Official Title:	Dose-Finding (Phase 1) Study of Continuous Infusion Cladribine, Cytarabine and Mitoxantrone (CI-CLAM) for Adults With Relapsed/Refractory Acute Myeloid Leukemia or Other High-Grade Myeloid Neoplasms Treated at UW/SCCA
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Fred Hutchinson Cancer Research Center
University of Washington School of Medicine
Seattle Cancer Care Alliance

Consent to take part in a research study:

DOSE-FINDING (PHASE 1) STUDY OF CONTINUOUS INFUSION CLADRIBINE, CYTARABINE AND MITOXANTRONE (CI-CLAM) FOR ADULTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA OR OTHER HIGH-GRADE MYELOID NEOPLASMS TREATED AT UW/SCCA

Principal Investigator: Elihu H. Estey, MD: Member, Fred Hutchinson Cancer Research Center; Professor, University of Washington; phone [redacted]. Email: [redacted]

Emergency number (24 hours):

- Call the paging operator at the University of Washington Medical Center at 206-598-6190, and ask for the Fellow on call for Hematology/Oncology.

Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is to examine continuous infusion CLAM (CI-CLAM), a chemotherapy regimen consisting of Cladribine, Cytarabine (also called Ara-C), and Mitoxantrone, in which all three drugs are delivered in a steady, continuous infusion over several days.

People who agree to join the study will not be asked to attend any extra visits outside of their usual clinical care. We think they will be in this study for up to 3-6 months. The exact length of treatment will depend on the side effects and response to the treatment.

The study involves procedures that are part of your usual care, such as a physical exam, blood tests, and a bone marrow examination.

We do not know if CI-CLAM would help treat your cancer, and it could even make your condition/disease worse. CI-CLAM could cause side effects such as fatigue, nausea/vomiting, low blood counts (low WBC, RBC, platelets), and others as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat your cancer instead of participating in this study. We will give

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you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

We would like you to join this research study.

Since you are a patient who has been diagnosed with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS), and your disease is refractory to treatment or has relapsed after achieving a remission, we would like to ask you to join this research study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in this study. You are free to say yes or no, or to drop out after joining. There is no penalty or loss of benefits if you say no. Whatever you decide, your regular medical care will not change.

Why are we doing this study?

We are doing this study to examine continuous infusion CLAM (CI-CLAM), a chemotherapy regimen consisting of Cladribine, Cytarabine (also called Ara-C), and Mitoxantrone, the latter three drugs to be delivered in a steady, continuous infusion over several days.

Contrast this to the conventional form of G-CLAM, whereby these same drugs are delivered to the patient over a shorter amount of time, usually 2-4 hours each, for several consecutive days.

Conventional G-CLAM is a common treatment, developed here, for newly diagnosed, as well as certain cases of relapsed/refractory AML or high-risk MDS. We want to know if the chemotherapy drugs in G-CLAM can be safely given to patients if delivered in the continuous infusion form. We are hoping to identify the ideal dose of CI-CLAM with this study. The doctors will watch patients carefully for side effects. We also hope to gain some preliminary knowledge whether CLAM given in this continuous infusion fashion might be more effective than conventional G-CLAM.

What research tests, procedures, and treatments are part of this study?

If you decide to join this study, we will do these tests and procedures:

- **Baseline Assessment.** You will need tests, including a bone marrow and/or peripheral blood analysis, and a physical exam to see if you are eligible for the trial. Please tell your medical team of any past or current medical problems. These tests and physical exam are usually considered part of regular cancer care. If you have recently had some of these tests, they may not need to be repeated. You may also need a catheter inserted to receive chemotherapy and to simplify blood draws and transfusions.
- **Study Treatment.** Given that the aim of this study is to find the best dose of CI-CLAM, different study participants may be treated with different doses. This depends on when you enroll in the study, and other medical factors. There are six different "dose levels," with the concentration of each respective drug remaining the same but the number of days of treatment increasing incrementally with each progressive dose level. At dose level 1, the drugs will be given as follows:
  - Cladribine will be given in your vein as a steady, uninterrupted infusion over 3 consecutive days, starting on day 1. The dose will be 5mg/m^2.
  - Cytarabine will be given in your vein as a steady, uninterrupted infusion over 3 consecutive days, starting on day 1. The dose will be 2g/m^2.
  - Mitoxantrone will be given in your vein as a steady, uninterrupted infusion over 2 consecutive days, starting on day 1. The dose will be 10mg/m^2.

    If the initial patients treated have acceptable side effects we will gradually increase the number of days for which each drug is given, from 2 to 3 for mitoxantrone and from 3 to 4, 4 to 5, and finally 5 to 6 days for the other drugs. Each increase would only occur if the patients treated for previous number of days had acceptable side effects. "Acceptable" is defined using criteria established by the National Cancer Institute (NCI).
- **Monitoring during Study.** During the trial you will need routine procedures, tests and close follow-up. This care is part of routine monitoring for patients receiving chemotherapy. Some examples of these tests, procedures, and care include the following:
  - A medical history
  - Physical examinations
  - Blood tests
  - Bone marrow examinations (i.e., aspiration and/or biopsy)

- Radiology tests such as a chest x-ray if clinically indicated
- Ultrasound of your heart or other heart tests if there are any concerns about your heart function
- Red blood cell or platelet transfusions

How long will I be in this study?

We think you will be in this study for up to 3-6 months. The exact length of treatment will depend on the side effects and your response to the treatment.

If you still have your cancer after one cycle of CI-CLAM, you may be eligible to have this therapy repeated. If this is the case, your doctors will discuss this with you. If you fail to achieve a good response ("remission") after two cycles of therapy, you will not be eligible for additional therapy as part of this clinical trial.

If you achieve a good response with CI-CLAM (i.e. achieve what is called a "remission"), you will be able to receive additional chemotherapy on this study to further reduce the amount of cancer cells that may be left in your body. This chemotherapy, also known as "consolidation" chemotherapy, will be continuous infusion CLA (CI-CLA), consisting of cladribine and cytarabine (this regimen does not include mitoxantrone). The consolidation will be given after your blood counts are better and you have recovered from side effects that you may experience. Some doctors or patients may elect to use therapies other than CI-CLA for your consolidation (e.g. transplantation), and your doctors will discuss these options after your initial treatment.

After you have finished the study treatment, you may return to your primary oncologist or choose to receive additional care at the Seattle Cancer Care Alliance (SCCA). As with any patient receiving such therapy, you will need monitoring. This future care will likely include visits to your doctor, physical examinations, and routine tests. These tests may include repeat bone marrow evaluations. The investigators may want to know about your health after you leave the SCCA. The investigators may contact you or your doctor to see how you are doing. The plan is to follow patients for 5 years after treatment.

The study doctor or your doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You are unable or unwilling to follow study procedures.
- The whole study is stopped.

If you are thinking about dropping out of this study, please tell the study doctor. The doctor can tell you about the effects of stopping G-CLAM. You

and the doctor can talk about what follow-up care and testing would help you the most.

If you leave the study, your test results and information cannot be removed from the study records.

What are the side effects (risks)?

In this part of the consent form, we tell you the side effects we expect from the tests and treatments in this study. There may be side effects we do not know about yet. If we learn about other side effects, we will tell you.

We carefully watch everyone in the study for side effects. If you want more information about side effects and risks, ask the doctor, pharmacist, or nurse.

This form lists side effects of *individual* drugs. When we use these drugs *together*, there may be other side effects.

Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study treatment. In some cases, side effects can last a long time or never go away. There also is a risk of death.

You should talk to your doctor about any side effects that you have while you are in this study.

Cladribine

Likely side effects (>20% of patients) of Cladribine are:

- Nausea and vomiting
- Tiredness or fatigue
- Rash
- Fever during times of low blood counts (i.e., “neutropenic fever”)
- Low blood counts (low WBC, RBC, platelets)

Less likely side effects (≤20% of patients) of Cladribine are:

- Headache
- Dizziness
- Cough or shortness of breath
- Abdominal pain, possibly with diarrhea or constipation
- Muscle or joint pain
- Pain at the place of injection
- Bruising

- Itching

Rare but serious side effects of Cladribine are:

- Stevens-Johnson syndrome
- Allergic reactions (fever, chills, shortness of breath, fast heartbeat, loss of consciousness, sweating, swelling of face or tongue, tightness of throat, wheezing)

Cytarabine

Likely side effects (>20% of patients) of Cytarabine are:

- Fatigue
- Low blood counts (low WBC, RBC, platelets)
- Diarrhea, nausea, vomiting, and loss of appetite
- Irritation, inflammation, or damage to the mouth, throat, esophagus (tube between the mouth and stomach), stomach, intestines or colon
- Fever during times of low blood counts (i.e., “neutropenic fever”)
- Rash
- Abnormal liver tests or liver function

Less likely side effects (≤20% of patients) of Cytarabine are:

- Chest pain
- Fluid collection around the heart
- Shortness of breath
- Headaches
- Dizziness
- Irritation or inflammation of nerves which causes pain in various parts of the body
- Itching
- Jaundice (yellow discoloration of the skin)
- Constriction of the lung airways causing shortness of breath or wheezing
- Inflammation of the pancreas (the organ in your abdomen that helps you digest food and controls your blood sugars)
- Difficulty in passing urine
- Inflammation or irritation of the eye or surface of the eyelids
- Kidney problems

Rare but serious side effects of Cytarabine are:

- Inflammation around the brain

- Heart failure
- Diffuse pain in the muscles, bones, chest, and eyes
- Severe skin rash with flat discolored areas and raised bumps
- Weakness
- Muscle damage
- Life-threatening liver damage

Mitoxantrone

Likely side effects (>20% of patients) of Mitoxantrone are:

- Fatigue
- Low white blood cell counts
- Fever during times of low blood counts (i.e., “neutropenic fever”)
- Nausea / vomiting
- Temporary discoloration of the urine and other body fluids (due to blue color of medication)

Less likely side effects (≤20% of patients) of Mitoxantrone are:

- Skin rash
- Fast or irregular heart beat
- Fever or chills
- Lower back or side pain
- Painful or difficult urination; decrease in urination
- Swelling of feet and lower legs
- Sore, red eyes
- Yellow eyes or skin
- Pain or inflammation at injection site
- Blue skin at place of injection

Rare but serious side effects of Mitoxantrone are:

- Allergic reactions (fever, chills, shortness of breath)
- Heart failure
- Secondary acute myeloid leukemia from drug treatment

Reproductive risks

Chemotherapy may make you sterile (unable to have children).

Also, the drugs in this study may affect a baby, before or after the baby is born.

For women who can become pregnant:

- You should not become pregnant while you are in this study.
- You should not nurse a baby while you are in this study.

For women and men:

- If you are having sex that could lead to pregnancy, you should use birth control while you are in this study.
- Check with the study doctor about birth control methods and how long to use them. Some common methods might not be appropriate while you are in this study.

Non-physical risks

Non-physical risks are:

- You may not be able to work.
- Breach of confidentiality.

What are the benefits?

We do not know if this study will help patients. We are testing CI-CLAM to see to find the best dose for people with AML and high-risk MDS. Patients who get this study treatment may get better, but their condition could stay the same or even get worse. We hope the information from this study will help other people with AML or high-risk MDS in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.

If you do not join this study, you have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor about them.

Your other choices may include:

- Another research treatment.
- Standard treatment.
- No treatment.
- Comfort care.

Protecting your Privacy as an Individual and the Confidentiality of Your Personal Information

Some people or organizations may need to look at your research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect your rights as a research participant.
- Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance.
- US National Institutes of Health, Office for Human Research Protections, U.S. Food & Drug Administration, and other agencies as required.

We will do our best to keep your personal information confidential. But we cannot guarantee total confidentiality. Your personal information may be given out if required by law. For example, a court may order study information to be disclosed. Such cases are rare.

We will not use your personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

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.

Information about your participation in this study such as the title of the study and the names of the researchers involved in the study will be made a part of your permanent medical record. If you authorize others to see your medical record, they will find out about your participation in this study.

Will you pay me to be in this study?

There is no payment for being in this study.

How much will this study cost me?

There may be some extra costs for being in this study. You or your insurer will have to pay these costs. Some insurers will not pay for research. Check with your insurer before you join this study.

The extra costs may be:

- Cost of tests that are given more often than usual.
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care you may need because of this study.

You or your insurer will have to pay for the costs of treating your cancer in this study.

What if I get sick or hurt in this study?

If you get sick or hurt in this study, tell the study doctor in person or call 206-667-3599.

Emergency medical treatment is available at the usual charge. You or your insurance company will have to pay for medical care or hospitalization. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family.

If you get sick or hurt in this study, you will get medical treatment. You or your insurer will have to pay for treatment.

What will my information be used for?

In addition, be aware that by agreeing to participate in this study, your information could be used for future research studies or sent to other investigators for future research studies without additional consent from you.

These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information. If you do not want your information to be used for future research studies without your consent, you should not participate in this study.

Your rights

- You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.
- If you join this study, you do not have to stay in it. You may stop at any time (even before you start). There is no penalty for stopping. Your regular medical care will not change.
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we may learn new information you need to know. For example, some information may affect your health or well-being. Other

information may make you change your mind about being in this study. If we learn these kinds of information, we will tell you.

For more information

If you have questions or concerns about this study, you may talk to your doctor anytime. Other people you can talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	[redacted] (Dr. Elihu H. Estey)
If you get sick or hurt in this study	[redacted] (Dr. Elihu H. Estey)
Your rights as a research participant	*206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center)* *206-543-0098 or email hsdinfo@uw.edu (Human Subjects Division, University of Washington)*
Your bills and health insurance coverage	206-606-1113

Signature

If you have read this form (or had it read to you), asked any questions, and agree to participate, please sign:

Participant / Printed Name, Signature, and Date

If you served as an interpreter or impartial witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the participant's apparent understanding of and willingness to participate in the research.

Impartial Witness or Interpreter / Printed Name, Signature, and Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature / Printed Name, Signature, and Date

Copies to: Patient, Medical Records, Research File