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THE FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE, DIVISION OF ONCOLOGY

Consent to Participate in the Study of 2-Chlorodeoxyadenosine (2-CdA) as a Pretransplant Immunosuppressive Agent to Prevent Graft Failure in Patients Transplanted with T Cell-Depleted Marrow

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EMERGENCY PHONE# (24-hours): (206) 667-5001.

Attending Physician:_____ Phone:_____

BACKGROUND AND PURPOSE

Patients with leukemia or lymphoma can sometimes be cured by marrow transplantation even when chemotherapy has not been successful. Results of marrow transplantation are best when the donor and recipient have the same tissue type, but not all patients have such a donor. When the donor and patient have different tissue types, a severe immunological reaction of donor cells against patient tissues often occurs. This reaction called graft-versus-host disease (GVHD) causes inflammation in the skin, liver, stomach and intestines, frequently leading to infections and death. The donor cells that cause GVHD are called T cells. GVHD can be very effectively prevented by removing T cells from the donor marrow, but when this is done, patients often reject the marrow. The purpose of this research study is to determine whether treatment of the patient with an additional immunosuppressive medication before transplantation can prevent rejection when T cells are removed from the donor marrow in order to avoid GVHD. There are no guarantees or promises that T cell depletion will prevent GVHD or that the additional immunosuppression will prevent rejection.

PROCEDURES

Patients usually receive high dose chemotherapy and total body irradiation (TBI) before transplantation in order to kill malignant cells. In this study, you will also receive a new immunosuppressive drug called 2-chlorodeoxyadenosine (2-CdA). The 2-CdA will be given continuously for seven days through the Hickman catheter (you will be given a separate form for placement of the Hickman catheter). On the second and third days after the 2-CdA treatment is finished, you will receive high dose chemotherapy with a medication called cyclophosphamide given through the Hickman catheter over a period of one hour on each day. Two days after the second dose of cyclophosphamide, TBI will be administered, and then the marrow with T cells removed will be infused. Marrow aspirations, blood counts and other laboratory tests will need to be done frequently in order to check the response to treatment. This type of testing is standard procedure for patients being treated with high dose chemotherapy and TBI.

RISKS, STRESS or DISCOMFORT

Cyclophosphamide may cause nausea, vomiting, diarrhea, temporary hair loss, temporary bladder irritation and possibly bleeding from the bladder. Some patients may have prolonged bladder damage and bleeding. Cyclophosphamide will destroy malignant cells and also decreases production of red blood cells, white blood cells and platelets, causing risks of infection or bleeding until the donor marrow begins to produce new blood cells. There is a chance that the donor marrow will fail to produce new blood cells because of rejection or other problems. In this situation, there is a high chance of infections, bleeding and death. Blood samples will be taken daily in order to count the different types of cells and determine the need for platelet and red cell transfusions. Cyclophosphamide causes decreased immunity which increases the risk of infections for several months after the transplant. Cyclophosphamide may also cause heart damage in a small number of patients.

Total body irradiation may cause nausea, vomiting, diarrhea, temporary hair loss and painful swelling of the salivary glands for a few days. TBI will destroy normal marrow cells in addition to the malignant cells, similar to the effects of cyclophosphamide. The TBI will probably result in sterility. Even if sterility does not occur, there is a major risk of genetic damage in any children conceived after transplantation.

2-CdA. When given as a single agent, 2-CdA has caused few, if any, significant side effects. When given together with cyclophosphamide and TBI, however, 2-CdA may cause significant side effects not usually seen in marrow transplant patients. Nerve damage causing severe weakness of the lower body occurred in approximately one-third of patients when high doses of 2-CdA were given together with cyclophosphamide and TBI. The doses to be used initially in the present study are 4-9-fold lower than those used in the previous study. It is not known whether nerve damage will occur with lower doses of 2-CdA. Kidney damage also occurred in approximately 20% of the patients who received 2-CdA together with cyclophosphamide and TBI. Depending on results in the first patients treated in this study, doses of 2-CdA may be increased or decreased in later patients. Doses of 2-CdA will not be increased if severe side effects occur with lower doses.

Removal of T cells from donor marrow. GVHD may occur if T cells are not effectively removed from donor marrow. In addition, removal of T cells will increase the chance of rejection unless the 2-CdA treatment is effective.. GVHD can be treated with immunosuppressive medications after transplantation. If rejection occurs, a second marrow transplant may be necessary. In patients with chronic myelogenous leukemia, removal of T cells from the donor marrow may increase the risk of relapse after transplantation.

ADDITIONAL RISKS

1) Infections and pneumonia are common during the first few months after marrow transplantation because of abnormal immunity.
2) Leukemia and lymphoma can relapse even if the transplant is successful.
3) The chemotherapy and radiation can cause damage to the heart, kidneys, lungs, brain, liver or other body parts. The danger is increased in patients who have been heavily treated previously with chemotherapy or radiation.
4) Cataracts may develop resulting in partial loss of vision which can be restored by surgery.
5) Blood samples and marrow aspirates must be obtained in order to determine the result of treatment. Discomfort and bruising can occur at the site of needle insertion.

BENEFITS

This treatment is being offered to between 10 and 20 patients who have a high chance of developing GVHD because they have different tissue types from their donors. Successful removal of the T cells from donor marrow can prevent GVHD much more effectively than the usual approach of using immunosuppressive medications after transplantation. If 2-CdA has an immunosuppressive effect before transplantation, then graft rejection may be prevented.

ALTERNATIVES

Transplantation can be done without removing T cells from the donor marrow but there is a 90% chance of developing GVHD which could be severe or life threatening in 65% of patients. In addition, treatments other than marrow transplantation can be considered.

OTHER INFORMATION

In agreeing to participate in a research study, you are choosing to receive therapy that is not yet available outside of research centers. This therapy is based on laboratory studies and exchange of information with other research centers. Although we expect that removal of T cells from donor marrow will prevent GVHD and that treatment with 2-CdA will prevent rejection, we cannot be sure of success, and minor or major (possibly fatal) complications could occur.

Your participation in this study is voluntary, and you may withdraw your consent at any time, for any reason, without notice and without prejudice. However, withdrawal from this study after administration of chemotherapy and TBI but before marrow transplantation would result in death due to marrow failure. You will be advised regarding any new information resulting from this study or from other studies which could affect your willingness to participate in this study.

The Division of Cancer Treatment, National Cancer Institute will provide you with the investigational agent 2-CdA free of charge for this study. Should this agent become commercially available or approved for prevention of rejection during the course of this study, you may be asked to purchase subsequent doses of the medicine. It is understood that you and/or your insurance company will pay for all medical expenses relating to or arising from other procedures.

Financial compensation is not available in the event of physical injury, adverse effects or death resulting from participation in this research study. Medical care will be authorized by the marrow transplant attending physicians if necessary. You and/or your insurance company or both will be responsible for all costs resulting from the medical care.

In order to evaluate the results of this study, your medical records will be available to physicians and researchers associated with this study. Authorized personnel at the Food and Drug Administration and the National Cancer Institute will also have access to this information. A qualified representative of the drug manufacturer may inspect patient or study records. All precautions will be taken to maintain confidentiality of medical records. Your personal identity will not be revealed in any publication of results. Study records will be maintained indefinitely for the purpose of analysis and follow-up.

If you have any questions about the research, please contact the marrow transplant physician in charge of your care. If you have questions about your rights as a research participant, please contact Karen Hansen in the Institutional Review Office of the Fred Hutchinson Cancer Research Center at (206) 667-4867.

Investigator's Statement

I have provided an explanation of the research study described above. The subject was given an opportunity to discuss the procedures and possible alternatives and to ask questions. A signed copy of this consent form has been given to the subject.

Investigator's Signature /Date

Subject's Statement

I understand that I have a life-threatening disease and that treatment is provided by this research center. I have chosen to undergo this treatment in spite of the uncertain outcome and possible harmful effects because the possible benefits outweigh the danger.

I agree to participate in this study according to conditions outlined in the Basic Oncology Consent Form which I have read and signed. I have had an opportunity to ask questions about risks, benefits and alternative treatment. The marrow transplant physicians have answered all questions to my satisfaction. I understand that future questions about the research will be answered by one of the investigators listed above or by another member of the marrow transplant team. I also understand that any questions about my rights as a research subject will be answered by Karen Hansen or by another qualified individual. No promises or guarantees have been made regarding the anticipated outcome of any tests or procedures. I am aware that I will not be charged for the 2-CdA, but that other costs incurred during the therapy and costs related to adverse effects must be paid by me and/or my insurance company. I give permission for my medical records to be available to physicians and personnel for this study at the Fred Hutchinson Cancer Research Center, the University of Washington, the National Cancer Institute and the Food and Drug Administration. I acknowledge that I will receive a copy of this consent form.

Patient /Date

Witness's Signature /Date

Parent/legal guardian /Date
(for patients <18 years old)

Other parent /Date
legal guardian (if reasonably available)

#126.8A - 05/07/92
Copies to: Patient
Medical Records
Research File

IRB APPROVAL
JUN 0 1 1992