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THE FRED HUTCHINSON CANCER RESEARCH CENTER
AND THE UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE, DIVISION OF ONCOLOGY
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1. Autologous [redacted] Transplantation for Patients with High Risk Stage II - III and Metastatic Breast Cancer Using a Conditioning Regimen of Busulfan and Cyclophosphamide and Anti-TNF α Therapy

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2. Introduction

This protocol replaces protocol #329.2 which currently uses busulfan (BU) + cyclophosphamide (CY) in a dose escalation, toxicity trial plus CD34 selected autologous marrow for the treatment of patients with advanced breast cancer. Changes are proposed in order to have an "all inclusive" treatment protocol for patients with breast cancer receiving BU/CY.

The proposed changes are to alter the BU + CY dose escalation schema so that the next higher dose levels will increase the doses of BU rather than increasing the CY as in the old schema. In addition, patients will all receive anti-TNF therapy similar to protocol #554 (recently reviewed by the CIC). Preliminary results of autologous marrow transplantation for breast cancer using BU and CY indicate promising anti-cancer activity with 4/8 evaluable patients who had stage IV disease achieving a complete response. This protocol is designed to determine the maximum tolerated doses of the Bu + Cy regimen when used with drugs that inhibit tumor necrosis factor (TNF-α). The sources of marrow have changed from only CD34 selected marrow to CD34 selected marrow, untreated marrow or G-CSF stimulated peripheral blood mononuclear cells (protocol #656). Patients who do not have adequate numbers of marrow cells harvested for treatment or who cannot have marrow stored can thus be treated on this dose escalation study.

Background

A. Conditioning Regimen.

Combination chemotherapy has been employed as the major means of treatment for patients with both recurrent or disseminated estrogen receptor (ER) negative breast carcinoma, as well as estrogen receptor positive carcinoma which has become refractory to hormonal manipulation. The response rate of ER-negative metastatic breast carcinoma (MBC) to chemotherapy regimens incorporating Adriamycin is 70 to 80% and a complete response occurs in 15 to 20% of such patients (1,2). The overall response rate of ER-positive MBC is on the order of 50 to 60% (3). However, the survival of these patients remains poor and essentially all patients eventually die of MBC. The respective median survival from initial recurrence is 12 to 18 months for ER-negative and about 30 months for ER-positive disease, with expected 5 year survivals of <5% and 20%, respectively. Based on the experience of high-dose chemoradiotherapy and bone

D. Dose Selection and Patient Allocation

The goal will be to determine the dose level that approximates the regimen related toxicity (RRT) of 20%. Patients will be allocated to these levels based on a modification of Hsi's method (32). The first group of four patients will be treated at dose level 2 (BU) 15 (Cy) 150 mg/kg. RRT will be determined according to the criteria for toxicity outlined in Appendix A. The development of Grade 3 or 4 toxicity of any of the major organ systems outlined in Appendix A that occurs within the first 28 days after transplant will be defined as RRT. These grades will be determined by the Principle Investigator and reported to the Registration Office at (667-4728) and the Clinical Coordinator (667-4324). Further dose escalation will be determined in the following manner:

1. At any level if there is reasonable evidence that the RRT level exceeds 20%, then the dose will be dropped and will not return to the higher level. Specifically, we will not treat additional patients at or above a dose level where the upper (i.e., interval from one to some lower limit) 90% one-sided confidence interval for the true probability of RRT exceeds 0.20. That is, the dose is dropped in the # of RRT/subjects is 2/2, 3/4, 3/5, 3/6, 4/7, 4/8, 4/9 or 5/10.
2. Patients transplanted for high risk Stage II-III disease will only be entered at the next lower level of Bu/Cy. When 4 patients with metastatic disease have been entered at the next higher level without toxicity, Stage II-III patients may then be entered at that dose level.
3. If no patients have been treated at a dose level and
   a. Dose escalation is allowed, then the dose will be escalated if the # RRTs/# of subjects is 0/4. If 2/4 are observed, the study will drop to the next lowest dose. If the dose is at the lowest dose, then up to a total of ten subjects will be observed as long as no more than two RRTs are observed. If 2/4 are observed, this will be the MTD. If three events are observed at the lowest dose, the study will be stopped at this time.
   b. If dose escalation is not allowed, the dose will drop to a lower level (if there is one). Otherwise, the study will stop if any of the numbers in 1) above are attained. Otherwise, data will be collected until ten subjects are observed at the level or two RRTs are observed. If 0/10, 1/10 or 2/10 are observed, this will be the MTD. If two RRTs occur before observing ten subjects, then the study will drop down one dose.
4. If the protocol returns up to a previously studied level (which then must have two RRTs with fewer than ten subjects studied), subjects will be studied until either a) 2/10 is observed and this will be considered the MTD, or b) a third event is observed in which case the dose will be reduced and this dose not returned to, or c) rule one requires reducing the dose.
5. If the protocol returns down to a previously studied dose, then up to ten subjects will be studied until either a) rule one requires reducing the dose, or b) 0/10, 1/10 or 2/10 are observed in which case this dose is the MTD, or c) a third event is observed in which case the dose is to be reduced and not returned to.
6. If the protocol is on the lowest possible dose and cannot escalate and if three RRTs are observed, the study will be stopped and the possibility of getting more data at the low dose will be evaluated.

This study will terminate when the MTD is defined, or level 7 is reached without toxicity.

E. Anti-TNFα Therapy

All patients will receive double therapy including:

Pentoxifylline 400 mg orally 5 times/day - days -9 - +21. (Administration times 07:00, 11:00, 15:00, 19:00, 23:00).

and

Ciprofloxacin 500 mg po BID days -9 until day 30 or hospital discharge. (Intravenous ciprofloxacin will be given 400 mg BID for patients unable to take oral medication).

F. Marrow or Peripheral Blood Stem Cell Infusion

Patients who receive marrow and peripheral blood stem cells shall have the peripheral blood stem cells infused first, if more than one day is required to give back the stored cell products. Infusion is performed 36-48 hours following chemotherapy. Single-bag aliquots containing approximately 120 ml volume of cryopreserved cells are thawed quickly in a 37oC waterbath and infused rapidly in 5-10 min/bag in an adult depending on the estimate of total blood volume/infused volume. Thawed cells are infused intravenously without a filter. Cells can be infused over a 2 hour period during the day; if marrow volume is large or if side effects occur, infusions can be continued the following day. Refer to Standard Practice Policy Manual for Administration Guidelines.

In addition, obtain the following:

1. Toxicity:
   a. Stored cells results in an unpleasant odor of DMSO (garlic-like) excreted by the lungs and should be explained to the patient in advance. DMSO toxicity has not been detected following stored marrow infusions in man.
   b. Volume overload. This can be avoided by centrifugation and removal of plasma, or by phlebotomy prior to infusion. This is of particular importance in small recipients who have previously received granulocyte or platelet transfusions.
   c. Pulmonary emboli. Usually not a problem, but occur due to fat and marrow emboli. The latter problem, when it occurs, is transient although temporary administration of O_2 may be necessary.
   d. Allergic reactions. Chills, fever, and hives occasionally occur, presumably due to antigenic plasma components. These reactions are never severe and respond to parenteral Benadryl.
   e. A modest and transient rise in blood pressure commonly occurs. Increased intravascular volume or a specific effect of DMSO could be responsible for this effect. Specific treatment is not usually required but if necessary the first approach should be blood or plasma removal.

2. Evaluation of Engraftment

   Engrafument will be assessed by conventional means (increase in WBC counts, platelets, and red cells; examination of marrow aspirates).

G. Growth factors - All patients will receive rhGM-CSF 250 $\mu g/m^2$ from day 0-21.