INSTITUTE:	National Cancer Institute		
STUDY NUMBER:	15-C-0039	PRINCIPAL INVESTIGATOR:	David C. Halverson, M.D.
STUDY TITLE:	Biomarkers in Acute Graft-Versus-Host Disease (GVHD) and Extracorporeal Photopheresis added to Investigator Chosen Therapies of Steroid Refractory Acute GVHD		
Initial Review Approved by the IRB on 11/26/14		Date Posted to Web: 12/06/14	

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This study is being done to learn more about the acute graft-versus-host disease (GVHD) after allogeneic stem cell transplantation. Acute GVHD is a risk after any allogeneic transplant (a transplant from a related or unrelated person). The doctors of your transplantation study have already discussed your risk of acute GVHD with you as a part of that study. Acute GVHD is different in every patient but is caused when the new immune system acquired from your donor causes damage to your organs. It can primarily effect the skin (rash), intestines (nausea, vomiting and/or diarrhea), or liver (jaundice). This study allows us to sample blood (for measurement of

biomarkers) as patients go through their transplant to try and better understand why some patients get acute GVHD while others do not and why some treatments work better than others for acute GVHD. If your doctor determines that you have developed acute GVHD after your transplant, you will be treated first with corticosteroids by your transplant doctor. In the event that these corticosteroids alone are not an adequate treatment in your case (called steroid refractory acute GVHD), participation in this study gives you and your doctor the option of adding an experimental treatment for steroid refractory acute GVHD called Extracorporeal Photopheresis (ECP). ECP on this study, if used, would be added to the same treatments you would receive for steroid refractory acute GVHD whether or not you participate in this study. This decision that corticosteroids have not worked and what treatments you get for steroid refractory acute GVHD, with or without ECP, will remain entirely between you and your doctor. Whether or not ECP helps treat steroid refractory acute GVHD has not been proven. ECP is an FDA-approved technique currently used for the treatment of a type of lymphoma that affects the skin. It is a procedure in which a part of the blood is removed from the body through an intravenous (IV) catheter by a special machine and then treated with a light-sensitizing agent, methoxsalen. The removed white blood cells are then exposed to ultra-violet light before being returned to you through a different IV. The ECP procedure has been used in other studies in more than 50 patients with acute GVHD with some improvement in symptoms being seen and no serious side effects reported.

ECP will only be potentially a part of your treatment on this study if you develop steroid refractory acute GVHD. Those patients that do develop steroid refractory acute GVHD and receive ECP on this study as a part of their treatment will help us understand more about the ECP procedure when combined with other current treatments for steroid refractory acute GVHD. We also will be studying how certain markers in your blood may help us predict who should get ECP in the future and the effects of ECP on the immune system. This procedure has not been approved by the FDA for the treatment of steroid refractory acute GVHD.

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

You are being asked to take part in this study because you are currently enrolled on an allogeneic transplantation protocol at the NCI and are at risk for developing acute GVHD.

How many people will take part in this study?

A total of 450 patients will take part in the study.

Description of Research Study

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

Before you begin the study

To qualify, you must be enrolled on an NCI allogeneic hematopoietic stem cell transplant protocol. You will not need to have additional examinations, tests or procedures to qualify for the study. All of the tests, with the exception of the pregnancy testing, that are needed are performed as part of your regular medical care with your transplant.

If you agree to be in the research study, you will be asked to sign this informed consent to participate.

During the study

If you never develop acute GVHD, you will simply provide multiple blood samples for 3 months as described below.

If you develop acute GVHD, you will receive treatment with corticosteroids for your acute GVHD as prescribed by your transplant physician. Your doctor will decide if corticosteroids alone are effective for you and, if not, whether ECP on this study should be part to your treatment.

If you and your doctor determine that ECP should be part of your treatment for steroid refractory acute GVHD, the ECP is usually done according to the following schedule. The exact schedule for your ECP will be determined by your doctor using ongoing evaluation of your progress.

- Twice weekly for 1 month
- Twice during every other week for 2 months
- Twice during one week per month for 4 months for a total of up to 7 months of treatment.

ECP will usually be done in your hospital room, the outpatient department, or you may be asked to have it in the Department of Transfusion Medicine.

If it is determined that the veins in your arms are not adequate for the procedure, you may be asked to have a catheter placed in a larger vein in your chest or groin (if you do not already have one). This may be left in place for future procedures or removed and placed again prior to additional procedures. You will be counseled what is appropriate for your situation.

During ECP, you are hooked up to a machine and your blood is circulated through tubes into a sealed, sterile chamber to separate the blood components so that your white blood cells can be

collected separately. The procedure requires access to veins in both arms with a needle that is slightly larger than a standard blood draw needle or a central catheter in a larger vein in your neck, chest, or groin. Blood is taken into the machine and sorted by their density and weight with the white blood cells saved in a special place in the machine. The white blood cells are then treated with a light-sensitizing agent called methoxsalen and a special ultraviolet light and then returned to you.

Methoxsalen is a naturally occurring substance, produced by a variety of fruits and vegetables (figs, limes, parsnips, celery) and in larger quantity by the common weed, Queen Anne's lace. It is known to be activated by ultraviolet light.

The cells and plasma are then mixed with an anticoagulant (a product used to keep the blood from clotting) and normal saline and returned to you through a second needle in the opposite arm. The procedure usually takes 2-3 hours. Before the ECP procedure is started, the nurse will also draw blood for laboratory and research tests. You also may be asked to provide a urine or blood sample for pregnancy testing before you begin the procedure.

The actual number and length of the treatment sessions will be decided by the doctor and will depend on how you respond to the treatment and any side effects that you may experience.

When you are finished with the study

If you don't get GVHD, you will have blood samples taken for the last time 3 months after your transplant. If you get acute GVHD but never get ECP, you will have blood samples and a GVHD assessment for the last time approximately 6 months after your transplant. If you receive ECP, you will have an overall assessment, a GVHD assessment, blood samples taken for the last time approximately 6 months after you complete all the ECP procedures.

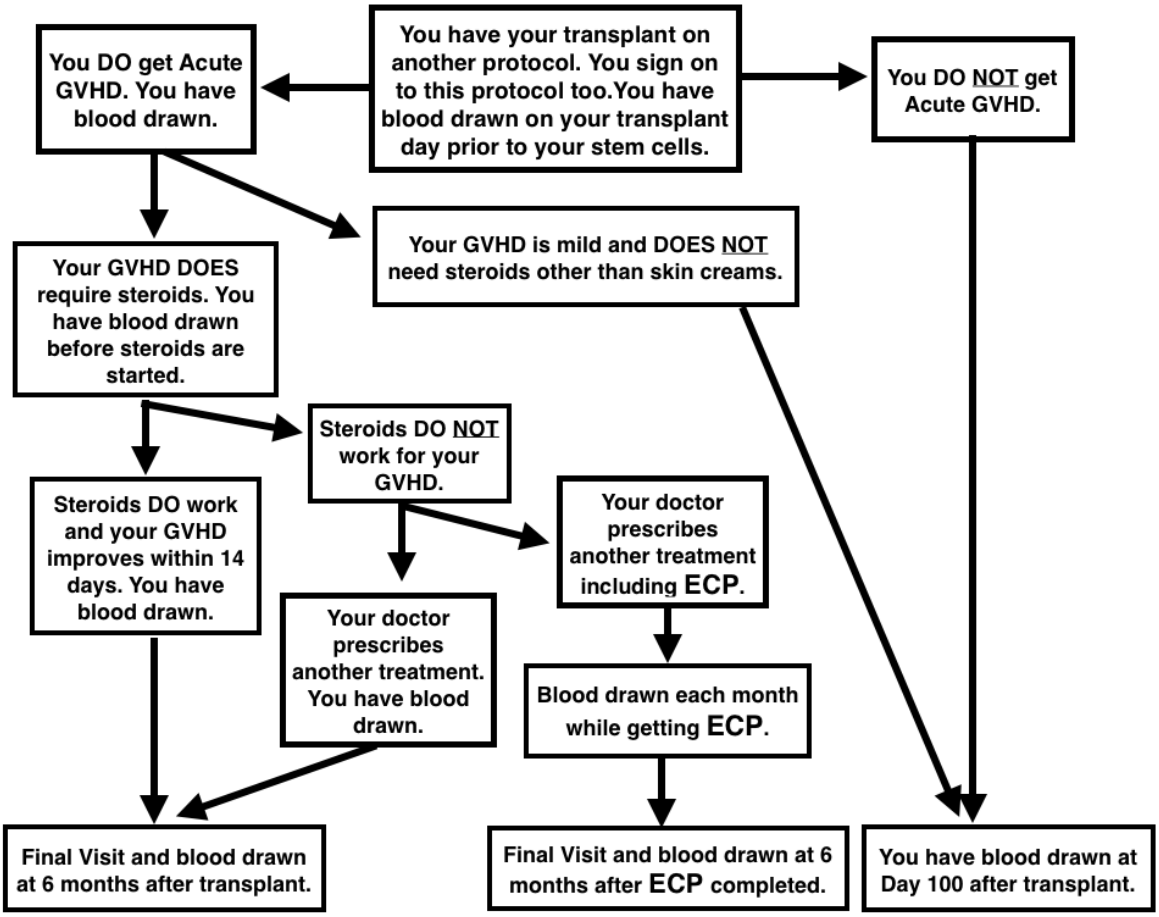
Study Chart

Day	***What you do***
At enrollment. All Patients	• You are already enrolled on an NCI allogeneic transplant protocol • Sign this consent after discussing with your physician • Research bloods (a little over 3 tablespoons)

Day	***What you do***
Day of transplant	• Research bloods (a little over 3 tablespoons)
Day you are diagnosed by your doctor with acute GVHD	• Research bloods (a little over 3 tablespoons)
The day that your doctor decides whether or not your GVHD has responded to corticosteroids.	• Research bloods (a little over 3 tablespoons)
The day of the first ECP if you and your doctor decide it will be part of your treatment for steroid refractory GVHD.	• Have the ECP procedure • Pregnancy test if applicable • Research bloods (a little over 3 tablespoons)
On any other days of ECP treatment	• Have the ECP procedure • Research bloods at first treatment of the week (a little over 3 tablespoons) • Pregnancy test if applicable (every 28 days)
On your Day +100 if you never get acute GVHD or approximately 6	• Have a physical exam by a clinician. • Research bloods (a little over 3 tablespoons)

Day	***What you do***
months after transplant if you get acute GVHD but never get ECP.	
End of ECP treatments and 6 months later.	• Have a physical examination by a clinician. • Research bloods (a little over 3 tablespoons)

Study Schema



Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because Methoxsalen is in a class of agent that is known to cause miscarriages or birth defects. 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 4 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.

If you are a woman that can have children, you will also undergo regular pregnancy testing every 28 days.

Effective forms of birth control include:

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

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options:

- Getting treatment or care for your GVHD without being on this study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the GVHD. It does not treat the GVHD directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

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

Related to Blood Collection

Taking blood from a vein may cause some discomfort, bleeding or bruising where the needle enters the body, and in rare cases, it may result in fainting. There is a small risk of infection. Some people have not felt well when having their blood taken. Some people have felt dizzy while having their blood drawn or later on. Let us know if you would prefer to lie down while you have your blood drawn.

Related to Methoxsalen Exposure

Exposure to this agent has a risk of eye damage. You should wear UVA absorbing, wrap-around sunglasses and cover exposed skin or use sunblock (SPF 15 or higher) for 24 hours after each

treatment, if you are outdoors or exposed to sunlight through a window. The sunglasses will be provided to you if they are necessary.

Related to ECP Procedure

ECP uses standard well-established medical procedures that can be done with minimal risk or discomfort to you. However, there are some risks that you should be aware of prior to participation in this study.

Possible side effects:

Likely side effects:

- Pain or discomfort at the site of insertion of intravenous catheters.
- Bruising or inflammation around the needle site(s)

Less Likely side effects:

- All intravenous catheters carry a small risk of thrombosis of the vein or infection of the skin or blood that rarely could lead to death.
- Nervousness, lightheadedness, decreased blood pressure, fainting, chills, redness of skin, or nausea with or without vomiting.
- The needle site(s) may become infected.
- A reaction to the anticoagulant (a drug that prevents your blood from clotting), which may include tingling around the mouth and face or muscle cramps. If you experience these symptoms, you should notify the staff immediately so that the procedure will be slowed down while your symptoms are treated.
- Blood loss from inability to return red blood cells resulting in a mild anemia (decrease in the number of red blood cells which carries oxygen to all parts of the body), usually without symptoms. May result in the procedure being discontinued and deferral from the ECP procedure and/or whole blood donation for 8 weeks.

Rare side effects:

- The rare possibility of an allergic reaction to material used to sterilize the plastic blood containers. Symptoms may include hives, nasal stuffiness, or shortness of breath, if this happens, the procedure will be discontinued and treatment administered.
- A small number of white blood cells will be removed during the procedure. Your body will replace the white blood cells, however the long-term effect of white blood cell removal is not clear.
- The extremely rare risk of hemolysis (bursting) of red blood cells, which may show up as red urine a few hours after the procedure.
- The remote possibility of accidental infusion of air when cells or fluid are put back into your body. Machines used for this procedure are equipped with alarms and monitors to prevent infusion of air.
- There may be other risks or discomforts associated with this study procedure which are currently unforeseeable.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to understand better our treatments for acute GVHD and to help understand the potential role of ECP in the treatment of patients with acute GVHD.. If you have only blood drawn there is no personal medical benefit from taking part in this study. If you get ECP on this study,it is possible that you will benefit, but we cannot be certain. These potential benefits could include improvement of your GVHD if your doctor decides to add ECP to your treatment. Because there is not much information about the ECP procedure's ability to treat acute GVHD, we do not know if you will benefit from ECP , although the knowledge gained from this study may help others in the future who have acute GVHD.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care related to the procedure will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

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

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
- the investigator of your primary transplant protocol requests that you stop the ECP procedure

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. However, according to FDA guidelines, information collected on you up to that point may still be provided to collaborators or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be 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 decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer or other health problems.

Yes No Initials_____

2. Someone may contact me in the future to ask permission to use my specimens and/or data in new research 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, **David Halverson**, M.D., Building 10, Room **3-3330**, Telephone: 301-312-3607. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

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 NOVEMBER 26, 2014 THROUGH NOVEMBER 25, 2015.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____