. It should not be administered to subjects who are pregnant or who have a history of increased sensitivity reaction to cytarabine or idarubicin.

Drug-related risks

Cytarabine can cause some or all of the following**:**

Common

- low white blood cell count with increased risk of infection
- low platelet count with increased risk of bleeding
- low red blood cell count (anemia) with symptoms like weakness, tiredness, shortness of breath
- nausea
- vomiting
- stomach pain
- tiredness (fatigue)
- sores in mouth or on lips

Less common

- diarrhea
- loss of appetite
- rash
- hair loss or thinning (may include face and body hair)

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- fever
- muscle and bone aches
- liver damage
- blood clots and inflammation of the vein where the drug was given

Rare

- red or swollen eyes
- sleepiness
- muscle weakness
- trouble walking
- trouble writing
- slurred speech
- kidney damage
- fetal changes that may lead to birth defects, prematurity, or serious illness in the newborn if you become pregnant while taking this drug
- allergic reaction with itching, dizziness, trouble breathing, or swelling of the face, mouth, or throat
- death due to infection, bleeding, or other causes

At high doses, cytarabine can cause neurologic complications such as altered mental state, headaches, seizures, inflammation of the linings of the brain, dementia, weakness, numbness and tingling in extremities, nerve damage and uncoordinated muscle movement. Please tell your study doctor if you experience any of these symptoms.

Idarubicin can cause some or all of the following:
Common

- decreased white blood cell count with increased risk of infection
- decreased platelet count with increased risk of bleeding
- nausea
- vomiting
- stomach pain
- decreased appetite
- sores in mouth or on lips
- hair loss or thinning
- skin rash

Less common

- darkening of nail beds

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- diarrhea
- fever
- abnormal blood tests which suggest that the drug is affecting the liver (Your doctor will discuss the importance of this finding, if any.)

Rare

- inflammation of the liver
- heart damage with shortness of breath and swollen feet and ankles, which can happen months or years after treatment
- irregular heartbeat
- tumor lysis syndrome, kidney damage
- pain, tingling, blistering, or peeling skin on palms and soles of feet

Idarubicin may cause serious or life-threatening heart problems at any time during the study or months to years after the study has ended. Your doctor will order tests before and during the study to see if your heart is working well enough for you to safely receive idarubicin. These tests may include an electrocardiogram (ECG; test that records the electrical activity of the heart) and an echocardiogram (test that uses sound waves to measure your heart's ability to pump blood). Your doctor may tell you that you should not receive this medication if the tests show your heart's ability to pump blood has decreased. Tell your doctor if you have or have ever had any type of heart disease or radiation (x-ray) therapy to the chest area. Tell your doctor if you are taking or have ever received certain cancer chemotherapy medications such as daunorubicin (cerubidine), doxorubicin (Doxil), epirubicin (Ellence), mitoxantrone (Novantrone), cyclophosphamide (Cytoxan), or trastuzumab (Herceptin). If you experience any of the following symptoms, call your doctor immediately: shortness of breath; difficulty breathing; swelling of the hands, feet, ankles or lower legs; or fast, irregular, or pounding heartbeat..

Risks of Drug Infusions

Cytarabine and idarubicin are to be given as an infusion through a vein. Common reactions to infusions include: flushing; shortness of breath; headache; chills; back pain; tightness in the chest; and low blood pressure. In most people, these reactions resolved over several hours to 1 day once the infusion was completed. In some people, the reaction stopped when the speed of the drug being given was slowed down.

Risks of Donor Lymphocyte Infusions

Graft-versus-host disease results from certain donor white blood cells (called lymphocytes) recognizing the host (patient) environment as being foreign, causing a reaction in which the donor cells may attack the recipient's body. These lymphocytes may start an immunological reaction. This graft-versus-host reaction may affect the patient's skin (in the form of a rash), the liver (by causing jaundice), and/or the

gastrointestinal tract (gut) (by causing nausea, cramps and diarrhea). Most patients develop some degree of graft-versus-host disease but it is usually controllable with medications.

However, some patients develop severe graft-versus-host reactions that can lead to death. Medications that suppress the immune system will be given to help prevent this complication.

Transfusion of white blood cells can transmit infectious diseases to the recipient such as CMV (cytomegalovirus), hepatitis B and C and HIV (human immunodeficiency virus, which is the virus that causes acquired immunodeficiency syndrome [AIDS]). All donors are screened for these viruses, but there still remains a possibility that these infectious diseases could occur as a complication of receiving donor cells. There is a possibility of having a reaction to one of the solutions that is used to grow or process them. Signs of a transfusion reaction include a fever, rash, and difficulty with breathing, low blood pressure, or changes in your heart rate. You will be given medications prior to the infusion to help counteract these side effects and will be monitored closely during the infusion.

The cells in an infusion (DLI) may cause the release of cytokines, chemicals in the body that produce a type of inflammatory response similar to that found in severe infection, including a significant decrease in blood pressure, fever and chills/shivering. You may feel unwell, as you do with a high fever. Deaths due to cytokine release syndrome have been reported. However, if treated appropriately, it is usually not dangerous.

Risks of Drawing Blood

Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Risks from Bone Aspiration

A bone marrow aspiration is a procedure in which an area of the hip (either one hip or both hips) is numbed and a small sample of bone marrow is withdrawn. When the local anesthesia (numbing medication) is given, you may initially feel a burning sensation in your skin and bone surface for several seconds. During the procedure, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely, infection can develop.

Drug and Food Interactions

For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are

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taking before you start the study and before starting to take any of these products while you are on the study.

For Those of Reproductive Potential

Female

Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you can continue in this study. If sexually active, you must agree to use two appropriate contraceptive measures for the duration of the study and for 1 month afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

Male

Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for 1 month afterward. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may be direct medical benefit to you such as disease remission, however, this cannot be guaranteed. We hope that in the future the information obtained from this study will benefit other people with leukemia and MDS.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?

Instead of being in this study, you have the following alternatives:

- Receive cytarabine and idarubicin without participating in this study

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- Receive other chemotherapy combinations
- Take part in another research study
- You may choose to get comfort care only, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier (other than those mentioned above) in records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, your initials and a unique study number will be used. The information linking your name to the study number will be kept in the DUHS Division of Hematologic Malignancies and Cellular Therapies database on a secure server and in their locked research offices.

Some of these tests and procedures would have been done as part of your regular care. The test results will be used both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the sponsor or their representatives. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record.

The study results will be retained in your research record forever. Any research information in your medical record will also be kept indefinitely.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives of the Food and Drug Administration (FDA), the Duke University Health System Institutional Review Board (DUHS IRB), the Center for International Blood and Marrow Transplant Research (CIBMTR), the Foundation for Accreditation for Cell Therapy (FACT) and the Duke Cancer Institute. If any of these groups review your research record, they may also need to review your entire medical record.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the federal privacy regulations.

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While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

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 ARE THE COSTS?
You or your insurance provider will be responsible for all costs related to your medical care, including the cost of cytarabine and idarubicin as well as collection and infusion of cells. You may wish to contact your insurance representative to discuss this further before making your decision about participating in the study, as there may be extra uncovered costs. In order to make sure that tests and studies done solely for research purposes are charged correctly, we will carefully monitor your Duke Hospital and Clinic charges as long as you are participating in this study. These tests and studies are not a part of routine care, and people who are not part of the study do not usually have them performed. Please ask Dr. Sung if you would like to know more about which tests and studies are being done solely for research purposes.

WHAT ABOUT COMPENSATION?
You will not be paid for participating in this study.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Sung at 919- 668-5710 during regular business hours and at pager number 919- 684-8111 after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
Your participation is voluntary. You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be collected by the study team.

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Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Sung in writing and let him know that you are withdrawing from the study. His mailing address is Box 3961, 2400 Pratt Street, Durham, NC 27710. Your study doctor may ask you to complete the tests that would ordinarily occur when a person completes the study and discuss what follow-up care and testing could be most helpful for you. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, if you do not follow the study rules or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at anytime without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr.Sung at 919- 668-5710 during regular business hours and at pager number 919-684-8111 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____		
Printed Name of Subject		
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time
_____		
Printed Name of Person Obtaining Consent		