INSTITUTE: National Cancer Institute

STUDY NUMBER: 16-C-0009 PRINCIPAL INVESTIGATOR: Mark Gilbert, M.D.

STUDY TITLE: Phase II Trial of Carboplatin and Bevacizumab for the Treatment of Recurrent Low-grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma in Adults: A Multi-Center Trial

Continuing Review Approved by the IRB on 08/07/17
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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?

This is an investigational study. Carboplatin is designed to interfere with the growth of cancer cells by stopping cell division, which may cause the cells to die. Carboplatin is FDA approved

and commercially available for the treatment of advanced ovarian cancer. Bevacizumab is designed to prevent or slow down the growth of cancer cells by blocking the growth of blood vessels. Bevacizumab is FDA approved and commercially available for the treatment of glioblastoma multiforme (a type of brain tumor). The use of these drugs in combination in ependymoma is investigational. At this time, this combination is only being used in research.

The goal of this clinical research study is to learn if the combination of bevacizumab and carboplatin can help to control recurrent ependymoma. The safety of this drug combination will also be studied.

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

You are being asked to take part in this study because you have a brain or spinal cord tumor called an ependymoma that is recurrent (has returned after treatment). Clinical trials include only patients who choose to take part. Your participation in this study is entirely voluntary.

How many people will take part in this study?

Up to 46 participants will take part in this multicenter study. Up to 13 participants will be enrolled at NCI.

Description of Research Study

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

Before you begin the study

You will have screening tests to help the doctor decide if you are eligible to take part in this study. If some of these tests have been performed within the past 14 days, they may not need to be repeated. These tests include medical history, physical exam, routine blood and urine tests, CT scan or MRI of your brain, CT scan or x-ray of your chest, an EKG and you will also complete a questionnaire about your quality of life. Tumor tissue left over from a previous procedure (such as disease diagnosis slides or tumor tissue leftover from a previous biopsy) will be collected to confirm your diagnosis and to test for biomarkers.

During the study

If you are found to be eligible to take part in this study you will receive carboplatin by vein over 30 minutes on Day 1 of each 28-day cycle. You will receive bevacizumab by vein over 90 minutes on Days 1 and 15 of each cycle.

Study Visits

Every week:

- Blood (about 1-2 teaspoons) will be drawn for routine tests.

Every 4 weeks:

- Urine will be collected to check your kidney function.
- You will be asked about any drugs you may be taking and if you have had any side effects.

Every 8 weeks:

- Your medical history will be recorded.
- You will have a physical exam, including measurement of your vital signs.
- You will have a neurological exam.
- Your performance status will be recorded.
- You will complete the quality of life questionnaire.
- You will have an MRI scan or CT scan of the head and/or spine to check the status of the disease.

At any time during the study, extra tests may be performed if the doctor thinks they are needed for your safety. The study doctor will tell you more about any extra tests.

How long will I be in this study?

You will receive up to 6 cycles of the study drug combination. You will be taken off study early if the disease gets worse or you experience intolerable side effects.

If the disease has not gotten worse after 6 cycles of receiving the study drug combination, you will be able to continue receiving bevacizumab alone for as long as the doctor thinks it is in your best interest. You will continue to follow the same study visit schedule detailed above.

When you are finished taking the drugs

After you stopped taking the study drugs, the study staff will call you every 3 months to check how you are doing. Each phone call will take about 5 minutes.

Birth Control

Because taking part in this study can result in risks to an unborn or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active.

Birth Control Specifications: If you are able to become pregnant or father a child, you must use acceptable birth control while on study and for 1 month after the last dose of study drug(s). Medically acceptable birth control types include approved hormonal birth control (such as birth control pills, Depo-Provera, or Lupron Depot), barrier methods (such as a condom or diaphragm) with spermicide, or intrauterine device (IUD). Talk to the study doctor about acceptable methods of birth control.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

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**:**

- You may choose to receive other treatments for recurrent ependymoma (such as chemotherapy [such as temozolomide], radiation therapy, or a combination of both)
- Taking part in another study, if available.
- 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?

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases, side effects may be serious, long-lasting or permanent, and may even cause death.

Tell the study staff about any side effects that you may have, even if you do not think they are related to the study drugs.

Carboplatin and bevacizumab each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Carboplatin Side Effects

Likely (occurring in more than 20% of patients)		
• abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• vomiting • low blood counts (red, white, platelets) • pain	• abnormal liver tests (possible liver damage) • abnormal kidney test (possible kidney damage

Less Likely (occurring in 3-20% of patients)		
• nerve damage (possible numbness, pain, and/or loss of motor function) • hair loss (partial or total) • abdominal pain • nausea	• constipation • diarrhea • abnormal taste • mouth blisters/sores (possible difficulty swallowing)	• weakness • abnormal liver tests (possible yellowing of the skin and/or eyes) • allergic reaction • infection

Rare but serious (occurring in fewer than 3% of patients)		
• high blood pressure • low blood pressure (possible dizziness/fainting) • heart failure • stroke • dehydration	• multiple blood clots (possible organ dysfunction and/or failure) • reduced blood supply to the arms and legs • visual problems	• difficulty breathing due to narrowing of the airways • tissue death at the injection site caused by drug leakage • life-threatening allergic

• blood vessel blockage • anemia due to destruction of red blood cells	• blindness • hearing loss	reaction (such as difficulty breathing, low blood pressure, and/or organ failure)

Carboplatin may cause you to develop another type of cancer (such as skin cancer and lung cancer).

Bevacizumab Side Effects

Likely (occurring in more than 20% of patients)		
• high blood pressure • blood clots in a vein (possible pain, swelling, and/or redness) • pain • nerve damage (loss of sensory function) • headache • dizziness • fatigue • hair loss (partial or total) • abdominal pain	• loss of appetite • constipation • diarrhea • mouth blisters/sores (possible difficulty swallowing) • digestive system bleeding • upset stomach • vomiting • abnormal taste	• failure of the ovaries to produce hormones, which may be permanent (possible stopped menstrual cycle) • bleeding • nosebleed • low white blood cell counts • difficulty breathing • weakness • abnormal kidney test (possible kidney damage)

Less Likely (occurring in 3-20% of patients)		
• blood clots in an artery (possible organ damage such as stroke and/or heart attack) • low blood pressure (possible dizziness/fainting) • heart failure • fainting • bleeding in the brain and/or spinal cord • stroke	• shedding and scaling of the skin (possible fatal loss of bodily fluids) • change of skin color • low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • dehydration • gas • dry mouth • hole in the intestines	• inflammation or paralysis of the intestines • weight loss • nausea • uterine and/or vaginal bleeding • low platelet cell counts • pain (back/muscle) • voice changes • runny nose • lung inflammation (possible difficulty

• difficulty walking • dry skin • skin sores • opening of a wound	(possibly leaking contents into the abdomen) • bleeding gums	breathing) • infusion reaction (possible chills and/or hives)

Rare but serious (occurring in fewer than 3% of patients)		
• severe heart problems • heart attack • chest pain due to heart trouble • severe increase in blood pressure (possible stroke) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss) • decreased brain function due to high blood pressure • decreased blood flow to part of the bowel (possibly causing death of tissue) • bleeding around the brain • temporary stroke symptoms • intestinal blockage	• stomach and/or small intestine ulcer • vein blockage in the abdomen • hole in the gall bladder (possible abdominal pain, gall stones, nausea, and/or infection) • hole in the bladder • destruction of red blood cells • low red blood cell counts • bone destruction (including destruction of the jaw bone) • inflammation inside the eye • blurry vision • increased pressure in the eye (possible pain and/or blurry vision) • detached retina (possible partial blindness)	• deafness • kidney failure • decreased kidney function (possible kidney failure) • coughing up blood • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • blockage in the lung (possible pain, shortness of breath, and/or failure to breathe) • abnormal hole inside the nose • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • wound healing problems

Bevacizumab may rarely cause an abnormal opening that develops between one area of the body and another (for example, an abnormal connection and opening in one or more places between the trachea [breathing tube] and esophagus, which may interfere with swallowing, digestion, and/or choking). This may result in death.

Rarely (in about 1-2% of patients), bevacizumab may cause bleeding in the brain in patients who have received bevacizumab for the treatment of primary brain tumors. You will be monitored for this complication and removed from the study if this were to occur.

If you are taking Coumadin (warfarin) or other blood-thinning drugs, you may be at higher risk of blood clots and/or bleeding.

Using the **study drugs together** may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study chair.

This study may involve unpredictable risks to the participants.

Potential Benefits of Participation

What possible benefits can I expect from taking part in this study?

The aim of this study is to determine a safe dose and to see if this experimental treatment will cause your tumors to shrink. 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 drug'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.

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.
- You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely. If the carboplatin and bevacizumab are stopped, you can decide whether or not to let your study doctor continue to provide medical information to the organization running the study.

Your doctor may decide to stop your therapy for the following reasons:

- if your disease comes back during treatment
- if you become pregnant while on study therapy
- 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.

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 the National Cancer Institute IRB 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.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Optional Procedures for the Study

If you agree, blood (about 1 teaspoon) will be drawn for biomarker testing before you begin receiving the study drugs and then every 8 weeks while you are on study. Biomarkers are chemical "markers" in the blood that may be related to your reaction to the study drug.

There are no benefits to you for taking part in the optional procedures. You may stop taking part at any time. The optional procedure will be performed at no cost to you.

You do not have to agree to take part in the optional procedures in order to receive treatment on this study.

Optional Procedure Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Circle your choice of "yes" or "no" for each of the following optional procedures:

Do you agree to have extra blood drawn for biomarker testing?

YES NO

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, Mark Gilbert, M.D., Building 82, Room 235A, Telephone: 240-760-6023. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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 AUGUST 07, 2017 THROUGH AUGUST 06, 2018.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name