PRINCIPAL INVESTIGATOR: Mark Roschewski, M.D.

STUDY TITLE: Dose-Adjusted EPOCH Chemotherapy and Rituximab (CD20+) in Adults and Children with Previously Untreated Aggressive Non-Hodgkin's Lymphoma

STUDY SITE: NIH Clinical Center

Cohort: Standard

Consent Version: 04/20/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being enrolled is a minor then the term "you" refers to "you and/or your child" throughout the remainder of this document.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

You have a disease called non-Hodgkin's lymphoma which your doctor's think would be better treated with chemotherapy than surgery or radiation. For your particular kind of non-Hodgkin's

lymphoma, previous studies have shown that combinations of drugs are much more likely to make the disease go away for appreciable periods of time than single drugs, which have only very limited effectiveness against this group of lymphomas. Studies have also shown that more intensive (i.e. higher dose) treatments have a greater chance of success than more gentle approaches. Studies conducted at the National Cancer Institute suggest that certain chemotherapy drugs may be more effective if given by continuous infusion into the vein rather than by the standard method of rapid intravenous injection. One such combination, which we call EPOCH (each letter stands for one of the drugs used in the combination), seems to have a high degree of effectiveness in patients whose tumors have stopped responding to standard regimens. We therefore plan to test this combination in patients who have never received chemotherapy previously. Research indicates that the effects of chemotherapy with EPOCH may be improved by the use of a drug called Rituximab. Rituximab is a special kind of drug called an antibody which binds to a specific molecule (called CD20) present on some types of lymphomas called B-cell lymphomas. If you/your child have/has one of the lymphoma types which have the CD20 molecule present, then you will also receive rituximab along with the EPOCH chemotherapy.

How many people will take part in this study?

Approximately 348 patients will take part in this study.

DESCRIPTION OF RESEARCH STUDY

Objectives and design of this study

The general purpose of this study is to develop treatments for lymphoma that are more effective than existing therapies. In this study five chemotherapy drugs are given together in an intensive combination called EPOCH. Each series of treatments is called a cycle; a cycle is repeated every three weeks and drugs are administered during the first five days of every cycle. EPOCH consists of prednisone by mouth on days 1-5, and etoposide, doxorubicin, and vincristine as a continuous infusion on days 1 through 5 (total of 96 hours). In addition, cyclophosphamide is given by intravenous injection over about 30-60 minutes on day 5. If your tumor has the CD20 molecule, you will also receive a dose of rituximab on day 1, immediately before the chemotherapy begins. Each cycle lasts 3 weeks: 5 days of chemotherapy followed by 16 days of no chemotherapy. You will receive repeated cycles of EPOCH until remission (disappearance of tumor) is achieved or until the tumor shows no further evidence of shrinkage. Between cycles of treatment we give another drug, G-CSF, whose purpose is to help your normal bone marrow cells recover from the chemotherapy and produce normal white cells. The use of G-CSF in this way may help us increase the total amount of chemotherapy you can receive.

We will test whether giving the drugs by continuous infusion with G-CSF will allow us to give more intensive and more effective therapy than was possible previously. If you are individually capable of tolerating more drug than the initial amount you receive, the treatment plan allows us to increase your doses of some of the drugs in later treatment cycles, so that we can be sure of giving you as much drug as you can tolerate without unacceptable side effects. However, the doses of rituximab, vincristine and prednisone will not be increased. In summary, then, the specific objective of this study is to assess whether EPOCH (and possibly rituximab) has excellent clinical response in patients like you and to see whether the use of continuous infusion of some of the drugs, coupled with the use of the bone marrow stimulator G-CSF, will permit us to give

significantly higher quantities of drug than is possible when the treatment is given in standard fashion.

A laboratory objective of this protocol is to study why some patient's tumors are not cured by therapy. To help determine this, we will do some experimental tests on your tumor biopsies, blood and other fluids from you to look at different genes and proteins. However, we will not examine mutations of normal genes from your tissue without obtaining additional permission from you. It may be important to obtain repeat biopsies of tumor tissue, even if you have already had such a biopsy before coming here. We do this sometimes to confirm the diagnosis or to obtain fresh tumor tissue for research purposes. 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. You may decide not to have a biopsy for research purposes and this will not affect your eligibility for this study. We may request biopsies after you sign the consent form, at Cycle 4 and at Cycle 6.

If you agree to have the optional biopsy, you will be asked to sign a separate procedure consent before you have the procedure.

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

Treatment consists of the following drugs:

1. Doxorubicin, etoposide, and vincristine - These three drugs are given by continuous IV infusion over four days, beginning on day 1 and ending on day 5 of each cycle. We deliver these drugs with the aid of one lightweight, portable infusion pump, each about the size of a portable tape recorder; this permits treatment on an outpatient basis. The pumps deliver the therapy through an intravenous catheter which is placed in your vein beforehand. You will be taught about the use and care of the pump and what to do if it stops working.
2. Cyclophosphamide - This is given over about 30-60 minutes on day 5 of each treatment cycle.
3. Prednisone - These are pills given by mouth twice a day for the first 5 days of every cycle.
4. Rituximab – Administered only in patients with CD20+ B-cell lymphomas. This drug is given by vein over several hours on the first day of each cycle, immediately before the chemotherapy infusion begins.
5. G-CSF - This is given by injection under the skin once daily beginning on day 6 of each cycle and continuing until recovery of the white blood cell count. If your white blood cell count is still very low on the day treatment is due to begin again, the chemotherapy may be deferred and the G-CSF restarted until fuller recovery of the white count. You will be taught how to administer the G-CSF to yourself during the first treatment cycle.

EPOCH-R Treatment Schema

	Day of Treatment														
	1	2	3	4	5	6	7	8	9	10	11	12	13	…	21*
Rituximab	X														
Etoposide	X ⟶														
Prednisone	X	X	X	X	X										
Vincristine	X ⟶														
Cyclophosphamide					X										
Doxorubicin	X ⟶														
G-CSF						X** ⟶									

* This twenty-one day (21) period will be known as a "cycle" of therapy. Therapy will be repeated for a total of 6-8 cycles.

** G-CSF will continue to be given to you until your blood counts have reached acceptable levels.

We expect that treatment will be given for approximately 6 to 8 cycles (about 18 to 24 weeks). In general, you will receive two cycles past the point of maximum response. In very rare situations, your study doctors may recommend radiation treatment to a specific area of your body after you complete the chemotherapy. If this occurs, your study doctors will explain the radiation therapy, other treatment options and side effects to expect.

Since several of these drugs can lower your resistance to infection, we also require that you take a combination antibiotic, trimethoprim/sulfamethoxazole (SeptraR or BactrimR) for three days each week while you are receiving EPOCH chemotherapy (Monday, Wednesday and Friday is the preferred schedule). If allergic to these preparations, you will receive another drug, pentamidine, by inhalation once monthly or other standard treatment.

Hepatitis B testing and prophylaxis:

As part of our study, we will test you for infection with Hepatitis B. We will tell you what the results mean and if you will require more frequent testing for Hepatitis B and need to take medicine to prevent Hepatitis B reactivation while on the study.

If you need to take medicine, you will take one, such as entecavir, by mouth every day until 12 months after your last chemotherapy.

Treatment of disease in the nervous system

It occasionally happens that lymphomas spread to the coverings of the brain (the meninges) at some point during the illness. If this should happen, the treatment usually includes the instillation of one of two chemotherapy drugs (methotrexate and cytarabine) directly into the fluid (the

cerebrospinal fluid, or CSF) surrounding the brain. This is usually done by first placing a small reservoir (an Ommaya reservoir) under the skin of the scalp; this reservoir is connected to a catheter that is placed through the brain itself into the fluid. This procedure is performed by a neurosurgeon under general anesthesia. These drugs may also be administered through a spinal tap (also called a lumbar puncture). Depending on how you respond to this therapy, it may be necessary to modify it and to also administer radiation to your brain and spinal cord. Each of these therapies will be discussed with you if they are needed. Patients who have lymphoma in their bone marrow or who have certain sub-types of lymphoma are at higher risk of developing lymphoma in the brain areas. To reduce this risk, patients at higher risk will receive methotrexate by a spinal tap on days 1 and 5 of cycles 3-6 of their EPOCH chemotherapy. This will be discussed with you by your treating physicians.

When you are finished taking the treatment

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. 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.

RISKS OR DISCOMFORTS OF PARTICIPATION

What side effects or risks can I expect from being in this study?

In order to determine whether this study is suitable for you, a number of tests will have to be done. This period of evaluation may take up to two weeks and is usually done on an outpatient basis. Depending on the tests you have already had before coming here, these may include blood and urine tests, studies of lung function, CAT or MRI scans, radioisotope scans, and biopsies of tumor tissue, bone marrow, liver, or other sites. Biopsies will, when possible, be done under local anesthesia. The risks associated with blood draws include pain, blood clots, bruises, infection and nerve damage. The risks associated with bone marrow biopsies include pain, bleeding, and 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.

In order to receive this therapy, 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

is necessary for infusion of chemotherapy 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 reinflate. 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.

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious or long-lasting or may never go away. There is also the risk of death from either the treatment or your disease.

You should talk to your doctor about any symptoms that you experience while taking part in the study.

Risks and side effects related to the treatment are identified below:

Side Effects from Treatment

Side Effects of EPOCH

Likely

- Lowered white blood cell count that may lead to infection.
- Lowered platelets which may lead to an increase in bruising or bleeding.
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath.
- Should low counts occur, they can be treated with blood products (transfusions), antibiotics, and there may be a reduction in the amount of drug given to you.
- Constipation.
- Fatigue or tiredness.
- Tingling of fingers and/or toes.
- Hair loss.
- Fever and/or chills.
- Time away from work.
- Urine colored red for a day or two after the doxorubicin infusion.
- Fingernail and toenail changes.
- Tearing or dry eyes.
- Runny nose.
- Bony pain.

Less Likely

- Nausea and/or vomiting.

- Loss of appetite, change in taste and weight loss.
- Headaches.
- Muscle aches and muscle weakness.
- Hoarseness or pain in the jaw.
- Elevated blood sugar levels.
- Elevated or decreased blood pressure.
- Confusion.
- Mouth & throat sores. Temporary irritation to the mouth may lead to mouth ulcers (similar to canker sores). Medications to numb the mouth may ease the mouth discomfort.
- Stomach ulcers.
- Skin rashes and/or dry skin.
- Loss of control of muscles or reflexes.
- Abnormalities in blood results such as elevated liver enzymes, low blood protein and low blood calcium.
- Mood changes such as agitation or depression.
- Trouble sleeping.

Rare but Serious

- Severe constipation may result in abdominal pain and cramping.
- Bladder irritation with painful and bloody urine.
- Damage to the heart muscle.
- Hand and foot syndrome, a condition that causes the skin on your hands and feet to become reddened, peel and be painful.

Side Effects of Rituximab

Likely:

- Lowered lymphocyte (a specific white blood cell) count
- Tiredness
- Fever and chills while receiving rituximab
- Nausea

Less Likely:

- Temporary shortness of breath or dizziness while receiving rituximab.
- Flushing, rash, itching and/or hives while receiving rituximab
- Lowered platelets which may lead to an increase in bruising or bleeding.
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath.
- Lowered white blood cell count that may lead to infection.
- Runny nose and sneezing

- Cough, wheezing, and/or infiltrates in your lungs
- Abnormal heart rhythms including a heart attack
- Allergic reaction that may be severe or life-threatening. Symptoms may include difficulty breathing, low blood pressure, fast heart rate, and sweating.
- Serum sickness or acute infusion reaction (both similar to allergic reactions)
- Elevated or decreased blood pressure
- Muscle or joint aches
- Pain at the site of your tumor
- Headache
- Abdominal pain, diarrhea, and/or vomiting
- Bowel perforation
- Infections with other viruses, such as JC virus, varicella zoster, herpes simplex, and West Nile virus could occur during or after treatment with rituximab. You will be closely monitored and appropriately treated for any infections.
- Abnormalities in blood results such as low calcium, high glucose, potassium, and uric acid
- Seizure
- Mood changes such as anxiety

Rare, But Serious:

- Skin rash that may be serious and life-threatening.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Patients who may have had prior exposure to the hepatitis B and C virus may be at an increased risk of recurrence of the virus that may lead to severe liver damage that can be life-threatening. You doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection, and you will be treated, if appropriate, by your doctor.
- Tumor lysis syndrome, which causes abnormal levels of chemicals in your blood and kidney failure. This is the results of rituximab killing a very large number of tumor cells in the blood and decreased oxygen in the blood.
- Lung problems such as adult respiratory distress syndrome (ARDS)

Infection Risks

It is important to emphasize that when you have a decreased white blood cell count, you are at risk of infection. Such infections can be very serious and can even cause death if not quickly and properly treated. Therefore, if you have a temperature greater than 38.3° C (101° F), you must call your doctor immediately.

Hepatitis B Reactivation

Hepatitis B reactivation has occurred in patients treated with combination chemotherapy and rituximab. Signs of hepatitis B reactivation may include: fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, clay colored bowl movement, joint pain and yellowing of

the skin and/or eyes (jaundice). It may lead to long-term health problems, including liver damage, liver failure, liver cancer, and even death.

Secondary Malignancy

A number of established chemotherapy agents have an inherent risk of causing another cancer (known as a "secondary malignancy"). Certain drugs in use today, not currently known to be associated with this risk may be shown at a later time to result in the development of these secondary malignancies.

Reproductive Risks

Many of the drugs used in this treatment program are toxic to the cells in the ovary and testicle and may produce sterility. Recovery of normal fertility is not well studied although we know that some patients treated with this combination have remained fertile after the therapy has been completed. 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. These drugs, as well as the scans performed to assess your disease may also be very toxic to an unborn child or nursing baby.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 12 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Complications of Treatment of the Central Nervous System

Complications of Ommaya insertion are uncommon when done by an experienced physician but could include infection and bleeding at the operative site or in the brain itself. Complications of lumbar puncture may include pain or bleeding at the site of needle insertion (the low back), infection, and headache. Most patients tolerate this treatment without serious side effects, although drugs placed into the brain fluid (CSF) may cause headache, stiff neck, and confusion that resolve when they are stopped. With long-term treatment, confusion and a slowing of thought processes may occur. If this treatment becomes necessary for you, the complications of the lumbar puncture or Ommaya insertion and methotrexate instillation will be discussed in more detail.

Risks from Other Study Procedures

Blood sampling

The blood samples collected as part of this study are not expected to produce any important decrease in the total amount of blood in your body. Side effects may include pain and discomfort, bruising, and rarely inflammation of the vein, bleeding or infection. Additionally, some patients can experience light-headedness or fainting. The most amount of blood to be drawn during any study visit/cycle is expected to be about 3 tablespoons. This includes testing for standard of care tests (i.e., complete blood counts) as well as blood for research.

Biopsy

Once treatment is complete as part of follow-up assessments, you may agree to the biopsy now and change your mind later. If at any time you do not want to have a biopsy done, please tell us, it will not affect your care. If you agree to have the biopsy, you will be asked to sign a separate procedure consent before you have the procedure(s). The likely side effects include discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion. Bleeding from the site of the needle insertion is a less likely risk. Rarely, significant infection or bleeding from this procedure, allergic reaction to the anesthetic, or formation of a scar at the site of needle entry occurs. If you will have sedation with the procedure, these risks will be discussed with you prior to the procedure. You will be asked to sign a separate consent form prior to any biopsy procedure.

Bone Marrow Aspiration

These procedures usually cause only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site. A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow biopsy. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. As the bone marrow liquid is taken from the bone, there may be a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all patients experience discomfort. The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.

Imaging – CT scans and MRI

Risks from CT scans:

CT scans are used to monitor your disease while you are in this study. CT scans expose you to radiation; the amount depends on the number of body areas scanned. In addition, scans involve use of contrast (oral and/or IV) that the cancer may be seen better on the images. You will have scans done (based on your disease at the discretion of your doctor) prior to treatment (if these need to be repeated from screening), after you sign the consent, at Cycle 4, and at Cycle 6.

The below describes more information about the risks of the contrast and imaging:

- Contrast Agents: There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the test to confirm that it is safe you to receive the contrast.

For IV contrast: You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach.

For oral contrast: You may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

- CT Scans: The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures showing the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan and you will be instructed to hold your breath. The scan itself will only take a few minutes to complete, the entire visit will take about 30 minutes. For the risks, see "Radiation" below & "Contrast Agent" above.

Radiation Risks:

During your participation in this research study, you may be exposed to radiation from up to a maximum of 5 CT Scans in a single year. The amount of radiation exposure from these procedures is equal to approximately 5.3 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT Scans that you get in this study will expose you to roughly the same amount of radiation as 17.7 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.5 out of 100 (0.5%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

Risks related to MRI:

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone

having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Risks related to Gadolinium enhanced MRI:

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes. It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

Risks: The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level. Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your study.

Risks of Lumbar Puncture

The lumbar puncture may cause pain at the site where the needle goes in and the spinal fluid is taken. There is a small risk of infection or bleeding. After the lumbar puncture you may get a headache. About a third of adults report a headache after an LP. To minimize the risk of a headache, the doctor will use a small needle and may prescribe bed rest for one or more hours after the procedure. If a headache occurs, it is usually mild and can be controlled by bed rest, drinking lots of fluids and a pain pill, such as acetaminophen. Rarely, the headache is severe and may require additional treatment with a "blood patch". In this procedure, a small amount of your own blood is injected into the lumbar puncture site. This procedure is generally effective in stopping the headache. A rare but serious complication of a LP, if it is done when the pressure inside the head is higher than normal (such as when a brain tumor is present), is known as

medullary herniation which can result in death. Increased intracranial pressure is very unlikely to be present. The LP will not be done if there are any clinical indications that you have increased intracranial pressure, a skin infection in the lower back area, or bone malformation of the lower back (including severe scoliosis) which would make a LP difficult.

To minimize these risks, the lumbar puncture procedure will be performed by a medical professional specifically trained to do this procedure.

Urine Collection

There is no physical risks involved with urine collection.

POTENTIAL BENEFITS OF PARTICIPATION

The aim of this study is to see if this treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. The potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. We do know that the information from this study will help doctors learn more about EPOCH-R as a treatment for aggressive lymphoma. We do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help future patients diagnosed with lymphoma.

ALTERNATIVE APPROACHES OR TREATMENTS

What other choices do I have if I do not take part in this study?

It should be emphasized that we do not know at this point whether the combination of drugs we propose to give you is superior, inferior, or equivalent to standard combination chemotherapy for your disease. Alternative procedures that could be used to treat your disease include:

1. Other combination drug regimens and other schedules of the same drugs used in this study. For example, a chemotherapy called CHOP given in the conventional manner would be suitable standard therapy for your condition.
2. Treatment with single drugs. This is known to produce brief responses of a few months' duration in many patients but to have little beneficial effect in long-term control of the disease.
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. Waiting, without active therapy. Although a period of watchful waiting is appropriate treatment for some kinds of tumors, in lymphomas similar to yours the disease will often grow and spread rapidly if no treatment is administered.

STOPPING THERAPY

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

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

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. 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 cannot be recalled and destroyed.

BLOOD COLLECTION FOR RESEARCH

You may be asked to donate a small amount of blood for research. If you agree to this, you will have blood collected for research before, during and after you complete treatment. The amount of blood collected will be kept within the safe range set by the Clinical Center. The blood collected is exclusively for research purposes and will not benefit you.

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, 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 they 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.

PAYMENT

Will you receive any type of payment for taking part in the study?

You will not receive compensation for participation in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

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.

CONFLICT OF INTEREST(COI)

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for additional information or a copy of the COI Guide. Investigators 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.

Investigators 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 regulations and is not a conflict of interest.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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 NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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 Roschewski, M.D., Building 10, Room 4N115, mark.roschewski@nih.gov, 240-760-6183. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Assent: I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Minor:

Signature of Minor	Print Name of Minor	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.