

IRB Protocol

**Prospective Randomized Controlled Trial of Ibandronate
and Rosuvastatin as Adjuvant Therapy in the Treatment of
Locally Advanced Breast Cancer**

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A. Study Purpose and Rationale

Hypothesis

When added to standard practice treatment regimens for locally advanced Stage III breast cancer, bisphosphonates, statins or both will decrease the rate of progression to local recurrence or metastatic disease and increase survival time.

Purpose and Rationale

The purpose of this prospective randomized controlled trial will be to investigate the benefit of adding bisphosphonates and/or statins in the adjuvant period to standard therapy for Stage III, or locally advanced, breast cancer. The rationale is that approximately 30% of patients with Stage III breast cancer have recurrence or progress to metastatic disease and that 5-year survival is approximately 50% (1). Statins and bisphosphonates, by inhibition of isoprenylation of proteins involved in cellular proliferation and survival, have been proposed to be anti-tumor and/or anti-metastatic agents (2). These drugs are safe medications that may be easily added to the standard of care of Stage III breast cancer patients.

Background and Literature Review

Breast cancer is the most common malignancy in women and the second most common cause of cancer death in women (3, 4). The American Cancer Society estimates that there will be nearly 185,000 new breast cancer cases in 2008 with over 40,000 deaths (4). Breast cancer is staged using the TNM staging system which takes into account the size of the tumor and local extension, the presence or absence of lymph node involvement and the presence or absence of metastasis. Prognosis and current standards of treatment, including the use of surgery, radiation and chemotherapy differ for different stages of breast cancer. While 5 and 10 year survival rates are over 95% and 85% respectively for Stage I breast cancer and are over 80% and 65% respectively for Stage II breast cancer, the 5-year survival rate for Stage III, or locally advanced, breast cancer is only 54% and the 10-year survival rate is only 36%; likely related to both local and distant recurrences (5). Stage III or locally advanced breast cancer accounts for approximately 10-20% of all breast cancer cases in developed countries (up to 36,000 new cases a year in the United States) (6) and up to 60% of cases in developing countries (7). Clearly, there is a need for new treatments which may lead to an improvement in survival in these breast cancer patients.

Currently, locally advanced, or Stage III, breast cancer is treated with a combination of chemotherapy and locoregional therapy with surgery and/or radiation (5, 8, 9). Neoadjuvant chemotherapy using an anthracycline (e.g. doxorubicin) based regimen or a taxane (e.g. paclitaxel) is used. In addition, patients undergo either mastectomy or breast conservation surgery and lymph node dissection along with radiation therapy depending on the clinical response to the neoadjuvant therapy. Dependent on response, adjuvant chemotherapy after surgery may also be used. In addition, if the tumor overexpresses the protein Her2, the Her2 inhibitor trastuzumab is added to the chemotherapy regimen. If the tumor is estrogen receptor positive (ER+), an aromatase inhibitor such as anastrozole or the antiestrogen tamoxifen is used after chemotherapy, surgery and radiation are complete.

Stage III breast cancer patients are followed with annual mammography and every 3-6 month doctor visits for the first 3 years and then every 6-12 month doctor visits up to 5 years (5). Currently, for these types of patients, bone mineral density is followed in post-menopausal women, in all patients with chemotherapy induced premature menopause, and in all patients taking aromatase inhibitors. As for patients without breast cancer, a bisphosphonate is given to osteoporotic patients. Furthermore, fasting lipids are followed by age related guidelines or in all patients taking aromatase inhibitors and statins added for patients whose LDL is above goal based on the NCEP-ATPIII guidelines. However, neither bisphosphonates nor statins are routinely added in these patients.

The mevalonate pathway is the biochemical pathway which begins with production of mevalonic acid and leads through a multi-step process to the production of cholesterol but also to the production of molecules

called isoprenoids (2). These molecules play important roles in the post-translational modification of many proteins involved in cell signaling, cell growth and differentiation, cell proliferation and many other important processes that are often hijacked in tumor cells. For example, the small GTPases Rho, Ras, Rac and Rab which are involved in malignant transformation of cells all require prenylation. Statins are used for hypercholesterolemia based on their inhibition of HMG-CoA reductase, which is the first enzyme in the mevalonate pathway. Bisphosphonates are used for osteoporosis based on their inhibition of osteoclast activity and thus reduction of bone resorption and turnover. However, the bisphosphonates also inhibit farnesyl pyrophosphate synthase, another enzyme in the mevalonate pathway. Therefore, statins and bisphosphonates can be expected to lead to a decrease in isoprenoid synthesis and therefore prenylation of proteins.

There are many preclinical studies in cell culture and mouse models demonstrating the anti-tumor properties of bisphosphonates, possibly due to their inhibition of isoprenoid synthesis (2). Because of these studies, it has been proposed that bisphosphonates may also be useful in the prevention of metastasis in patients with nonmetastatic cancer (10, 11). There have been two prospective randomized controlled trials of clodronate in preventing metastasis in breast cancer, one using pamidronate and one using zoledronic acid (10). In Diel et al (12), clodronate reduced skeletal metastases in breast cancer patients from 29% in the control group to 13% in the treatment group. In Powles et al, clodronate reduced the risk of skeletal metastases from 13.5% in the control group to 9.6% in the treatment group. However, a third RCT did not show a reduction of skeletal metastases (13); therefore more recent studies have focused on the newer-generation bisphosphonates which possess greater antitumor properties (10). van Holten-Verzantvoort et al (14) found that pamidronate reduced skeletal metastases from 36% to 27%, however this was not statistically significant in this trial of 124 patients. Finally, Mystakidou et al (15) studied 40 patients randomized to receive either zoledronic acid or placebo and found that after one year, 60% of zoledronic acid patients had no bone metastases versus only 10% of placebo patients. These data support the hypothesis that bisphosphonates may not only be useful in the reduction of risk of skeletal complications of metastases (as they are currently used) but also may play a role in the prevention of metastases (10).

Similar to bisphosphonates, many preclinical studies exist showing the antitumor properties of statins, in such pathways as cell growth, metastasis and angiogenesis (16). The effects of statins and the risk of cancer is still debated; however two recent meta-analyses do not support a strong association between statin use and the risk of cancer in general (17, 18), and a review of the literature also did not show an association between statin use and breast cancer specifically (19). On the other hand, whether statins will be beneficial in cancer treatment is poorly studied. One randomized controlled trial looked at treatment of hepatocellular cancer patients with pravastatin and showed an increase in survival from 9 months to 18 months (16).

Based on the molecular biology of the mevalonate pathway, preclinical and limited clinical data on the use of bisphosphonates and statins in the prevention of metastases, it may be hypothesized that these drugs may prevent local and/or distant recurrence or progression to metastatic disease and increase survival in breast cancer patients.

B. Study Design and Statistical Analysis

Study Design

Patients with Stage III breast cancer will be recruited from multiple centers. Patients will be excluded from the study if they are already being treated with a bisphosphonate or a statin for established indications. Patients will be treated with chemotherapy, surgery and radiation according to the standard of care following a treatment algorithm (9). Acceptable chemotherapy regimens will be an anthracycline or taxane based chemotherapy regimen with or without trastuzumab based on Her2 expression. Estrogen

receptor positive patients will be treated with an aromatase inhibitor or tamoxifen. Patients will then be randomized to either treatment with the bisphosphonate ibandronate (Boniva®), the statin rosuvastatin (Crestor®), both ibandronate and rosuvastatin or placebo regardless of bone mineral density results or lipid levels. The patients will be followed for five years. The study primary outcome will be evidence of progression to metastatic disease, evidence of local recurrence, and overall survival. Patients who develop an indication for treatment with bisphosphonates and statins during the follow-up period will not be denied these therapies; the study drug will be stopped and the appropriate drug added by the patient's physician. Subjects will be analyzed in an intention to treat analysis.

Statistical Analysis

The number of patients who develop local and/or distant recurrence, progress to metastatic disease, and who expire during the follow-up period will be counted in each group. The rates of each of the primary endpoints and a composite of the primary endpoints will be compared in the three drug treatment groups versus the placebo group using a Chi-square test.

Sample Size

It is estimated that 30% of patients with Stage III breast cancer will progress to local or distant recurrence (metastasis). A reduction with either or both drugs of 8% to at least 22% of patients would be considered significant. Using an alpha error of 5% and a beta error of 80%, 500 subjects will be needed in each group.

$$N = 8(p_1q_1 + p_2q_2/\text{effect}^2) + 2/\text{effect} + 2$$

$p_1 = 0.30, p_2 = 0.22, q_1 = 0.70, q_2 = 0.78, \text{effect} = 0.08$

Using 500 subjects per group and assuming 50% mortality for patients with Stage III breast cancer at the end of the 5 year follow-up period, a significant reduction to at least 41% mortality can be detected.

C. Study Procedures

Procedures for standard of care therapy for Stage III breast cancer will be followed. Once patients are randomized to bisphosphonate, statin, both or placebo, the patients will be given unlabelled pills of either ibandronate, rosuvastatin, combined or placebo to be taken on a daily basis. Patients will be followed every 3 months according to standard of care; in addition blood will be taken for analysis of renal function and liver function tests.

D. Study Drugs

1. Ibandronate (Boniva®)

- FDA approved for osteoporosis
- Dosing and route of administration will be according to standard regimen: 2.5mg PO daily
- Side effects and frequency: Common side effects are dysphagia, esophagitis, dyspepsia, stomach or esophageal ulcers, and diarrhea. Rare serious side effects are uveitis, scleritis, osteonecrosis of the jaw, musculoskeletal pain, and renal failure.

2. Rosuvastatin (Crestor®)

- FDA approved for hypercholesterolemia, hypertriglyceridemia, and atherosclerosis
- Dosing and route of administration will be according to standard regimen: 20mg PO daily
- Side effects and frequency: Common side effects are headache, myalgia, abdominal pain, asthenia, constipation, nausea, myopathy, liver enzyme abnormalities. Rare serious side effects are rhabdomyolysis, acute renal failure, and hypersensitivity reactions.

E. Medical Devices

None

F. Study Questionnaires

None

G. Study Subjects

Inclusion criteria

- 1) Women age 18 and over
- 2) Histologically confirmed primary invasive adenocarcinoma of the breast at stage IIIA, IIIB, IIIC
- 3) Completion of standard of care treatment (chemotherapy with anthracycline or taxane based regimen, mastectomy or breast conservation therapy, and radiation).

Exclusion criteria

- 1) Evidence of metastatic disease
- 2) Already on a bisphosphonate for osteoporosis
- 3) Already on a statin for hypercholesterolemia
- 4) Creatinine clearance as measured by MDRD less than 30 as ibandronate is contraindicated for these patients
- 5) Active liver disease as evidenced by elevated AST or ALT, as rosuvastatin is contraindicated for these patients.

H. Recruitment of Subjects

Subjects will be recruited from the breast cancer treatment clinic at the study centers. The patient's oncologist will determine if the patient is suitable for the study and will ascertain that the patient is willing to discuss the study before being approached by the investigators.

I. Confidentiality of Study Data

All data will be confidential. Patients will be assigned a unique code that is separate from the medical record number, social security number, initials, phone number or address. Data will be stored in a secure location.

J. Potential Conflict of Interest

There are no conflicts of interest.

K. Location of Study

The study will be conducted at New York Presbyterian Hospital Columbia University Medical Center and associated sites.

L. Potential Risks

The potential risks of the study include the known side effects of ibandronate and rosuvastatin.

M. Potential Benefits

The potential benefits include a reduction in progression to metastatic disease and overall survival.

N. Alternatives:

None

O. Compensation to Subjects:

Compensation will not be provided.

P. Costs to Subjects:

There will be no costs.

Q. Minors as Research Subjects:

Not applicable

R. Radiation or Radioactive Substances:

Not applicable

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