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: *Randomized*

Consent Version: 09/21/2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

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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 for the treatment of hairy cell leukemia (HCL) with cladribine (also called 2-chlorodeoxyadenosine or CdA) and rituximab. 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, also called rituxan, 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 is not considered standard treatment and it has not been used as long as cladribine for this disease. Rituximab works by attacking cancerous white blood cells, which helps to destroy the hairy cells; it is an infusion given intravenously (through a vein in your arm) over a several hours. Rituximab has been approved by the Food and Drug Administration (FDA) for use in patients with a form of cancer called low-grade or follicular Non-Hodgkin's Lymphoma (NHL), diffuse large B-cell Non-Hodgkin's Lymphoma (NHL) and for certain patients with rheumatoid arthritis.

The first goal of the trial is to treat all patients with cladribine. You will be randomized as to whether or not you will get rituximab at the same time as cladribine. Both groups will get the rituximab at least 6 months later only if hairy cells are detected in your blood at that time. Patients who received their 1st course of rituximab at least 6 months after starting cladribine may receive a 2nd course of rituximab at least 6 months after the beginning of the 1st course of rituximab, if hairy cells are still detected in the blood at that time. The cladribine is given intravenously (by vein) over 2 hours every day for 5 days. The rituximab is given over about 2 hours, although it may be given more slowly if needed, especially the first few times. Rituximab is given once per week for 8 weeks. If rituximab begins at the same time as cladribine, you may begin the rituximab just after the first dose of cladribine. Whether you receive rituximab early or delayed is not up to you, but is determined in a random way which you and your doctors cannot control. It is like the flip of a coin. It is not known whether either method of timing the rituximab is better than the other. This research trial allows you to receive up to "16" infusions of rituximab. Even if the treatment is shown to be of benefit to you, your doctor may not continue to give you additional infusions of rituximab beyond that allowed in the protocol while you are participating in this trial. As part of this study, you will have many lab tests, including bone marrow biopsies and blood tests, to determine whether you have hairy cells left during or after treatment. Some of the tests may be performed by your local physician, but some will need to be performed at NIH.

Plan of the study

This study plans to randomize 132 patients: 68 patients who had no prior treatments with cladribine or pentostatin, and 62 patients who had 1 prior treatment with cladribine or pentostatin with 2 extra patients for replacements if needed. No patients are allowed to have had rituximab prior to being randomized. Half of the patients in each of these 2 groups will receive cladribine and rituximab starting at the same time, and half will receive cladribine alone and only receive rituximab at least 6 months later if and when they have evidence of hairy cells in the blood or bone marrow biopsy. Up to 20 patients with the variant HCLv may be treated with cladribine and rituximab without being randomized, whether patients in this group had 1 or no prior courses of cladribine or pentostatin. It is important for the study for each group to be tested at several time points to determine if they have evidence of minimal residual disease with hairy cell leukemia.

Before you begin the study

Before you begin study therapy, you will have several tests performed to check whether the study is suitable for you. This is called screening. Your doctor will review your medical history and the drugs that you are currently taking as well as the previous treatments of your disease to determine whether you can participate in this study.

Some of these tests or procedures are part of regular care and may be done even if you are not being considered to join the study. If you have had some of these tests or procedures recently, they may or may not have to be repeated. The following tests and procedures will be performed prior to starting treatment:

You will also have additional samples collected for research tests.

- Lab blood and urine tests will be collected to check your health. Other blood samples will be collected for research (up to 16 tablespoons of blood)
- Electrocardiogram (EKG) of the heart will be done to check the electrical activity of your heart
- Echocardiogram of the heart will be done to check how well your heart pumps.
- Stress test to check how your heart works during physical activity
- Test to test how well your lungs work
- CT scan and/or MRI
- Abdominal ultrasound to check the major organs in the abdominal cavity

During the study

Up to 16 tablespoons of blood may be drawn every 4 weeks while you are participating in the study. Every effort will be made to keep blood tests to a minimum. You will be monitored for anemia and given blood transfusions if needed.

- Day 0-1: Routine lab tests
- Days 3, 5: Routine blood tests
- CBC at 1, 2, and 3 months after beginning cladribine or delayed rituximab, then every 3 months during the first 2 ½ years and every 6 months after 2 ½ years
- Research blood to determine the amount of Hairy cells in your blood. (about 3 tablespoons)
    - Week 5 and every 3 months for the 1st year after beginning cladribine, then every 6 months for 2 ½ years, and then every year.
    - For patients that take delayed rituximab
        - Blood will be drawn as above until hairy cells are detected and the decision is made to begin delayed rituximab. Then blood will be collected 0-7 days before delayed rituximab, Week 5 and every 3 months after starting delayed rituximab for the 1st year, then every 6 months for 2 ½ years, and then every year.
- Bone Marrow Biopsy with aspirate, CT or other imaging study of spleen and any other site of known disease, at:
    - 1 and 6 months after cladribine
    - Before and 6 months after beginning delayed rituximab

  - Yearly while in CR for 2 ½ years
  - Every 2 years while in CR thereafter
- The assessment 6 months after cladribine should be at NIH.
- We will follow you at least twice a year when the treatment is completed. This will be done at least by phone or email to determine your status.

Risks or Discomforts of Participation

In order to determine if you are eligible for this experimental use of rituximab with or after cladribine, several tests will have to be done. This period of evaluation may take several weeks and will most likely be done as an outpatient. These tests may include standard blood and urine tests, an electrocardiogram test of your heart, a chest X-ray, an echocardiogram, which is an ultrasound of the heart, computerized tomography (CT or CAT) scans, other X-rays, and a bone marrow biopsy. Many of these tests will have to be repeated several times to check your response to the treatment. These tests will be covered under the NIH screening protocol 01-C-0129 that you will sign prior to having any procedures/tests performed.

Summary of Cladribine toxicities:

Likely (50-70% of patients):
- Fever
- Damage to normal red blood cells which may cause fatigue, or worsen symptoms or heart or lung disease.
- Damage to normal white blood cells which may increase the risk of infection
- Damage to normal platelets which may increase the risk of bleeding

Less likely (25-50% of patients):
- Fatigue
- Nausea

Unlikely (5-25% of patients)
- Chills
- Sweating
- Body pain
- Decreased appetite
- Vomiting
- Diarrhea
- Constipation
- Abdominal pain
- Skin bleeding
- Bloody nose
- Numbness or tingling
- Headaches
- Liver damage

- Muscle pains
- Joint pains
- Swelling
- Fast heart rate
- Rash, itching, redness of the skin

Rare (less than 5% of patients)

- Serious bleeding or infection, although rare in HCL (< 5%), could cause death
- Stress on the heart due to low red blood cells, while rare in HCL (< 5%), could cause death

Rituximab toxicity

Cladribine is considered more toxic than rituximab. However, most of this consent form focuses on toxicities of rituximab since in patients like you who have had either no prior cladribine or pentostatin treatment or treatment with only one prior cladribine or pentostatin course, the standard treatment is cladribine without rituximab.

Rituximab is generally well tolerated by most patients. However, it can cause side effects. You may have none, some, or all of the effects listed below, and they may be mild, moderate, or severe. In some instances, patients who have used rituximab have died. You will be closely monitored by medically trained staff for any side effects and should report any changes in the way you feel to your study doctor. Some side effects may require treatment with medications, procedures, or other therapies. If you develop certain side effects, you may need a break from taking rituximab. Many side effects will improve or go away; however, some can be long lasting or permanent. If you have questions about the risks of rituximab please talk to your study doctor.

Likely (50-60% of patients):
- Fever

Less likely (25-50% of patients):
- Decrease in lymphocyte type of normal white blood cells
- Chills
- Infection
- Fatigue

Unlikely (10-25% of patients):
- Nausea
- Headache
- Night Sweats
- Rash
- Abdominal pain
- Decrease in normal white blood cells
- Decrease in neutrophil type of normal white blood cells (neutrophils are cells which help fight infection)

- Itching
- Increased cough,
- Low platelets (cells which help blood clotting)
- Runny nose
- Back pain
- Low blood pressure
- Diarrhea
- Vomiting
- Muscle pains
- Joint pains
- Dizziness

Infusion-Related Reactions - Rituximab may cause side effects associated with infusion of the drug through the veins. Such side effects are called infusion related reactions. Infusion-related reactions can occur up to 24 hours after receiving rituximab, but they usually happen within 30 minutes to 2 hours of beginning an infusion. Most infusion-related reactions are mild or moderate in severity, but they can be severe, and may even lead to death. Most reactions occur with the first infusion and improve with later infusions. Data indicate that symptoms of an infusion-related reaction occur in about 77% of people after their first dose of rituximab (severe symptoms occur in about 7%). By the eighth dose, the rate of such symptoms decreases to approximately 14%. The most common symptoms include fever, chills, nausea, dizziness, vomiting, headache, sweating, flushing, itching, skin rash, hives, runny nose, sneezing, cough, fatigue, joint pain, muscle pain, swelling of arms or legs, soreness or swelling at disease sites, and chest pain. Severe reactions may include tongue or throat swelling, wheezing or difficulty breathing, fluid or inflammation in the lungs, low blood pressure, irregular heartbeat, and heart attack. Notify your doctor immediately if you experience any of the symptoms above while receiving, or soon after receiving, an infusion of rituximab.

Tumor Lysis Syndrome – Some patients can develop tumor lysis syndrome after rituximab treatment. Tumor lysis syndrome is caused when cancer cells break down and release their contents into your blood. Tumor lysis syndrome can lead to high levels of potassium in the blood, changes in the blood levels of other electrolytes, kidney failure, and can cause death in severe cases.

Skin and Mucous Membrane Reactions – Reactions of the skin and/or mucous membranes (the lining of the mouth, nose and eyes) may occur with rituximab. Examples of this type of reaction include peeling, rashes, blisters, and open sores. While these reactions appear to be rare, they can be severe or even lead to death when they occur. They usually occur from 1 to 13 weeks after receiving rituximab. If you experience any of these symptoms contact your study doctor immediately.

Infections - Rituximab may increase your risk of developing certain types of infections. Some of these infections can be serious or lead to death. It is important to tell your doctor immediately if you develop symptoms of an infection, such as a fever, chills, a stubborn cough or a cough that produces phlegm, persistent diarrhea, burning with urination, red or inflamed skin, or green or yellow discharge from a wound or sore. If you have HIV-associated lymphoma, you may be at increased risk for deadly infections after rituximab.

Hepatitis B – In rare instances, patients receiving rituximab have developed hepatitis B, a type of infection of the liver caused by the hepatitis B virus. Many of the patients who developed hepatitis already had the virus in their body before starting rituximab. Hepatitis B can occur more than a 1 year after stopping rituximab treatment. In some cases, it has resulted in liver failure and death. Your doctor may take a sample of blood from you to test you for the hepatitis B virus before starting treatment with rituximab. He/she may also take samples of blood during treatment to check your liver. If you develop pain in the area of your stomach, or a yellow discoloration of your skin (jaundice), contact your study doctor immediately.

Progressive Multifocal Leukoencephalopathy (PML) - Progressive multifocal leukoencephalopathy (PML) is a rare and severe viral infection of the brain that has developed in patients receiving rituximab. Some of these patients did not show signs of PML for up to 1 year after having rituximab. It is not clear whether rituximab increases the risk for PML. PML can cause brain damage, memory loss, trouble thinking, blindness, and death. Notify your study doctor immediately if you develop trouble thinking or walking, a decrease in strength in your arms or legs, or changes in your vision or hearing.

Bowel Obstruction and Rupture – Cancer patients treated with rituximab and chemotherapy may rarely develop blockage or rupture of the intestines. Some of these patients died. Notify your study doctor immediately if you develop pain or swelling in the stomach area or persistent vomiting.

Decrease Blood Counts - Rituximab may cause a decrease in the numbers of certain blood cells. This has caused patients to develop anemia (low levels of red blood cells that carry oxygen throughout your body), low numbers of platelets (the cells that help your blood clot), or low levels of white blood cells (the cells that help your body fight infections). The decrease in blood cells can last for as long as 1 year after rituximab treatment.

Interaction with Vaccinations - Rituximab may interfere with your body's ability to respond to a vaccination. Certain vaccines may not be effective. Other vaccines might lead to an infection if they contain live organisms (for example, measles, mumps, rubella, or polio vaccines). Talk with your doctor before receiving any vaccinations while taking rituximab, and for 1 year after treatment has finished.

Antibodies Against Rituximab - After receiving rituximab, your body might make antibodies against rituximab. Antibodies are part of the body's normal response to foreign substances. However, these antibodies might also interfere with how well rituximab works, or they might increase your risk for certain side effects.

Reproductive Risks - The effects of rituximab on pregnant women, fetuses, new-born children and sperm, are unknown. If you are pregnant or breast feeding, or you are a man seeking to father children, you should not take this drug. If you are a woman who is able to have children, you must agree to avoid becoming pregnant while taking rituximab and for 1 year after treatment has finished (because the drug can stay in your body for a long time). Your doctor may take a sample of blood from you to test if you are pregnant before starting treatment with rituximab. If you are a man, you must agree to use contraception to prevent pregnancy while taking the drug and for twelve months thereafter. If you suspect that you, or your partner, have become pregnant, you must notify the study doctor immediately.

Other Effects - Other side effects that may occur during treatment with rituximab include heart failure, irregular heartbeats, and lung problems such as scarring or inflammation. If you have a history of heart problems, including irregular heartbeats, heart attacks, and/or angina (a condition where the heart doesn't receive enough blood), rituximab may worsen these conditions. Notify your study doctor immediately if you develop difficulty breathing, fainting, or pain in your chest. Immune system problems can also occur while taking rituximab. These problems can include inflammation of the eyes, nerves, blood vessels, joints, or lining of the lungs.

In addition to the effects listed above, unanticipated side effects may occur that have not been previously reported.

If you have any unusual symptoms, you should report them immediately to your doctor.

You will be kept fully informed of any events that occur during the course of the trial which might affect your safety and change your decision about continuing to participate in this trial.

Because rituximab is a mouse antibody that has been changed to make it similar to a human antibody, treatment with rituximab may cause your body to make human antibodies to the mouse-based antibody. These antibodies are called human anti-mouse antibody (HAMA) or human anti-chimeric antibody (HACA). This has happened in 1.1% (4/356) of patients and the potential response may lead to limiting the effectiveness of mouse-based antibody therapies for you in the future.

Unanticipated side effects may occur that have not been previously reported. If you have any unusual symptoms, you should report them immediately to your doctor.

Combination of cladribine and rituximab

There have been insufficient reports of cladribine being used at the same time as rituximab to predict toxicities of the combination which might be worse than cladribine or rituximab alone.

Premedications:

Acetaminophen (Tylenol): side effects are unlikely. Regular use of acetaminophen can cause liver damage especially at high doses (more than 4000mg/day or 12 regular strength tablets per day). To minimize this possibility, you should not take over-the-counter products containing acetaminophen during the time periods you are taking scheduled acetaminophen doses on this study.

We will carefully monitor you to detect any of these side effects; in addition, you will be taught about side effects, which you may experience and must report immediately. Although side effects of this treatment usually last for a short period of time and completely resolve, you may experience side effects that are permanent. Although not expected, death could occur from this experimental treatment. It is very important that you notify us as soon as possible if you experience any type of side effect so that you can be carefully examined. All precautions will be taken to prevent these side effects and you will be treated promptly (if treatment is required and possible) if they occur. Treatment on this study will require a significant amount of your time and may be stressful. Participating in this study may prevent you from being in other research studies in the future.

Risks Associated with Routine Procedures:

Blood Drawing

To monitor the effects of therapy frequent blood tests will be necessary. Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting.

Urine collection

There is no risk related to urine collection.

Bone Marrow Biopsy

Your hip bone will be numbed with anesthesia, a small needle will be inserted into the hipbone, and about two tablespoons of bone marrow will be removed through the needle. This procedure usually causes only brief discomfort. 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

Electrocardiogram (EKG)

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.

Echocardiogram

There is no physical risk involved with echocardiogram.

Stress test

A stress test, also called an exercise stress test, shows how your heart works during physical activity. Because exercise makes your heart pump harder and faster, an exercise stress test can reveal problems with blood flow within your heart. A stress test usually involves walking on a treadmill or riding a stationary bike your heart rhythm, blood pressure and breathing are monitored.

A stress test is generally safe, and complications are rare. Risk of complications, include:

- Low blood pressure. Blood pressure may drop during or immediately after exercise, possibly causing you to feel dizzy or faint. The problem should go away after you stop exercising.
- Abnormal heart rhythms (arrhythmias). Arrhythmias brought on by an exercise stress test usually go away soon after you stop exercising.

Heart attack (myocardial infarction). Although exceedingly rare, it's possible that an exercise stress test could cause a heart attack.

Pulmonary function tests (PFTs)

Pulmonary function tests (PFTs) are a group of tests that measure how well your lungs work. This includes how well you're able to breathe and how effective your lungs are able to bring oxygen to the rest of your body. PFTs are usually safe for most people. However, because the test may require you to breathe in and out quickly, you may feel dizzy and there's a risk that you may faint. If you have asthma, the test may cause you to have an asthma attack. In very rare cases, PFTs may cause a collapsed lung.

Abdominal/splenic ultrasound

There is no physical risk involved with abdominal ultrasounds.

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 up to four CT Scans (including the one you had during screening). The amount of radiation exposure you will receive from these procedures is equal to approximately 5.2 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." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The four CT Scans that you get in this study will expose you to the roughly the same amount of radiation as 17.3 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.5 out of 100 (0.5%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

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

While we hope that cladribine treatment with rituximab at the same time or delayed will be beneficial to you, we do not know if you will receive personal, medical benefit from this treatment. You may have improvement in your leukemia such as reduction in cancer-related symptoms. Your participation in this study may help us advance the understanding of the best treatment of hairy cell leukemia early in the disease process.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of receiving rituximab with or after the cladribine, you may decide to receive the cladribine alone, as is standard practice for hairy cell leukemia. You may decide now not to receive treatment in this protocol or you may choose at any point in time to stop the drugs and withdraw from the protocol. In either case you would be returned to the care of your referring physician.

Because of the type and extent of your tumor, chemotherapy is felt to be more beneficial than surgery or radiation alone. Alternative approaches that could be used may include:

1. Other forms of treatment:
    a. Several drugs besides cladribine and rituximab can be useful in patients with HCL, alone or in combination. These may include Pentostatin, fludarabine and interferon, which are also drugs which can produce responses in HCL, but they also can hurt the immune system.
    b. Radiation treatment, which sometimes can control tumor growth in local areas such as lymph nodes, spleen and bones. However, this approach will not effectively treat disease that has spread beyond the areas that are irradiated.
    c. Surgery, which can be used to remove the spleen (if this has not already been done).
2. Experimental agents.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest

- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Genentech and/or Biogen IDEC (the manufacturers of the rituximab molecule) or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The National Institutes of Health and the research team for this study are using drugs developed by Genentech and Biogen IDEC through a joint study with your researchers and the company. The company also provides financial support for this study.

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 and 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 have not already been used or shared 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.

Some of these research studies will be performed under the companion protocol 10-C-0066. You will be asked to sign a consent for that study prior to having any samples collected.

- 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. Leukemia cells from the blood, bone marrow, or other tissues may be tested with anti-cancer drugs to determine if the malignant cells can be killed outside the body. Requires 1-3 tablespoons.
- Soluble CD25, CD22, and other tumor markers: To estimate the amount of cancer cells in the body by measuring proteins which fall off cancer cells and go into the blood. Requires about 1 teaspoon.
- HLA 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.
- Assays which could have an impact on both patients and their children, including studies of genetic cancer risk, will not be done.

Flow cytometry assays to quantify tumor markers on the malignant 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.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

You will not receive compensation for participation in this study.

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

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more 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 companies who produces the 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: _____.