INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0116 PRINCIPAL INVESTIGATOR: Steven A. Rosenberg, M.D., Ph.D

STUDY TITLE: A Phase II Study of Lymphodepletion followed by Autologous Tumor-Infiltrating Lymphocytes and High-Dose Aldesleukin for Human Papillomavirus-Associated Cancers

Continuing Review Approved by the IRB on 01/11/16
Amendment Approved by the IRB on 07/22/15 (J) Date posted to web: 02/05/16

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.

Why is this study being done?

We have developed an experimental therapy that involves taking cells called lymphocytes from patients' tumors, growing them in the laboratory in large numbers, and then giving the cells back to the patient. These cells are called Young Tumor Infiltrating Lymphocytes, or Young TIL and the therapy is called cell therapy. Before receiving the cells, the patients receive 2 chemotherapy drugs to temporarily suppress the immune system to improve the chances that the tumor fighting

cells will be able to survive in the body. After the cells are given, the patients receive aldesleukin (IL-2) to help the tumor fighting cells stay alive longer.

The purpose of this study is to see if these tumor fighting cells (young TIL) can cause tumors that are associated with the human papilloma virus (HPV) to shrink and to evaluate the toxicity of this treatment.

Why are you being asked to take part in this study?
You are being asked to participate in this study because you have been diagnosed with an HPV-associated cancer such as cervical, vulvar, vaginal, penile, anal, or oropharyngeal cancer.

How many people will take part in this Study?
Up to 73 patients will be enrolled in this study.

Description of Research Study
The Cell protocol has several stages:

Stage	Timeframe	Location	Comments & Instructions
Work up	1-2 weeks	Inpatient and out patient	Scans, x-rays, labs leukapheresis other tests as needed
Chemotherapy (day -7 to -1)	1 week	Inpatient	Receive IV chemotherapy to prepare your immune system for the cells
Cells and aldesleukin (Day 0-4)	1-5 days	Inpatient and possibly ICU	Receive the TIL cells IV and then high dose aldesleukin about every 8 hours for up to 15 doses
Recovery	1-2 weeks	Inpatient unit	Recover from the effects of treatment
Follow -up	Ongoing until disease progression	Outpatient	Return to clinic for physical exam, review of side effects, labs, scans every 1-6 months.

What will happen if you take part in this research study?

Before you begin the study

Cell harvest and growth
We will be obtaining your cells for treatment from a biopsy of your tumor or during surgery, so we can grow Young TIL from your tumor cells in the laboratory. In 1 out of 5 patients, we are not able to successfully grow the cells for this procedure. If your cells do not grow or show HPV reactivity to certain cancer targets, you will not be able to receive the cell infusion. If that happens, we will look at alternative treatments for you (best available care) or return you to the care of your referring physician. We usually know after about 4 weeks whether the cells will grow well enough to be used as an experimental treatment on this protocol. At the time we determine that your cells are not growing, we will inform you and discuss your options with you.

Work up

Prior to receiving the experimental treatment you will undergo many tests. These include imaging procedures, heart and lung function tests, and laboratory tests. If you are a woman, you will undergo a pregnancy test. You will also have a large catheter inserted into a vein and leukapheresis will be performed (see below). You may be admitted to the hospital for these tests. However, you will be allowed to leave on pass on the days that you are not having tests performed.

Catheter insertion

Prior to beginning the experimental treatment, you will have an intravenous (IV) catheter placed in your upper chest. The area will be numbed with an anesthetic before the catheter is put in. Although rare, putting these catheters in can sometimes cause collapse of a lung or cause bleeding. Lung collapse is treated by putting a tube into your chest for a few days to allow your lung to expand. Pressure is placed on any area that might bleed. Other IVs may be needed in one or both of your arms if we need to give you extra fluids, medicines, or nutrition.

Leukapheresis

Leukapheresis is a procedure that allows us to remove certain types of blood cells from you and return the rest of your blood. It is a very common procedure that is done routinely here at the NIH with very few risks. During leukapheresis, blood is removed from you through a needle in your arm, circulated through a machine that divides whole blood into red cells, plasma (the serum part), and lymphocytes (or white cells), and then the plasma and red cells are returned to you through a second needle in your other arm. The white blood cells may be used to help grow the cells. In addition to the leukapheresis you will undergo as part of your work up, we will also ask you to undergo one additional pheresis procedure between 4 and 6 weeks after your cell treatment to see the impact of this therapy on the immune system and see if cells we gave you are still active.

Chemotherapy Regimen (Day -7 through Day -1)

After we have grown the Young TIL cells to large numbers in the laboratory, you will be admitted to the hospital to begin your experimental treatment. You will be given two chemotherapy medicines, cyclophosphamide and fludarabine, to make space in your immune system so the Young TIL can work without any interference from the cells in your immune system. These medicines may cause your tumor to shrink some, but this shrinkage is anticipated to be only partial and of small duration. The main purpose of the chemotherapy is to see if we can make the cells more effective in fighting cancer tumors. Animal experiments have indicated that chemotherapy can make the cells more effective in fighting cancer tumors, but it is not known whether this is true in humans. The cyclophosphamide will be given into your catheter over 1 hour for two days (Day -7 and Day -6) and the fludarabine will be given into your catheter for 30 minutes every day for the next five days (Day -5 through Day -1). The side effects of these medicines are described on the following pages.

Cell Infusion and Aldesleukin Regimen (Day 0 through Day 5)

All patients will be given the cells through their IV over 20-30 minutes one to four days after the last dose of chemotherapy. Within 24 hours after your cell infusion you will be given high dose aldesleukin through one of the IVs. It will be given as a 15-minute infusion about every 8 hours for up to five days after the cell infusion. Aldesleukin is a cell growth factor and it is thought that it will help the cells live longer in your body.

The day after your cells are infused, we will give you G-CSF (filgrastim) as a shot or injection under the skin every day to stimulate your blood cells until they increase to a sufficient number. We will watch you closely during this entire time for any side effects of this experimental regimen. We will discuss the side effects below and we will include in your care all the medicines and treatments to prevent as many of these side effects as we can and to make you as comfortable as we can.

Recovery

You will recover in the hospital until you are well enough to go home. This usually takes 7-12 days after you have received cells or your last dose of aldesleukin; however, you may need to stay in the hospital for longer than this before you are well enough to go home. We will continue to give you support medications, do laboratory tests, and watch you closely for any side effects until we feel your condition is stable.

In addition to the laboratory tests to monitor your condition, we will remove between 1 and 9 teaspoons of blood daily to study the effects of this regimen on your immune system. If you experience side effects in you kidneys, we will collect 1 additional teaspoon of blood and about 6 teaspoons of urine to see if we can determine the cause of these side effects. The maximum amount of blood for research is approximately 2.3 cups in 8 weeks.

Follow up and Evaluation of Experimental Regimen

You will need to continue to take Bactrim, an antibiotic, for at least 6 months following your treatment to prevent you from catching a certain type of pneumonia seen in patients who have low white blood cell counts. We will ask you to return to NIH 4-6 weeks after completing your regimen for evaluation. This visit will probably take 2 days. If your tumor shows evidence of shrinking, we will ask you to return for evaluation every 4-6 weeks for 1 year and then every six months after that for up to 5 years, and then yearly thereafter. If your tumor appears to be growing, we will look for other investigational therapies you may be eligible for, or refer you back to the care of your local physician. At some of your follow up visits, you may undergo leukapheresis so that we can see the effect this therapy has had on your immune system and if the cells we gave you are still alive.

Retreatment

If your tumor shrinks or disappears following the initial treatment and then recurs you may receive one additional treatment if you tolerated the treatment well and if all the side effects have

resolved. You will receive the same medications and cell infusion on the same schedule as with the first treatment.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not participate in the study because we don't know how this medicine would affect your unborn child or your baby. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for four months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:
• abstinence
• intrauterine device (IUD)
• hormonal [birth control pills, injections, or implants]
• tubal ligation
• vasectomy

Alternative Approaches or Treatments

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

If there are effective salvage regimens (regimens used when standard regimens have failed), you will be directed to undergo these regimens before participating in this protocol.

Other options for treatment of your cancer include:

- Standard chemotherapies, including targeted therapies;
- experimental vaccines;
- experimental chemotherapies; or biotherapies;
- other combination therapies; or
- getting no treatment; or getting comfort care which is 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.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

The risks and discomforts of this research study can be significant. This experimental treatment can lead to long-term decrease in your immune function. If you have received radiation therapy, you will need to recover completely (usually at least 4 weeks) from the side effects of the radiation before beginning treatment on this protocol. It is also possible that you may lose your fertility following this experimental treatment. It is possible, although unlikely, that this experimental treatment may cause your death.

We will discuss the side effects of this experimental treatment with you. You will be given medicines, transfusions, and treatments to prevent or treat the side effects including drugs to prevent and/or treat different types of infections. We will try to make you as comfortable as possible.

Leukapheresis

During the leukapheresis procedure, you may have some tingling in your face and lips due to the medicine used to keep your blood from clotting during the procedure. The nurses may give you a calcium-containing antacid to chew that takes away this tingling. Rarely, people may experience lightheadedness or dizziness. We ask that you eat prior to the procedure to prevent this. Rare complications of this procedure are lowered blood pressure, bleeding or bruising where the needles are put in your arms.

Young TIL Cell Infusion

All Young TIL cells will be given through your catheter while we keep you in the patient care unit so we can watch you closely.

Potential risks include:

- Fever, chills and shortness of breath, which are common and may last for a few hours
- Lung congestion causing shortness of breath
- Immune-type reaction, such as pharyngitis and vaginitis. *Note:* In similar clinical trials with cells targeting a melanoma protein, we have observed the following immune-mediated toxicities: loss of skin pigment (known as vitiligo), and inflammation of the eye (uveitis). The skin and the eye are all sites where that targeted melanoma protein is known to exist.
- As this is a new experimental therapy, side effects that we do not anticipate that may cause your condition to deteriorate may be encountered. Any new information that becomes available during the course of this study will be shared with you.

Medications

The side effects of cyclophosphamide, fludarabine, high dose aldesleukin and some of the other medications you will receive are listed below:

Cyclophosphamide and Fludarabine side effects		
Common	Less Common	Rare
▪ Changes in blood counts including: low red cell count (causing fatigue and shortness of breath), low platelet count (increasing the risk of bleeding and bruising), decrease in white blood cells (increasing the risk of infection and the need for treatment with antibiotics or other treatment) ▪ Loss of appetite, nausea, vomiting, ▪ Diarrhea, stomach pain ▪ Mouth sores ▪ Hair loss ▪ Fatigue ▪ Muscle or joint aches	▪ Bleeding ▪ Infection ▪ Bladder irritation with bloody urine ▪ Severe allergic reaction (difficulty breathing/swelling) ▪ Headache or dizziness ▪ Sweating ▪ Swelling of arms or legs ▪ Skin changes, rash, blisters ▪ Weakness ▪ Hearing loss	▪ Heart damage ▪ Lung damage ▪ Kidney damage ▪ Inflammation of the eye resulting in blindness ▪ Inflammation of nervous system resulting in death ▪ Epstein Barr Virus Lymphoma. This can be fatal (Two patients on other studies in the Surgery Branch developed EBV lymphoma, and one died as a result of this disease.) ▪ Loss of fertility ▪ Two out of the first 81 patients enrolled on the initial young TIL study died from complications resulting from suppression of the immune function which resulted in a severe infection (one of these patients also received radiation as part of their treatment regimen).

IL-2 (aldesleukin) side effects		
Common	Less common	Rare
▪ Fever, chills, and fatigue ▪ Lowered platelet and red blood cell levels that may require transfusions ▪ Significant fluid retention causing weight gain (as much as 20 pounds). ▪ Low blood pressure ▪ Increased heart rate ▪ Low urine output ▪ Swelling in your extremities, ▪ Fluid in your lungs that can require oxygen ▪ Dry mouth, nausea, vomiting and diarrhea; ▪ Rash, itching; and changes in skin or hair pigmentation, called vitiligo; ▪ Changes in mental status, including confusion, difficulty sleeping or vivid dreams; this can be severe and require sedation and monitoring in the ICU	▪ Decrease in thyroid function that may require daily thyroid hormone replacement; ▪ Abnormal kidney and liver function that can be severe; ▪ Abnormal heartbeats or low blood pressure that may require treatment in the ICU. ▪ Breathing problems which may need monitoring in ICU and insertion of a breathing tube.	▪ Bowel perforation (a hole) requiring longer hospitalization or surgery. ▪ Autoimmune disease, where your immune system attacks cells in organs of your body. Should this occur, you will be treated with steroids to stop the immune response. ▪ Damage to the heart muscle or heart attack ▪ Loss of blood flow to the extremities due to medicines used to treat very low blood pressure and shock. In one instance a patient had to have her lower arm amputated after treatment with these medicines. ▪ IL-2 is mixed with human albumin which could cause an allergic reaction or potentially transmit viral infections, although we have not had this occur.

Support Medications – side effects		
Common	Less common	Rare
Filgrastim (To increase production of white blood cells)		
▪ Bone Pain	▪ Severe headache	▪ Severe breathing problems ▪ Rupture of your spleen
Bactrim (To prevent a specific type of pneumonia)		
	▪ Fever ▪ Nausea, vomiting, ▪ Skin rash with itching ▪ reduced number of white blood cells ▪ Allergic reaction	
Fluconazole: (To prevent fungal infections)		
▪ Headache ▪ Nausea, vomiting, diarrhea, abdominal pain ▪ Itching		▪ A skin disorder called Stevens Johnson Syndrome, which can be fatal ▪ Liver damage which may be permanent
Acyclovir and Valacyclovir		
	▪ Temporary decrease in kidney function which may not cause any symptoms ▪ Nausea, vomiting, diarrhea, constipation ▪ Pain and irritation at place of injection	▪ Skin rash, hives, itching ▪ Tremors, dizziness, Confusion, seizures ▪ Fatigue ▪ Blood in the urine

Potential Benefits of Participation

Are there benefits to taking part in this study?
The aim of this study is to see if this new experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the Young TIL therapy effect on your type of cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may benefit others in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs even if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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 National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- NCI Institutional Review Board
- The study Sponsor (Steven A. Rosenberg, M.D., Ph.D.)
- Prometheus Laboratories, Inc.

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.

Stopping Therapy

Your doctor may decide to take you off this study under the following circumstances:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

In this case, you will be informed of the reason for that decision.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. If you refuse to participate or withdraw from the protocol or at the completion of the protocol, we will attempt to offer you participation in other NIH protocols if these are available, or will refer you to your home physician for further management.

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 the Sponsor. 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.

You should understand that this study involves research and that your participation is voluntary. Unexpected or unforeseeable side effects may also occur. Your participation in this protocol may be terminated without your consent if your physician feels that it would not be safe for you to continue. Any significant new findings that relate to this protocol will be discussed with you.

Conflict of Interest

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

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

It is possible that the information obtained from your participation on this study may become valuable for commercial research and development purposes (including patentable inventions), which may be of significant benefit to society, the sponsor of this study, individual researchers or other third parties. You will not receive direct financial benefit from such research and development. The NIH and 2 of the investigators on the research team have developed the cell process being used in this research and have a patent pending. This means that it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions.

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, Steven A. Rosenberg, M.D., Ph.D., Building 10 CRC, Room 3-3940, Telephone: 301-496-4164. 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 JANUARY 11, 2016 THROUGH JULY 10, 2016

_____	_____	_____	_____
Signature of Investigator	Date	Signature of Witness	Date
_____		_____	
Print Name		Print Name	