INSTITUTE: National Cancer Institute

STUDY NUMBER: 05-C-0185 PRINCIPAL INVESTIGATOR: Thomas Waldmann, M.D.

STUDY TITLE: Phase II Study of the Efficacy and Toxicity of Ontak (Denileukin Diftitox) in the Therapy of Adult T-Cell Leukemia

Continuing Review Approved by the IRB on 6/27/2011
Amendment Approved by the IRB on 6/13/2011 (F) Date Posted to Web: 8/5/2011
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Description of Research Study

You have a form of cancer called adult T-cell leukemia/lymphoma (ATL). This is a disease caused by a virus, which infects the white blood cells. In addition to being present in the blood, the malignant cells can be found in the skin, lungs, lymph nodes, liver, bone, bone marrow, spleen and the tissues covering the brain. This is a serious condition and many patients die within one year of diagnosis.

You are being offered admission to a study to test the anti-tumor actions and side effects of a protein called Denileukin Diftitox (Ontak). We are now testing deniluekin diftitox in up to 38 patients with Adult T cell leukemia/lymphoma. The primary purpose of the study is to determine the ability of the deniluekin diftitox to fight the malignant cells. Denileukin

diftitox is considered experimental for the treatment of ATL since it has not been approved by the FDA for this purpose. However it is currently approved by the US Food and Drug Administration (FDA) to treat patients with a cancer called Cutaneous T cell lymphoma. The FDA has approved two dose levels for denileukin diftitox, 9mcg/kg/day and 18mcg/kg/day for five consecutive days every 3 weeks.

The malignant cells of the form of cancer that you have, adult T cell leukemia/lymphoma (ATL), have a protein (antigen) on the surface of the cell called CD25, also known as the interleukin-2 receptor (IL2-R). Denileukin Diftitox is known as a recombinant immunotoxin. It is made of two parts: a protein, IL-2, which binds to the CD25 on the cancer cell and a toxin (a type of poison) that kills the cell to which it binds. The theory behind this drug is that the IL-2 would attach to the cancer cell allow the diphtheria toxin to get into the cell and would kill it. Diphtheria toxin is very powerful and a single molecule of the toxin getting into the cell is considered sufficient to result in the death of the cancer cell. The toxin part is a portion of the diphtheria bacteria but it has been changed so that it will not make you sick with diphtheria.

Prior to enrollment on the protocol a number of tests shall be performed. You will have blood tests for hepatitis B and C virus and HIV. You will sign a separate consent for the HIV test. The HIV test must be negative for you to be in the study. If any of the tests are positive, the results will be provided to your regular doctor and you will be referred for follow-up care. You will have a bone marrow biopsy prior to start of therapy to accurately establish the extent of your disease, and if it is positive initially, it shall be repeated after the therapy has stopped. In addition, skin or lymph node biopsies may be taken to help in the diagnosis of your condition and to study the malignant cells in the lymph nodes or skin. If such a biopsy is needed, a separate consent to participate will be presented to you. You will undergo standard X-rays, CT-scans, and possibly a PET (positron emission) scan and/or a magnetic resonance imaging (MRI) scan prior to treatment and at specific intervals during and after your treatment. Standard X-rays, CT-scans and PET scans result in small, but significant doses of radiation being delivered to your body. The medical risks of radiation delivered in these circumstances are believed to be small. MRI scans do not use radiation to image, but rather radio-magnetic pulses. The specific indications for, risks, side effects and discomfort for each imaging scan will be explained to you prior to the procedure

Because the company (Eisai Inc.) has recently had a problem with the production of denileukin diftitox, Eisai will only supply the drug to patients who have demonstrated an ongoing response to prior denileukin diftitox treatment. Eisai has also required that you receive treatment every 3 weeks rather than every 2 weeks as our protocol had used. Therefore, you will receive treatment with this drug at a dose of 18mcg/kg/day for 5 days in a row intravenously (into the vein), every 3 weeks. We do not believe that this change in the treatment schedule will make any difference in the possibility denileukin diftitox will improve your condition. Nine patients treated with the lower dose of denileukin diftitox showed only short duration reductions in their disease that did not persist. Seven patient have been treated at the higher dose of denileukin diftitox and while the first 5 patients treated at 18mcg/kg/day showed no significant reductions in their disease, the last 2 patients had evidence of improvements. One of these patients had to discontinue treatment due to treatment related side effects, but the other patient continues to be treated. Higher doses may prolong the period of benefit but this is unproven. The 3 week period equals one cycle of therapy. You will remain in hospital on the days when you are receiving Denileukin Diftitox. The infusion takes 60 minutes each day. You will be monitored closely by the medical and nursing staff during the 5 day period. Your dose of denileukin Diftitox will depend on your body weight at the time you enter the study, and your dose may increase or decrease depending if your weight has increased or decreased by a significant amount. To help reduce possible side effects of denileukin diftitox during the drug administration that could be an allergic reaction to the antibody, you will also be given acetaminophen (Tylenol®) and diphenhydramine (benadryl®). These drugs are not experimental and may cause side effects including sleepiness and rarely affects on the liver.

During the study frequent blood samples will be taken (up to approximately 100 teaspoons (=2 cup full) in any six week period to determine the effect of the drug on your disease and to monitor for potential side effects. Blood drawing is associated with slight discomfort.

You will be assessed initially after 4 weeks, by history and physical examinations, looking at the number of cancer cells in your blood and by examining CT-scans to measure the size of tumors in your body. Your treatment will be stopped if the cancer is growing or if there are severe side effects from the treatment. After the initial assessment you shall be re-assessed every 8 weeks. The treatment shall continue for up to a period of 12 months if there is evidence of benefit to you.

You may be asked to undergo a procedure called apheresis which allows us to remove specific parts of the blood and return the red blood cells. Several blood tests must be performed to make sure you are eligible for apheresis. Apheresis will not be performed if you have any of the following: 1) severe anemia or low platelet count; 2) a history of a positive test for HIV; 3) a history of a positive test for Hepatitis B or Hepatitis C; 4) a history of heart disease or any other medical condition that in our judgment should exclude you from the study; 5) a history of allergy to the anticoagulant used during the procedure; 6) pregnancy. In some instances you may still be permitted to undergo apheresis in spite of anemia or low platelet counts as long as your physician and the Department of Transfusion Medicine physician believe the procedure would be safe. The cells collected during the apheresis will be analyzed in the research laboratory of Dr. John Brady, an NCI investigator, and a portion frozen and stored with SAIC-Frederick, a government contractor. Your name will be removed from the samples at the time of analysis or storage and given an identifier to protect your identity.

The procedure takes about one hour and is done in the Department of Transfusion Medicine. Apheresis is similar to donating a unit of blood. First you will have your pulse, blood pressure, and temperature taken, then you will lie down on a couch or bed. Blood will be withdrawn through a needle placed in one arm, and channeled into a special machine which will separate the white blood cells from the remaining parts of your blood. Your red blood cells and your plasma will be returned to you through the same needle or possibly a needle placed in your other arm.

There will be minimal discomfort due to the needle stick. The procedure is generally very safe for healthy individuals (without anemia, bleeding problems, or heart problems). As with other kinds of blood drawing, donors may have lowered blood pressure and may sometimes faint. A small amount of anti-coagulant ("blood thinning" medication) is in the blood that is returned to you, but your body rapidly eliminates this. This medication may cause chills, nausea, heart burn, nasal stuffiness, or a tingling feeling when the blood is returned to your body. These symptoms are brief and may often be stopped by slowing the procedure. There is a very small chance of introducing infection at the site of the needle. There may be bruising at the site of the needle stick.

ALTERNATIVE APPROACHES TO TREATMENT:

Your cancer cannot be cured by surgery or radiation therapy.
Alternatives to participation in this study include:

- Treatment with chemotherapy or interferon in combination with zidovudine (AZT).
- Other experimental approaches such as treatment with other monoclonal antibodies, monoclonal antibodies that have been tagged with radioisotopes to deliver radiation to the sites of the tumor, and other immunotoxins, which are antibodies that have been modified by the attachment of bacterial products that are toxic to the cell are also being tested.
- Stem cell transplantation has also been used in a small number of patients with ATL.
- You may choose to have no further therapy and instead getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not

treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

RISKS AND DISCOMFORTS OF PARTICIPATION:

The purpose of this study is to define how well Denileukin diftitox works to eliminate the leukemic cell from your body. As with any drug, this study may involve risks that are unpredictable. It is possible that you will receive no benefit from this experimental treatment while risking the possibility of experiencing side effects, or even death. The side effects seen with Denileukin diftitox can be broken down into several categories.

Likely (has occurred in over 20% of patients)

- Acute infusion reactions:
  Reactions that may occur during or soon after receiving the treatment include: low blood pressure, back pain, shortness of breath, rash, itching, chest pain, rapid heart rate, headache, fever, chills, weakness, stomach upset and joint or muscle aches. You will be given medicines to help prevent or lessen these symptoms. If you do have a reaction during or after you receive the treatment, you may be given acetaminophen (Tylenol), diphenhydramine (Benadryl), or epinephrine, and the treatment may be slowed down or stopped early. Rarely patients experience a severe allergic response to Denileukin diftitox which required discontinuation of its treatment.
- Vascular leak syndrome:
  This syndrome includes low blood pressure, swelling in the tissues, weight gain, and a decrease in a normal protein in the blood called albumin. These symptoms usually resolve on their own, but if necessary we will give you medicines to decrease the swelling and weight gain and support your blood pressure.
- Risk of Infection
  The normal cells that fight infection in your body may be affected by this treatment. Without these cells you may be at higher risk for infection. We will teach you ways to help prevent infections and will monitor you closely for signs of infection. You will be treated with medications including trimethoprim-sulfamethoxazole in an attempt to prevent pneumonia.
- Nausea, vomiting, loss of appetite or diarrhea
- Flu like symptoms which may start several hours to days after the treatment
- Fatigue

Less Likely (less than 20% risk of happening)

- Changes in blood counts (anemia) which can cause fatigue
- Low blood levels of magnesium, potassium and sodium have been seen with this drug, as well as high blood sodium levels.
- Blood clots:
  If this occurs you will be hospitalized to treat the clot. Two patients with lymphoma who also had a history of heart disease experienced a heart attack while receiving treatment with Denileukin diftitox. Therefore we are not allowing patients with a known history of active heart disease to participate in this study because of the possible increased risk of heart problems.
- Temporary increase in liver enzymes may also occur.
- Temporary damage to the kidneys may occur causing blood, protein or white cells to leak into the urine

Rare (These serious side effects have been reported in less than 1% of patients treated and in many cases were seen in only one individual)

- Changes in vision:
  Loss of visual acuity, in particular with color vision has been seen following treatment. Some patients vision recovered after the drug was stopped but most patients reported persistent visual problems.
- Tumor lysis syndrome
  As a result of killing the cancer cells a syndrome known as tumor lysis has occurred rarely in patients. We may administer a medication called allopurinol, if necessary in an attempt to prevent it and give you the appropriate treatment should it occur, with additional fluids, medicines to increase your urine output and keep your urine alkaline.

If severe side effects occur that might threaten you life during your participation on this study, your treatment will be stopped.

You should avoid pregnancy during the course of this study. Female patient-volunteers of childbearing potential will be tested for pregnancy; pregnant patients will be excluded from the study. Breast feeding women should not participate in this study because of the potential risk to the nursing child. Male subjects should use contraception to prevent pregnancy in their partners during treatment. Birth control should be maintained for six months following completion of therapy. There may be risks and side effects to you or an unborn baby if you become pregnant during the study that we cannot predict. You should not become pregnant or father a child while on study. You should not nurse your baby while on study or until three months after treatment is completed.

Side effects of blood draw

- Minor physical discomfort (needle stick pain),
- Bruising at the site of the needle puncture,
- Inflammation, or rarely, infection.

Risks related to the CT scans

- Small exposure to radiation, which should not cause a significant risk to your health.
- Bruising, swelling at the injection site of the contrast which may be given at the time of the CT
- A sensation of warmth and flushing in response to the contrast injection.
- Allergic reactions including skin rash, low blood pressure, wheezing and organ damage. Kidney damage can occur but usually is not permanent.

Biopsies of skin, lymph nodes, lymph node aspirates and bone marrow aspirates may be performed before and after treatment to establish the full extent of the disease and follow the response to treatment of Denileukin diftitox. Lymph node aspirates will be obtained in all patients with lymph nodes that can easily be felt on physical exam. Internal lymph nodes that would require a CAT scan to obtain the biopsy will not be done. The risks and discomforts of these procedures are described.

- Lymph node biopsies if necessary would be performed by the Surgery Branch, NCI in the Clinical Center, and would generally be done under local anesthesia. If a lymph node biopsy is required the procedure will be described to you and a separate consent form will be given to you for that procedure. An alternative procedure to lymph node biopsy is a lymph node aspirate. For this procedure a small needle is inserted into the lymph node and gently moved back and forth to dislodge some of the cells. A pathologist will examine the cells under the microscope at the time of the procedure to be sure the specimen is adequate. The lymph node may need to be aspirated two or three times to obtain enough cells to examine. There may be some discomfort similar to that you experience while having blood drawn during this procedure.
- For the skin biopsy a circular piece (about 1/8 inch) of skin will be surgically removed following numbing of the skin by injection of a local anesthetic (lidocaine).
- A bone marrow aspirate and biopsy involves a numbing of the skin and bone of the back of the hip with a local anesthetic and removal of a small piece of bone and marrow by a needle. There is some pain and discomfort during the procedure and possibly for a few days afterward.

Risks related to any biopsy

- Pain or discomfort during the procedure and possibly for a few days after
- Bruising or bleeding at the site of the biopsy
- Infection, which is rare and generally treatable with antibiotics

Biopsies are performed to understand the extent of the disease and to assess the response to treatment, however if lymph node biopsy is performed that part of the sample may be processed for research purposes should you agree. If

you do not want to partake in research biopsies, this will not affect your ability to enter the protocol and receive study drug.

POTENTIAL BENEFITS OF PARTICIPATION:

If the Denileukin diftitox binds to the cancer cells they may be killed. The immunotoxin has been shown to help people with Cutaneous T cell lymphoma. The present research may or may not be of direct benefit to you. However, the results may aid in the treatment of other patient volunteers.

RESEARCH SUBJECTS RIGHTS:

Your participation in this experimental research study is voluntary. Refusal to participate will not result in penalty or loss of benefits to which you would otherwise be entitled. You may withdraw from the study at any time. Please feel free to ask any questions you wish concerning research or your disease. You may call the Principal Investigator Dr. Thomas Waldmann (301-496-6653) with any questions about this study, about your rights as a research subject or about any inquiry you feel is related to the study. In addition you may contact the Clinical Center Patient Representative (301-496-2626) if you have any questions regarding your rights under this protocol. The patient representative is not directly involved in the study.

Participation in the present study may render patients ineligible to participate in other research studies that limit the number or type of treatments they may have received. Participation in this protocol does not constitute a promise of long-term care at the NIH Clinical Center.

LEGAL RIGHTS

You will not lose any of your legal rights as a research subject by signing this consent form.

OTHER PERTINENT INFORMATION

1. Confidentiality. 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.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. 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, Thomas Waldmann, M.D.; Building 10, Room 4N115, Telephone: 301-496-6653.

You may also call the Clinical Center Patient Representative at 301-496-2626.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 27, 2011 THROUGH DECEMBER 26, 2011.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____