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Outcome of Patients With Early Breast Cancer Receiving Nitrogen-Containing Bisphosphonates: A Comparative Analysis From the Metropolitan Detroit Cancer Surveillance System

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Abstract

Background—Preclinical data suggest that bisphosphonates exhibit antitumor activity. However, clinical studies indicated conflicting results. In this study, we compared the overall survival (OS) of postmenopausal patients with non-metastatic invasive breast cancer who received any of the second-generation nitrogen-containing bisphosphonates for osteopenia or osteoporosis, with the survival of those who did not.

Patients and Methods—We conducted a retrospective study at the Wayne State University/Karmanos Cancer Institute (KCI) in Detroit, Michigan and extracted data from the Metropolitan Detroit Cancer Surveillance System (MDCSS), a Surveillance, Epidemiology and End Results (SEER) registry. Patients > 50 years of age with stage I, II, or III invasive breast cancer between the years 2000 through 2003 were included. Information regarding medications was extracted from the patients' medical records.

Results—A total of 696 women with stage I–III breast cancer were included. Ninety-seven women (14%) used nitrogen-containing bisphosphonates. The difference in OS between bisphosphonate users and nonusers was not statistically significant ($P = .32$) at 3 years. After adjusting for differences between the groups in age, stage of disease, hormone receptor status, endocrine therapy, vitamin D, and calcium use, there was a marginally significant ($P = .07$) difference in survival; bisphosphonate users had poorer survival than nonusers.

Conclusion—Our results indicate that the use of nitrogen-containing bisphosphonates is not associated with improved OS in patients with nonmetastatic breast cancer, even after adjusting for known prognostic factors, but with a marginally worse OS. Further research is awaited to clarify the role of bisphosphonates in the adjuvant setting.

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Disclosures

All of the authors report that they have no relevant relationships to disclose.

Keywords

Alendronate; Ibandronate; MDCSS; Risedronate

Introduction

Bisphosphonates are effective inhibitors of bone resorption and have become integral in the management of bone health in patients with malignant bone disease.¹ Bisphosphonates can be classified into at least 2 groups with different modes of action: the first-generation bisphosphonates that closely resemble pyrophosphate (such as clodronate and etidronate) can be metabolically incorporated into non-hydrolysable analogues of ATP that may inhibit ATP-dependent intracellular enzymes; and the second-generation more potent, nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, zoledronate, and ibandronate) that inhibit enzymes in the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds, essential for the posttranslational modification of small GTPases.² They are also bone-specific agents and their strong affinity for bone, and not for other tissues, makes them potent inhibitors of bone resorption and bone remodeling activity, with limited potential for side-effects in non-skeletal tissues. By inhibiting farnesyl diphosphate synthase, the nitrogen-containing bisphosphonates block the mevalonate pathway, the end product of which is an essential signaling component in many cancers.³ Therefore, in addition to reducing skeletal morbidity, nitrogen-containing bisphosphonates may have direct and indirect anti-tumor activity potentially extending survival. Preclinical data suggest that bisphosphonates exhibit antitumor activity through a variety of mechanisms, including inhibition of angiogenesis, an essential process for tumor growth that is commonly targeted by new therapeutic agents.⁴ In addition, data suggest that bisphosphonates may inhibit cellular proliferation, cause cell-cycle arrest, induce apoptosis in cancer cell lines, and inhibit multiple steps required for the development of tumor metastasis in vitro and in animal models.^{5,6} Earlier clinical data on the prevention of bone metastases were inconclusive.⁷⁻¹¹ Recently, Gnant et al reported that zoledronate, in an adjuvant setting, significantly prolonged disease-free survival beyond the time achieved with endocrine therapy alone (HR, 0.64; $P = .01$) in premenopausal women with endocrine-responsive breast cancer.¹² Investigations in multiple tumor types are currently ongoing to determine whether preclinical findings translate into consistent clinical results.

Five nitrogen-containing bisphosphonates are currently approved in the United States. The primary indications are for treatment of osteoporosis (alendronate, ibandronate, and risedronate) and treatment or prevention of skeletal-related events in patients with multiple myeloma, breast cancer, and prostate cancer (ibandronate, pamidronate, and zoledronic acid). In the current study, we compared overall survival (OS) of postmenopausal patients with nonmetastatic breast cancer who received any of the new-generation bisphosphonates: alendronate, ibandronate, risedronate, and zoledronic acid for osteopenia or osteoporosis, with the survival of those who did not, adjusting for other factors that may affect survival. An association between the use of bisphosphonate and improved survival in breast cancer patients who take one of these anti-osteoporosis drugs would have clinical and public health implications on breast cancer management.

Patients and Methods

This retrospective study conducted at the Wayne State University/Karmanos Cancer Institute (KCI) in Detroit Michigan was based on the Metropolitan Detroit Cancer Surveillance System (MDCSS), a Surveillance, Epidemiology and End Results (SEER) registry. We identified all KCI patients > 50 years of age diagnosed with stage I, II, or III

invasive breast cancer between the years 2000 through 2003. Data were extracted on age, disease stage, date of diagnosis, type of breast cancer, estrogen receptor (ER) status, progesterone receptor (PgR) status, HER2/*neu* status, type and duration of treatments, and vital status. We then reviewed the medical records of these individuals and extracted information regarding medications used during the study period, starting from date of breast cancer diagnosis.

Demographic and disease characteristics of women who received bisphosphonates were compared with those of women who did not receive bisphosphonates using t tests for continuous variables such as age, tests for trend for ordinal variables such as disease stage and chemotherapy duration, and χ^2 tests for differences in proportions for binary variables. A logistic model was used to assess the statistical significance of differences in bisphosphonate use associated with age, stage, receptor status, endocrine therapy, and vitamin D and calcium usage. A log-rank test was used to evaluate the statistical significance of differences in survival between the groups. A proportional hazards model was used to assess differences in survival, adjusting for differences between groups in demographic and disease characteristics and the proportional hazards assumption was verified.

Results

We reviewed the records of 696 patients. There were 97 women (14%) among the 696 women with nonmetastatic breast cancer whose medical records indicated use of bisphosphonates (Table 1). The most commonly used bisphosphonate was alendronate (9%), followed by risedronate (3%) and zoledronic acid (3%). Approximately one third of users of each type had been using the bisphosphonate for more than 12 months.

Bisphosphonate users and nonusers were comparable with respect to demographic and disease characteristics with the exception of receptor status ($P < .001$; Table 2). Only 5% of bisphosphonate users' tumors were ER negative (ER⁻), PgR negative (PgR⁻), and HER2/*neu* negative (HER2/*neu*⁻) compared with 28% of nonusers; 61% of users had ER-positive (ER⁺), PgR-positive (PgR⁺), and HER2/*neu*⁻ tumors compared with 48% of nonusers; however, 24% of users had discordant ER/PgR receptors and were HER2/*neu*⁻ compared with 12% of nonusers; 11% of users and 12% of nonusers had HER2/*neu* positive (HER2/*neu*⁺) tumors. Chemotherapy, surgery, and radiation therapy did not differ between users and nonusers (Table 3). However, significantly more bisphosphonate users (80%; $P < .001$) also received endocrine therapy, especially aromatase inhibitors, than did nonusers (51%). Bisphosphonate users were also significantly ($P < .001$) more likely to have used vitamin D or calcium ($P < .001$) than nonusers (Table 4).

The crude difference in OS between bisphosphonate users and nonusers was not statistically significant ($P = .32$). At 3 years, OS was 94% (95% CI, 88%–98%) for bisphosphonate users and 88% (95% CI, 86%–91%) for nonusers.

After adjusting for differences between the groups in age, stage of disease, hormone receptor status, endocrine therapy, and vitamin D and calcium use, there is a marginally significant ($P = .06$) difference in survival, but the difference is in the unexpected direction; bisphosphonate users have marginally poorer survival than nonusers (Table 5). As expected, higher stage is associated with worse survival and endocrine therapy is associated with better survival. Neither age, ER/PgR/HER2 receptor status, nor vitamin D use nor calcium use is significantly associated with survival. There is no evidence of an interaction between bisphosphonate use and hormone receptor type, eg, that among individuals with each

specific hormone receptor profile bisphosphonate users had better OS than to nonusers ($P = .75$).

Discussion

In contrast with the consistent preclinical antitumor effects of bisphosphonates, clinical studies in breast cancer have produced conflicting results.^{7–13} Clinical data on the prevention of bone metastases by the early-generation bisphosphonate clodronate yielded mixed results.^{7–10} Diel et al investigated the effects of clodronate on the incidence and extent of new metastases in a prospective randomized trial of 302 patients with breast cancer and tumor cells in the bone marrow. Results of that trial showed that clodronate can reduce the incidence and number of new bony and visceral metastases.⁷ In a larger placebo-controlled randomized trial of 1069 patients with primary operable breast cancer, Powles et al concluded that clodronate significantly reduced the risk of bone metastasis, and improved the 5-year bone relapse-free survival, with a trend toward better OS.⁸ However, Saarto et al reported that adjuvant clodronate treatment worsened survival, especially in hormone-negative patients, among whom significantly more patients on clodronate experienced non-skeletal metastases than the control group.⁹ This study has been controversial and was criticized for the following: (1) the study population was stratified by menopausal status rather than hormone receptor status; (2) premenopausal patients received chemotherapy whereas no postmenopausal patients, including ER[−] and PgR[−] cases, received adjuvant systemic chemotherapy; (3) there was a significant imbalance between the treatment and control group of patients.¹⁴

More recent studies using the second-generation nitrogen-containing bisphosphonates, such as zoledronate, pamidronate, and ibandronate have suggested an antitumor effect of these compounds in vitro via the inhibition of farnesyl diphosphonate synthase in the mevalonate pathway.^{15,16} Nitrogen-containing bisphosphonates also have antiangiogenic effects, decreasing the serum vascular endothelial growth factor (VEGF) of patients with a variety of solid tumors.¹⁷ They also appear to enhance the antitumor activity of known cytotoxic agents that were commonly used in clinical settings.¹⁸

The results of our study indicate that the use of nitrogen-containing bisphosphonates is marginally associated with worse OS in patients with nonmetastatic breast cancer, even after adjusting for known prognostic factors. Our results appear to be consistent with the results from Van Holten-Verzantvoort et al,¹¹ a randomized, multicenter clinical study performed to determine the effect of oral pamidronate treatment on the first development of bone metastases in 124 patients with breast cancer, with either locally advanced disease ($n = 33$) or extraskelatal metastases ($n = 91$), but no bone metastases. The study showed that in patients with bone metastases, oral pamidronate given for a median period of about 20 months significantly reduced skeletal morbidity and had a favorable effect on selective aspects of the quality of life of the patients, but did not alter the radiologic course of the disease or the OS of the patients. In contrast, oral pamidronate given to patients with advanced breast cancer but no demonstrable bone metastases did not prevent or delay the appearance of the first clinical or radiologic manifestation of bone metastases. A subsequent review by the same authors¹⁹ emphasized that in a series of studies, the long-term efficacy of oral pamidronate was established in the prevention and treatment of skeletal metastases in patients with breast cancer and bone metastases. In contrast, oral pamidronate given to patients with advanced breast cancer but no demonstrable bone metastases did not prevent or delay the appearance of the first clinical or radiologic manifestation of bone metastases. This treatment is therefore very effective in patients with established metastatic bone disease. More studies are needed to define the place of pamidronate (and of other bisphosphonates) in the prevention of bone metastases in patients at risk. More recently, the results of the

Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG) trial,¹² including 1,801 women with stage I and II breast cancer showed that the addition of Zoledronic acid (4 mg every 6 months) to adjuvant endocrine therapy significantly prolonged disease-free survival (DFS) and recurrence-free survival at 4 years compared with adjuvant endocrine therapy alone in premenopausal women with endocrine-responsive breast cancer. Despite little similarity between our study and the ABCSG in regards to patient population and design, it is worth noting that our study is in possible conflict with the results of the ABCSG trial. Further trials are needed to investigate the possible role of bisphosphonates antitumor activity in premenopausal women versus postmenopausal women. Also, the association between the effect of bisphosphonate and hormone receptor status of breast cancer is not clear and needs further elucidation¹³. Recently, 3 parallel companion trials (Z-FAST, ZO-FAST, and E-ZO-FAST) have evaluated the efficacy of zoledronic acid for preventing aromatase-inhibitor bone loss in postmenopausal women with hormone-responsive breast cancer.²⁰⁻²² The effect of zoledronic acid on disease recurrence and DFS was evaluated as a secondary endpoint. All 3 studies showed that up-front zoledronic acid prevents bone loss in postmenopausal women with early breast cancer but only ZO-FAST trial²³ showed decreased disease recurrence with the up-front use of zoledronic acid at 36-month analysis (HR, 0.588; $P = .0314$; $n = 1064$). The ZFAST trial showed no survival or improvement in recurrence rate to date and the ongoing E-ZO-Fast trial showed a trend in the opposite direction²⁴

An important limitation to our retrospective study is that the use of bisphosphonates was based on the clinical decision to treat osteoporosis or osteopenia. Clinically, the choice among the various nitrogen-containing bisphosphonates depends on the preference of clinicians and the adherence of patients. We have made every attempt to assess compliance and duration of treatment by reviewing the medical charts and account of the treating physicians (Table 1). Another potential limitation is the relatively smaller number of patients using bisphosphonates compared with the nonusers, which in turn may affect the ability to draw definitive conclusions. Another limitation is that SEER does not collect information on recurrence of disease; therefore, we could not evaluate differences in DFS or disease-specific mortality. Finally, patients received a variety of nitrogen-containing bisphosphonates. Variation in the composition of the bisphosphonates makes it difficult to compare efficacy, although all patients received nitrogen-containing bisphosphonates that are believed to have a similar mechanism of action. However, we believe the assessment of commonly used oral bisphosphonates in this context is useful and has practical implications.

Conclusion

We believe that this analysis raises some questions regarding the use of bisphosphonates by women with nonmetastatic breast cancer. It suggests that further research into the role of bisphosphonates is needed. While these treatments have proven efficacy in women with established metastatic bone disease, more studies are needed to define the role of bisphosphonates for patients with early stage breast cancer. Bisphosphonate use can result in significant adverse events such as osteonecrosis of the jaw and renal impairment. Reports of improved OS or DFS in breast cancer should be interpreted with caution until definitive results from ongoing large randomized controlled trials are available. Several large randomized controlled trials, such as the B-34 trial, the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial, and the SWOG 0307 trial, are being conducted to clarify the role of bisphosphonates in the adjuvant setting. These studies will assess the direct or indirect antitumor effects of bisphosphonates, according to the rate of bone metastasis, other visceral metastasis, and OS.

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Table 1

Bisphosphonate Distribution Among Users (n = 97) and Nonusers (n = 696), and Duration of Use, in Women With Nonmetastatic Breast Cancer

Bisphosphonate	Number of Patients (%)
Any Bisphosphonate Use	
No	599 (86)
Yes	97 (14)
Alendronate	
No	635 (91)
Yes	61 (9)
Alendronate Duration	
< 6 months	28 (46)
6–12 months	12 (20)
> 12 months	21 (34)
Ibandronate	
No	692 (100)
Yes	0
Risedronate	
No	674 (97)
Yes	18 (3)
Risedronate Duration	
< 6 months	7 (41)
6–12 months	4 (24)
> 12 months	6 (35)
Zoledronic Acid	
No	673 (97)
Yes	19 (3)
Zoledronic Acid Duration	
< 6 months	6 (32)
6–12 months	7 (37)
> 12 months	6 (32)

Table 2

Demographic and Disease Characteristics of Bisphosphonate Users and Nonusers, According to on Age, Stage, and Hormone Receptor Status

Characteristic	Bisphosphonate Use		P Value
	Yes (n = 97)	No (n = 599)	
Mean Age, Years (SD)	64 (10)	63 (9)	.22
Stage, n (%)			
1	43 (45)	257 (43)	.48
2	44(45)	261 (44)	
3	8(8)	76 (13)	
Receptor Status, n (%) ^a			
ER ⁺ , PgR ⁺ , HER2 ⁻	52 (61)	235 (48)	< .001
Any ER/PgR, HER2 ⁺	9 (10)	64 (54)	
ER ⁺ or PgR ⁺ , HER2 ⁻	20 (24)	60 (13)	
ER ⁻ , PgR ⁻ , HER2 ⁻	4 (5)	134 (28)	

^aPatients were grouped in 4 major groups: triple-negative (ER⁻, PgR⁻, and HER2⁻); ER positive and PgR positive and HER2 negative (ER⁺, PgR⁺, HER2⁻); ER positive or PgR positive and HER2 negative (discordant ER/PgR, HER2⁻) and HER2 positives (any ER/PgR, HER2⁺).

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor; SD = standard deviation

Table 3

A Treatment Characteristics			
Characteristic, n (%)	Bisphosphonate Users (N = 97)	Bisphosphonate Nonusers (N = 599)	P Value
Chemotherapy			
No	45 (48)	294 (50)	.65
Yes	49 (52)	289 (50)	
Chemotherapy Duration			
< 6 months	37 (82)	237 (88)	.49
6–12 months	6 (13)	22 (8)	
> 12 months	2 (4)	9 (3)	
Anthracycline			
No	57 (62)	237 (88)	.48
Yes	35 (38)	196 (34)	
Taxane			
No	74 (80)	477 (83)	.48
Yes	18 (20)	95 (17)	
Other Chemotherapy			
No	76 (83)	483 (84)	.65
Yes	16 (17)	89 (16)	
Surgery			
No	1 (1)	28 (5)	.09
Yes	96 (99)	560 (95)	
Lumpectomy			
No	93 (98)	552 (99)	.40
Yes	2 (2)	6 (1)	
Mastectomy			
No	93 (98)	550 (99)	.62
Yes	2 (2)	8 (1)	

B Treatment Characteristics			
Characteristic, n (%)	Bisphosphonate Users (N = 97)	Bisphosphonate Nonusers (N = 599)	P Value
Radiation Therapy			
No	44 (47)	271 (47)	.98
Yes	50 (53)	310 (53)	
Endocrine Therapy			
No	18 (20)	281 (49)	< .001
Yes	74 (80)	298 (51)	
Endocrine Therapy Duration			

B Treatment Characteristics			
Characteristic, n (%)	Bisphosphonate Users (N = 97)	Bisphosphonate Nonusers (N = 599)	P Value
< 6 months	13 (18)	71 (25)	.40
6–12 months	13 (18)	40 (14)	
> 12 months	45 (63)	172 (61)	
Tamoxifen			
No	55 (60)	375 (65)	.37
Yes	37 (40)	205 (35)	
Raloxifene			
No	92 (98)	590 (98)	.65
Yes	2 (2)	9 (2)	
Aromatase Inhibitor			
No	50 (54)	482 (83)	< .001
Yes	98 (17)	42 (46)	
Other Endocrine Therapy			
No	90 (98)	572 (99)	.56
Yes	2 (2)	8 (1)	

Chemotherapy, surgery, and radiation therapy did not differ between bisphosphonate users and nonusers. More bisphosphonate users (80%) received endocrine therapy, especially aromatase inhibitors, than did nonusers (51%).

Chemotherapy, surgery, and radiation therapy did not differ between bisphosphonate users and nonusers. More bisphosphonate users (80%) received endocrine therapy, especially aromatase inhibitors, than did nonusers (51%).

Table 4

Distribution, Frequency, and Duration of Vitamin D, Calcium, and Calcitonin Use Among Bisphosphonate Users and Nonusers

Characteristic, n (%)	Bisphosphonate Users (N = 97)	Bisphosphonate Nonusers (N = 599)	P Value
Vitamin D			
No	83 (88)	582 (97)	< .001
Yes	11 (12)	17 (3)	
Vitamin D Duration			
< 6 months	0	7 (47)	.02
6–12 months	2 (22)	0	
> 12 months	7 (78)	8 (53)	
Calcitonin			
No	91 (98)	595 (99)	.15
Yes	2 (2)	4 (1)	
Calcitonin Duration			
< 6 months	0	1 (25)	.44
> 12 months	2 (100)	3 (75)	
Calcium			
No	66 (70)	535 (89)	< .001
Yes	28 (30)	64 (11)	
Calcium Duration			
< 6 months	4 (15)	20 (33)	.10
6–12 months	5 (19)	16 (26)	
> 12 months	17 (65)	25 (41)	

Table 5

Overall Survival Analysis

Overall Survival Measure	Overall Survival Hazard Ratio (95% CI)	P Value
Bisphosphonate Use		
Yes	1.29 (0.99–1.67)	.06
No	1.00	
Age	1.00 (0.99–1.01)	.41
Stage		
I	1.00	.0002
II	1.00 (0.84–1.22)	
III	1.66 (1.26–2.19)	
Receptor Status		
ER ⁺ , PgR ⁺ , HER2 ⁻	1.00	.54
ER ⁻ , PgR ⁻ , HER2 ⁻	0.95 (0.74–1.22)	
ER ⁺ or PgR ⁺ , HER2 ⁻	1.16 (0.90–1.50)	
Any ER/PgR, HER2 ⁺	1.11 (0.83–1.48)	
Vitamin D Use	0.45	
Yes	0.74 (0.45–1.21)	.23
No	1.00	
Calcium Use		
Yes	0.99 (0.72–1.34)	.93
No	1.00	
Endocrine Therapy		
Yes	0.67 (0.55–0.83)	< .001
No	1.00	

After adjusting for differences between the groups in age, stage of disease, hormone receptor status, endocrine therapy, and vitamin D and calcium use, bisphosphonate users have marginally poorer survival than nonusers.

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor