A Randomized Trial of Sequential Therapy with Exemastane after Two versus Three Years of Tamoxifen in Postmenopausal Women with Primary Breast Cancer

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A. Study Purpose and Rationale

Breast Cancer is the most common female cancer in the United States, the second most common cause of cancer in women and the main cause of death in women ages 45-55. In 2004, 217, 440 American women will be diagnosed with breast cancer and 40, 580 will die from this disease (1). Once the diagnosis of breast cancer is established, the choice of initial treatment depends on the stage or extent of disease. Initial treatment decisions include mastectomy +/- axillary lymph node dissection vs sentinel node dissection, breast conserving surgery followed by radiation therapy, neoadjuvant chemotherapy and adjuvant systemic therapy. Adjuvant systemic therapy (chemotherapy or hormone therapy) after definitive local therapy represents a major advance in the management of early breast cancer, significantly reducing recurrence and death.

Breast cancer is estrogen dependent in many cases and reduction of estrogen levels by ovariectomy or endocrine therapy is one of the main goals of therapy (2, 3, 4). Tamoxifen (a selective estrogen receptor modulator) has been shown to decrease risk of recurrence by 47% and risk of death by 26% when taken 5 years post surgery and is the current standard of treatment (5). Alternative endocrine therapy, include the aromatase inhibitors: Anastrazole, Letrozole (reversible nonsteroidal inhibitors) and Exemastane (irreversible steroidal inactivator). Studies performed using the aromatase inhibitors have shown them to be superior to tamoxifen in prolonging disease free survival without the increased risk of endometrial cancer (6). Furthermore, studies have revealed a higher rate of disease free survival in patients who received letrozole after five years of tamoxifen therapy (7).

Randomized trials directly comparing two years versus five years of tamoxifen therapy confirmed that there was a relative risk reduction of 18 to 19 percent with the longer therapy, suggesting that the bulk of therapy from tamoxifen was obtained from the shorter course of treatment (8). Recently, in a large, international, intergroup phase 3 trial, exemastane was found to significantly prolong disease free survival in postmenopausal women who were free of recurrence after anywhere from two to three years of tamoxifen therapy and then switched to exemestane (9). The purpose of this study is to determine the appropriate sequence of therapy. Thus, we will determine whether the drug, exemestane, prolongs disease free survival when given to postmenopausal women diagnosed with primary breast cancer after receiving adjuvant tamoxifen therapy for 2 years versus 3 years for the duration of five years. Our null hypothesis is that there is no difference in disease free survival at two versus three years of tamoxifen followed by exemestane. The alternative hypothesis is that there is prolonged disease free survival with sequential therapy of two years of tamoxifen compared to three years of tamoxifen followed by exemastane.

B. Study Design and Statistical analysis

This will be a phase 3, randomized, double-blind, multicenter study. Postmenopausal women who have been diagnosed with primary breast cancer and have undergone initial treatment either with mastectomy, breast conserving surgery, radiation therapy, neoadjuvant or adjuvant systemic chemotherapy therapy will be randomized to two arms. Randomization will be performed with the use of permuted blocks and will be stratified according to center. A total of 1123 patients will be randomized to each arm. One arm will include patients randomized to two years of tamoxifen followed by 3 years of exemestane therapy, while the second arm will include patients randomized to three years of tamoxifen

therapy followed by two years of exemestane. Dosage of exemestane given will be 25mg once a day, while tamoxifen will be given at 20mg once a day. Enrollment of a total of 2246 will be required to detect an absolute difference of 4% in disease free survival 5 years after randomization (90% power and p value of 0.05). The a priori expectation will be to conduct the principal analysis after 203 primary end points have occurred.

Analysis will be done according to the intention to treat principle. Statistical analysis to be employed include, hazard ratios, Kaplan-Meier curves, log rank tests and the Cox proportional-hazards regression model. Hazard ratios will be used to determine the primary end point, which is disease free survival. Disease free survival will be defined by time from randomization to recurrence of breast cancer, locally or distally, primary cancer in the contralateral breast, or death from any cause. Secondary end points will include overall survival, breast cancer free survival and incidence of adverse events, with a particular emphasis on the incidence of osteoporosis. Adverse effects will be graded according to the Common Toxicity Criteria of the National Cancer Institute (version 1.0). The Cox proportional-hazards regression model will be used to adjust for prognostic variables such as estrogen-receptor status, nodal status, use of chemotherapy or hormone replacement therapy. Two interim analyses will be conducted after one third and three quarters of the planned number of events. Early termination will be considered at the time of the interim analysis if the P value of the stratified log-rank test is less than the significance level calculated, with O'brien-Flemming stopping boundaries that maintained an overall significance level of 0.05.

C. Study Procedure

Patients will be evaluated at three months intervals during the first year after randomization, every six months during the second and third years and annually thereafter. Reported symptoms, adverse effects as well as clinical findings on exam will be recorded. Phlebotomy for blood draws will be done annually for hematologic and biochemical analyses including CBC, basic metabolic panel, liver function tests. These procedures involve minimal risk to the patient besides some local tenderness and minimal risk of infection. Mammography (as permitted by the local surgical procedure) will be performed annually according to the standard clinical care. Likewise, bone densitometry scans will be performed annually according to current standard care and T scores monitored. The duration of this study will be five years. Interim safety analysis will be reviewed by the data and safety monitoring committee.

D. Study drugs

Tamoxifen is an FDA approved drug in the treatment of advanced breast cancer and adjuvant therapy for early stage breast cancer. It is the current standard of therapy based on studies that have shown that the postoperative administration of tamoxifen for five years reduces the risk of recurrence by 47% and reduces the risk of death by 26% (5). In this study, tamoxifen will be administered at a dose of 20mg daily orally, which is the standard mode of treatment. The common side effects of tamoxifen include hot flashes, headaches, fatigue, nausea, vaginal dryness, vaginal bleeding, and muscle cramps. Serious, but rare adverse effects that have been reported include thromboembolic disease and endometrial cancer (10).

Studies on third generation aromatase inhibitors, to which exemestane belongs, have shown superiority over tamoxifen. Exemestane is superior to tamoxifen as first line therapy for metastatic disease (11), and has antitumor effects in patients who have no response to 3rd generation non steroidal aromatase inhibitors (12). Exemastane will be given at the standard dose of 25mg daily orally. Exemestane exhibits similar common side effect profiles like tamoxifen but less commonly, however it has been reported to result in a higher incidence of arthralgia, diarrhea, visual disturbances (9). Recent studies reveal that all 3rd generation aromatase inhibitors or inactivators increase bone resorption. Not surprisingly, studies have shown a slight increase in the incidence of osteoporosis and fractures, however there are reported studies to suggest that exemestane has a superior safety profile compared to other 3rd

generation aromatase inhibitors with regards to bone turnover (13). Studies are currently underway to further evaluate the degree of bone mineral loss.

E. Medical device

Not applicable

F. Study Questionnnaire

Not applicable

G. Study Subjects

a. Eligibility criteria
- Postmenopausal Women (>55 yrs) with amenorrhea for more than two years or more than one year at the time of diagnosis
- Histologically confirmed, completely resected unilateral breast cancer, ER + or unknown receptor status
- Adequate treatment of primary breast cancer including, mastectomy, breast conserving surgery with postoperative radiation therapy, neoadjuvant chemotherapy, or chemotherapy started within 3 months of diagnosis
- Received tamoxifen therapy for 0 to less than 1 month
- Patients should have normal CBC, renal, and liver function tests

b. Exclusion criteria
- ER negative tumor
- Local relapse or distant metastases
- Clinically significant skeletal, cardiac or endocrine disorder
- Use of HRT within 4 weeks prior to randomization or any other hormonal therapy (intermittent treatment with vaginal estrogen permitted)
- Severe osteoporosis or previous cancer diagnosis except carcinoma in situ of cervix or basal cell skin cancer
- Concurrent use of investigational drugs or anticoagulant agents

H. Recruitment of subjects

Patients presenting to any of the ten participating sites in the New York City area with diagnosis of early stage breast cancer and who fulfill the above eligibility criteria will be identified. Patients will represent a diverse ethnic population based on the different locations of the centers in the different boroughs of the city. Patients will be approached about the study and informed consent obtained from willing participants.

I. Confidentiality of Study data

All study data will have a unique code number for all study subjects and data will be secured in a location accessible only to the investigators.

J. Potential conflicts of interest

There is no conflict of interest. None of the investigators have a proprietary interest in the drugs used in this study.

K. Location of the study

This study will be a multi center study including ten participating sites in the New York City area. All studies will be performed in the Oncology department of all participating medical centers.

L. Potential risks

Potential risks include both the known common and rare side effects outlined in part D above. There will be no use of untested experimental drugs with unknown side effects.

M. Potential benefits

Based on published data, patients will benefit from the prolonged disease survival conferred by the sequential therapy of tamoxifen and exemestane than with tamoxifen alone, which is the current standard of care.

N. Alternative therapies

All the patients in this study will be receiving the drug tamoxifen, which is the standard of treatment as part of the sequential therapy with exemestane. No other alternative therapy will be offered.

O. Compensation to subjects

There will be no compensation to subjects participating in this study

P. Costs to subjects

There will be no additional costs to the subjects participating in this study

Q. Minors as research subjects

Not applicable

R. Radiation or Radioactive substances

Not applicable

S. References

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