Sequential High Dose Chemotherapy and Stem Cell Rescue Versus Conventional Dose Chemotherapy for Stage III Breast Cancer.

Nina Shah

A. Study Purpose and Rationale

The purpose of this study is to determine if there is any benefit in disease-free survival (DFS) at 5 years of Stage III breast cancer patients who are treated with 2 sequential regimens of high-dose chemotherapy and peripheral blood stem cell (PBSC) transplant when compared with patients receiving conventional dose chemotherapy.

Breast cancer affects 1in 8 women in the United States. 10-25% of these patients are Stage III (also known as "locally advanced) at diagnosis. This stage is particularly challenging because of the diversity of tumors (large, inflammatory) that it includes. Though adjuvant chemotherapy regimens have improved DFS in many Stage III patients, there is still a significant degree of recurrence. No more than 50% of patients achieve long-term disease-free status despite multi-modal treatment with surgery, chemotherapy (neo adjuvant or adjuvant), and radiation therapy (1).

The concept of high dose chemotherapy (HDC) has been present for over 20 years, but there is still debate over the most appropriate target population and regimen schema. The theory behind HDC is that a more intense dose (3-10 times the conventional dose) will have a greater chance of killing microscopic residual disease which may not be touched by conventional dose chemotherapy (CDC). Because these intense doses result in myeloablation, patients are then infused with their own stem cells that will have been collected in advance of the HDC. These progenitor cells are identifiable by the presence of the CD34 antibody. The patient's blood is run through an apheresis machine, the CD34+ cells are specifically collected on a special column and the cells are stored for future use. Growth factors and other supportive measures are also employed.

Several early studies provided encouraging data regarding this theory, with improvement in DFS in stage IV patients (2). This spawned a great deal of interest in this new strategy and investigations began to extend beyond stage IV disease.

Thus, the protocol has also been applied to stage II high risk and stage III disease. Initial non-randomized trials suggested that HDC was beneficial in both groups (2). Randomized trials done thereafter yielded equivocal results (2) and suggested the need for large, multicenter studies. Recent data from one randomized, multicenter trials have shown a significant effect for tumors with 10 or greater positive lymph nodes. However, this study did not specifically address stage III patients (3).

The most widely used sequence for HDC in Stage III disease is a course of CDC (this can be neoadjuvant or adjuvant) with stem cell collection followed by one cycle of HDC and stem cell reinfusion. There are several choices for CDC, such as doxorubicin/ cyclophosphamide/ paclitaxel or fluorouracil/ epirubcin / cyclophosphamide. A regimen will generally include one of the anthracyclines, as they appear to have excellent activity against breast cancers (12). The HDC is most commonly comprised of cyclophosphamide, thiotepa and carboplatin (CTCb). This HDC has, in an appropriate support setting, generally been well-tolerated with no significant acute mortality or long term sequelae (3, 4, 5). There is an increase in peri-HDC morbidity which is most often addressed by inpatient supportive care in a stem cell transplant unit.

Another, less widely studied HDC sequence consists of a tandem transplant regimen. This consists of two cycles of HDC, each with different agents, given in sequence, with autologous stem cell transplant after each cycle. This protocol has been employed by oncologists here at CPMC with a triple sequence of high dose paclitaxel, then high dose melphalan and finally, high dose CTCb, each with a

subsequent stem cell transplant. This was applied to metastatic breast cancer patients with good responses (6, 7). Similar results have been reported by other authors (8,9). The tandem transplant regimen has also been studied in Stage II/III patients with promising results and little toxicity (10). Therefore oncologists here at CPMC feel that this regimen should be studied in a randomized, controlled fashion to determine the actual (if any) benefit.

B. Study Design and Statistical Analysis

Women 18-60 with histologically confirmed stage III breast caner, otherwise healthy and with no evidence of metastatic disease will be eligible for this prospective, multi-center, randomized trial. Subjects will be approached by their primary oncologists. All patients will undergo induction CDC with fluorouracil, doxorubicin and cyclophosphamide (FAC) for at least 4 cycles. Subjects whose disease has responded to chemotherapy will be eligible for randomization to either a control arm (completion of CDC) or a treatment arm (HDC with stem cell support x 2). Patients will then be followed for up to 5 years.

A total of 920 subjects will be enrolled in the trial. This grants a power of 80% with an alpha of .05. This is based on a presumed effect size of the treatment of at least 10 % from the existing 5-year DFS of 50%, plus a 10% drop-out or ineligibility rate. Based on prior experience at CPMC, approximately 25 subjects are expected per institution per year. Differences in DFS will be assessed by Kaplan-Meier curves and the log-rank test. Cross-over will be permitted.

C. Study Procedure

a. Treatment Plan

All patients will undergo induction chemotherapy with FAC x 4 cycles. After the 4th cycle patients will be evaluated for response to the chemotherapy. Patients without a CR or PR to this initial chemotherapy will not be eligible to proceed in the study. At this point, all the remaining subjects will be stratified according to inflammatory breast cancer versus non inflammatory and Her-2/neu negative versus positive. The subjects will then be randomized to either the control or treatment arm.

b. Control Arm

Patients will complete their induction chemotherapy with another 2 cycles of FAC. After completion patients will again be evaluated for any areas of original disease. Radiation therapy and, if indicated, Tamoxifen will be suggested accordingly.

c. Treatment Arm

After randomization, the treatment arm patients will be administered G-CSF for 10 days. Peripheral CD34+ progenitor cells will then be collected via a commercially available aphaeresis unit. At least 1.9 x 10^6 CD34+ cells /kg must be collected for the patient to proceed. Patients will then be admitted to a stem cell transplant unit at one of the participating centers. An indwelling catheter will be placed upon admission. Thereafter, the first cycle of high dose chemotherapy will be administered: mitoxantrone (30 mg/ m2) on Day -4 (with Day 0 being the day of stem cell re-infusion) and melphalan 90 mg/m2 on Day -1 and -1 (for a total of 180mg/m2). Stem cells will be reinfused on Day 0, with 1.0 x 10^6 CD34+ cells/kg.

After transplant, patients will be given supportive care until marrow recovery. This may include, but is not limited to, growth factor administration, antibiotics and transfusions as necessary. The patients will be discharged home after recovery.

d. Eligibility for CTCb

- Afebrile off growth factors and antibiotics
- No life-threatening toxicity from prior therapy which would place the patient at undue risk
- Absolute neutrophil count > 1000/μl

- Creatinine Clearance > 60 ml/min
- Bilirubin < 1.5 x normal
- SGOT < 2.5 x normal

Patients will be eligible for the second cycle of HDC no sooner than 21 days after the administration of melphalan. If eligible, the patient will be re-admitted to the appropriate unit for further treatment. A new indwelling catheter will be placed. The second course of HDC will take place over 4 days. On Day -6 to Day -3 (with day 0 being the day of stem cell reinfusion) the patient will receive tiotepa at 125 mg/m2/d and carboplatin at 200 mg/m2/d. During these 4 days cyclophosphamide and mesna will be infused continuously for a total of 6000 mg/m2 and 7500 mg/m2 respectively. On Day 0 the patient will receive her second transfusion of autologous cells. Thereafter, she will be given supportive care until marrow recovery. This may include, but is not limited to, growth factor administration, antibiotics and transfusions as necessary. The patient will be discharged home after recovery. Radiation therapy and Tamoxifen, if indicated will be suggested as out-patients.

Patients in both arms will be followed closely as out-patients. They may choose to receive their follow-up care with physicians not affiliated with the study institution provided that there is established open communication between the physicians at both locations. Within the first 100 days the patient and her physician (if he or she is not a part of the study institution) will be contacted twice in order to follow-up on any toxicities after therapy. Thereafter, patients will be evaluated every 4 months with either primary contact at the study institution or communication between the institution and the patient plus her outside physician. Patients and their primary physicians will be educated and encouraged regarding report of any significant event to the study institution. Total follow-up is estimated at 5 years.

Treatment arm patients will be subject to more aggressive management and therefore, more procedures, such as blood draws and chest radiographs. In addition, the total in-patient hospital time is estimated at 40 days, 20 days for each admission. After treatment is complete, there will be little difference in the degree of follow-up between the control and treatment arms. However, the follow-up of every 4 months may be more than would be expected if not on study (though this is quite variable across patients).

D. Study Drugs

All drugs will be given intravenously except G-CSF which is given subcutaneously.

a. Dosing

- Fluorouracil: 500 mg/m2
- Doxorubicin: 50 mg/m2
- Cyclophosphamide (CDC): 500 mg/m2
- Melphalan: total 180 mg /m2, not FDA approved for breast cancer
- Mitoxantrone: 30 mg/ m2, not FDA approved for breast cancer
- Cyclophosphamide (HDC): 6000 mg/m2, not FDA approved for breast cancer at this dose
- Thiotepa: 500 mg/m2, not FDA approved for breast cancer at this dose
- Carboplatin: 800 mg/m2, not FDA approved for breast cancer
- Mesna (HDC): 1875 mg/m2
- G-CSF: 300 mcg SC

b. Potential toxicities of mitoxantrone/melphalan

Myelosuppression, mucositis, abnormal liver chemistries, cardiac toxicity, hypersensitivity reaction, renal dyscfunction, pulmonary toxicity, secondary cancers.

c. Potential toxicities of CTCb

Myelosuppression, hepatic dysfunction via veno-occlusive disease (this is rare but has a 50% mortality), nausea, vomiting, mucositis, dysphagia, diarrhea, reversible CHF, reversible pulmonary toxicity, cystitis, nephrotoxicity, SIADH, rash, alopecia, possible anaphylaxis, sterility.

The vast majority of these toxicities can be managed with supportive care or discontinuation of the offending agent.

The exact chemotherapeutic agents in this study will be, first, high dose mitoxantrone and melphalan followed by CTCb (with stem cell infusion after each of the 2 cycles). There are several reasons behind this choice. First, this is essentially the regimen used in the aforementioned studies with tandem transplants and breast cancer. In addition, the toxicities of high dose mitoxantrone and melphalan have been studied previously at this institution (unpublished data). These drugs were relatively well tolerated here when employed in a similar tandem regimen for lymphoma. Other studies have also shown the safety of mitoxantrone and melphalan at 50 and 200 mg/ m2 respectively (10, 11) as well as the safety of mitoxantrone plus melphalan at 60 and 180 mg/m2. These doses are higher than or equal to those that will be used in the current study. Though the previous tandem study at CPMC used paclitaxel, this study will include mitoxantrone in lieu. This will limit the previously observed peripheral neuropathy seen with high-dose paclitaxel. It will also allow for a high dose anthracycline (mitoxantrone). As previously mentioned, anthracyclines are known to be active against breast cancer cells. In addition, mitoxantrone is known to have less cardiac toxicity when compared with doxorubicin (12). This will allow the opportunity to use the high dose anthracycline in a patient who has likely already been exposed to doxorubicin without the same risk of cardiotoxicity to be expected from high-dose doxorubicin.

E. Medical Device

None

F. Study Questionnaire

None

G. Study Subjects

a. Inclusion criterial

- Female, age 18-60
- Histologically confirmed breast cancer
- Stage III
- Ineligible for any other high priority study
- CR or PR to 4-6 courses of a doxorubicin-based chemotherapy
- Non pregnant, non lactating
- Clinical parameters:
  - LVEF $\geq$45%
  - ECOG performance status = 0-1
  - Bilirubin < 2 x normal
  - Creatinine < 1.5 x normal
  - HIV negative
  - Brain CT or MRI negative for metastases
  - CT of chest, abdomen and pelvis negative for metastases
  - Bone scan negative for metastases
- Signed informed consent

b. Exclusion Criteria

- Metastatic disease
- Pregnant

- Lactating
- Chemotherapy-resistant disease

H. Recruitment of Subjects

Subjects will be approached and referred by their primary oncologist after confirmation of breast cancer by histology. The oncologists in the local area of the study institution will have been informed about the study via several mailings and possibly a phone call.

I. Confidentiality of Study Data

Study data will be coded and stored in a secure location in accordance with IRB regulations.

J. Potential Conflict of Interest

None.

K. Location of the Study

The study will be conducted through the department of medical oncology at CPMC as well as other medical oncology departments at large institutions (whose IRB's will be approached as well). The out-patient, inductive chemotherapy cycles can be given either at one of the study institutions or at the patient's preferred physician site, provided there is open communication with physicians at the study institution. Admission for HDC and transplant will be to a stem cell transplant unit at the respective study institutions. All follow-up studies such as radiological studies can be done at the location of the patient's choice, provided the study institution has access to reports and films as necessary.

L. Potential Risks

Control arm patients are subject to treatment risks that are common with CDC (nausea, diarrhea). Subjects would likely undergo this treatment regardless of affiliation with this study so there is no added toxicity.

Treatment arm subjects are at risk for significant toxicity just after administration of HDC. The most profound toxicity is myelosuppression, which will be addressed with autologous stem cell transplant. While engraftment is pending the patients will be at risk for infections and bleeding. Patients will be supported with growth factors, antibiotics and blood products as necessary. The most common side effect of immunosuppression is mucositis, which will be aggressively managed with anti-microbials and pain medication. Additionally, the patients will receive their HDC and stem cells in a stem cell transplant in-patient unit, where supportive care is optimal.

The data for HDC, especially in a tandem regimen, is still preliminary; however, we do not expect that the treatment arm will yield significantly worse results. It is possible that the HDC arm will show a greater benefit than expected, rendering the control arm patients less optimally treated. Patients will be informed of the potential at entry.

M. Potential Benefits

Enrollment in this study may be beneficial by assuring close follow-up of patients, in either arm, so that disease progression can be carefully monitored. In addition, any data gathered from this

experiment may provide useful information for future clinical decisions in women with stage III breast cancer.

N. Alternative Therapies

Alternates to the treatment arm include continuing CDC or undergoing HDC with one cycle only. Thus far, there is not enough data to comment on the relative advantages or disadvantages with either option in comparison to the treatment.

O. Compensation to Subjects

None.

P. Costs to Subjects

None. Insurance approval will be actively sought.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

Aside from conventional imaging studies performed for most cancer patients, there is no additionally radiation exposure in this study. Patients will be referred for radiation therapy after their chemotherapy as this is the standard of care. However, it is not an intervention in this particular study and patients may refuse.

S. References

1. Lipman, M. "Breast Cancer." Chapter 89 in Harrison's Principles of Internal Medicine, on-line ed. Editors: Eugene Braunwald, Anthony S. Fauci, Kurt J. Isselbacher, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson 2003.
2. Vahdat, L and K. Antman. "Dose-Intensive Therapy for Breast Cancer." Chapter 47 in High-Dose Cancer Therapy: Pharmacology, Hematopoiesis, Stem Cells. Third Edition. Edited by J. Armitage and K. Antman. Lipincott Williams & Wilkins, Philadelphia. 2000.
3. Rodenhuis et. al, "High Dose Chemotherapy with Hematopoiesis Stem-Cell Rescue for High Risk breast Cancer." *New England Journal of Medicine*. July 3, 2003. 349(1). 7-15.
4. Schrama JG, Holtkamp MJ, Baars JW, Schornagel JH, Rodenhuis S. Toxicity of the high-dose chemotherapy CTC regimen (cyclophosphamide, thiotepa, carboplatin): the Netherlands Cancer Institute experience. *British Journal of Cancer*. 2003 Jun 16;88(12):1831-8.
5. Sola Rocabert C, Mesia R, Mendoza L, Tabernero JM, Amill B, Maroto P, Bellet M, Ojeda B, Alonso MC, Verger G, et al. High-dosage chemotherapy and the autologous transplantation of peripheral hematopoietic progenitor cells in breast cancer: the initial results, analysis of toxicity and the necessary support means. *Medicina Clinical*. 1995 Oct 7;105(11):407-11.
6. Vahdat, LT et al. Phase I trial of sequential high-dose chemotherapy with escalating dose of paclitaxel, melphalan and cyclophosphamide, thiotepa and carboplatin with peripheral blood

progenitor support in women with responding metastatic breast cancer. *Clinical Cancer Research*. 1998:4. 1689-1695.
7. Vahdat LT, Balmaceda C, Papadopoulos K, Frederick D, Donovan D, Sharpe E, Kaufman E, Savage D, Tiersten A, Nichols G, Haythe J, Troxel A, Antman K, Hesdorffer CS. Phase II trial of sequential high-dose chemotherapy with paclitaxel, melphalan and cyclophosphamide, thiotepa and carboplatin with peripheral blood progenitor support in women with responding metastatic breast cancer. *Bone Marrow Transplant*. 2002 Aug;30(3):149-55.
8. Pecora, AL et al. Effect of induction chemotherapy and tandem cycles of high-dose chemotherapy on outcomes in autologous stem cell transplant for metastatic breast cancer. *Bone Marrow Transplant*. 2001 Jun; 27(12): 1245-53.
9. Broun, ER et al. Tandem autotransplantation for the treatment of metastatic breast cancer. *Journal of Clinical Oncology*. 1995 Aug; 13(8): 2050-5.
10. Kier, P et al. High doseage chemotherapy and autologous peripheral stem cell transplantation in breast carcinoma. *Acta Medica Austriaca*. 2000;27 Suppl 52:33-6.
11. Bowers, C et al. Dose escalation of mitoxantrone given wht thiotepa and autologous bone marrow transplantation for breast cancer. *Bone Marrow Transplant*. 1993 Nov; 12(5): 525-30.
12. Delozier T, Vernhes JC. Comparative study of adriamycin, epirubicin and mitoxantrone in cancer of the breast. Review of the literature. *Bull Cancer*. 1991 Nov;78(11):1013-25.