PRINCIPAL INVESTIGATOR: Robert J. Kreitman, M.D.

STUDY TITLE: Randomized Trial of Cladribine (CdA) with Simultaneous or Delayed Rituximab to Eliminate Hairy Cell Leukemia Minimal Residual Disease

STUDY SITE: NIH Clinical Center

Cohort: *Eligibility Screening*

Consent Version: *09/21/2022*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Study PI: Robert J. Kreitman, M.D
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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

Description of Research Study

This consent form is to determine your eligibility for our study involving treatment with cladribine (also called CdA) and rituximab for hairy cell leukemia. Cladribine is a chemotherapy agent

known to be very effective in the treatment of hairy cell leukemia and is considered standard of care, but it is not known to be able to cure the disease. Rituximab is a drug that attacks hairy cells and may kill them either by causing the cells to kill themselves, or by getting the immune system to kill the cells. Rituximab is effective in hairy cell leukemia but it is not considered standard treatment and it has not been used as long as cladribine for this disease. The goal of the trial is to treat all patients with cladribine, randomize patients to either getting rituximab at the same time as cladribine, or getting the rituximab at least 6 months later and only if evidence of the hairy cells is present. The purpose of this consent is to determine if you are eligible for this trial. If you are considered eligible, you will need to read and sign a larger consent form which describes the trial and the treatments in more detail. You may not yet be eligible for cladribine and rituximab for several reasons, like having a disease which is not considered hairy cell leukemia, or having results of blood counts which are not in the correct range to be eligible. If so, you may still be eligible in the future. Whether or not you are eligible for our study, we may obtain follow-up data on your outcome from you or your physician. This includes, if they occur at all, the date of tumor recurrence, tumor progression, and possibly death. Your blood, bone marrow, tumor or other tissue may also be tested for other factors for research purposes. However, this consent does not permit any additional studies that would test for genes (i.e. tendency for diseases) that might be inherited from you by your children.

Tests needed to determine whether you are eligible for this trial:

Blood samples will be drawn at your local medical doctor or previously obtained bone marrow samples will be sent to NIH. We may collect up to 8 tablespoons of blood to test for your eligibility and collect research samples for this study.

The following tests or procedures are needed to determine whether you are eligible for this trial:

- Medical history: A complete review of your medical history, including obtaining information about your diagnosis and previous treatments, and reviewing information about your other conditions.
- Physical examination including weight and height, and vital signs
- Performance status: an evaluation of your ability to perform everyday activities.
- Lab blood and urine tests, to check for blood counts, organ function, and for signs of infection.
- Pregnancy test in women who can have children. Pregnant women will not be allowed on study.
- Test for hepatitis B and C.
- HIV test. As part of this study, we will test you for infection with HIV, the virus that causes AIDS. If you are infected with HIV, you will not be able to take part in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infections, and the importance of informing your partners at possible risk because of your HIV infection
- Flow cytometry of the blood.
- Electrocardiogram (EKG)
- CT scan or MRI

- Bone marrow biopsy samples, whether they obtained at NIH or elsewhere, and whether the bone marrow test has already been done or not yet done. Your tumor tissue may be obtained from prior surgeries or from a biopsy that you might elect to have for purposes of determining if you are eligible for this study. Any biopsy or other procedure would be done only if needed and only after you sign an additional informed consent related to the specific procedure.

Use of Specimens and Data for Future Use

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect, use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Samples to be saved for additional tests:

You will be given the chance to decide if you would like to have your blood and bone marrow samples saved for the optional studies described below.

- Bone marrow biopsy samples, whether they obtained at NIH or elsewhere, and whether the bone marrow test has already been done or not yet done. Requires about 1/2 teaspoon.
- Neutralizing antibodies: Antibodies a patient might make to certain protein drugs which block their effect against cancer cells. You may or may not consider receiving these protein drugs in the future. Requires about 1 teaspoon.
- Cytotoxicity assays. Hairy cells from the blood or bone marrow may be tested outside the body with anti-cancer drugs to determine if they can be killed. Requires 1-3 tablespoons.
- Soluble CD25, CD22, and other tumor markers: Your hairy cells make these proteins and since they fall off the cells and go into the blood, the blood can be tested for them to estimate the amount of hairy cell leukemia cells in your body. Requires about 1 teaspoon.
- HLA (Human leukocyte antigen) typing to better understand the immune system in patients with hairy cell leukemia. HLA is the human leukocyte antigens, a complex of proteins on

your white blood cells which allow your body to determine whether the cell is yours or not. Requires about 1 teaspoon.

- PAX-gene tube: To obtain RNA to study the mechanism of how leukemia cells form, and to detect very low levels of leukemia cells in patients. PAX-gene tubes contain a special liquid that keeps RNA in the blood stable, and it mixes with your blood only after it is drawn. Requires about 1/2 teaspoon.
- RNA samples can also be used, in an assay called micro-arrays, to study why some patients may not respond as well as others to treatments for leukemia. The genes to look at would include those that trigger cells to die, and those that help make hormones which cause inflammation. Taken with PAXgene tube.
- Samples of blood to study certain toxicities of other treatments used for hairy cell leukemia, including hemolytic uremic syndrome (HUS). Requires about 1/2 teaspoon.
- DNA samples to look for abnormalities which might make a patient more susceptible to HUS. Requires about 1/2 teaspoon.
- Flow cytometry assays, where your hairy cells are tested with antibodies outside your body to determine how much of each tumor marker is present on the hairy cells. In flow cytometry, your blood after being drawn goes into a tiny tube where lasers determine whether the tumor markers are present and, if so, how much. Requires about 1/2 tablespoon.
- Samples of blood to look for factors in the malignant cells which might explain how fast or slow they grow or how they respond to treatment.
- Samples to determine the presence of BRAF and related proteins on the malignant cells, to better understand what causes and stimulated the leukemia cells to form and grow.

Assays which could have an impact on both patients and their children, including studies of genetic cancer risk, will not be done. Your research blood samples, when sent outside the NIH, will only be identified by the study code, subject number, and date and time of collection.

Risks or Discomforts of Participation

Blood draws

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting and infection.

Urine collection

There is no risk related to urine collection.

Electrocardiogram (ECG)

Some skin irritation can occur where the ECG/EKG electrodes are placed. Once the electrodes are placed, the test will begin, is completely painless, and generally takes less than a minute to perform. After the test, the electrodes are removed.

Bone marrow biopsy

Your study doctor may need to take bone marrow samples from you to study how your disease is responding. Your hipbone will be numbed with anesthesia, a small needle will be put into the hipbone, and about 10 mL (2 teaspoons) of bone marrow will be taken out through the needle. A bone marrow biopsy may also be obtained. This procedure usually causes some pain. Very rarely, infection or bleeding may occur at the needle site.

Local anesthesia

Biopsy may be done under local anesthesia. Potential side effects of local anesthesia include drowsiness, headaches, blurred vision, twitching muscles or shivering, continuing numbness, weakness or pins and needles sensation.

Imaging/Scans

You may receive a contrast agent injected into your arm as part of your scan. Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives but can also result in a serious life-threatening emergency from difficulty breathing. If this occurs, it is treatable. You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach. Please ask the study doctor if you have questions about the risks of these scans.

MRI

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. We will obtain pictures of your chest, abdomen and pelvis for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Risks from Gadolinium

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for both research and medical purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body.

What are the risks of radiation from research?

During your participation in this research study, you will be exposed to radiation from one CT scan. The amount of radiation exposure you will receive from these procedures is equal to approximately 1.3 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The one CT Scan that you get in this study will expose you to the roughly the same amount of radiation as 4.3 years' worth of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Potential Benefits of Participation

There may be no direct benefit from allowing us to test your blood or other tissue. However, this testing may make you eligible for our trial of cladribine and rituximab. If you become eligible for our treatment study, you would need to give additional informed consent regarding the risks of the treatment.

Alternative Approaches or Treatments

You may choose not to be tested for eligibility or to have any other studies done.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from Genentech and/or Biogen IDEC, the pharmaceutical company who produces rituximab molecule.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Robert Kreitman, kreitmar@mail.nih.gov, 301-480-6187. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.