Effects Of Consolidation Therapy With Pamidronate In Breast Cancer Patients Who Have Completed Autologous Bone Marrow Transplant

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A. Study Purpose

Bisphosphonates are pyrophosphate analogues that inhibit the formation and dissolution of calcium phosphate crystals in vitro. In vivo, bisphosphonates bind to hydroxyapatite on the surface of bone. These drugs are used therapeutically to inhibit osteoclast-mediated bone resorption. Recent clinical trials have demonstrated the anti-osteolytic effect of bisphosphonates in patients with breast cancer and bony metastases. Although overall survival was not improved, bisphosphonates used in breast cancer patients reduced the incidence of hypercalcemia, bone pain, and pathologic fractures. A recent clinical trial also demonstrated that therapy with a bisphosphonate could reduce the incidence of new bony and visceral metastases in women with primary breast cancer at high risk for metastases. In this study, the number of metastatic bony lesions and visceral metastases per woman was twice as high in the control group as the bisphosphonate group. Although the mechanism of action by which these drugs may inhibit metastases is not fully understood, a recent paper demonstrates that the bisphosphonate alendronate can enhance the degradation by plasmin of a metalloproteinase by inhibiting tissue inhibitor of metalloproteinase 2 which protects the metalloproteinase from degradation. There has been research suggesting that tumor cells may secrete metalloproteinases to allow for invasion of bone and other tissues and the creation of metastatic lesions. Bisphosphonates may act as direct inhibitors of the ability of tumor cells to metastasize.

The purpose of this study is to observe the effect of treatment with pamidronate, a bisphosphonate, on breast cancer patients who have completed autologous bone marrow transplant and are at high risk for recurrent disease (80 % of stage IV patients with breast cancer who have undergone bone marrow transplant develop recurrent disease) and whether it alters the rate of recurrent disease, bony and visceral metastases, or survival. In addition, markers of bone resorption and of metalloproteinase activity will be monitored in an effort to gain more insight into the mechanism through which bisphosphonates work.

B. Study Design

The study will be a randomized double blind, placebo-controlled clinical trial. Patients will be followed for 36 months after enrollment in the trial. One hundred twenty women (sixty in each group) with breast cancer who have undergone autologous bone marrow transplant will be randomly assigned to monthly treatment with Pamidronate versus placebo. The study subjects must be women with breast cancer stage II, III at high risk for developing advanced disease or stage IV who have undergone high dose chemotherapy followed by autologous bone marrow transplant. The subjects will be excluded from the study if they have bony metastases or a positive bone scan after BMT or if they have a second malignancy. The subjects must be over the age of 21 and will be recruited from CAMP protocol trials for bone marrow transplant of breast cancer patients. The patients included in the study will be randomized to a monthly 2-hour infusion of pamidronate or to infusion with placebo. Randomization will occur after bone marrow transplant has been completed and there is no evidence of disease by physical exam, CT scan, or bone scan.

During the coarse of the study, if a patient in the placebo group develops bony metastases, the patient will discontinue treatment with the placebo drug and will be treated with pamidronate.

Follow up investigations will take place at Columbia Presbyterian according to a standard protocol. The patient will be required to come for follow-up visits every few months for the 36 months they are followed for this study. At each visit, a history will be taken and a physical performed. A chest x-ray, bone scan, ultrasound of the liver and mammogram will be done at least twice yearly. Laboratory tests (CBC, C7, Electrolytes, LFTS, and measurements of tumor antigens) will be done every three months. In addition, measurements of N-telopeptides and C-telopeptides will be measured in the urine of subjects to monitor bone turnover. Serum levels of tissue inhibitor of metalloproteinase 2 and pro-metalloproteinase 2 will be measured to ascertain if there is a difference between the two groups. If there is evidence by history or exam of metastases to bone, additional x-rays and scans will be done of the affected areas. If there are abnormalities on neurological exam, the appropriate scans and tests will be done. Bone lesions identified on radiographs will be assessed by two independent radiologists.

C. Statistical Analysis

Current analysis of the Camp protocol data on breast cancer autologous bone marrow transplant patients show that 80% of stage IV patients and 15-20% of stage II and III patients develop recurrent disease after 5 years. The initial projection in this study is that after 24 months of follow up there should be a 20 % decrease in the reoccurrence of new bony or visceral disease in BMT patients. The studies of bisphosphonates in breast cancer have not demonstrated a survival benefit thusfar, however the use of bisphosphonates in multiple myeloma have shown a survival benefit in patients who had severe disease requiring salvage therapy of 33%. Based on this literature, we estimate a survival benefit of 20%. These parameters will be evaluated by chi-square test.

D. Study Drugs

The drug used in this study will be Pamidronate which is approved by the FDA for use in the treatment of osteoporosis and of bony metastases in cancer. The dose of drug used will be 90mg given intravenously every 4-6 weeks. The patients will come to the study center for infusion of the drug once a month. Reported side effects of the drug are erosive esophogitis, gastrointestinal discomfort, transient fever, fatigue, constipation, bone pain, asymptomatic hypophosphatemia, hypokalemia, hypocalcemia. There also have been isolated reports of nephropathies and of uveitis.

E. Recruitment of Subjects

Patients who have breast cancer Stage II or III at high risk for the development of metastatic disease or Stage IV breast cancer who are eligible for bone marrow transplant will be recruited for this study at the same time they are recruited for participation on the CAMP protocol for bone marrow transplant. Patients referred for consideration for the bone marrow transplant protocol will also be screened for participation in this study.

F. Risks and Benefits of Participation

Potential risks to the participants include the development of a side effect to Pamidronate as listed above or the development of a complication secondary to gaining intravenous access for infusion of the drug. Potential benefits of participation on the study are increased disease free survival, decreased bony and visceral metastases at the time of recurrence , and increased time to recurrence.