

ARGININE BUTYRATE + GANCICLOVIR IN EBV (+) MALIGNANCY
**A PHASE ONE TRIAL OF BUTYRATE IN COMBINATION WITH GANCICLOVIR IN
EBV-INDUCED MALIGNANCIES AND LYMPHOPROLIFERATIVE DISEASE**

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BACKGROUND AND PURPOSE

You are being asked to participate in this research study because you have been diagnosed with either lymphoproliferative disease or a cancer, which developed from a virus called Epstein Barr Virus (EBV). This virus is the cause of many common diseases, such as mononucleosis. However, in individuals who have a decreased ability to fight infection (due to medications or other illnesses), the EBV can cause more serious diseases such as lymphoproliferative disease or certain diseases. The current standard treatment for diseases caused by EBV is chemotherapy and/or radiation therapy. In this study, the investigational drug Arginine Butyrate (not FDA approved) will be given with ganciclovir. The combination of these two drugs is also "investigational". These two drugs will be given together in the attempt to increase the effectiveness of ganciclovir.

When cells infected with EBV divide in order to multiply, an enzyme is produced. When this occurs, the virus (and the cells containing the virus) can be killed by the drug ganciclovir. In some diseases produced by EBV (lymphoproliferative disease and certain cancers), the virus does not produce this enzyme and therefore cannot be killed by ganciclovir. Although not proven in humans, it has been shown in the lab that when cells are infected with EBV, a protein is produced.

The purpose of this study is to (1) determine the safety and effectiveness of this treatment in controlling his/her disease, (2) to evaluate any side effects he/she may experience, and (3) measure the drug levels of Arginine Butyrate in the blood during and after treatment.

PROCEDURES

If you choose to participate in this study, some of the following tests may be necessary for your doctor to determine the extent of your disease and to closely monitor the effects of the treatment on your disease: (1) physical examination, (2) multiple blood tests, (3) tissue biopsies - under local anesthesia a small piece of tissue is taken from an area of disease, (4) bone marrow aspirate and biopsy - a needle is inserted into the bone to obtain a sample of the marrow, (5) CAT scans - X ray procedure, (6) chest x-ray, (7) bone scan -X ray procedure, (8) urine test (including pregnancy test).

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Throughout your participation in this study, it may be necessary to obtain up to 4 tissues biopsies, tissue samples and/or bone marrow biopsies. The tissues samples (e.g. skin biopsy, lymph node biopsy, fine needle aspirate, thoracentesis) will be taken from an area that was previously involved with tumor. These samples will only be taken if the tumor tissue can be obtained by a minor procedure. The type of procedure chosen will be explained to you and can usually be done in your hospital room. If samples can not be obtained, treatment will continue as long as there is no evidence of your disease becoming worse. The purpose of the samples may be necessary to evaluate your tumor tissue in the laboratory in order to determine if the treatment is working.

Before treatment begins, an intravenous catheter (a tiny tube also called a central line) will be placed into one of the large veins in your upper chest. The catheter placement takes approximately 1 hour, and is done in the outpatient department by a surgeon. This catheter is used to give the drug and for blood drawing. Problems associated with this catheter include pain, bleeding, formation of blood clots, temporary injury to the lung causing difficulty with breathing, infection, or clogging of the tubes which could lead to the catheters being removed. A separate consent form will need to be signed for this procedure. If you already have had a central line catheter placed for other therapies you will not need to undergo another procedure.

Treatment in this study will be given as an inpatient at Boston Medical Center. Treatments with Arginine Butyrate are given in cycles. There is a maximum of 3 cycles of treatment within this study and each cycle is 28 days long (21 days on treatment and 7 days off treatment). One day before the first dose of Arginine Butyrate (cycle #1), you will come to the outpatient clinic to receive Gancyclovir. Gancyclovir is given twice a day over one hour through a vein. Ganciclovir is not given before cycle #2 and cycle #3. Ganciclovir will start the same day as Arginine Butyrate during cycles #2 and #3. Depending on how well you tolerate each cycle of treatment, you may need to remain in the hospital for the 7 days between each cycle of treatment for a total of approximately 90 days in the hospital.

Arginine Butyrate treatments are given through the central line catheter, continuously, for 21 days in a row. While receiving treatment with Arginine Butyrate, ganciclovir will continue as described above until treatment in this cycle is completed (21 days). Side effects will be evaluated on the third day of the first cycle of Arginine Butyrate treatment. If the side effects are acceptable, the dose of Arginine Butyrate will be increased. This evaluation process will be repeated once more for a maximum of two dose increases. Extra blood tests (2 teaspoons) will be drawn 30 minutes, 1, 2, 4, and 24 hours after any dose increase and at day 21 of Arginine Butyrate treatments. These blood tests will be necessary only during the first cycle. In order to obtain blood samples without requiring multiple needle sticks, the catheter that was inserted in your upper chest for the purpose of giving the drug treatments can be used or an intravenous tube (a small catheter) can be placed in a vein in your arm.

During treatment with Arginine Butyrate, physical exams and blood tests (approximately 2 - 3 teaspoons) will be done daily in order to (1) monitor side effects, (2)

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monitor response to treatment, and (3) measure blood levels of Arginine Butyrate. Urine will also be collected and tested on days 2, 4, 6, and 8 of treatment with Arginine Butyrate.

After the completion of each cycle of treatment, some of the tests and exams which were done at study entry will be repeated in order to monitor your response to treatment, and to make any necessary dose adjustments. Depending on your response to treatment and any side effects you may experience, cycle #2 will start approximately 7 days after the completion of cycle #1 (day 29). If at any time during treatment there is evidence of disease spread, or if the side effects are too severe, then whether you agree or not, your doctor may decide to discontinue treatment within the study. The maximum number of treatment cycles in this study is 3 (for a total of approximately 90 days in the hospital).

Once off treatment, you will continue to be evaluated on a regular basis and your physician will discuss with you your future treatment options.

The potential known side-effects of this treatment are listed below:

RISKS/DISCOMFORTS

TISSUE and BONE MARROW BIOPSIES: There may be some pain during this procedure. Medications will be given to decrease any discomfort you may be experiencing.

The most common side effect is soreness in the area where the biopsy is taken. This can last for a few days but can usually be relieved by taking Tylenol. Other uncommon side effects may include bleeding and/or local infection in the area where the biopsy is taken. Measures will be taken to lessen the chances of these effects occurring. A separate consent form may need to be signed for this procedure.

Side effects from the drugs used in this study are as follows:

ARGININE BUTYRATE:

Butyrate has been given to many adults and children with other conditions without any serious side effects occurring. However, it has not been given in combination with ganciclovir, to treat these diseases. Since this is the first study in which this drug combination has been used to treat these diseases, you will have to remain in the hospital for the entire course of each treatment cycle (approximately 22 days) or 90 days for all three cycles.

The most common reported side effects are nausea and vomiting. Giving anti-nausea medicine before Arginine Butyrate usually controls these. All of the patients who received Arginine Butyrate experienced lower potassium in the blood that can cause symptoms such as muscle weakness, leg cramps, dizziness and stomach upset. The potassium level returned to normal after the treatment was stopped. Other uncommon side effects include fatigue, fever, diarrhea, and protein in the urine, which usually does not cause symptoms. Five patients experienced single episodes of low blood pressure, shortness of breath, muscle aches, chest and arm pain, insomnia and anxiety. This drug also has an odor that can be unpleasant.

One patient reported a temporary loss of appetite. One patient had a mild increase in a liver enzyme that did not cause any symptoms and was reversed when the drug was stopped. There were no life-threatening side effects observed with Arginine Butyrate.

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GANCICLOVIR:

Ganciclovir is an approved drug that has been used to treat many thousands of patients. The most frequently reported side effect of ganciclovir is a decrease in the blood cells in the bone marrow which could lead to: 1) decreased white cells which may lead to an increase risk of infection, 2) lower number of red cells which can cause shortness of breath, weakness and fatigue, 3) lower platelet which can result in easy bruising or bleeding. The drugs' effect on the bone marrow is only temporary and transfusions of red blood cells and/or platelets are available if needed to increase these cells until the bone marrow recovers. Blood will be drawn and monitored on a regular basis. Other side effects may include headache, confusion, rash, and loss of appetite and fatigue. Although Arginine Butyrate and ganciclovir have caused the side effects described above, other side effects may occur which were not seen before. In addition, whether using these two drugs in combination will result in worsening the known side effects of each or in developing new side effects is not known. Although the side effects are usually temporary and manageable, it is possible they could be serious or fatal.

Blood samples and injections may result in fainting, pain, bruising, or bleeding at the site of injection. All appropriate measures will be taken to avoid these occurrences.

The effects of this treatment on a fetus are unknown. Therefore, if you are pregnant or nursing a child, you cannot take part in this study (women of child bearing potential will be asked to take a urine test to see if they are pregnant before starting in this study). If you are sexually active, you must practice effective birth control measures (oral contraceptives, diaphragm with spermicidal gel, IUD, condoms).

BENEFITS

There are no proven benefits to participation in this study.

ALTERNATIVES

If you decide not to participate in this study, other experimental treatments may be available. You also have the option of choosing no treatment.

COSTS

Arginine Butyrate will be provided free of charge. If your insurance carrier does cover the cost of ganciclovir while you are being treated in this study, the drug will be supplied free of charge. You or your insurance company will be responsible for the cost of the hospitalizations and lab tests. Financial arrangements will be discussed with you prior to the start of treatment.

All information obtained in this study will be held in confidence. You will not be identified by name on any study-specific records. The Food and Drug Administration, the National Cancer Institute, and a qualified representative from Boston University Medical Center and of the drug manufacturer reserves the right to review study data that may include identifying information. No publications will identify participants by name or initials.

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You understand that in the event injury occurs resulting from the research procedures, medical treatment will be available at Boston Medical Center. However, no special arrangements will be made for compensation or for payment for treatment solely because of your participation in this experiment. You understand that this paragraph is a statement of policy of Boston Medical Center and of Boston University, and does not waive any of your legal rights.

If you have any questions regarding the research or your participation in it, either now or at any time in the future, please feel free to ask them. The research team, particularly Dr. Douglas Faller, who may be reached at (617) 638-4173, will be happy to answer any questions you may have. You may obtain further information about your rights as a research subject by calling the Coordinator of the Institutional Review Board for Human Research of Boston University Medical Center at 638-7266. If any problems arise as a result of your participation in this study, including research-related injuries, please call the principal investigator of this study, Dr. Faller.

You are not obligated to participate in this research. If you choose not to participate, your present and/or future medical care will not be affected in any way, and you will incur no penalty or loss of benefits to which you may otherwise be entitled. Also, if you participate, you may withdraw your consent and discontinue participation at any time without affecting your medical care or benefits to which you may otherwise be entitled.

SUBJECT'S STATEMENT OF CONSENT

I have read the above description of this research study, and I understand it. I have been informed of the risks and benefits involved, and all of my questions have been answered to my satisfaction. Furthermore, I have been assured that a member of the research team will also answer any future questions I may have. I understand that I will receive a copy of this form.

I understand that I am free to withdraw this consent and discontinue my participation in this research study at any time without prejudice. I voluntarily consent to my participation in the described research study.

Patient's signature Date

Patient's printed name

Physician's signature Date

Physician's printed name

Valid for use through _____ Per IRB _____

*****All patients must be called into extension 7276*****

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