Section of Hematology and Oncology

CYTARABINE PLUS CONTINUOUS INFUSION DAUNORUBICIN INDUCTION THERAPY FOR ADULTS WITH ACUTE MYELOID LEUKEMIA; A FEASIBILITY STUDY WITH CARDIAC MRI MONITORING

Informed Consent Form to Participate in Research
Bayard Powell, M.D., Principal Investigator

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have Acute Myeloid Leukemia. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to test the safety and ability of giving daunorubicin, a common drug to fight acute myeloid leukemia, over a longer period of time. Daunorubicin is approved by the FDA for the treatment of AML. This way of giving the drug is called continuous infusion and is believed to be just as effective to fight your leukemia but safer for your heart.

This study will test 2 things:

1) To see if it possible to give Daunorubicin over a longer period of time (24 hours), and
2) To see what effects (good and bad) it has on you and your condition. Researchers believe continuous infusion of Daunorubicin works just as well as standard of care treatment but has less toxicity to your heart.

This study will do this by seeing if you are able to complete the infusion process and to look at your heart to see how it is working through pictures and blood tests. This study will also want to determine how this therapy works at treating your cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

There will be 40 people at the Wake Forest Comprehensive Cancer Center research site that will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

After your study doctor has answered all your questions about this study and you have given written consent by signing this form. Several tests will be done to be sure you are able to enter this study. Many of the tests are the same as those you have had in the past to diagnose and treat your disease. Some of these same tests will also be done during the study to follow your progress.

If you take part in this study, you will have the following tests and procedures:

Blood draws:
These draws will occur during your cancer treatment and are considered a normal part of care or standard of care. A needle will be inserted into your vein and blood will be taken from the vein. A blood draw will occur before the study, at every treatment session, and after the all the treatments are completed. On two or three occasions this blood will also be used for research purposes to determine troponin levels.

Bone marrow aspirations and biopsies:
For this type of cancer, bone marrow aspirations and biopsies occur as a part of the standard of care and treatment of the cancer to find out how your cancer is responding to the medicine. Bone marrow aspirations and biopsies will occur before the study begins and after the induction period to determine how your cancer responded to treatment. For the aspirations, the doctor will insert a needle your bone and remove some bone marrow. For the biopsy, the doctor will insert another needle and remove a small piece of bone and marrow for testing.

Echocardiogram (ECHO):
This will be done for standard of care to determine how your heart is functioning. An echo will occur before the study, after induction, only if you need another cycle of induction, and 3 months after the study in completed or if your cancer comes back after treatment with in these 3 months.

Magnetic resonance imaging (MRI):
This is another way to look at your heart and will be used, like the ECHO, to determine how your heart is functioning. It will be done for research purposes. It will also be used to compare which method, ECHO or MRI works best in determining heart function during chemotherapy. You will have an MRI before the study, 3 months after the study is completed or if your cancer comes back after treatment, and 6 months after the study is completed or if your cancer comes back within this 6 month period.

Continuous infusion of Daunorubicin.
Giving Daunorubicin is part of the standard of care for this cancer. However, giving this drug by continuous infusion, or over a long period of time, in this case 24 hours, is being done for research purposes. Giving Daunorubicin and related drugs by continuous infusion has been reported to be safer for your heart.

Administration of Medicine
You will be administered medicine through your veins to treat your cancer. This is a part of the standard of care to treat your cancer.

In this study, your participation will be divided into different visits. These visits and the procedures involved are described below.

Screening Visit
In this visit, we will find out if you can participate in the study. If you have not already had this done, you will have a blood draw. A needle will be inserted in your vein and you will have approximately 2-3 teaspoons of blood taken from a vein. You may also have a sample of your bone marrow and bone taken (bone marrow aspiration and biopsy). These tests will be used to find out the how far along your cancer is. These tests will be performed periodically throughout the study, but would also be done as a part of your normal care, as well.

You will have approximately 2-3 teaspoons of blood withdrawn from a vein at the entry of the study and at each treatment. The total amount of blood withdrawn during the study will be approximately 36-54 teaspoons depending on how your cancer responds to the treatments.

Study Entry Visit
You will be asked to sign this form to enter the study. You will also be asked to provide personal information including medical history, where you live, your sex, age and other similar information. The following tests may be done at this visit:

- The study doctor or nurse will ask you about your medical history and what other medicine you are taking at this time.
- The study doctor or nurse will examine you to determine your performance status. This is to find out how your cancer is affecting your daily activities.
- A physical exam will be done and your vital signs (heart rate, blood pressure, breathing rate and body temperature), height and weight will be recorded.
- Approximately 2-3 teaspoons of blood will be drawn for routine lab tests and a test to determine how your heart is working.
- A bone marrow sample (aspiration and biopsy) (a little over ½ teaspoon)

A pregnancy test must be performed for women of childbearing potential within 1 week (7 days) before registering for the study.

You will also have two procedures that will look at your heart and how it is well it is working. These are painless procedures where the researchers take pictures of your heart. One test is called an Echocardiogram or ECHO and the other is called magnetic resonance imaging or MRI. The ECHO will take about 45 minutes to complete and is part of standard care. This procedure is similar to what someone would use to look at a developing baby while in a mother's stomach. You will have adhesive (sticky) electrodes placed on your chest. The person performing the ECHO will place a handheld instrument on your chest. This will allow the machine to see your heart and pictures will be taken. The MRI may take about 30 to 90 minutes. You will lie down on a table and adhesive electrodes will be placed on you. The table will slide into a machine that looks like a tube. During this time you will need to remain still as the person working the machine (the technician) takes pictures. The technician may ask you to hold your breath for a couple seconds so that they can take pictures. Movement can blur the pictures. Once the procedure is finished the technician will move the table out of the machine.

Treatment Visits and Procedures
This study has several parts. There will be 1 or 2 induction cycles depending upon how your cancer responds and then consolidation therapy, which may take up to 3 cycles. One cycle of

chemotherapy is one week of taking medicine and one week of rest.

Induction
The first part is induction. You will stay at the hospital for this part of the study. This is the first part of your cancer treatment. In this portion of the treatment you will be given cytarabine as it would normally be given. You will also be given Daunorubicin (one of the chemotherapy drugs) but this will be done over a 24 hour period. Induction may take 1 or 2 cycles.

Cycle 1
During the first week, treatment is given as follows:

Days 1, 2 and 3
- You will be given Daunorubicin as a continuous infusion over 24 hours
- Your vital signs will be taken
- About 2-3 teaspoons of blood will be taken for laboratory tests

Days 1, 2, 3, 4, 5, 6 and 7
- You will be given cytarabine as a continuous infusion (Standard of care)
- Your vital signs will be taken
- About 2-3 teaspoons of blood will be taken for laboratory tests

The second week of the cycle is a rest week (no treatment).

Day 14 (+/- 2 days)
You will have a bone marrow aspiration and biopsy to see if your disease has responded (just like you would if you were not on the study). Depending on your bone marrow biopsy results, you may need another Induction cycle.

Depending on your bone marrow aspiration and biopsy results you may need another cycle of induction, if so; you will have another ECHO at this point. If you need another cycle (Cycle 2) of induction therapy, the second Cycle will be as follows:

Days 1 and 2
- You will be given Daunorubicin (continuous infusion)
- Your vital signs will be taken
- About 2-3 teaspoons of blood will be taken for laboratory tests

Days 1, 2, 3, 4, 5
- You will be given cytarabine (continuous infusion)
- Your vital signs will be taken
- About 2-3 teaspoons of blood will be taken for laboratory tests

After this cycle, you will have a bone marrow biopsy so the doctor can see if your disease is responding. This would happen even if you were not in the study.

Consolidation
If you respond to the induction treatment you may move on to the next phase called consolidation therapy. This will occur within 2 weeks (14 days) after induction therapy once you have recovered from induction therapy. This phase of therapy is to kill any remaining cancer cells that may be in your body. You will stay at the hospital for this part of the study. Consolidation therapy may need to be done for up to 3 cycles (42 days) as recommended by your doctor. Because patients with CBF AML benefit from additional high dose cyarabine consolidation therapy, we recommend 4 cycles of consolidation therapy. So if you have CBF AML you may have 4 cycles of consolidation therapy. Consolidation therapy will consist of you taking cytarabine at a higher dose than you had during induction. The treatment is as follows:

Days 1, 3 and 5
- You will be given cytarabine (over 3 hours), every 12 hours
- Your vital signs will be taken
- About 2-3 teaspoons of blood will be taken for laboratory tests

Days 2, 3, 6 and 7
- No Treatment

After consolidation therapy is completed we would like to follow your progress for 6 months or if your leukemia relapses. After 3 months or if your leukemia relapses you will do another MRI and ECHO to determine your heart function. After 6 months or if your leukemia relapses you would come back in to do an MRI.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

HOW LONG WILL I BE IN THE STUDY?
You may be in the study for up to 292 days. Of this time, about 120 days or about 4 months will be focused on giving the medicine for the treatment of your cancer. After that you will come back to Wake Forest Cancer Center at 3 months for an MRI and ECHO and 6 months for an MRI, or if your cancer comes back.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the procedures (MRI) and the test drug, (Daunorubicin) we are studying include:

Risks Related to Daunorubicin

Common (≥20%)

- Hair loss
- Nausea, vomiting
- Pink or red colored urine, sweat or saliva

Less common (<20%)

- Damage to the heart which may cause shortness of breath, tiredness
- Infection
- Anemia
- Bruising, bleeding
- Pain and sores in the mouth and throat
- Dark discoloration of the nail and skin
- Loss of nails
- Redness and pain at the site of previous radiation
- Swelling and redness at the site of injection
- Diarrhea

Rare (≤ 3%)

- Cancer of the bone marrow
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Risks Related to Continuous Infusion of Daunorubicin

There are no known risks to administering Daunorubicin by continuous infusion; however, there may be unknown risks.

Risks Related to Cytarabine

Some common side effects observed in patients taking cytarabine include:

- Anemia
- Low white blood cells
- Low platelets
- Serious infections
- Nausea
- Vomiting
- Diarrhea
- Stomach pain
- Loss of appetite

- Inflammation of the mucus membranes lining the mouth
- Hair loss
- Muscle or joint pain
- Tiredness
- Sore or red eyes
- Anemia
- Low levels of white blood cells
- Increased risk of infection
- Weight loss
- Decreased liver function
- Fever
- Increased risk of bleeding

Rarely, cytarabine has been associated with sepsis (whole-body infection and inflammation), pneumonia, difficulty urinating, decreased kidney function, nerve damage, sores in the throat, chest pain, inflammation of the lining that surrounds the heart, pancreatitis (inflammation of the pancreas), jaundice (temporary yellowing of the skin and eyes), eye infection, dizziness, shortness of breath, and headache.

Risks Related to MRI

Common:

- Anxiety/stress
- Claustrophobia (if you are claustrophobic you should let your doctor and the MRI technician know)
- Discomfort

Rare, but serious:

- Injury related to the presence of metallic or surgical implants or metal pieces in the body and the MR magnet; it is important that you let the MRI team know about whether you have these before the MRI procedure.

Risks Related to Echocardiogram

You may experience some discomfort when the technician removes the electrodes, similar to that of pulling off a band aid.

Risks Related to Blood Draws

You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and

any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

Contraceptive Measures for Males

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for ***3 months*** afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be:

- Better tolerance or fewer side effects to Daunorubicin.

Based on experience with Daunorubicin in patients with AML, researchers believe continuous infusion of Daunorubicin is as good as standard therapy you could receive without being in the study but with fewer side effects. Because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:

- Other chemotherapies
- Standard Chemotherapy
- Comfort care, which is an option if you decide that you do not want any more active treatment for your cancer. Comfort care includes pain medication and other types of support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends, and your doctor.

You could be treated with Daunorubicin even if you do not take part in the study.

The most common standard of care procedure would be to have induction therapy as described here (cytarabine and Daunorubicin or idarubicin) but with Daunorubicin given in a normal fashion, which is called a bolus (all of the medicine given in a short amount of time). The consolidation therapy would be the same or similar to what it described here. The risks associated with standard of care treatment are similar as to what are described in this study.

WHAT ARE THE COSTS?

The study will pay for MRIs on pre-study evaluation and on 3 month and 6 month follow-ups or relapse. The study will also pay for the troponin lab tests at pre-study evaluation, day 4 of cycle 1 and day 3 of cycle 2. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and/or effectiveness of Daunorubicin when given as a continuous infusion over 24 hours; the results will be provided to the Food and Drug Administration and other federal and regulatory agencies, as required.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study. Parking validation will be provided for study-related outpatient visits.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest Comprehensive Cancer Center.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call **Bayard Powell, M.D**.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you] and/or [information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:**

- Your health history
- How you respond to study procedures
- Laboratory and other tests
- Physical examinations

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. The only people that will be granted access to your Protected Health Information are:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

1) Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

2) Representatives from government agencies such as the US Food and Drug Administration (FDA)

3) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

4) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-

identified. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Bayard Powell, M.D. that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Bayard Powell, M.D.
Comprehensive Cancer Center
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped
You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

You are encouraged to ask question regarding your treatment.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, **Bayard Powell, M.D.**

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB.

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00040792
Meeting Date Approved 12/30/2019
Version Valid Until: 7/9/2020