INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0099 PRINCIPAL INVESTIGATOR: Udo Rudloff, M.D

STUDY TITLE: Regional Chemotherapy in Locally Advanced Pancreatic Cancer: RECLAP Trial

Continuing Review Approved by the IRB on 9/23/13
Amendment Approved by the IRB on 11/15/12 (E) Date Posted to Web: 10/4/13
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?

Pancreas cancer is the fourth leading cause of cancer death in the United States. Surgery offers the only chance at cure however, by the time most patients are diagnosed with pancreas cancer their tumors are too large to be removed. Standard intravenous chemotherapy may shrink some of the tumor, but even with chemotherapy, only about 25% of patients will live for one year following diagnosis. Researchers have been studying different ways of giving chemotherapy which will be more effective at shrinking the cancer so that it is small enough to be surgically removed. Several phase 1 studies have shown that administration of chemotherapy directly into the pancreas in the area of the tumor is safe. Studies have

also shown that giving gemcitabine over a longer period of time increases the amount of drug that is available to the tumor. In this study, we plan to give gemcitabine (a chemotherapy approved to treat pancreas cancer) directly into the pancreas in the area of the cancer and at a slow rate of infusion. Giving the gemcitabine directly to the tumor and at a slow rate of infusion is an experimental treatment and we are looking to find the safest dose of gemcitabine to give patients and also to see how well patients tolerate the drug given in this manner.

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

You are being asked to participate in this study because you have pancreas cancer which is currently too large to be removed but has not yet spread to other organs that are not near your pancreas.

How many people will take part in this Study?

Up to 46 subjects will be enrolled here at the National Institutes of Health for this initial study.

Description of Research Study

This is an intra-inter patient dose escalation study (see below*) of gemcitabine given at a slow rate of infusion through a catheter which is threaded into one of the blood vessels in the pancreas and connected to a conventional vascular access device (port). Subjects who meet the eligibility criteria will undergo pancreatic angiography and embolization (see *During the Study* for a description of angiography and embolization) as necessary to isolate the blood vessels supplying the tumor. Subjects will receive up to 3 courses (6 months) of Gemcitabine given through this catheter directly into the pancreatic circulation. The dose for each subject will be increased at the beginning of each cycle until the maximum dose is reached provided no dose limiting toxicities were experienced. Subjects will be assessed every 8 weeks to see if the tumor is shrinking.

*intra-inter patient dose escalation study – a study where each group (cohort) of 3-6 patients enrolled in the study receives a higher dose of medication than the previous group unless 2 of 6 patients have a dose limiting toxicity (DLT – a specified list of side effects.) In addition, patients in each cohort who do not experience a DLT, will receive a higher dose with each cycle of chemotherapy until the maximum dose is reached.

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 six (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 a history and physical examination, and your recent lab work and imaging studies will be reviewed to see if you are eligible for the study and to see if it is safe for you to be in this study. If you haven't had recent blood work or imaging studies, they will be repeated. If the exact size and location of your tumor is not clear on the MRI or CT scan, you will have a laparoscopy performed to be sure that you are eligible for the study. This is a minor surgical procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen. A laparoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

During the study
Within about two weeks following your initial evaluation visit, you will be admitted to the NIH Clinical Center patient care unit and will undergo pancreatic angiography and embolization. This procedure is performed in the Interventional Radiology (IR) Suite by a radiologist while you are under either general or local anesthesia with sedation. The radiologist will thread a catheter (long thin flexible plastic tube) through the femoral artery (in your groin) to the blood vessels supplying the pancreas. He will then inject dye into the catheter and take x-rays in order to see the blood circulation to the tumor, the pancreas and other nearby organs (angiogram). In order to separate the blood flow to the tumor from the blood flow to the other organs, he will embolize or close off, vessels that supply both the tumor and the other organs. He will then thread another catheter into the main vessel that supplies the tumor. The other end of the catheter will then be tunneled under your skin and attached to a conventional "port" under the skin in your hip. This will allow the medication to be given into the catheter throughout the course of treatment. If the catheter cannot be placed through the femoral artery due to the location of your tumor and/or the shape of your blood vessels, then the catheter may be placed through one of the blood vessels in your neck or arm and the port will be placed in your chest – like a conventional port. After you have completed treatment the port will be removed. The whole procedure takes approximately 2 hours to complete. The principle investigator will review the procedure with you and you will be asked to sign an additional consent for the treatment.

After the catheter has been inserted, you will be monitored over night in the intensive care unit (ICU). The following morning, you will return to the IR suite to start your first dose of chemotherapy. The radiologist will inject dye and take x-rays to be sure the catheter is in the correct place. If it is not – he will re position it. A special needle will be inserted into the port and the gemcitabine in fusion will be

started. Once the physicians are certain you are tolerating the infusion, you will return to the ICU for the rest of the infusion – 24 hours total. During the infusion you will be monitored, have blood drawn at least once daily and received routine care. In order to prevent blood clots from forming in or around the catheter you will be placed on a blood thinner given by injection. The nurses on the patient care unit will instruct you on how to give the injections before you are discharged.

Once you are discharged, you will need to have blood drawn weekly (this may be done by your home oncologist) and we will give you a diary to record any side effects from the treatment and your blood thinner doses. If you do not return to the Clinical Center to have blood drawn, the research nurse will contact you and ask you about any side effects you may be having.

Two weeks after the first infusion, you will return to the Clinical Center every two weeks to receive your second, third and fourth infusions. Prior to each infusion the research nurse or physician will review your diary, you will have a physical exam, lab work and another angiogram, CT, or x-ray performed to check the placement of the catheter. You may receive the second (and subsequent) infusions in the ICU or on the patient care unit. Your will be monitored during the infusions and have labs drawn and receive standard care as needed. If you tolerated the second infusion without experiencing any DLTs your dose will be increased for the third and fourth infusions. Once you are discharged you will have blood drawn and complete your diary as noted above. If you have abdominal pain or other GI symptoms following your treatments, you will have an endoscopy prior to your next treatment to be certain that it is safe for you to continue treatment. An endoscopy is similar to a laparoscopy except that a flexible tube is inserted through your esophagus and into your stomach to look for signs of bleeding or irritation

Two weeks after the fourth treatment (course 1) you will return to the Clinical Center for imaging studies, a physical examination and lab work. If your tumor is shrinking you will continue with treatment for 2 more courses. If at any time your tumor becomes small enough to be surgically removed, your physician will discuss this option with you.

When you are finished taking the treatments

You will be seen in the clinic every 3 months for 2 years following your last treatment and then every 6 months. At each evaluation you will have a physical examination, blood work drawn and imaging studies. If you are unable or un-willing to return to the Clinical Center for follow up visits, the research nurse will contact you by phone.

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 chemotherapy or surgery for your cancer without being in a study
- Taking part in another experimental 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.

Risks or Discomforts of Participation: What side effects or risks can I expect from being in this study?

The risks involved in participating in this study have been summarized below according to each part of the experimental treatment. Because gemcitabine has not been given in this way before, there may be additional risks that we do not know about.

Pancreatic Angiography and Embolization

Likely	Less Likely	Rare but Serious
• Abdominal Pain (12-24 hours) • Fever (99-102 degrees F) • Nausea and/or Vomiting	• Abdominal Fluid Buildup (Ascites) • Bleeding (at catheter insertion site) • Infection (at catheter insertion site) • Allergy to Iodine Contrast agent • Mild pancreatitis	• Liver Failure • Kidney Failure • Liver Abscess Formation • Stomach or Duodenal Ulcer • Pancreatitis - severe • Cholecystitis • Arterial Injury at catheter insertion site

Gemcitabine

Likely	Less Likely	Rare but Serious
• Fatigue, may be due to due to low red blood cell counts • Increased risk of infection due to low white blood cell counts • Bleeding due to low platelet counts • Mucositis (mouth sores) • Nausea and vomiting	• Diarrhea • Rash • Change in lab values that may not cause any symptoms and may not require treatment	• Liver damage • Kidney damage

Indwelling catheter

Likely	Less Likely	Rare but Serious
• Mild Pain (12-24 hours)	• Infection • Formation of blood clots which could break off and travel to your legs and other organs	• Pancreatitis • Bleeding

lovenox

Likely – at the site of injection	Less Likely	Rare but Serious
• Mild irritation • Pain • Bruising • Redness	• Change in lab values that may not cause any symptoms and may not require treatment	• Hemorrhage or bleeding

Are there benefits to taking part in this study?
The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinkage of your tumor(s), possibly making your tumors small enough to be removed, lessening of your symptoms, such as pain, that are caused by the cancer or slowing the growth of your cancer. Because there is little information about the giving gemcitabine at a slow rate directly to pancreas tumors, we do not know if you will benefit from taking part in this study (improved survival), although the knowledge gained from this study may help others in the future who have pancreas 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.

Stopping Study Participation

Your doctor may decide to take you off of the study if he/she believes that it is in your best interest, if your disease does not respond to the treatment, if you have side effects that are too severe, or if new information shows that another treatment may be better for you. In this case, you will be informed of the reason therapy is being stopped. You will also be counseled regarding other treatment options as in "Alternative Approaches or Treatments."

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.

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.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process *http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf*. 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, Udo Rudloff, M.D., Building 10, Room 4-5940, Telephone: 301-496-3098.

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 23, 2013 THROUGH SEPTEMBER 22, 2014.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name