INSTITUTE: National Cancer Institute

STUDY NUMBER: 00-C-0080 PRINCIPAL INVESTIGATOR: William Dahut, M.D.

STUDY TITLE: A Double Blind Randomized Crossover Phase III Study of Oral Thalidomide versus Placebo in Patients with Stage D0 Androgen Dependent Prostate Cancer Following Limited Hormonal Ablation

Latest IRB Review: Continuing Review 10/1/04
Latest Amendment Approved: Amend H 4/28/05
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.

The purpose of this document is to explain the nature of the treatment you are being offered and what is known about the side effects, risk, inconveniences, and discomforts associated with the drugs and the way in which they are given so that you can better decide whether you wish to participate. You are encouraged to ask any questions you have about this study.

Description of Research Study

This study involves your voluntary participation in a research protocol. The purpose of this study is to develop a more effective treatment for prostate cancer. To do this, we propose treating you with the drug leuprolide or goserelin (drugs already approved for the treatment of prostate cancer) followed by either thalidomide or placebo. This is an experimental treatment. Thalidomide is an investigational (research) drug that was initially developed as a sedative. Sedative drugs help a person sleep. It was found to cause birth defects in the children of pregnant women who had received the drug in the early 1960's. Recently, thalidomide has been studied for its ability to block the growth and development of blood vessels. The growth and development of blood vessels is called angiogenesis, and therefore, this drug is known as an angiogenesis inhibitor. Many researchers believe that the growth of blood vessels is one way that cancers grow and progress. This study is an attempt to see if thalidomide will block the growth and development of blood vessels in prostate cancer. Previous experimental studies in humans with noncancerous conditions have determined the highest tolerable dose of thalidomide. In addition, we have already treated approximately 50 patient-volunteers with advanced prostate cancer (patient-volunteers that had progressive cancer despite the removal of testosterone from their body) at different doses (200 mg/day and up to 1200 mg/day). Although some patient-volunteers in that study had clinical benefit, we think that thalidomide may be more effective when given with leuprolide or goserelin (a drug that reduces the amount of testosterone in your body, and as a result, reduces the size of the prostate tumor in most patients) to patient-volunteers such as yourself.

Therefore, you are being asked to voluntarily enter this randomized study. A randomized study means that you have a 50/50 chance of receiving either treatment (like the flip of a coin). First, you will be randomized to either thalidomide or a placebo (a sugar pill). Neither you, nor your doctor, will have a choice in the treatment regimen you will receive. The treatment regimen you will receive will consist of either leuprolide or goserelin followed by thalidomide, or leuprolide or goserelin followed by placebo. Patient-volunteers will remain on thalidomide or placebo until their PSA returns to its starting value (prior to leuprolide or goserelin), or 5ng/ml, whichever is lower. You will then receive leuprolide or goserelin for an additional six months followed by thalidomide or placebo (whichever drug you did not receive the first time), and remain on this until your PSA returns to its starting value (prior to beginning the second six months of leuprolide or goserelin) or 5ng/ml, whichever is lower. If your PSA rises while on leuprolide or goserelin, never falls below 5ng/ml, or if you develop cancer which has clearly spread (become metastatic), then you will be taken off the study.

Before receiving any form of treatment, you will be evaluated in the outpatient clinic to see if you are eligible for this therapy. This evaluation may take up to 2 weeks, and will be done on an outpatient basis. Some studies for determining the extent your cancer has spread may be done for the first time, or repeated if you have previously had these tests (e.g., CT scans, Bone scans).

You may be asked to undergo a complete neurologic examination as part of a nerve conduction study. The nerve conduction study is performed by attaching metal electrodes to your skin on your arms and legs and then applying brief electrical shocks. The conduction of these electrical shocks is recorded. Most patient- volunteers do not find this painful; most patient- volunteers perceive this as a tingling or twitching sensation. If your doctors feel it is necessary for your care, you will be asked to undergo a study called an EMG, or nerve conduction test. An EMG is a study which measures the electrical activity of muscles. A thin disposable needle is inserted into the muscle which lies next to your skin. The EMG is slightly uncomfortable, but not more so than routine blood drawing. We will ask you to undergo one or both of these tests while on treatment, and at any point at which it is deemed clinically indicated.

Blood and urine studies will be needed to determine if the experimental drug (thalidomide) can be safely administered to you. We will collect about 70 cc of blood (approximately 4 tablespoonfuls) from you during each month of treatment. The collected blood will be used to study the amount of drug in your body, and to look for other markers associated with your cancer.

The treatment is designed for you to participate as an outpatient. We anticipate having 280 men similar to you enrolled on this study. Eight other institutions will be participating in this study. Each of those institutions will have the same eligibility requirements and treatment design.

First, you will be randomized to either thalidomide (200 mg every evening) or placebo (a sugar pill). Following randomization, you (regardless of the treatment regimen) will receive six monthly injections of leuprolide or goserelin. After this time, you will be given four capsules of either thalidomide or the placebo to take by mouth each evening. We will be monitoring your prostate-specific antigen [(PSA) a protein secreted by your prostate gland] closely since changes in PSA are helpful in evaluating tumor progression. We will also look at other forms of assessing your disease such as bone scans and CT scans. At any point that your doctors feel your disease is not under control, we will give you six more injections of monthly leuprolide or goserelin, and then you would receive the opposite treatment (thalidomide or placebo, depending on what you initially received). Again, we will be monitoring your PSA closely (as well as other means of assessing your tumor such as bone scans, CT scans).

We will be comparing the time you are off leuprolide or goserelin for each treatment. In addition, we will be obtaining blood routinely from you to assess molecular changes (investigative/abnormal changes in your disease and/or the way your body is responding to the drug/placebo treatment). These data will not be available to you. They may, however, be available to a qualified representative of the drug manufacturer (in addition to NCI researchers). If your disease recurs after the second treatment, then you will be taken off the study and have the option of receiving standard treatments from you local doctor. You will also have the option of enrolling on other studies we have to offer, assuming you are eligible for those studies.

Alternative Approaches or Treatments

It has been explained to you that you have cancer of the prostate. There is some evidence that it is still present despite initial treatment with either radiation or surgical removal of the prostate. One option may be to receive radiation to your pelvis. Hormonal therapy is often used in the treatment of your disease. Hormonal therapy may involve routine injection of a drug called leuprolide or goserelin that decreases the amount of the male hormone, testosterone, in your body, or the surgical removal of your testes. Some researchers are recommending short periods of treatment with leuprolide or goserelin, followed by breaks in therapy and then the restarting of therapy when your PSA begins to increase. Any of these treatments would be acceptable for the treatment of your disease now. Treatment alternatives you could now consider include: 1) other forms of commercially available drug(s) or hormonal treatment(s), 2) other forms of experimental drug(s) or hormonal treatment(s), and 3) you may also elect to receive no treatment for your cancer now, and wait until symptoms or complications develop. At this point, you may receive supportive care or other therapies at that time in order to lesson or eliminate symptoms.

Your doctors have told you that although the "standard" treatments listed above could be administered to you, there is no known cure for your cancer. For this reason, we are offering you experimental treatment on this research study. Although we hope that this therapy may benefit you, and that tumor growth will be delayed, there is no guarantee that your tumor will respond.

Risks or Discomforts of Participation

We are asking you to participate in this study, and cannot guarantee that you will receive a benefit from this treatment. Likewise, we can not guarantee that you will not have complications from these treatments. However, all of these drugs have been given to humans, and therefore, we have a good idea of the potential side effects you may develop.

You may experience complications associated with the frequent collection of blood samples (bruising and possible infection). In addition, you may have some bruising where the needle is inserted for the EMG in the neurological portion of the study.

Side Effects of Thalidomide

The possible side effects of this drug include: hypersensitivity reaction (rash, fever, itching, fast heart rate, low blood pressure); decreased white blood cell count (which affect your body's ability to fight infection); effects on your cardiovascular system may include a slowing of the heart rate, lowering of the blood pressure when you change position, edema (swelling), clots in blood vessels, and in very rare cases sudden or unexpected death. There may be shortness of breath. . You may also experience fatigue, muscle aches, muscle weakness (not due to neuropathy), confusion, depressed level of consciousness, mood changes (depression), dizziness, lightheadedness, or extreme sleepiness. Due to the possibility of these side effects, you should be extremely cautious driving and operating heavy machinery while taking thalidomide. There may be dry or itchy skin, rash, or Stevens-Johnson Syndrome a disorder that involves skin ulceration, sloughing and could lead to death. Effects on the GI system include constipation, mouth dryness, nausea, and heartburn. There may be changes in some tests that measure liver and pancreas function, or reduced function of the thyroid gland, which may be permanent and require medication. You may experience numbness and tingling, shooting pains, motor neuropathy (weakness to the arms and legs), seizures, and tremor. In some cases, the nerve damage has lessened or gone away after the discontinuation of thalidomide, however, there is a chance of permanent nerve damage. There may be dry eyes or blurred vision. There has been a report of Amaurosis Fugax "Fleeting Blindness" which is a temporary loss of vision to one eye that can last up to one minute.

Patients on other NCI sponsored cancer trials who were taking thalidomide have reported vomiting, anorexia (loss of appetite), weight loss, syncope (transient loss of consciousness/fainting), abdominal pain, hyperglycemia (increase in blood sugar level), anxiety, apnea (loss of breathing), supraventricular tachycardia (abnormally rapid heart rate and rhythm), atrial fibrillation (abnormal heart rhythm), thrombocytopenia (low level of platelets in the blood needed for clotting), pancreatitis (an inflammation of the pancreas which could cause severe abdominal pain) and "sick sinus syndrome" which is an abnormal slowing of the heart that may require implanting of a pacemaker.

Most of these side effects are self-limiting or resolve after the thalidomide has been discontinued.

There have been reports of significant abnormal kidney function in patients taking bisphosphonates along with thalidomide. Examples of bisphosphonates, commonly used to strengthen bones, include residronate (Actonel), alendronate (Fosamax), zoledronic acid (Zometa), and pamidronate (Aredia).

Barrier birth control measures are necessary for all participants and their sexual partners for 8 weeks.
The reason this is so important is that Thalidomide causes severe birth defects in unborn babies if females who are pregnant take it. The risk of thalidomide causing damage to the embryo is up to 50 percent for females taking thalidomide during the "sensitive period." This period is estimated to range from 35 to 50 days after the last menstrual

period. It is not known whether or not thalidomide may cause birth defects in unborn babies if it is taken after the "sensitive" period. A single dose of thalidomide may cause birth defects.

Birth defects observed in babies exposed to thalidomide during pregnancy include absent or abnormal legs and arms; spinal cord defects; cleft lip or palate; absent or abnormal external ear; heart, kidney and genital abnormalities; and abnormal formation of the digestive system, including blockage of necessary openings. A 1994 article by Stromland and others describes an association between thalidomide and autism.
Because of the severity of these abnormalities, and the fact that it is not known if thalidomide is present in male ejaculate (semen), it is extremely important that pregnancies do not occur in your sexual partner while you are taking thalidomide. Therefore, you must be counseled about the possibility that thalidomide may be present in semen. You must use a latex condom every time you have sexual intercourse with a woman during therapy and for 8 weeks after discontinuing thalidomide, even if you have had a successful vasectomy. Remember, however, that no method of birth control besides complete abstinence provides 100 percent protection from pregnancy.

It is possible that you may experience some, all, or none of the side effects described above. It is also possible that thalidomide will produce some unanticipated side effects. For that reason, you will be monitored closely while you are receiving treatment for any signs, which might signal the earliest stage of toxicity so that appropriate intervention can be done.

Side Effects of Leuprolide or Goserelin

The major toxicities associated with leuprolide or goserelin (a drug that blocks an enzyme in your body [LHRH] which helps produce testosterone) are those of androgen withdrawal (the removal of testosterone from the body). These include: hot flashes/flushing, failure to achieve an erection and loss of sexual interest. Other adverse effects include, nausea and vomiting, swelling of the feet and rare shortness of breath. Some patient-volunteers have reported pain at the site of injection. Patients taking leuprolide or goserelin for long periods of time may be at risk for thinning of the bones.

If new information is gained regarding your disease or related to the drug being studied, we will discuss that information with you.

Potential Benefits of Participation

This is a "double blind randomized crossover Phase III study," which means that we are trying to determine if the experimental treatment is more effective that the existing treatment for early stage (D0) prostate cancer. Benefit cannot be promised, nor can the chance of benefit be accurately predicted. However, because all of these drugs have independently been shown to have benefit in the treatment of prostate cancer, and we hope that the combination of these drugs will be even more effective.

It is possible that you may experience some, all, or none of the side effects described above. For this reason, we will continue to monitor you closely throughout your treatment. We will also closely monitor the progression of your disease. If it is determined that your disease has become significantly worse, we will propose treating you with 6 more months of leuprolide or goserelin, followed by the other treatment regimen (thalidomide or placebo, whichever you did not receive the first time).

Cost and Reimbursement

If you choose to participate in this study, your medical care and the costs of the laboratory and radiographic studies done at the Clinical Center, National Institutes of Health will be at no charge to you. The NIH cannot reimburse you for the costs of medical care delivered outside the NIH, even if you are seeking medical attention as a result of side effects of treatment given on this study. Similarly, you cannot be reimbursed if you choose to have diagnostic radiographic tests (such as chest x-rays or CT scans) performed locally (outside of the NIH), even if they are done for the purposes of this study.

Communication

The NCI physicians involved in your care are available to answer all of your questions concerning this protocol. If you have any concerning or questions, you may contact Dr. William Dahut, the Principal investigator at (301) 496-4916, Dr. William Figg, the Protocol Chairperson, at (301) 402 3622, or an Associate Investigator, or the research nurse, Jane Carter, R.N. at (301) 435-5614. If you have any complications when you are not in the Clinical Center (e.g., at home or in a local hotel), you must call the page operator at (301) 496-1211 and ask for the NCI Medical Oncology Clinical Research Unit physician on call. Laura Cearnal, the NIH Patients' Rights Representative, will be available to answer questions concerning your involvement in this study or your rights as a research subject. She is not directly associated with this study and can be contacted at (301) 496-2626.

Research Subject's Rights

You will be told if no benefit occurs to you as a result of taking part in this treatment program and the program will be stopped.

You will receive a copy of this informed consent for your own records. In addition, a copy of the informed consent is on file with the Medical Oncology Clinical Research Unit of the National Cancer Institute and a copy will be made available to you whenever you want to see it. Your records will be kept confidential, with the exception that the FDA, either drug company that manufactures these drugs may have access to your medical record, as well as the staff of the National Cancer Institute may inspect and study your medical records.

Your participation in this study is entirely voluntary, and you may refuse to participate, or withdraw from this protocol at any time and receive care from a physician of your choice. Your participation in this study may be ended by the Principal Investigator or an Associate Investigator without your consent if they feel termination is medically indicated.

Upon completing this study, you may be given the choice of taking part in other research protocols that may be appropriate for you. Otherwise, you will be returned to the care of your referring physician. It is important to stress that your participation in this study does not constitute a promise of long term care at the NIH Clinical Center. If there is no research study that can help you, you will be returned to the care of your private doctor. If you do take part in this study, you may be unable to take part in certain other research protocols because these protocols may not allow patient-volunteers who have been on certain drugs to enter. You may decide now not to receive treatment in this protocol, or you may choose at any time to stop the drug and withdraw from the protocol. In either case, you would be returned to the care of your referring physician.

Your signature on this form indicates that you agree to participate in this medical research study under the direction of the principal investigator as listed above. Important Information and Warnings for All Patients Taking THALOMID (Thalidomide):

WARNING: SERIOUS HUMAN BIRTH DEFECTS IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

Consent For Men

INIT_____1. I understand that I must not take Thalomid (thalidomide) if I cannot avoid unprotected sex with a woman, even if I have had a successful vasectomy.

INIT_____2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy.

INIT_____3. I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse, or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID (thalidomide) and for 8 weeks after I stop taking the drug, even if I have had a successful vasectomy.

INIT_____4. I also know that I must inform my doctor if I have had unprotected sex with a woman, or if I think, FOR ANY REASON, that my partner may be pregnant. If my doctor is unavailable, I can call 1-888-668-2528 for information on emergency contraception.

INIT_____5. I understand that Thalomid (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of reach of children and should never be given to women who are unable to have children.

INIT_____6. I understand that Thalomid (thalidomide) can cause side effects including nerve damage (numbness, tingling or pain in the hands or feet that may not be reversible) and drowsiness. (If I become drowsy, I will not operate heavy machinery or drive a car. Also, I will avoid alcohol and other medicines not prescribed by my doctor). If I develop a red itchy rash, I will contact my doctor immediately. If I feel dizzy, I will sit upright for a few minutes before standing up from a lying or sitting position. I understand all of the other possible side effects explained to me by my doctor. I know that I cannot donate blood while taking Thalomid (thalidomide).

NIT_____7. My doctor has answered any questions I have asked.

Authorization

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive Thalomid (thalidomide). I now authorize my doctor to begin my treatment with Thalomid (thalidomide).

Patient Name (please print) Patient, Parent/Guardian Signature Date(mo./day/yr.)

I have fully explained to the patient the nature and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with Thalomid (thalidomide), and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed.

Physician Name (please print) Physician Signature Date(mo./day/yr.)

Thalidomide

Thalidomide is supplied as 50 mg capsules

Thalidomide should be stored at room temperature

Thalidomide is administered Orally

Side effects of thaliomide: Drowsiness and sleepiness, headache, constipation, nausea, dry mouth, rash, numbness in feet and fingers, increased appetite, weight gain, loss of sex drive, swelling due to water retention, dry skin, bone marrow suppression, itching, hair loss, somnolence, depression and, of course, teratogenic effects (birth defects).

Warning: There is an extremely high risk that a deformed infant will result if pregnancy occurs to your partner while you are taking thalidomide even for short periods. Therefore, this teratogenic action of thalidomide necessitates:

Male patients must be counseled about the possibility that thalidomide may be present in semen. Men must use a latex condom every time they have sexual intercourse with a woman during therapy and for 8 weeks after discontinuation of thalidomide, even if they have had a successful vasectomy.

The bottle label will bear: Thalidomide must not be used by males and females who are sexually active.

In addition, all bottles should have affixed a warning label similar to the following: This medication may cause drowsiness, alcohol may intensify this effect. Use caution when driving or operating machinery.

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 other authorized people.

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.

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, William Dahut, M.D.; Building 10, Room 12N226, Telephone: (301) 496-4916. Other researchers you may call are: William Figg, Pharm.D. (301) 402-3622; Cathy Parker, R.N. (301) 435-5613; Jane Carter, R.N. (301) 435-5614, Alisa Trout, R.N. (301)-496-7955.

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 _____

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 _____

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 _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM OCTOBER 1, 2004 THROUGH OCTOBER 1, 2005.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____