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Does The Use Of Intravenous Zoledronic Acid, In Combination With Chemotherapy Regimens, Arrest The Development And Spread Of Cancer Cells To Increase Disease-Free Survival In Breast Cancer Patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2011

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Does the use of intravenous zoledronic acid, in combination with chemotherapy regimens, arrest the development and spread of cancer cells to increase disease-free survival in breast cancer patients."

STUDY DESIGN: Review of three English language primary randomized controlled trials published between 2009 and 2010.

DATA SOURCES: Randomized controlled trials and open label, randomized, phase 2 trial comparing the use of zoledronic acid in combination with chemotherapy to the use of chemotherapy alone were found using Medline/PubMed and Cochrane Databases

OUTCOMES MEASURED: The outcomes measured were incidence of metastasis, progression of disease, and disease-free survival. Mammography, breast ultrasound, MRI, CT scans, and histopathologic studies were used to measure these outcomes after treatment was received.

RESULTS: Two randomized controlled trials and one open label, randomized, phase 2 trial were analyzed in this review. In Aft et al, patients treated with zoledronic acid and chemotherapy had fewer detectable disseminated tumor cells at 3 months than at baseline (p=0.054). In Coleman et al, the residual invasive tumor size after treatment and resection had an adjusted mean difference of 12mm between the two treatment groups (95% CI: 3.5-20.4mm, p= 0.006). Gnant et al demonstrated that the use of zoledronic acid in combination with chemotherapy had a 36% reduction in the risk of disease progression and a 35% reduction in the risk of recurrence compared to chemotherapy alone (p= 0.01 and 0.02, respectively).

CONCLUSION: Based on these three trials, the results of this review were inconclusive. The studies analyzed suggest possible anti-tumor effects leading to increases in disease-free survival. Further research should be aimed at determining a particular chemotherapy plus zoledronic acid regimen and a specific patient population for which zoledronic acid is most effective.

KEY WORDS: Breast Cancer; Breast Neoplasm; Zoledronic Acid

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women and the second most common cause of cancer related death in women across the United States[1]. By definition, "breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast"[1]. With its primary route of metastasis being via lymphatics, aggressive forms of breast cancer can metastasize to the bone, liver, lungs, and brain[1].

For 2011, it is estimated that 230,480 women with be newly diagnosed with breast cancer, with approximately 39, 520 deaths resulting from the disease[2]. Its incidence rate from years 2004 to 2008 was 124:100,000 women per year, with the overall median age of diagnosis being 61 years of age[2]. The overwhelming statistics in relation to incidence and mortality have a large impact on the overall economics of breast cancer. In 2008, approximately 21.2 million mammograms were ordered from physician office visits as screening for breast cancer[3]. Because of increasing incidence and awareness for this disease, the total national expenditure for breast cancer reached an estimated $13.9 billion in 2006 and an estimated $631.2 million on research in 2010 [3,4]. In addition to the financial aspects of the disease, a diagnosis of breast cancer has a significant impact on the physical and mental health of both the patient and their families.

The etiology of breast cancer is multifaceted with several genetic and environmental risk factors identified. The BRCA1, BRCA2, and p53 tumor-suppressor genes normally function to produce proteins that help to repair damaged DNA[1]. Mutations in these genes cause defective proteins to be produced, which results in accelerated and unregulated growth of breast tissue thereby increasing the patient's risk. It has been found that women who inherit a mutated BRCA1 gene have a 60-80%

lifetime chance of developing breast cancer[1]. Environmentally, there are a myriad of non-modifiable and modifiable risk factors associated with oncogenesis. Age, early onset menstruation, late onset menopause, nulliparous, history of radiation therapy, smoking, obesity, and hormone replacement therapy are all linked to breast cancer development[1].

In attempts to treat this disease, researchers are looking to alternative and adjunctive therapies to use in combination with the previously implemented chemotherapy regimens, surgery, radiation, and hormone treatments. Recent studies suggest that the addition of intravenous zoledronic acid (ZA), a third generation bisphosphonate, to chemotherapy regimens may provide additional benefit to breast cancer patients by arresting tumor growth and preventing the spread of malignant cells[5,6,7]. Although chemotherapy alone has shown to be successful, the addition of zoledronic acid promises to increase disease free survival and decrease the incidence of metastasis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does the use of intravenous zoledronic acid, in combination with chemotherapy regimens, arrest the development and spread of cancer cells to increase disease-free survival in breast cancer patients."

METHODS

All three studies met the criteria for subjects who were female breast cancer patients over the age of 18 who where prescribed chemotherapy regimens plus intravenous zoledronic acid treatments. One of the studies used was an open label, randomized, phase 2 trial which compared neoadjuvant IV zoledronic acid plus

epirubicin/docetaxel chemotherapy to epirubicin/docetaxel chemotherapy alone[5]. The other two studies used were randomized control trials; one comparing neoadjuvant IV zoledronic acid plus chemotherapy to chemotherapy alone[6]; the other comparing adjuvant IV zoledronic acid plus goserelin plus tamoxifen or anastrozole to goserelin plus tamoxifen or anastrozole alone[7].

In the Aft et al study,[5] patients received 4 mg of IV zoledronic acid every 3 weeks plus epirubicin 75 mg/m^2 plus docetaxel 75 mg/m^2 every 3 weeks for 1 year. In the randomized control trial by Coleman et al,[6] patients received 6 doses of 4 mg IV zoledronic acid every 3-4 weeks in combination with their chemotherapy treatment. In the Gnant et al study,[7] patients received 3.6 mg of subcutaneous goserelin plus either tamoxifen 20 mg per day orally or anastrozole 1 mg per day orally with or without 4 mg of IV zoledronic acid every 6 months.

A detailed search was completed by the author using the following search engines: Medline/PubMed, Cochrane Database of Randomized Controlled Trials, and Cochrane Database of Systemic Reviews. The key words “breast cancer” “breast neoplasm” and “zoledronic acid” were used. All articles were published in the English language in peer reviewed journals. One meta-analysis exists on this topic and was last updated in 2010. Gnant et al was published in 2009 but was not included in this meta-analysis. No information from the meta-analysis will be used as part of this paper. All other articles used were published after March of 2010. The articles were selected based on their relevance and the importance of the outcome to the patient (POEMS). Studies that were included were those that were randomized, controlled, not included in a meta-analysis or were published after March 2010, and based on patient oriented outcomes.

Studies excluded were those that included male patients, prior history of neoplasm, pregnancy, or contraindications to chemotherapy or zoledronic acid. Statistics utilized in these studies were p-values with a value <0.05 being statistically significant, 95% confidence intervals, numbers needed to treat (NNT), and numbers needed to harm (NNH). Table 1 outlines the demographics and characteristics included in these studies.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Aft, 2010	Open label, randomized, phase 2 trial	120	29-68	Women with clinical stage II-III newly diagnosed breast cancer, Staged $\geq$ T2 and/or $\geq$ N1, ECO Group performance of 0 or 1, Normal cardiac, renal, and liver function	Evidence of distant metastasis, Prior malignancy, Disorders of the heart, liver, or kidneys, Pregnancy, Women < 18 years old	31	Patients received 4 mg of IV ZA every 3 weeks for 1 year plus prescribed chemotherapy treatment (epirubicin 75 mg/m^2 plus docetaxel 75 mg/m^2 every 3 weeks)
Coleman, 2010	RCT	205	41-57	Women receiving neoadjuvant chemotherapy, Staged $\geq$ T3 and/or $\geq$ N1, Scheduled to receive surgery and/or radical radiotherapy, curative intent within 6 months of initiating therapy	Prior malignancy, Women < 18 years old	10	Patients received 6 doses of 4 mg IV ZA every 3-4 weeks in combination with their neoadjuvant chemotherapy treatment, followed by surgical resection tumor

Gnant, 2009	RCT	1803	25-57	Premenopausal women, surgery for stage I or II breast cancer, Estrogen receptor positive and/or progesterone receptor positive, Less than 10 positive lymph nodes, Prescribed goserelin for chemotherapy	Stage T1a, T4d, or yT4, Prior history of neoplasm, Preoperative radiation, Pregnancy, Lactation, Contraindications for study medications	150	Patients received goserelin plus tamoxifen or anastrozole with ZA (4 mg every 6 months) for 3 years

OUTCOMES MEASURED

The outcomes measured were those of patient oriented evidence that matters (POEMS), which includes incidence of metastasis, progression of disease, and disease-free survival. Mammography, breast ultrasound, MRI, CT scans, and histopathologic studies were used to measure these outcomes after treatment was received [5,6,7].

RESULTS

Two randomized controlled trials and one open label, randomized, phase 2 trial are analyzed in this review. All participants are female patients diagnosed with breast cancer and prescribed a chemotherapy regimen without or without zoledronic acid treatment. The results were presented in dichotomous form in the Aft et al[5] and Gnant et al[7] studies, but presented as continuous data in the Coleman et al study[6].

The Aft et al study assessed the incidence of detectable disseminated tumor cells (DTC) in the bone marrow of breast cancer patients three months after treatment[5]. In the control group, 28 of the 58 patients had DTCs at baseline compared to 26 of 60 patients

in the chemotherapy plus zoledronic acid group. After three months and four cycles of treatment, 25 of 53 patients in the control group had detectable DTCs compared to 17 of 56 patients in the zoledronic acid group (p=0.054). However, of the patients without detectable DTCs at baseline, 15 of 25 patients in the control group remained negative compared to 27 of 31 patients in the zoledronic acid group (p=0.030) (Table 2)[5].

Table 2- Efficacy of chemotherapy plus zoledronic acid in reduction of disseminated tumor cells compared to chemotherapy alone

	Chemotherapy Alone	Chemotherapy + ZA	p-value
Baseline DTCs	28/58 (48.3%)	26/60 (43.3%)	-
No Baseline DTCs	30/30	34/34	-
Evidence of DTCs at 3 months	25/53 (47.2%)	17/56 (30.4%)	0.054
DTC negative at baseline and 3 months	15/25 (60%)	27/31 (87.1%)	0.030

The control event rate (CER) was determined as those who had detectable DTCs after three months of the treatment without zoledronic acid. The CER was calculated to be 47.1%. The experimental event rate (EER) was determined as the number of patients who had detectable DTCs with zoledronic acid treatment. The EER was found to be 30.4%. From this data, the absolute benefit increase (ABI) was -16.7% with a number needed to treat (NNT) of -6 and a number needed to harm (NNH) of 13 (Table 6)[5,7].

Coleman et al assessed the residual invasive tumor size in breast cancer patients treated with neoadjuvant therapy[6]. Patients in this study had primary end points evaluated by surgical resection specimens. The data was presented as continuous data that could not be converted into a dichotomous format. There were 182 patients assessed for residual invasive tumor size (RITS), the primary end point, in both groups. Adjusted means were calculated taking into account biological and clinical factors known to affect tumor

response. The adjusted means for the control group and the chemotherapy plus zoledronic acid group (CT + ZA) were 27.4 mm and 15.5 mm, respectively, revealing a difference in means of 12 mm (95% CI 3.5-20.4mm, p=0.0059) (Table 3)[6].

Table 3 – Efficacy of chemotherapy plus zoledronic acid on residual invasive tumor size compared to chemotherapy alone

	CT Alone	CT + ZA	Estimate	s.e.	95% CI	p-value
RITS (adjusted means)	27.4 mm	15.5 mm	12	4.3	(3.5, 20.4)	0.0059

The Gnant et al study assessed the effects of chemotherapy plus zoledronic acid on disease-free and recurrence-free survival[7]. A median follow up period of 47.8 months was used to assess the status of the 1803 patients followed in this study. In the experimental group, 845 of the 899 patients (94.0%) were free of disease compared to 821 of the 904 (90.8%) patients in the control group (p=0.01). Similarly, 845 of the 899 (94.0%) patients in the experimental group were recurrence-free as compared to the 822 of the 904 patients (90.9%) in the control group at the same 47.8 month follow up period (p=0.01) (Table 4)[7]. For disease-free survival, the absolute benefit increase (ABI) was 3.2%, with a numbers needed to treat (NNT) of 32 patients, and a numbers needed to harm (NNH) of -32 patients. For recurrence-free survival, the ABI was 3.1%, the NNT was 33 patients, and the NNH was -33 patients (Table 6)[5,7]. Using Cox analysis, patients who received zoledronic acid had a 36% reduction in the risk of disease progression and a 35% reduction in the risk of recurrence compared to the control group (Table 4)[7].

Table 4- Efficacy of Zoledronic Acid on Disease Free Survival

	Chemotherapy Alone	Chemotherapy plus ZA	p-value	% Risk Reduction	Cox p-value
Disease-Free Survival	821/904 (90.8%)	845/899 (94.0%)	0.01	36%	0.01
Recurrence-Free Survival	822/904 (90.9%)	845/899 (94.0%)	0.01	35%	0.02

The primary end point for the Gnant et al[7] study was disease-free survival. This was defined as "a period of time beginning at randomization to the occurrence of one or more of the following: a local or regional recurrence, cancer in the contralateral breast, distant metastasis, second primary carcinoma, or death from any cause." As outlined in Table 5 below, the addition of zoledronic acid had fewer events in all categories.

Table 5- Events in the Intention-to-Treat Population

Event	Chemotherapy Alone	Chemotherapy plus ZA
Locoregional Recurrence	20	10
Distant Metastasis	41	29
Contralateral Breast Cancer	10	6
Secondary Primary Cancer	10	9
Death	26	16

As illustrated below in Table 6, a negative NNT was calculated for the Aft et al[5] trial due to the fact that the study is measuring the incidence of metastasis. This negative NNT suggests that for every six patients treated with zoledronic acid there is one less patient who will experience metastatic disease in the experimental group when compared to the control group. Similarly, the data provided in both the Aft et al[5] and the Gnant et al[7] studies allowed for a numbers needed to harm to be calculated. In the Aft et al[5] study, for every 13 people treated with zoledronic acid, 1 patient would be harmed in the experimental group compared to the control group. In the Gnant et al[7] trial, negative numbers needed to harm were obtained for both disease-free and recurrence-free survival. For disease-free survival, this suggests that for every 32 patients treated with zoledronic acid in the experimental group, one patient in the control group will be harmed. Likewise, for recurrence-free survival, for every 33 patients treated with zoledronic acid in the experimental group, one patient in the control group will be harmed. In these instances, harm refers to disease progression or recurrence.

Table 6- Comparison of Dichotomous Data

Study		CER	EER	ABI	NNT	NNH
Aft, et al						
	Reduction of DTCs	47.1%	30.4%	-16.7%	-6	13
Gnant, et al						
	Disease-Free Survival	90.8%	94%	3.2%	32	-32
	Recrrence-Free Survival	90.9%	94%	3.1%	33	-33

Because of the condition and treatments analyzed in these studies, the safety and health of the patients involved were closely monitored throughout the trials. In the Aft et al[5] trial, a safety analysis was performed on 119 patients using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The most common adverse events noted were infection, thrombosis/DVT, and neutropenic fever. In the Coleman et al[6] trial, there were 63 serious adverse events (SAE) reported, 36 events in the chemotherapy alone group versus 27 in the chemotherapy plus zoledronic acid group. The most commonly reported SAE was neutropenic sepsis. In the Gnant et al[7] trial, the most commonly reported adverse events were arthralgia, bone pain, and fever. The methods used for reporting adverse events in the Coleman et al and Gnant et al trials were not noted.

Table 7- Adverse Events Across Trials (number of patients monitored)

	Aft et al (119)		Coleman et al (205)		Gnant et al (1803)	
	CT alone	CT + ZA	CT alone	CT + ZA	CT alone	CT + ZA
Adverse Event						
Infection	6	5				
Thrombosis/DVT	2	5				
Fever	2	3			20	80
Neutropenic Sepsis			16	14		
Arthralgia					164	215
Bone Pain					222	317

DISCUSSION

In the RCT conducted by Aft et al, the use of zoledronic acid in combination with epirubicin and docetaxel did not have a statistically significant impact on reducing detectable DTCs after three months of treatment[5]. It did, however, show statistically significant results for patients who were initially DTC negative that remained DTC negative after treatment[5]. Unfortunately, this was not the aim of this study and therefore requires further investigation. Even though the results were not statistically significant, patients treated with the combination of chemotherapy and zoledronic acid had fewer detectable DTCs at 3 months than at baseline.

Results collected by Coleman et al found that the residual invasive tumor size was significantly influenced by the use of zoledronic acid in combination with chemotherapy treatments[6]. Considering residual invasive tumor size is the estimated amount of tumor remaining post surgical resection, lower values suggest longer disease-free survival for these patients[6]. As the primary end point, the comparison between treatment groups revealed a mean difference of 12mm, with the lowest values in the experimental group, thus showing a positive benefit to adding zoledronic acid to the chemotherapy regimen.

Furthermore, in the Gnant et al study, statistically significant data was collected supporting the use of zoledronic acid as an adjunctive therapy to increase disease-free and recurrence-free survival[7]. The outcome of this study also identified a possible patient population for which zoledronic acid is beneficial; those with low to intermediate risk, endocrine-responsive early breast cancer tumors[7].

Unfortunately, many limitations exist in this patient population, which affect the validity of these results and thus the outcome of this review. Multiple chemotherapy

regimens were used, both premenopausal and menopausal patients were analyzed, and various outcomes were measured to assess the effects of zoledronic acid as an adjunctive therapy for breast cancer patients. Additionally, the outcomes were measured using mammography, breast ultrasound, MRI, CT, and histopathologic studies. Limitations of these studies include interpretation of the data, specifically in regards to the presence of DTCs in Aft et al[5], and in the inter-pathologist variation as noted in Coleman et al[6].

Zoledronic acid is a third-generation bisphosphonate currently used as treatment for osteoporosis in men and postmenopausal women, hypercalcemia of malignancy (HCM), and bone metastases caused by solid tumors[8]. It primarily works to prevent bone resorption by inhibiting osteoclast activity and promoting osteoclast apoptosis[8]. The FDA approved "Zometa" in 2001 as a treatment for HCM and oncology-related indications[8]. In 2007, the same drug was approved under the name "Reclast" for the treatment of osteoporosis and Paget's Disease[8].

CONCLUSION

Based on the three trials analyzed in this review, the evidence is inconclusive if the use of zoledronic acid in combination with chemotherapy arrests the development and spread of cancer cells to increase disease-free survival. As discussed, there is mounting evidence in favor of this adjunctive therapy with results trending in favor of its antitumor and anti-metastatic effects.

In addition to larger patient populations evaluated over longer periods of time, future trials would benefit from using a single type of chemotherapy, be exclusive of premenopausal or postmenopausal patients and a specified hormone-receptor status, and address an optimal dosing schedule for zoledronic acid administration.

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