

CHR# H7015-06457-17

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UNIVERSITY OF CALIFORNIA SAN FRANCISCO

Consent to be a Research Subject

¹³¹I-Labelled MIBG

(Metaiodobenzylguanidine) Therapy for Metastatic
or Unresectable Pheochromocytoma and other Related Tumors
A Phase II Study: CHR# H7015-06457-17 CC# 03991

INVESTIGATORS

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BACKGROUND AND PURPOSE

I have advanced (metastatic) pheochromocytoma or a related tumor. The above physicians are investigating a method of treating metastatic pheochromocytoma with a radioactive compound called ¹³¹I-metaiodobenzylguanidine (¹³¹I-MIBG) which is taken up by the pheochromocytoma (and related tumor) cells. This compound delivers the radioactive iodine to the cancer cells selectively and result in their destruction. There have been reports of short-term effectiveness in metastatic pheochromocytoma using ¹³¹I-MIBG, but the long-term effectiveness is not yet known.

PROCEDURES

- 1) **Pretreatment body scan** with low dose ¹³¹I-MIBG or ¹²³I-MIBG will be required. A small amount of radioactive iodine is attached to MIBG and is injected intravenously. I will need to return in 1 to 3 days to Nuclear Medicine to have my whole body scanned by a radiation detector that will determine if the MIBG has entered my tumor.
- 2) **Pretreatment evaluation** requires giving blood (about 35 ml or 7 teaspoons) and 24 hour urine specimens for laboratory evaluation. Radiological studies (such as x-ray, CT scan, MRI scan or bone scan) will be required to determine the extent of remaining tumor. An ultrasound (echo) study of the heart may also be done. If the lungs have tumor, pulmonary (breathing) tests will be done. A bone marrow biopsy may be done, if there is a chance that my tumor has spread to bones.

- 3) **Collection of stem cells** – Peripheral blood stem cells (PBSC) may need to be collected from me. To collect PBSCs, granulocyte colony stimulating factor (G-CSF) must first be given. G-CSF is given by myself (or someone of my choosing) as daily injections under the skin with a needle. G-CSF helps push bone marrow cells (stem cells) into the bloodstream. G-CSF is continued daily for several days until PBSC collections are completed.

To collect peripheral blood stem cells, I would first have a central venous catheter (intravenous line) placed. This is a catheter placed under my collar bone, or at the base of my neck, which enters into one of the large veins which leads to my heart. This is placed using local numbing medicine in the entry area first. When my white blood count (WBC) is high enough, I will have my PBSCs collected through a process called leukapheresis. My blood would be run out through my central venous catheter and circulated into a machine which separates off my peripheral blood stem cells and transfers them to a bag. The remainder of my blood is returned to me. Leukapheresis is performed daily for one to four collections as an outpatient. My peripheral blood stem cells are then frozen.

- 4) **¹³¹I-MIBG Treatment** involves injection of the radioactive compound into the vein as often as once every 12 weeks. If my bone marrow is involved with cancer, I will be treated with a lower dose of ¹³¹I-MIBG. Depending on my response to treatments, I may require additional doses. The injection will be given in the hospital, and will require a 5 - 7 day hospitalization for observation, radiation precautions, and intravenous fluids. I will require a bladder catheter for about three days. For the first 3 days at bed rest, I may receive an injection of an anti-clotting medication (such as enoxaparin) to reduce the likelihood of blood clots developing in my veins.

Following the ¹³¹I-MIBG injection, I will be in an isolation room in the hospital behind a lead shield. Visits will be limited according to the potential radiation exposure, 0.5-2 hours the first day and 1-6 hours the second day behind a lead shield. I will be discharged when radiation levels have fallen adequately, usually about 5 to 7 days after the injection.

- 5) **Follow-up** requires blood drawing for laboratory tests twice weekly for 4 - 6 weeks, then weekly for 4 weeks, then monthly until normal. Blood tests for endocrine studies will be required at 1, 3, 6 and 12 months post-treatment, and at least every 6 months thereafter. A 24-hour urine will be collected about every 3 months for 12 months and at least every six months thereafter. Lifetime follow-up is required.

If the heart has significant uptake of the isotope, a cardiac ultrasound will be repeated after treatment. If the lungs are involved with tumor, pulmonary (breathing) function tests will be obtained after treatment and as necessary.

Physicians (home town or U.C.S.F.) visits will be necessary every 1-2 weeks for the first 2 months, then monthly for the first year after treatment, every 2 months during the second year and every 3 months thereafter. I will require regular follow-up for my entire life. After one year following ¹³¹I-MIBG treatment, I will see a physician at least every 3 months.

If having follow-up with a hometown physician, written follow-up with U.C.S.F. physicians will be required after each visit. Copies of laboratory and radiologic tests will need to be sent to U.C.S.F. so that my progress can be monitored.

RISKS AND DISCOMFORTS

- 1) **Low Blood Counts:** This treatment will likely (greater than 50% of the time) cause a lowering of the white blood cell count and a decrease in red blood cell count and/or platelet count, thus increasing the risk of infection or bleeding. The lowered blood counts are usually transient, lasting about 2 - 3 weeks. Low blood counts may necessitate blood (20% chance) and/or platelet (75% chance) transfusions; I may require G-CSF (20% chance) to stimulate my white blood cells. Bone marrow function usually returns with time. If bone marrow function does not return after this possible side effect, a peripheral blood stem cell (PBSC) infusion will be necessary. This procedure would return my PBSCs that have been removed prior to treatment with ¹³¹I-MIBG. There is an additional risk that the returned cells may contain residual cancer cells or will not adequately replace the damaged bone marrow, leaving me open to increased infections, bleeding and possible death. The infusion of peripheral blood stem cells can occasionally be associated with nausea, a metallic taste, shortness of breath, flushing, a slowing of the heart rate, and temporary high blood pressure. It can also occasionally cause headache, flushing and red urine for one day. Occasionally (1-10% of the time), without stem cells, reduced blood counts may never return to normal.

A serious condition known as “myelofibrosis” can occasionally occur months to years after treatment with ¹³¹I-MIBG. Myelofibrosis may occur alone or in association with leukemia and causes permanent bone marrow failure that can be treated but that that is likely fatal.

- 2) **Breathing Problems:** Rarely, patients with pheochromocytomas can spontaneously develop serious shortness of breath, due to the release of substances from the tumor that causes the lungs to suddenly fill with fluid that interferes with breathing. This condition is known as “acute respiratory distress syndrome” (ARDS) and is frequently (10 – 50% of the time) fatal. Therapy with ¹³¹I-MIBG can occasionally trigger an attack of ARDS.
- 3) **Other Organ Failure:** Decreased function of the thyroid gland may rarely (less than 1% of the time) occur; this could cause fatigue and weight gain, but is correctable with thyroid medication. Decreased function of the adrenal glands might rarely occur; this could cause low blood pressure that might progress to shock and death. The decreased function is correctable with adrenal hormones. Decreased heart function might occur rarely; this could rarely cause permanent heart failure symptoms such as fatigue, shortness of breath, swelling of my body or even death; heart medications may help, but not permanently cure heart failure. Decreased lung function may occur occasionally

after multiple treatments if the tumor has spread through the lungs; this could cause permanent shortness of breath or death. Decreased liver function might rarely occur; this could cause jaundice, swelling, bleeding, and death.

- 4) **Infertility** - The ^{131}I -MIBG treatment may make me infertile (unable to produce eggs or sperm needed for pregnancy).

Women: The risk of female infertility in the general population is about 10%. It is estimated that the risk of female infertility (and premature menopause) after ^{131}I -MIBG treatment may be increased to about 30% after one therapy, 50% after two therapies, and 70% after three therapies.

Men: The risk of male infertility in the general population is about 10%. It is estimated that the risk of male infertility after ^{131}I -MIBG treatment may be increased to about 20% after one therapy, 30% after two therapies, and 40% after three therapies.

- 5) **Risk to the Unborn Child:** The ^{131}I -MIBG treatment poses risks to the unborn child.

Women: ^{131}I -MIBG treatments are hazardous to a growing fetus or a baby. Therefore, if I am pregnant or breast-feeding, I may not take part in this study. It is important that I not become pregnant during this treatment and for 4 months thereafter. If I am sexually active, I (and my partner) should use abstinence or an effective method of contraception that is medically appropriate based upon my personal doctor's recommendation at the time. If I should become pregnant during this treatment program, I should notify my personal doctor and immediately contact Dr. Fitzgerald or his associates for advice.

Women Caretakers: Caregivers (i.e., spouse, parent, other family member, guardian, friend) will be exposed to radiation after I receive ^{131}I -MIBG. The amount of radiation will be approximately equivalent to less than one abdominal X-ray or less than 1/3 of a lumbar spine X-ray. Caregivers may not be pregnant while caring for me during this study, because exposure of the fetus to radiation may increase the risk that the unborn child will later develop cancer or other health problems. If my parent/caretaker is pregnant, then special precautions will be used to avoid contact with me during and for 4 weeks after ^{131}I -MIBG therapy. Should my spouse/parent/caretaker become pregnant within 4 weeks after ^{131}I -MIBG therapy, we will immediately contact Dr. Fitzgerald or his associates for advice.

Men: Abnormalities of sperm can be seen for up to 6 months after radiation therapy, which could possibly result in malformations in a baby conceived during this time. If I am sexually active, I (and my partner) should use abstinence or an effective method of contraception (based upon my/her personal doctors' recommendations) so as not to cause a pregnancy within 6 months after treatment with ^{131}I -MIBG.

- 6) **Blood Pressure:** High or low blood pressure occurs frequently (10 - 50% of the time), but is

usually mild. Treatment for high blood pressure is occasionally required during the infusion of the ¹³¹I-MIBG; this might rarely result in dizziness or fainting.

- 7) **Urine Infection:** The required bladder catheterization may occasionally cause a urinary tract infection.
- 8) **Blood Clots:** Prolonged bed rest may rarely cause blood clots to form in the veins of the legs that can travel to the lungs; such clots can cause death.
- 9) **Anti-coagulants:** Anti-clotting medication, such as heparin or enoxaparin, may be given by injection to reduce the risk of blood clots developing in the veins while at bed rest. Such anticoagulants can rarely cause major hemorrhage (such as intestinal bleeding), spinal bleeding with paralysis, heart failure, pneumonia, fluid in the lungs, fever, severe allergic reactions such as rash or shock, bruising, injection site bleeding, and injection site pain.
- 10) **Phlebotomy:** The risks of drawing blood include temporary discomfort from the needle stick, bruising and rarely, infection. A peripheral intravenous line may cause some discomfort, bruising, and rarely infection. A peripheral intravenous line may cause discomfort, bruising, and rarely infection. A "central" intravenous line may occasionally be required; the placement of this line would likely cause temporary discomfort and rare complications such as nicking and collapse of a lung (for subclavian vein lines) that would require treatment with a chest tube.
- 9) **Bone Marrow Biopsy:** Bone marrow biopsy, if required, involves pain and the risk of infection (rare) or bleeding (occasional) at the sites.
- 11) **Leukapheresis:** The leukapheresis procedure for the collection of peripheral stem cells can occasionally cause a temporary lowering of blood pressure. This might make me feel faint and is treated with intravenous fluids. During leukapheresis, a blood thinner (anti-coagulant) is added to my blood as it circulates through the machine. This will temporarily anticoagulate the blood within me and may occasionally result in some numbness and tingling around my lips, feet and hands. Leukapheresis requires a large venous catheter for blood circulation. This catheter is usually placed under the collarbone or in the neck. Placement of the catheter frequently causes local discomfort, bruising, and occasionally a partial or complete collapse of the lung. If collapse of the lung is severe enough, surgical placement of a temporary chest tube would be necessary. Chest tubes are placed between two ribs and expand the lung through a vacuum system. Chest tubes are generally in place for 3-4 days and often cause local discomfort and would require hospitalization.

12) G-CSF: G-CSF has a number of potential side effects. The side effects may include bone pain, fluid retention, weight gain, headache, low blood pressure, decreased appetite, spleen enlargement, fever and chills. Of these side effects, bone pain is most likely and the others are rare. Occasionally patients have allergic reactions to G-CSF (hives, wheezing, fever, local pain and swelling at the site of injection). These allergic reactions generally resolve with the administration of an antihistamine drug.

13) Cancer: In the general population, the lifetime risk of developing cancer is about 35%. This treatment will slightly increase the lifetime risk of developing a second cancer, such as leukemia or thyroid cancer. Following the ¹³¹I-MIBG therapy in adults, the lifetime malignancy risk is estimated to be increased by 0.5 - 1%. Following one ¹³¹I-MIBG therapy in children or adolescents, the lifetime risk of malignancy is estimated to be increased by 1-2%. Multiple treatments with ¹³¹I-MIBG will further increase lifetime risk of developing a second cancer.

14) Other Risks: This treatment usually causes temporary gastrointestinal upset with some loss of appetite, nausea, and sometimes vomiting. Tenderness in the salivary glands frequently occurs. Dry mouth (xerostomia) occasionally may occur and may persist many months or become permanent.

BENEFITS & ALTERNATIVES

There is a chance that the radioactive MIBG will cause a decrease in size of my tumors, or a decrease in symptoms; however, this possibility cannot be guaranteed. ¹³¹I-MIBG may be helpful in the future in combination with other therapy to cure patients who have widespread disease. It is also possible that the treatment will not directly help me. The alternative treatment available may be a combination of chemotherapeutic drugs or no further treatment of the pheochromocytoma. The best supportive care will be given regardless of the treatment selected.

COSTS

At the present time, the ¹³¹I-MIBG and hospitalization is to be paid for by the patient and his/her usual insurance coverage. Because this therapy may be considered experimental, the costs of treatment may not be covered by a third party carrier.

Estimated costs per patient for this treatment include:

- 1) Bone marrow biopsy and peripheral blood stem cell harvests (up to about \$10,000).

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- 2) Hospital and nuclear medicine costs for ¹³¹I-MIBG treatment (about \$30,000 per 5 day treatment).
- 3) Nuclear medicine, nuclear pharmacology, radiology, medicine, oncology, and endocrinology professional fees (up to about \$10,000 per 5-7 day treatment).
- 4) The treatments may be repeated if indicated. If a peripheral blood stem cell infusion is required, the costs could be considerable, since prolonged hospital stays might be required.

SPECIAL POINTS

- 1) If I am injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University depending on a number of factors. The University of California does not normally provide any other form of compensation for injury. For further information about this, I may call the office of the Committee on Human Research at (415) 476-1814.
- 2) My records will be handled as confidentially as is possible within the law. In order to verify the study data, monitors from the Food and Drug Administration may need to see some specific records, including my records.
- 3) This treatment is toxic to a fetus (baby in uterus). If I am pregnant, this treatment will not be used. I will ensure against becoming pregnant. Should I become pregnant after the treatment is started, I will immediately contact Dr. Fitzgerald or his associates.

QUESTIONS

I have discussed this with Dr. Fitzgerald or his associates. All my questions have been answered. If I have other questions, I can call Dr. Fitzgerald at (415) 665-1136.

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CONSENT

Participation in this study is voluntary. I can refuse to participate or I can withdraw at any time. If I choose to refuse or withdraw, there will be no jeopardy to my relationship with the Department of Medicine or to future care. The physician can also take me off study if it is in my best interest to do so. I have been given a copy of the consent form and the Experimental Subject's Bill of Rights to keep.

Date

Subject

Date

Physician obtaining consent

PARENT/GUARDIAN CONSENT (for minors under age 7 years)

Date

Parent or legal guardian

Date

Physician obtaining consent

CHILD & PARENT/GUARDIAN ASSENT (For minors age 7 years or older):

Date

Child

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Date

Parent or legal guardian

Date

Physician obtaining assent