INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 00-CH-0093 PRINCIPAL INVESTIGATOR: Karel Pacak, M.D., Ph.D., D.Sc.

STUDY TITLE: Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma and Paraganglioma

Continuing Review Approved by the IRB on 7/22/09
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Adult for Romidepsin

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.

OVERVIEW OF THE STUDY

The main goal of this study is to develop a new approach to increase the entry of a radiocompound called [^{131}I]-MIBG used for radiation treatment of metastatic pheochromocytoma and paraganglioma. We hypothesize that pretreatment with romidepsin a drug that increases histone acetylation in these tumors may also increase the uptake of [^{131}I]-MIBG in these tumors. This would result in a higher expose of tumor cells to radiation and, therefore, more efficient treatment to kill metastatic pheochromocytoma or paraganglioma cells. Romidepsin is an investigational and experimental anti-cancer agent that has not yet been approved by the Food and Drug Administration for use in this form of cancer.

You will not be paid for your participation in this study. However, all protocol-related tests, procedures, and hospitalization at the NIH are without cost to you. In addition to this consent form, you will be asked to sign the adult consent form for participating in this research study.

You are free to withdraw from the study at any time. Should you do so, we will not continue further diagnostic tests and we will not perform surgery at the NIH. Any information obtained from this study is research related and will be made available to you and your physician only upon a special request (see attachment).

Pretreatment [^{123}I]-MIBG scintigraphy

This part of the study will be done to find out whether you are eligible to receive romidepsin (in case that your tumors will take [^{123}I]-MIBG). If so, then you will receive romidepsin (as described below) and you will undergo 2nd (research indicated) [^{123}I]-MIBG scintigraphy. We hypothesize, that the uptake of radioactive [^{123}I]-MIBG will be enhanced by pheochromocytoma or paraganglioma cells after injection of romidepsin.

In order to block the accumulation of [^{123}I]-MIBG in the thyroid gland, you will be required to take medication called SSKI or potassium perchlorate (if you are allergic to iodides), 1 day before and 3-7 days after [^{123}I]-MIBG administration. You will not be permitted to eat anything for at least 3 hours before the [^{123}I]-MIBG test is started, but will be allowed to drink as much water as you wish. If possible you should drink 2 to 3 glasses of water before the test.

The scanning is done at the Nuclear Medicine Department of the NIH Clinical Center. The scanner is shaped like a doughnut, and the part of your body being scanned is in the hole. The procedure will consist of two [^{123}I]-MIBG scans, one before and one after 5 days of the treatment with romidepsin. A plastic catheter is inserted into an arm vein for injection of [^{123}I]-MIBG preferable at 1:00 PM. This first scan will be called "a baseline scan". During the injection you should feel nothing unusual. The first phase of the scanning takes next day at 8:30 AM - approximately 20-24 hours after the injection. Additional images will be taken for another 45 minutes (SPECT). You may be repositioned in the scanner in order to increase the field of view. In total, this test will take approximately 1.5 hours. Planar images will start approximately at 1:00 PM.

Romidepsin Administration

Before you are given romidepsin, additional tests and procedures must be further performed, and those are listed under the "adult consent form" (that you will sign as the part of this protocol) to find out if you are eligible for the present study.

To be eligible for romidepsin administration you will also need to undergo:

- ECG (recording of the electrical activity of your heart)
- Echocardiogram (special ultrasound of the heart performed to test heart function)
- MUGA scan (a special x-ray of the heart performed to test heart function as an alternative to the echocardiogram) and routine blood tests
- Cardiac MRI
- Cardiology consult by a trained cardiologist

If we find that your cardiac function is not impaired, you will be eligible to receive romidepsin through n peripheral iv catheter over 4 hours. Romidepsin will be administered on the first, third and fifth days. The chart below shows what will happen to you during treatment. You will undergo all cardiac monitoring measurements as an inpatient in telemetry unit on days of romidepsin pretreatment.

Time table is outlined below.

Day	*What you do*
Within 1 - 4 weeks of starting study	• Chest x-ray • ECG • CAT scan/ MRI • Echocardiogram
Before starting study	• Check-in to the hospital before starting study • Routine blood tests
Entry exam	• 1st [^{123}I]-MIBG scan before treatment to establish the tumors uptake and eligibility for the study
Day 1	• Routine blood tests • ECG will be done 1 hour before starting romidepsin and within 1 hour after ending romidepsin • Romidepsin will be given iv over 4 hours per dose
Day 3	• Routine blood tests • ECG will be done 1 hour before starting romidepsin and within 1 hour after ending romidepsin • Romidepsin will be given iv over 4 hours per dose
Day 5	• Routine blood tests • ECG will be done 1 hour before starting romidepsin and within 1 hour after ending romidepsin • Romidepsin will be given iv over 4 hours per dose
Day 6	• [^{123}I]-MIBG injection
Day 7	• 2nd [^{123}I]-MIBG scan after treatment to establish the posttreatment tumors uptake • Routine blood tests • ECG • Discharge from hospital if any health complications recorded

Risks and side effects related to the romidepsin include those which are:

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the romidepsin. In some cases, side effects can be serious, long lasting, or may never go away. Although not expected, death could occur from this experimental treatment.

You should talk to your study doctor about any side effects that you have while taking part in the study, particularly about:.

- Nausea
- Vomiting
- Taste changes
- Loss of appetite

- Fatigue
- Fever (some patients have fever immediately following romidepsin treatment. This fever should disappear on its own.)
- Decrease in potassium, magnesium calcium, or phosphate blood levels (levels of these minerals will be measured in your blood before and after romidepsin treatment. You will be treated with extra infusion of minerals or oral supplements of minerals if needed.)
- Decrease in red blood cells (anemia, a decrease in the red blood cell count, may result from your disease, repeated blood draws, or chemotherapy. If your anemia is severe, we may recommend a blood transfusion.)
- Decreased white blood cells (it is important for you to know that at the times that you have decreased white cell counts, you may be at risk of serious infection. Such infections can be very serious and even cause death if not quickly and properly treated. This may occur several days after treatment while you are at home. Therefore, if you have a temperature greater than 38 ^{0}C (100 F), you must call your a physician immediately).
- Decreased platelets (a decrease of platelets may place you at increased risk of bleeding, which may be serious and even cause death. If you experience bleeding, call your doctor at once.)

Less Likely you may develop:

- Mouth sores
- Weight loss
- Headache
- Increased level in blood levels of liver-associated enzymes

Rare but serious reactions include:

- Accumulation of fluid in lungs
- Increase in blood levels of uric acid (which comes from the breakup of cancer cells, and could be associated with kidney damage)
- Heart palpitations, a sign of rapid heart beat
- Death (At a few centers in the United States, several patients with pre-existing heart disease with risk factors known to increase the chance of sudden death due to arrhythmia have died suddenly while enrolled on trials with romidepsin (around 1% of 400 enrolled patients). The role of romidepsin in these events is unknown; however, the deaths may have been related to romidepsin and sudden death could occur from this experimental treatment. Protocol candidates will be evaluated for heart disease prior to enrollment and patients with heart disease who are at risk for sudden death will be excluded.

It is of the utmost importance that you notify us as soon as possible if you experience any type of side effect so that you can be carefully examined before any more romidepsin is given. All precautions will be taken to prevent these side effects and you will be treated promptly should they occur.

Food stuffs to avoid:

Grapefruit Juice
Star Fruit

Prescription medications to avoid:

Generic names:

Amantadine	Dofetilide	Halofantrine	Moexipril/HCTZ	Saquinavir
Amiodarone	Dolesetron	Haloperidol	Moxifloxacin	Sotalol
Aprepitant	Domperidone	Ibutilide	Naratriptan	Sparfloxacin
Arsenic Trioxide	Droperidol	Indapamide	Nefazodone	Sumatriptan
Bepridil	Erythromycin	Indinavir	Nelfinavir	Tacrolimus
Chloral hydrate	Ethinyl-estradiol	Isradipine	Nicardipine	Tamoxifen
Chloramphenicol	Felbamate	Itraconazole	Norfloxacin	Telithromycin
Chlorpromazine	Flecainide	Ketoconazole	Octreotide	Thioridazine
Cimetidine	Fluconazole	Levofloxacin	Pentamidine	Tizanidine
Ciprofloxacin	Fluoxetine	Levomethadyl	Pimozide	Troleandomycin
Cisapride	Fluvoxamine	Lithium	Procainomide	Venlaflaxine
Clarithromycin	Foscarnet	Mesoridazine	Quetiapine	Verapamil
Clotrimazole	Fosphenytoin	Methadone	Quinidine	Ziprasidone
Delaviridine	Gatifloxacin	Mibefradil	Risperidone	Zolmitriptan
Diltiazem	Gestodene	Miconazole	Ritonavir	
Disopyramide	Grepafloxacin	Mifepristone	Salmeterol	

HAZARDS, RISKS, INCONVENIENCES, AND DISCOMFORTS

Pain: Inserting an i.v. catheter can cause local discomfort, clotting, bleeding, or infection. There is a slight, but definite risk of entering an artery, rather than a vein, and this could result in bleeding, bruising, or communication between the artery and vein. We have a sound wave detector available that enables us to "see" the vein even in difficult cases. We estimate less than a 1% risk of local complications other than bruising. Bruising or mild discomfort can last for several days following the procedure. These complications are generally transient and permanent damage is extremely rare.

Allergy: Some people are allergic to iodinated radiographic contrast agents. If you have any allergy to those agents, you must let us know to ensure that alternative imaging studies are used, appropriate pretreatments are given, and to ensure that appropriate allergy medications are made immediately available.

Cardiac problems: Some people can experience cardiac toxicity like ventricular or other arrhythmia and cardiac dysrhythmia. All patients will be closely monitored with ECGs for asymptomatic ST and T wave changes. The level of cardiac enzymes will be measured.

Unexpected findings: Because of the investigational nature of this study, we may not understand the significance of all findings. For instance, [^{123}I]-MIBG scanning may identify abnormalities that are not tumors. Such results are called false positive results. If unexplained or unusual findings occur we may recommend other tests to help explain these findings to determine their significance.

RADIATION

[^{123}I]-MIBG

In summary, you will receive as the part of this study as well as the other studies under this protocol (see adult consent form) the radiation exposure from:

Option (A) fluorodopamine scans (up to3 per year; 1 mCi each), fluorodopa scans (up to 2 per year; 12 mCi each), [^{123}I]-MIBG (1 scan for research, 10 mCi) and in [^{99m}Tc] sestamibi scans (1 scan for research, 20 mCi). As part of these procedures, transmission scans of the body (to aid quantification and localization) will be performed with CT (with each fluorodopamine scan), [^{68}G] (with each fluorodopa scan) and [^{99m}Tc] (with [^{123}I]-MIBG scan).

This radiation exposure is not required for your medical care and is for research purposes only. The total amount of radiation you may receive in this study is ***4.4 rem*** which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

Option (B) fluorodopamine scans (up to3 per year; 1 mCi each), fluorodopa scans (up to 2 per year; 12 mCi each), [^{123}I]-MIBG (1 scan for research, 10 mCi). As part of these procedures, transmission scans of the body (to aid quantification and localization) will be performed with CT (with each fluorodopamine scan), [^{68}G] (with each fluorodopa scan) and [^{99m}Tc] (with [^{123}I]-MIBG scan).

This radiation exposure is not required for your medical care and is for research purposes only. The total amount of radiation you may receive in this study is ***3.6 rem*** which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

Option A includes a [^{99m}Tc] sestamibi scan where as Option B omits this scan. All other imaging procedures are the same. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, *An Introduction to Radiation for NIH Research Subjects.*

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes X-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

One concern some people may have about radiation exposure is the effect on fertility or on the possibility of causing harm to future children (i.e., genetic risk). The doses received in the research study are well below the levels needed to affect fertility.

Please let us know if you have participated in research studies at the NIH or other institutions that have involved the use of radiation, to ensure that the total radiation dose from all studies is not excessive. Examples of such studies include X-ray studies, cardiac catheterization, fluoroscopy, or nuclear medicine studies.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY AND RIGHTS UPON REFUSAL OR WITHDRAWAL FROM THIS STUDY

The choice to enter or not enter this study is entirely voluntary. Before you decide to enter or not, you should understand what the doctor has explained and what you have read about the research study. If you decide not to participate your enrollment in any other NIH protocol will not be affected. If you choose to begin this study you have the right to withdraw at any time.

As noted above, many other physicians and centers are experienced in the evaluation and treatment of patients with pheochromocytoma and paraganglioma. These centers will commonly rely on many of the same tests that we use to determine the cause of your symptoms. While some tests that we perform are not widely available (such as fluorodopamine PET scanning) they may not be critical to your specific case.

We cannot predict which patients will benefit from the additional tests offered in this study. If you are not sure that you wish to participate in this study, let us know at any time, and we will refer you to other physicians and medical centers experienced in the evaluation and treatment of patients with pheochromocytoma and paraganglioma.

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, Karel Pacak, M.D., Ph.D., D.Sc.; Building 10, CRC, Room 1E-3140, Telephone: 301-402-4594 or Karen T. Adams, CRNP; Building 10, CRC, Room 1E-3140, Telephone: 301-402-7785. 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 JULY 22, 2009 THROUGH JULY 21, 2010.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____