INSTITUTE: National Cancer Institute

STUDY NUMBER: 13-C-0114 PRINCIPAL INVESTIGATOR: Jeremy Davis, M.D.

STUDY TITLE: Phase II Trial of Surgical Resection and Heated Intraperitoneal Peritoneal Chemotherapy (HIPEC) for Adrenocortical Carcinoma

Continuing Review Approved by the IRB on 09/25/17

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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?

Adrenocortical carcinoma (ACC) is a rare tumor that has a very poor prognosis; few patients diagnosed with this disease live beyond 5 years after being diagnosed. Those whose tumors have spread throughout their abdomen have an especially poor prognosis and traditional chemotherapy is not very effective. At the NIH Clinical Center, we have treated patients with other types of cancer whose tumors have spread throughout their abdomen with aggressive surgical removal of their tumors followed by heated

chemotherapy with good results. We think that this type of treatment may help patients with ACC. In this study, we would like to determine if this type of surgery plus heated chemotherapy can improve survival in patients with ACC.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have been diagnosed with ACC and although your tumor has spread throughout your abdomen, we think that we will be able to remove most of the tumors with an operation. Standard chemotherapy usually does not prevent tumors like yours from growing following surgery but we think that giving heated chemotherapy directly into your abdomen may prevent or increase the length of time that it takes for the tumors to grow back.

How many people will take part in this study?

Approximately 30 patients with ACC will take part in this study.

Description of Research Study

In this study patients will undergo a major surgical operation to remove as many of their visible cancer tumors as possible. At the end of the surgical procedure, while still in the OR (and under general anesthesia) patients will receive heated intraperitoneal peritoneal chemotherapy with a drug called cisplatin (HIPEC). At the NIH Clinical Center, we have used surgery and HIPEC to treat patients with several different types of cancers that have spread to their abdominal organs. These have included gastric cancer, appendiceal cancer, peritoneal mesothelioma and other GI cancers that have spread to the peritoneum (the thin membrane that covers all of the abdominal organs). Following the procedure, patients will likely remain in the hospital for 10-21 days and are then will be seen in clinic every few weeks following discharge until fully recovered. Patients will be asked to complete a Quality of Life Questionnaire several times throughout the study so that we can see how the procedure affects their quality of life. Patients will be followed for survival.

Stage	Timeframe	Location	Events
Work up	1-2 weeks	Inpatient and out patient	Scans, x-rays, labs, QOL questionnaire, other tests as needed
Surgery, HIPEC and recovery	4-12 weeks	In-patient, ICU and out-patient	Number of days in the hospital and length of recovery will depend on the size and location of tumors
Follow up	Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months	NIH Clinical Center as possible	Includes physician visit, labs, scans and QOL questionnaires.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. 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 6 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

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

Before you begin the study:

You will have several tests performed to be certain it is safe for you to have the operation and the HIPEC. This may include blood tests, CT and MRI scans, pulmonary and heart function tests; you may also have consultations with a cardiologist and an anesthesiologist.

Surgery to Remove All of Your Tumors:

Once you have completed all of the testing and your physician has reviewed the results to determine that this procedure is safe for you, you will be admitted to the hospital. Most patients are admitted 1-2 days before their operation. Your physician will explain the surgical procedure and HIPEC and will answer any questions you may have. You will be asked to sign a separate consent for the operation.

In order to remove all of the tumors in your abdomen, you will need to have a major operation. This will include removing the tumors as well as parts of any organs that the tumors may be attached to (for example liver, intestines.) If you have tumors in your peritoneum (the thin film of tissue that covers all of your abdominal organs) this will be removed. After we have removed all of the tumors that we can see, you will undergo HIPEC while you are in the operating room. If your surgeon cannot remove the majority of your tumors or if the surgeon considers it unsafe you will not receive the HIPEC.

HIPEC

Two catheters (or thin tubes) will be put in your abdomen. The cisplatin will be diluted in a heated solution and will be given to you through one catheter in your abdomen and drained out through another, bathing the inside of your abdomen with cisplatin. This chemotherapy solution will be washed through your abdomen over 90 minutes at a temperature of about 104 – 105 degrees, which is above your normal body temperature. After your abdomen has been bathed for 90 minutes, the chemotherapy will be rinsed out and the catheters will be removed. During this procedure we will carefully monitor your temperature. If your body temperature goes up during the procedure, we will use cooling blankets and ice packs to keep your body temperature normal.

In order to reduce the risk of side effects (especially kidney damage), from any of the cisplatin that may leak into your bloodstream while it is in your abdomen, a second medicine called sodium thiosulfate will be given to you through your vein during the HIPEC treatment. Sodium thiosulfate binds to cisplatin in the blood and makes it less harmful.

Recovery

After the operation you will be admitted to the Intensive Care Unit (ICU) where you will be monitored closely for 1-4 days. As with any major operation, you may have a breathing tube and be connected to a breathing machine for 1-2 days following the operation. You will have a tube in your stomach, a catheter (tube) in your bladder and several IVs during this period. As soon as you are able, you will be helped to get out of bed, to cough and take deep breaths and to walk. Once your bowel function has returned to normal, you will be allowed to eat – this usually takes 5-7 days.

When your condition is stable, you will be transferred to the regular patient care unit until you are ready to be discharged to home, usually 7-14 days following the operation. Throughout your hospitalization, you will receive pain medications, IV fluids, antibiotics, and blood transfusions as necessary.

Follow Up

You will be asked to return to the NIH Clinical Center for follow up examinations every few weeks until you have fully recovered from the operation and HIPEC. After that, you will be seen about every 3 months for the first year; every four months for the next year and then every six months thereafter. If you are not able to come to the NIH Clinical Center, we will contact you by phone or e-mail and may ask that you send copies of your scans, lab works and physician notes to us.

Health Related Quality of Life Forms (HRQOL)

At several points during this study, we will ask you to complete 2 health related quality of life questionnaires. This will take about 15 minutes and we will ask that you complete the questionnaires by yourself. We will ask you to do this before you have your operation and then

during your follow up visits. You can decide not to complete the questionnaires at any point and this will not affect your treatment.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study? The operation to remove the tumors throughout your abdomen is likely to be quite extensive and will incorporate HIPEC as well. The risks from this operation, HIPEC and general anesthesia include:

Likely

- Pain
- Temporary slowing or stopping of bowel function, known as an ileus. This could take several days to resolve and may require that the tube in your nose that drains your stomach stay in place longer
- Laboratory studies of the liver, particularly bilirubin may be elevated. This may be due to handling or removing part of the liver during surgery or it may be as a result of the cisplatin. Other lab tests may be elevated as well but these too, will usually not cause any symptoms and resolve in a few days.
- This surgery may also cause changes in your bowel pattern, either constipation or diarrhea. Fluid may develop in your abdomen, known as ascites. This may go away on its own, or may need to be drained if it becomes too uncomfortable.

Less Likely

- Leakage of bowel contents may occur from an area where the bowel was sewn together or from any area of your bowel due to the effects of the chemotherapy, the increased temperature during HIPEC, or from the surgery itself. This may cause an infection in your abdomen that may be life threatening and may require an additional operation to repair the leak. Rarely this will cause openings to form from the bowel through the skin or into the abdomen (fistulas) that may require you to stay in the hospital longer, may require antibiotics, or require a second operation to repair.
- The chemotherapy in your abdomen may also cause irritation to structures surrounding the abdomen, particularly the lining of your lungs. This irritation may result in a condition called "pleural effusion" which means that the lung lining is irritated. This may cause pain and some fluid may collect between the lining and the lung. The fluid usually resolves by itself, but on occasion it may need to be drained with a needle and syringe, if it is causing difficulty breathing.
- Bleeding which might require transfusions or a second operation to correct
- Blood clots that have the risk of moving to the lungs causing difficulty breathing

- Infection in the abdomen, where the incision was made, or in the lungs (pneumonia). All types of infections would be treated with antibiotics.
- Breathing problems which may require oxygen or rarely reinsertion of the breathing tube and breathing machine for a few days.

Rare but serious:

- Heart failure, lung failure, kidney failure, liver failure, blood clots in your extremities or lungs and stroke. This may require treatment in the ICU including need for a breathing machine, dialysis, and blood pressure medications.
- Damage to the various organs of your body which may cause your death.

Risks: Cisplatin		
Likely – these may be mild to severe	Less Likely – these may be mild to severe	Rare but Serious
• Thinning of your hair • Decrease in blood counts including white blood cells (which increase the risk of infection), red cells (which may cause fatigue and weakness) and platelets (which increase the risk of bleeding). • Tiredness, insomnia, muscle aches, dizziness • Changes in taste and smell • Cough, shortness of breath	• Nausea • Vomiting • Hearing loss	• Permanent kidney damage (requiring dialysis)

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will prevent your tumors from growing back. 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 treatment's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it 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.

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 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.
- National Cancer Institute Institutional Review Board

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 stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if you have side effects from the treatment that your doctor thinks are too severe

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 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 can**not** 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 Protocol Review Guide. You may ask your research team for 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.

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, Jeremy Davis, M.D., Building 10, Room 4-3760, Telephone: 240-760-6229. 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 SEPTEMBER 25, 2017 THROUGH SEPTEMBER 24, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____