Kathryn Hamilton

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

ORIGINAL CHART COPY

Consent To Participate In Autologous Transplantation
For Patients With High Risk Stage II - III or Metastatic Breast Cancer
Using A Conditioning Regimen Of Busulfan And Cyclophosphamide and anti-TNFα Therapy

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BACKGROUND AND PURPOSE

Patients with early breast cancer who have 10 or more positive lymph nodes are at very high risk of developing metastatic disease. The remissions obtained by treatment with chemotherapy in metastatic east cancer are almost always temporary. They usually last for months rather than years. vestigators have not proven, but hypothesize, that high dose combination chemotherapy will reduce the number of tumor cells in the patient over that achieved with "standard doses." This intensive combination therapy destroys the normal bone marrow so no new blood cells are produced. The patient's stored marrow is given to repopulate the marrow spaces to produce red cells, white cells and platelets.

This new treatment program has been designed with the hope that it will prove to be much more effective than standard treatments now available. We hope that your life will be lengthened by this treatment. There is, however, a chance that your life will be shortened because of the treatment. Because the treatment is designed to eliminate as many cancer cells as possible, the treatment will have many side effects which will be unpleasant and can result in your death.

This new treatment program has been designed to determine the maximum tolerated doses of the chemotherapy drugs busulfan and cyclophosphamide when used in combination with drugs which inhibit tumor necrosis factor (Anti-TNF therapy). Tumor necrosis refers to cell damage or death. Anti-TNF therapy utilizes pentoxifylline, (PTX) and ciprofloxacin, (CIPRO), drugs which may prevent cell death in healthy cells.

PTX has been safely prescribed for more than 10 years to treat leg cramps due to poor circulation with little or no side effects. Recent studies suggest that PTX prevents kidney, lung and liver damage in patients receiving transplants. When PTX was given along with an antibiotic called ciprofloxacin (CIPRO) to patients undergoing bone marrow transplant, no kidney, liver or lung damage was seen in 10 patients. We plan to see if the combination of these drugs can prevent damage to the kidney, liver lungs in patients receiving bone marrow transplant. Initial information in patients undergoing bone

marrow transplants suggests the earlier PTX/CIPRO is started the better are the chances for preventing organ damage.

During the time of bone marrow transplant, you have an increased risk for developing serious infection because of low white blood cell counts. Therefore, this treatment regimen will also include the drug recombinant human granulocyte macrophage-colony stimulating factor or rhGM-CSF. Results from the use of rhGM-CSF in human trials (over 1000 cases) suggest the rhGM-CSF is well tolerated and may shorten engraftment time by stimulating white blood cell growth.

Sometimes it is not possible to harvest sufficient bone marrow because of previous treatment or the nature of your disease. In such situations, the peripheral stem cells, a cell which is the source of all the blood cells in your body, may be obtained from your peripheral blood. In this case, your peripheral blood can be used to perform a successful transplant.

There are no guarantees or promises the procedure will be successful.

PROCEDURES

Marrow Harvest
After your bone marrow is collected, an untreated portion will be frozen.

Separation of Hematopoietic Stem Cells
If your marrow is treated to select stem cells, it will be incubated with the monoclonal antibody 12.8, which comes from mice and reacts with the stem cells. The marrow is then passed over a column containing the protein avidin, which will bind these antibody-labeled stem cells. The other marrow cells including the tumor cells pass through the column and are eliminated. The stem cells which are bound to the column are recovered and stored until your transplant. When the stored 12.8-positive marrow cells are required for transplant, they are thawed and infused.

Conditioning Regimen/Dose Escalation
You will then be given high dose of busulfan and cyclophosphamide prior to your transplant. The dosages you will be given will be administered to four patients in all. Only after a group of four patients shows no severe reactions to the chemotherapy treatment will the dosage be raised to the next dosage level. Busulfan will be given orally for four consecutive days, then cyclophosphamide will be given on three or four days depending on the dose levels.

Anti-TNF Therapy
The Anti-TNF therapy will be administered orally for 31 days starting nine days before the transplant. In the outpatient department while you are pre-transplant you will receive oral PTX and CIPRO. The PTX and CIPRO will be given for 21 days after your transplant. Either drugs may be given through your Hickman catheter if your physician thinks you may not be absorbing the medicine when you take it by mouth. Routine blood tests will be performed daily. Some of these tests are routine medical care and some are part of the study . Study samples of blood (2-4 tablespoons) will be taken once a week to measure the levels of the drugs in your blood and your body's own response to them. In addition, samples (2-4 tablespoons) will be drawn daily to make sure you don't have an infection.

ransplant
After the chemotherapy, the previously stored bone marrow which has been treated with antibody will be infused through the Hickman catheter, similar to a blood transfusion. In the event the number of cells harvested is insufficient or if the marrow sample being treated is difficult to process, your stem cells may not be able to be isolated with this procedure. In this case, you will receive the unprocessed marrow. In some cases the amount of marrow harvested is less than the amount normally harvested. In this situation you will receive both marrow and peripheral blood as your transplant.Therefore, you will receive as your transplant either your unprocessed marrow, processed marrow treated to remove breast cancer cells, both marrow (treated or untreated) and peripheral blood, or, alternately, your untreated peripheral blood.

GM-CSF
The rhGM-CSF will given intravenously (by vein) for 22 days starting on the day of transplant.

You will then remain in the hospital for approximately three weeks to allow complete bone marrow recovery.

RISKS, STRESS, OR DISCOMFORT

usulfan. The immediate effects of busulfan may include vomiting, diarrhea, and seizures. Medication l be given to minimize or prevent these side effects. The late effects which are usually temporary may include hair loss and hyperpigmentation (changes in skin color). Some patients may develop a rash. Some patients may develop mucositis (mouth sores). Some patients may develop abnormal function of the liver or lung.

Cyclophosphamide may cause nausea, vomiting, diarrhea, temporary bladder irritation, and, at times, bleeding from the bladder, and temporary hair loss. A small portion of patients may have prolonged bladder damage and bleeding. Cyclophosphamide also suppresses production of red blood cells, white blood cells, and platelets, causing a risk of infection and/or hemorrhage until the graft begins to function. Cyclophosphamide causes decreased immunity which may also lead to increased infections for several months following transplant. Heart damage may occur in a small number of patients. Cyclophosphamide may result in sterility. Even if sterility does not occur, there is a major risk of genetic damage to any future offspring. There may be some as yet unknown consequences to the patients health resulting from the administration of cyclophosphamide.

Pentoxifylline, an Anti-TNF agent, has been safely used in the oral dosage form for other treatments with few side effects in the United States for over 7 years at the same amount that will be used in this study. The most frequent reactions have been a 5-10% increase in the incidence of nausea and vomiting. Also theoretical side effects include abnormal heart rhythms or seizures and coma but none of these have been observed in over 50 patients treated with the dose of PTX to be used for this study. Intravenous pentoxifylline is an investigational drug. Therefore, the risks of this form of the drug are not completely know at this time. Although we do not anticipate any serious side effects from intravenous pentoxifylline, the rare side effects reported are the same as those reported for the oral
n of the drug.

Ciprofloxacin, the other Anti-TNF agent, is a widely used antibiotic with no major side effects. The most common side effect includes stomach upset or headache.

RhGM-CSF appears to cause transient muscle and bone pains during the time of treatment in 25% of patients. Occasional headaches, facial flushing, hypotension, partial loss of consciousness, rapid heart rate, difficult breathing, episodes of nausea and low grade fever have also been observed in patients receiving rhGM-CSF.

Marrow or Peripheral Blood Stem Cell Transplant. There is a risk of increased infections or even death prior to engraftment or in the event your marrow does not function adequately after engraftment. Blood counts will be done frequently to monitor the return of marrow function. Platelet and red cell transfusions will be given as necessary to maintain adequate levels. There is a risk that the graft may not grow. Such a graft failure might be fatal unless a second transplant could be carried out.

ADDITIONAL RISKS

a) Blood samples must be drawn at frequent intervals to follow the treatment and to monitor the return of marrow function. Granulocyte, platelet and red cell transfusions will be given as necessary to maintain adequate levels. There is small discomfort at the site of needle insertion and bruising may occur.

b) Marrow incubated with antibodies or stored without incubation can be damaged by the processing, freezing and thawing with resultant poor or no engraftment.

c) If the monoclonal antibody-treated marrow does not grow in 2-3 weeks the untreated marrow will be infused.

d) In addition to the above risks, there is the risk of organ failure, including heart, kidney, lung, brain, liver or other body parts. This risk is increased in patients who have already had significant chemotherapy and/or radiation therapy.

e) The malignancy may recur even if the transplant is successful.

f) Marrow is stored in dimethyl sulfoxide (DMSO). This compound has an unpleasant odor which is given off through the lungs (and breath) for several days.

BENEFITS

Standard chemotherapy-induced remissions are almost always temporary. This new treatment has the potential of prolonging life for patients with metastatic breast cancer.

ALTERNATIVES

Alternate treatment programs might involve other forms of chemotherapy, without bone marrow storage or intensive consolidation treatment as well as other investigational treatments and investigational chemotherapeutic drugs. These alternate programs may be less risky, but may also be less effective. This is a new approach so information about its usefulness compared to standard treatment is not available.

OTHER INFORMATION

This treatment is being undertaken for the above described fatal disease. In agreeing to participate in a research program you are choosing to receive therapy that is not yet available outside of research institutions. This therapy is based on laboratory studies and/or exchange of information with other research centers. Although we expect it to benefit your condition, there is no assurance that it will do so, and it is possible that you may have unfavorable complications which might also be fatal.

Your decision to participate in this study is voluntary. You can decide whether or not to participate in this study. You may decide not to participate in this study at any time, for any reason, without notice. However, early withdrawal from treatment during the conditioning regimen without subsequent marrow transplantation could be fatal.

It is understood that all medical expenses relating to, or arising from, these procedures will be paid by you and/or your insurance company.

There is no financial compensation for participation in this program.

Medical care will be authorized by the attending physician. You and/or your insurance company will be responsible for all costs arising from the medical care. In order to evaluate the results of this study, your medical records will need to be available to other physicians and researchers associated with the research project. Cell Therapeutics Incorporated (the company supplying the drug, IV Pentoxifylline), the Food and Drug Administration, and National Cancer Institute will also have access to this information. All precautions to maintain confidentiality of medical records will be taken. Your personal identity will not be revealed in any publication or results. Study records will be maintained indefinitely for the purpose of analysis and follow-up.

If you have questions about the research or related injury, please contact your attending physician.

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

Investigator's Statement

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

Investigator's Signature /Date

Patient

534-40-3433 RE1231 01/26/93
HAMILTON, KATHRYN L F
CD BUCKNER 58
INS-998 IP 34000

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 uncertainties of the outcome and the possible harmful effects because the possible benefits outweigh the risks.

I agree to this study and to the conditions outlined in the Basic Oncology Consent Form which I have read and signed. I have had an opportunity to ask questions of the physicians, including questions about risks, benefits and alternatives to treatment. These questions have been answered to my satisfaction. I understand future questions I may have about the research will be answered by one of the investigators listed above and that any questions I have about my rights as a research subject will be answered by the person identified above. No promises or guarantees have been made regarding the anticipated outcome of any tests or procedures. I am aware that I and/or my insurance carrier is responsible for the costs incurred in the therapy provided, including adverse effects. I give permission for my medical records to be available to physicians and personnel for this study at the University of Washington, Fred Hutchinson Cancer Research Center, Food and Drug Administration, as well as Cell Therapeutics Incorporated (the company supplying the drug, IV Pentoxifylline). I acknowledge that I will receive a signed copy of this consent form.

X see other side for Fred Appelbaum signature
Patient Investigator /Date

X Kate G Anderson mem 1/6/93
Witness /Date

Parent/legal guardian /Date
[for patients <18 years old]

Other parent/legal guardian /Date
[if reasonably available]

#681.1 - 09/02/92
Copies to: Patient, Medical Records, Research file

IRB APPROVAL
SEP 23 1992