INSTITUTE: National Cancer Institute

STUDY NUMBER: 07-C-0081 PRINCIPAL INVESTIGATOR: Kieron Dunleavy, M.D.

STUDY TITLE: A Phase I/II Study of Flavopiridol in Relapsed or Refractory Mantle Cell lymphoma (MCL) and Diffuse Large B-cell Lymphoma (DLBCL)

Continuing Review Approved by the IRB on 6/13/11
Amendment Approved by IRB on 06/02/11 (I) Date Posted to Web: 06/10/11
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.

DESCRIPTION OF RESEARCH STUDY

You have been invited to participate in this study because you have either relapsed mantle cell lymphoma (MCL) or diffuse large B-cell lymphoma (DLBCL). This is a clinical research study using a drug called flavopiridol. Flavopiridol is an investigational drug that has been shown in the laboratory to work in a different way to standard chemotherapy. Its effectiveness may depend on the amount of drug (dose) and schedule (timing of drug dose). Earlier studies of flavopiridol given on a different schedule were not successful. The schedule that you will be receiving has been tested on patients with a different type of disease called chronic lymphocytic leukemia (CLL). Some of the patients with CLL who received flavopiridol developed a complication called tumor lysis syndrome (TLS) which is where there is a quick death of tumor cells which may cause the amount of potassium and other substances in the bloodstream to rise to dangerous levels. The dose was then lowered and certain patients with very high white cell counts most at risk for developing TLS were not treated with flavopiridol until their white count was lowered. Since these changes, the dose and schedule that you will be

receiving in this study has been given to at least 42 patients safely. In this study, we are trying to determine what the maximum dose of flavopiridol is that can be given safely to patients with your tumor type as a 30 minute initial infusion followed by a 4 hour infusion, given weekly for 4 consecutive weeks followed by a 2 week treatment break. There will be 4 different dose levels of flavopiridol in this study and when you are enrolled, the dose level that you receive depends on when you are enrolled in relation to the other patients and the side effects that other patients on the study have had. Our goal is to enroll up to 71 patients on this study.

There are several abnormalities in mantle cell and diffuse large B-cell lymphoma cells which may be targeted by flavopiridol. For example, a type of protein called cyclin D-1 has high expression in mantle cell lymphoma cells and probably prevents the tumor cells from dying. Cyclin D-1 is a target of flavopiridol and we hope that by targeting this it will cause tumor cells to die. There are several other proteins in both mantle cell and diffuse large B-cell lymphoma cells which may be targeted by flavopiridol. We hope that by using this new schedule, which is very effective in CLL, we will see good responses which will translate into clinical benefit in patients with mantle cell and diffuse large B-cell lymphoma.

Study Design: Before being enrolled in the study, you will undergo a series of tests to determine if you are eligible for the study and to determine the extent (called stage) of your lymphoma. If you are found not to be eligible for the study, you will be referred back to your home physician. If you are eligible and decide to participate, we will ask you to undergo a lymph node biopsy before you start any treatment. As part of your clinical evaluation and follow up we will use CT scans to determine the extent of your disease and response to treatment.

Administration of flavopiridol: Flavopiridol is given intravenously (IV—into a vein). It may be given in a little catheter inserted on the day of the infusion or through a venous access device (also called central venous catheter). If you already have a central venous catheter, a new one will not be placed. If it is determined that you need a central venous catheter, you will be given an appointment for an outpatient surgical procedure to place the catheter into a vein in the arm or chest. You will receive further information about the procedure and the catheter from the clinic that performs these procedures.

You will be admitted to the hospital to receive flavopiridol for the first infusion. Flavopiridol is given as a 4 and a half hour infusion. Some of the drug dose is given over the first 30 minutes; the remainder is infused over 4 hours. You will receive medications for nausea and diarrhea. For the first treatment, you will be given the drug allopurinol by mouth and fluid into your veins to prevent an unlikely, but serious, side effect called tumor lysis syndrome (which occurs when cancer cells die too rapidly). The study doctor will decide if on subsequent cycles you need treatment to prevent tumor lysis syndrome. If you do not have serious side effects, you will go home the following day. This treatment will be repeated weekly for 4 weeks in a row, followed by 2 weeks with no treatment. This 6 week time period is called a "cycle."

After the first infusion, the remaining treatments will be in the outpatient clinic as long as you do not develop serious side effects. You may go home 2-3 hours after outpatient treatments. If you have serious side effects as an outpatient, you will be hospitalized. Any further flavopiridol would then be given to you in the hospital.

If you develop low white blood counts during flavopiridol treatment, we will begin treatment with Neupogen (G-CSF) which can cause your neutrophil count to rise. Once we start Neupogen, we will continue it throughout the course of your treatment with flavopiridol.

Research tests: We would like to perform research studies on your blood, bone marrow, tumor tissue or other fluids to look at different genes and proteins that may be involved in the development of your lymphoma or the reaction of the immune system. We will not examine mutations of normal genes from your tissue without obtaining additional permission from you. We plan to do a tissue biopsy before you start treatment and in selected cases a second biopsy after treatment

has begun. These biopsies will give us important information about your tumor and the effects of flavopiridol on it. Biopsies requiring major surgery (e.g., in the chest or the abdomen) will not be performed for research purposes alone but only if absolutely necessary for your medical care. Some of the research tissue and samples obtained may be sent to centers outside of the National Cancer Institute for tests to better understand how flavopiridol works in cancer cells.

Lymph node biopsy:

The purpose of the lymph node biopsy is to identify biomarkers that may predict how a patient will respond to flavopiridol. Please clearly check the appropriate box below:

☐ I am volunteering to take part in the optional lymph node biopsy

☐ I am **NOT** volunteering to take part in the optional lymph node biopsy

Some patients may also undergo up to two biopsies under CT guidance for research purposes. This radiation is for research purposes only and is not necessary for your medical care.

Certain patients who have tumor cells in their blood stream may be asked to undergo a procedure called lymphapheresis or apheresis for research purposes. Lymphapheresis or apheresis is done by circulating your blood through the apheresis machine. To do this you must have two places where IV needles are placed. There are two ways to do this procedure. In the first method, a needle is placed into each of your arm veins. The second method uses a vascular access device. Both methods provide a route for your blood to be circulated through the apheresis machine. Your blood is removed from one IV site, and then flows through the tubing into the machine. The machine has a centrifuge that separates the part of the blood that is to be removed. Only a small portion of your blood is circulated through the machine at any one time. The blood then returns to you through the other IV site. The procedure takes 2 - 4 hours to complete. Once the procedure is done, all of your blood is returned to you. You will be taken off the machine by the nurse. The needles are then removed and pressure is put over where the needles were to be sure that bleeding stops. After a period of rest, you will be told when to come in for your next procedure. The procedure may be done more than once.

You may have some discomfort when the nurse puts the needles into your veins. Keeping your arms in one position and staying still during a 2 - 4 hour procedure may also be a little uncomfortable. Some patients may feel dizzy, light-headed, nauseated, or cold during the procedure. Tell the staff right away if you feel any of these side effects. It is normal to feel tired for a short time after this procedure.

What happens after treatment is completed: This depends on how you have responded to the therapy. If all evidence of disease has disappeared, we will schedule periodic visits to the Clinical Center for follow-up examination and tests. If the disease does not disappear entirely or if it should recur after having disappeared for a period of time, then you may need further therapy. At that time you will be given the opportunity of participating in additional research protocols that may be appropriate for you. If no such protocols are available, you will be returned to the care of your local physician. We will continue to contact you and/or your local physician to see how you are doing even after you have completed treatment on this protocol. It is important to stress that participation in this protocol does not constitute a promise of long-term medical care here at the Clinical Center. It is conceivable that participation in this study may make you ineligible to participate in certain other research protocols because the requirements for entry onto these protocols may not allow patients who have already been treated with certain drugs or who have had certain side effects from previous treatment. You may decide now not to receive treatment on this protocol, or you may choose at any point in time to stop the treatment and withdraw from the protocol; in either case you will be returned to the care of your referring physician.

ALTERNATIVE APPROACHES OR TREATMENTS

Alternative procedures that could be used to treat your disease include:

1. Combination drug regimens. There are several drugs which are very active in diffuse large B-cell lymphoma and mantle cell lymphoma.
2. Treatment with single drugs.
3. Radiation (X-ray) treatments. This can stop tumor growth in particular locations, such as bone, abdomen, and other sites but is not successful in controlling the disease overall unless the disease is very localized at the start of therapy.
4. Surgery. As with radiation, surgery can be successful in removing tumor from particular locations but cannot be used successfully to remove all lymphoma cells from the body, since the disease is almost always present in multiple locations. Also, surgery cannot be used against tumor in some of the organs most commonly involved by lymphoma, such as the liver or the lungs.
5. Bone marrow transplantation may be an alternative type of treatment. This can be curable in some patients with relapsed or refractory mantle cell lymphoma or diffuse large B-cell lymphoma.
6. Watching and waiting may be an option for select patients without symptoms.
7. Getting no treatment; getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

RISKS OR DISCOMFORTS OF PARTICIPATION

In order to determine whether this study is suitable for you, a number of tests will have to be done. Some or all of these tests will be repeated during and after the flavopiridol at different times. Depending on the tests you had before coming here, these may include blood and urine tests, studies of lung function, CAT or MRI scans, radioisotope scans (for example a PET scan), colonoscopies, and biopsies of tumor tissue, bone marrow, liver, or other sites. Biopsies will, when possible, be done under local anesthesia. The risks associated with bone marrow biopsies include pain, bleeding, and local infection. Risks of biopsies include pain, bleeding, infection, and the risks to the particular area undergoing surgery. General anesthesia itself is generally very safe but has a very small risk of major complications such as heart attack or stroke. The surgical and anesthetic risks will be explained to you in more detail at the time of surgery, if this is needed. Risks of colonoscopy with biopsies include discomfort and bleeding from the rectum; rarely the colon may be punctured and if this occurs, it is serious and may require surgery. A separate consent describing all of the complications and side effects of colonoscopy with biopsies will be obtained from you.

In order to receive this therapy it is possible that you will need to have an intravenous catheter placed. This catheter is usually placed in the arm, chest or neck area into a major vein inside your chest. We usually remove the catheter after each cycle but on occasion it can be left in for several cycles. The catheter may be necessary for infusion of flavopiridol and for the drawing of blood. It is usually inserted under local anesthesia. The risks associated with the procedure include pain, bleeding, infection, and puncture of the underlying lung. Lung puncture can result in lung collapse, which might require that a chest tube be placed into the chest cavity (usually for a day or two) to help the lung re-inflate. The long-term risks of the catheter include infection and clotting of the vein in which the catheter sits. If these occur, it may be necessary to remove the catheter. These risks will be explained to you in more detail at the time of the insertion.

Possible side effects of Flavopiridol:

Likely:

- Lack of enough red blood cells (anemia)
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Decrease in the total number of white blood cells (leukocytes)

Less Likely:

- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Belly pain
- Chills
- Fever
- Pain
- Potentially life-threatening condition during a drug infusion which may cause low blood pressure, rash, fever, chills, difficulty breathing, rapid heartbeat, nausea, and kidney damage
- Infection
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Decreased number of a type of white blood cell (lymphocyte)
- Loss of appetite
- High blood sugar level
- Decreased levels of a blood protein called albumin
- Decreased blood level of phosphate
- High or low blood calcium
- Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure
- Increased creatinine (blood test that indicates kidney function)
- Muscle pain
- Pain in the area of the tumor
- Taste changes
- Bleeding from the brain
- Shortness of breath
- Hair loss
- Low blood pressure
- Fainting
- Formation of a blood clot that breaks loose and is carried by the blood stream to plug another blood vessel

If you receive Neupogen, the possible side effects include:

- Bony pain
- Skin rash
- Skin reddening around the injection site
- Muscle cramps
- Decreased platelets (not clinically significant)
- Pain or numbness and tingling around the chin
- Worsening of certain pre-existing inflammatory conditions (such as psoriasis eczema, or vasculitis)
- Fever, body aches
- Alterations in certain laboratory tests
- With prolonged administration Neupogen has been associated with hair thinning and enlargement of the spleen.

In addition to the above listed side effects, unforeseeable or unexpected risks, including death may be involved with this drug. Your physicians will watch you closely for side effects and will stop treatment if any side effects become a serious threat to your life or well-being. Your physicians will also stop the treatments if it becomes clear that the treatment is not successfully controlling your disease.

You should not become pregnant or father a baby while on this study because the drug in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Flavopiridol may be toxic to the cells in the ovary and testicle and may produce sterility. Recovery of normal fertility is not well studied. For this reason, men who are about to receive this treatment should, if they wish to have children in the future, consider sperm banking before start of the treatment. Women of childbearing age will have a pregnancy test, which must be negative at the time of study entry. This test requires that a urine sample be obtained within one week prior to the study. The results of the pregnancy test will be made available to you prior to the initiation of the study.

Rarely, patients may develop a dangerous side effect from blood transfusions called graft versus host disease (GVH). This disease is caused by white cells from the blood transfusion that can attack your normal tissues and cause death. GVH is preventable by radiating the blood before you receive it. It is important to emphasize that you will not receive any radiation from the blood and the radiation procedure done on the donated blood will not harm you. If you require a blood transfusion at the NIH during this study, you will receive blood that has been radiated. However, if your local physician gives you a blood transfusion, it is important that you make sure the blood has been radiated.

This research study involves exposure to radiation from one to two CT scans. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. If you are an adult, the total amount of radiation you will receive in this study is from 1-2 CT scans.

Using the standard way of describing radiation dose, from participating in this study, you will receive (from two CT scans) a total of 8.0 rem to your kidneys and 5.2 rem each to your stomach, gallbladder wall and lower large intestine. All other organs will receive smaller amounts of radiation. Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 1.2 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guideline established by the NIH Radiation Safety Committee for research subjects. The guideline is for an effective dose not to exceed 5 rem received per year in adults.

The NIH Radiation Safety Committee, a group of experts in radiation matters, has reviewed the use of radiation in adults in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earths air and soil. The dose that you will receive from two CT scans is about the same amount you would normally receive in 4 years from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, *An Introduction to Radiation for NIH Research Subjects.*

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in the chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is estimated at 0.05 percent. Therefore, the total risk of fatal cancer may be estimated to increase from 25 percent to up to 25.05 percent. This change in risk is small and cannot be measured directly. Compared with other everyday risks, such as flying in an airplane or driving a car, this increase is considered slight.

Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider 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 would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

If you are pregnant you may not participate in this research study. It is best to avoid radiation exposure to unborn children since they are more sensitive to radiation than adults.

POTENTIAL BENEFITS OF PARTICIPATION

We hope that some patients will have tumor shrinkage with flavopiridol. However, it is possible that you may not respond to any of this treatment.

RESEARCH SUBJECT'S RIGHTS

Any complication arising from this treatment will receive full and prompt medical attention. However, the National Cancer Institute, Federal Government, and the Clinical Center do not provide financial compensation for injury or long-term

medical treatment for such injuries, except as may be provided by remedies available under law. The study drug flavopiridol will be provided by CTEP. You will not be paid for taking part in this study. Your participation in this research study may contribute to the development of commercial products from which Sanofi Aventis Pharmaceuticals, Inc. or others may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit. Your medical care and the costs of the laboratory and radiographic studies done at the Clinical Center, NIH will be at no expense to you. If the blood tests needed to monitor the effects of treatment are to be done by your local physician, you can be reimbursed for the costs if your insurance does not cover this expense; permission for this must be obtained by your NIH physician in advance. The NIH cannot, however, reimburse you for the costs of other types of medical care delivered outside the NIH, even if you are seeking medical attention as a result of side effects from treatment given here, unless permission is granted in advance by the principal investigator of this study. Similarly, we do not ordinarily reimburse the costs of diagnostic radiology tests (such as CT scans, MRI, or chest X-rays) done outside the NIH, even if they are done for the purposes of this study.

NEW INFORMATION

You will be informed of any new findings related to the development or safety of flavopiridol that may affect your willingness to continue to take part in this study.

EARLY TERMINATION

You will be discontinued from this study for any of the following reasons:

- You may be withdrawn from the study if you do not comply with the study requirements.
- Your doctors do not feel it is in your medical best interests to be continued on this study.
- You have had unacceptable toxicity which does not permit safe continuation on the study
- You require another treatment.

MAKING YOUR CHOICE

We would like to keep some of the blood/tissue that is left over for future research. These specimens will be identified by a number and not your name. The use of your specimens will be for research purposes only and will not benefit you. It is also possible that the stored specimens may never be used. Results of the research done on your specimens will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your blood/tissue can be kept for future research, you can change you mind at any time. Just contact us and let us know that you do not want us to use your blood/tissue. Then any remaining blood/tissue that remains will be destroyed.

Please read each sentence below and think about you choice. After reading each sentence, circle and initial the answer that is right for you. If you have any questions, please talk to your doctor or nurse. No matter what you decide to do, it will not affect your care.

1. My blood/tissue may be kept for use in research to learn about, prevent or treat cancer.

Yes No Initials_____

2. My blood/tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes No Initials_____

3. Someone may contact me in the future to ask permission to use my specimen(s) in new research at the NIH not included in this consent.

   Yes No Initials_____

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, Kieron Dunleavy, M.D.; Building 10, Room 4N115, Telephone: 301-435-1007.

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 JUNE 13, 2011 THROUGH JUNE 12, 2012.

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

Print Name _____ Print Name _____