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Research Paper

Exposure to alendronate is associated with a lower risk of bone metastases in osteoporotic women with early breast cancer

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ABSTRACT

Background: Bisphosphonate (BP) treatment to prevent bone loss in breast cancer patients is already well established. However, data on the association between oral BP exposure before cancer diagnosis and disease outcomes in patients with early breast cancer are still scarce. Limited information is available on alendronate, the most common oral agent for the treatment of post-menopausal osteoporosis, regarding the association with bone metastases.

Aim: To examine the association between oral bisphosphonate exposure before cancer diagnosis and the risk of bone metastases in osteoporotic women diagnosed with early breast cancer.

Subjects and methods: This historical cohort study was conducted at the oncology division at Tel Aviv Medical Center. The study population included post-menopausal women with early breast cancer, diagnosed between 2002 and 2012. Data on cancer characteristics, diagnosis of osteoporosis, prior bisphosphonate exposure and outcome were collected from medical files.

Results: Among 297 osteoporotic women identified, 145 (49%) were treated with bisphosphonates (alendronate in 90% of the cases) before cancer diagnosis. BP-treated women were significantly older than the BP-naïve ones (67.9 years vs 64.6 years, $p = 0.01$), but comparable in risk factors and disease characteristics. Over a mean follow up of 5.6 years, nine cases of bone metastases were identified, eight of them among BP-naïve patient (cumulative incidence of 9.9%) and one among BP-treated patients (0.7%). In a multivariable Cox's proportional hazards survival model the use of BP prior to cancer diagnosis was associated with a hazard ratio of 0.04 (95%CI:0.004–0.403, $p = 0.006$) for bone metastasis. The HR remained similar after further adjustment for tumor stage and cancer therapy.

Conclusions: History of alendronate use is associated with a lower likelihood of bone metastases in post-menopausal women with early breast cancer. Oral bisphosphonate treatment could be sufficient for reducing the risk of bone metastases.

Introduction

Breast cancer is the most common cancer in women, accounting for approximately 25% of all cancers [1,2], reaching 31% in Israel [3,4]. The long-term outcome has significantly improved, but recurrence and mortality rates are still substantial [5,6,7] with bone remaining the most common site of breast cancer metastases. The predilection of cancer cells for the bone is not entirely understood. In 1889, Paget suggested the "seed and soil" hypothesis proposing that tumor cells circulate to the bone which provides a favorable microenvironment for tumor cell seeding [8]. The bone is an attractive soil due to physical properties such as acidic pH and high calcium concentration, and the production of osteolysis-promoting growth factors such as transforming growth factor, insulin-like-growth factors, platelet-derived growth factor and members of the bone morphogenic protein family. The osteolysis process, in turn, leads to the release of tumor-promoting growth

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factors further contributing to this vicious cycle [9,10,11,12,13].

Bisphosphonates (BP) are potent inhibitors of bone turnover, and are approved and widely used for the treatment of osteoporosis. BP inhibit osteoclasts and affect T-cell function, and hence, could also be an effective adjuvant treatment, particularly in preventing or delaying recurrence in bone [14,15]. Improvements in bone-metastasis-free survival, disease-free survival, and overall survival in women with early breast cancer have been reported in some trials in which the oral bisphosphonate clodronate [16,17,18] or intravenous zoledronic acid [19,20,21,22] were used as adjuvant treatment. Zoledronic acid is the only bisphosphonate for which recent data on clinical outcomes for postmenopausal women in the adjuvant setting has been presented [23,24]. The earliest clinical trials which used the oral agent clodronate to reduce disease recurrence in women with early breast cancer were promising, albeit inconsistent [16,17,18,25]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) summarized the data on the topic and concluded that adjuvant bisphosphonates reduced the rate of breast cancer recurrence in the bone and improve breast cancer survival [26]. However, no data was available on alendronate [26].

In recent years, a few studies have examined the association between the new generation oral BP and breast cancer outcomes. Kremer et al. conducted a prospective study of a historical cohort of 21,664 women who had been diagnosed with breast cancer from 1998 to 2005; the principal outcome was the incidence of bone metastases. The pre-diagnosis use of BP and cessation at cancer diagnosis was associated with an increase in bone metastases incidence, whereas exposure before and continuing after the cancer diagnosis, or post-diagnosis exposure only was associated with a decrease in bone metastases incidence [27]. The study population included pre and post-menopausal women, osteoporotic and non-osteoporotic women, and the BP exposure was pre or post-breast cancer diagnosis which makes the results interpretation difficult. Recently, Rennert et al. published the results of a nested case-control analysis using data from a cohort of 3731 postmenopausal women with newly diagnosed breast cancer. They reported that the use of second-generation bisphosphonates (alendronate and risedronate) before diagnosis was associated with a significant improvement in overall and breast-specific odds of survival [28]. Lipton et al. published the results of a study on osteoporosis therapy and outcomes in postmenopausal hormone-receptor-positive breast cancer patients treated with adjuvant aromatase inhibitors. Oral osteoporosis treatment administered to postmenopausal breast cancer patients receiving adjuvant AI therapy was associated with improved event-free survival and distant disease-free survival [29]. Osteoporosis diagnosis and treatment were self-reported in this study, and no data were available on the kind of treatment received.

Alendronate is the most widely used oral agent for the treatment of post-menopausal osteoporosis over the past decades, and data is still needed on its association with breast cancer outcome. Our study aims to further assess the association between the previous use of oral bisphosphonate treatment for osteoporosis, specifically alendronate, and the incidence of bone metastases in a population of osteoporotic postmenopausal early breast cancer patients.

Subjects and methods

This historical cohort study was conducted at the oncologic clinic at Tel Aviv Medical Center between the years 2014–2016. The study population included post-menopausal women diagnosed with early breast cancer between January 1st 2002 and December 31st 2012, i.e., breast cancer that has not spread beyond the breast or the axillary lymph nodes, which includes invasive ductal stage I, stage IIA, stage IIB, and stage IIIA breast cancers. Women under the age of 50 and women with previous or other malignancy were excluded. The index date was at breast cancer diagnosis according to the patients' file, and the end of follow up was set as the last documented visit in the file (hospital or health services file), date of bone recurrence or date of death, whichever occurred first.

The study endpoint was the incidence of skeletal metastases. The diagnosis of breast cancer was extracted from the medical file and confirmed by pathological reports in all files. We collected data on, size, lymph nodes involvement, grade, estrogen progesterone receptors expression, Her-2 expression, and treatment regimen: adjuvant chemotherapy, radiotherapy, tamoxifen, and aromatase inhibitors (AI) agents. The diagnosis of cancer recurrence, metastases or death was extracted from the medical records, and pathological reports, bone scans, CT scans, and PET-FDG. The diagnosis of bone metastases was established if either a PET-FDG scan or CT scan indicated bone involvement. The diagnosis of osteoporosis was confirmed based on data retrieved from the patient files. We reviewed the medical history searching for a diagnosis of osteoporosis based on a history of previous major osteoporotic fracture (hip, vertebra, distal radius, humerus), a pathologic bone mineral density report (lumbar spine or femoral neck or total hip T-Score < -2.5 using GE Lunar Prodigy or Hologic Discovery DXA systems) or osteoporotic medications use. Subjects were considered osteoporotic if meeting at least one of these criteria.

Bisphosphonate exposure was established from the medical file. We searched the chronic medication list and computerized purchases from the health maintenance organizations. Telephone interviews were completed to collect accurate data on exposure duration. Any exposure of one-year duration, occurring at least one year before cancer diagnosis was considered as exposure. Subjects with less than one year of documented exposure were excluded.

We collected data on the following variables: age at diagnosis, body mass index (BMI), socio-economic status (SES), smoking, family history of breast cancer, and hormonal replacement therapy (HRT). Due to a high percentage of missing values, some of the variables were excluded from the models presented below (Tables 1–3).

We used Cox's proportional hazards regression model to build the multivariable survival model. The multivariate model was based on a stepwise forward selection of the data. The variables included were age at diagnosis, BMI, SES, smoking, HRT use, family history, tumor size, lymph nodes involvement, grade, estrogen progesterone receptors expression, Her-2 expression, and treatment regimen: adjuvant chemotherapy, radiotherapy, tamoxifen, and aromatase inhibitors (AI) agents (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The proportional hazard assumption was tested based on Schoenfeld residuals regressed on follow-up time, and it was met by all covariates ($p > 0.1$).

The study protocol was approved by the local medical ethical committee of the Tel Aviv Sourasky medical center and complies with the Declaration of Helsinki and principles of Good Clinical Practice. Informed consent was obtained from patients before the telephonic interviews.

Results

From 1000 breast cancer files reviewed, 297 osteoporotic women were identified according to data from the medical files. The mean age at diagnosis was 64.7.4 ± 10.4, as expected the osteoporotic women were older than the non-osteoporotic ones (66.8 ± 9.9 versus 61.5 ± 8.5, $p < 0.001$). Regarding BMI, Socioeconomic status, smoking status, parity, age at menopause there were no significant differences between the two populations. There were no significant differences between osteoporotic and non-osteoporotic women regarding grade at diagnosis, stage, and hormonal receptor status.

In the 297 osteoporotic subjects identified, 145 (49%) were treated with bisphosphonates before cancer diagnosis. Ninety percent of BP-treated subjects received alendronate, 10% received risedronate. Regarding the remaining 51%, the majority of them (62%) received calcium and vitamin supplements, and no BP use was confirmed from the files (Fig. 1). Treatment duration was not documented in the files and assessed by telephonic interviews for a sample of subjects

Table 1
Characteristics of the osteoporotic women within the study population: BP treated versus BP-naïve.

	All OP	NAIVE	BP users	p
N	297	81	145	
Age at diagnosis (mean (sd))	66.78 (9.97)	64.62 (9.52)	67.99 (9.76)	0.013
Age at menopause (mean (sd))	50.31 (4.71)	50.62 (4.54)	50.13 (5.01)	0.692
Smoking (%)				0.371
No	126 (43.0)	35 (43.2)	69 (47.6)	
Yes	54 (18.4)	19 (23.5)	23 (15.9)	
Missing	113 (38.6)	27 (33.3)	53 (36.6)	
Family history (%)				0.556
No	116 (39.6)	29 (35.8)	62 (42.8)	
Yes	68 (23.2)	21 (25.9)	31 (21.4)	
Missing	109 (37.2)	31 (38.3)	52 (35.9)	
BMI.grp (%)				0.605
< 20	6 (2.0)	1 (1.2)	4 (2.8)	
20–24	36 (12.3)	12 (14.8)	19 (13.1)	
25–29	48 (16.4)	18 (22.2)	24 (16.6)	
30–34	14 (4.8)	3 (3.7)	10 (6.9)	
35+	11 (3.8)	5 (6.2)	5 (3.4)	
Missing	178 (60.8)	42 (51.9)	83 (57.2)	
Parity (%)				0.422
0	30 (10.2)	9 (11.1)	14 (9.7)	
1	40 (13.7)	14 (17.3)	16 (11.0)	
2	99 (33.8)	28 (34.6)	46 (31.7)	
> = 3	94 (32.1)	24 (29.6)	49 (33.8)	
Missing	30 (10.2)	6 (7.4)	20 (13.8)	
HRT (%)				0.667
No	42 (14.3)	14 (17.3)	20 (13.8)	
Yes	51 (17.4)	18 (22.2)	29 (20.0)	
Missing	200 (68.3)	49 (60.5)	96 (66.2)	
DCIS = yes (%)	88 (31.0)	19 (24.4)	53 (37.1)	0.076
IDC = yes (%)	276 (95.8)	76 (96.2)	133 (93.7)	0.625
Grade(%)				0.471
1	26 (8.9)	9 (11.1)	10 (6.9)	
2	116 (39.6)	26 (32.1)	60 (41.4)	
3	50 (17.1)	14 (17.3)	23 (15.9)	
Missing	101 (34.5)	32 (39.5)	52 (35.9)	
ER (%)				0.373
No	31 (10.6)	6 (7.4)	18 (12.4)	
Yes	260 (88.7)	75 (92.6)	126 (86.9)	
Missing	2 (0.7)	0 (0.0)	1 (0.7)	
Lymph nodes positive(%)				0.479
No	177 (60.4)	48 (59.3)	91 (62.8)	
Yes	61 (20.8)	18 (22.2)	23 (15.9)	
Missing	55 (18.8)	15 (18.5)	31 (21.4)	
Tumor size (cm, mean SD)	1.69 (1.2)	1.90 (1.3)	1.64 (1.1)	0.169
T1 [%]		26	31	0.507
T2[%]		35	32	
T3 [%]		37	34	
AI (%)				0.005
No	126 (43.0)	38 (46.9)	62 (42.8)	
Yes	118 (40.3)	37 (45.7)	48 (33.1)	
Missing	49 (16.7)	6 (7.4)	35 (24.1)	
Radiotherapy (%)				0.163
No	58 (19.8)	13 (16.0)	31 (21.4)	
Yes	204 (69.6)	62 (76.5)	94 (64.8)	
Missing	31 (10.6)	6 (7.4)	20 (13.8)	
Chemotherapy (%)				0.018
No	184 (62.8)	58 (71.6)	88 (60.7)	
Yes	63 (21.5)	17 (21.0)	25 (17.2)	
Missing	46 (15.7)	6 (7.4)	32 (22.1)	
Established bone metastases	**9 (4)**	**8 (9.9)**	**1 (0.7)**	**0.001**

(supplement), the majority received BP for a period of 1–5 years. BP-treated women were significantly older than the naïve ones (67.9 ± 9.7 years 64.6 ± 9.5 years, $P = 0.013$). No significant differences were noted regarding BMI, smoking status, parity or socio-economic status. Cancer characteristics including tumor grade, size, positive lymph nodes and hormonal receptor status were similar between the two groups. The treatment received was slightly different: BP-naïve women received more aromatase inhibitors (45% vs 33%,

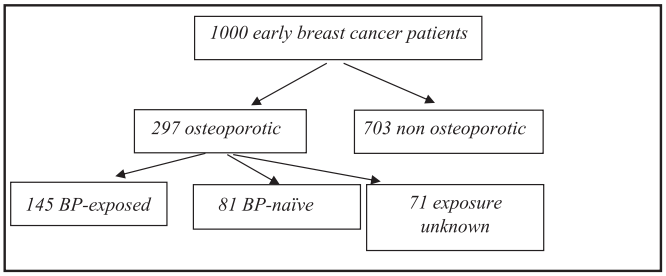

Fig. 1. The study cohort.

Table 2
Hazard ratio for bone metastases adjusted for age at diagnosis and BMI -parsimonious model.

	HR	CI lower limit	CI upper limit	*p* value
Age at diagnosis (per year)	1.039	0.964	1.120	0.315
BMI (per 1 Kg/m2)	0.975	0.777	1.224	0.829
Bisphosphonate exposure (any vs none)	**0.040**	**0.004**	**0.403**	**0.006**

Table 3
Hazard ratio for bone metastases adjusted for tumor stage.

	HR	CI lower limit	CI upper limit	*p* value
Age at diagnosis (per year)	1.108	0.998	1.231	0.057
BMI (per 1 Kg/m2)	0.919	0.702	1.202	0.536
Tumor size > 3 cm	0.414	0.051	3.327	0.407
Lymph nodes positive	7.429	1.347	40.988	0.021
Estrogen receptor positive	0.532	0.071	3.987	0.539
Bisphosphonate exposure	**0.032**	**0.004**	**0.451**	**0.009**

Table 4
Hazard ratio for bone metastases adjusted for treatment.

	HR	CI lower limit	CI upper limit	*p* value
Age at diagnosis (per year)	1.053	0.917	1.210	0.466
Lymph nodes	4.172	0.383	45.646	0.241
Estrogen receptor	0.097	0.003	3.490	0.202
Adjuvant chemotherapy	0.766	0.043	13.555	0.856
Radiotherapy	0.236	0.010	5.504	0.369
Tamoxifen treatment	0.571	0.041	8.042	0.678
Bisphosphonate exposure	**0.040**	**0.002**	**0.834**	**0.038**

$p < 0.05$) and slightly more adjuvant chemotherapy (21% vs. 17%, $p < 0.018$) (Table 1). The mean follow-up duration was 5.6 ± 3.8 years from the date of breast cancer diagnosis for the entire cohort, 6.1 ± 3.6 for the osteoporotic subjects. The mean follow up was similar for the two groups: 6.3 ± 4.5 for the BP treated women and 6.4 ± 3.4 for the non-treated women ($p = 0.310$).

We registered 45 cases of disease recurrence, 31 were local and 14 were distal: 9 cases of bone metastases, 3 cases of liver, 1 case of lung and 1 case of brain metastases. Only recurrence to bone was significantly lower in the BP treated subjects (Table 1). A Cox proportional hazards survival model adjusted for age at diagnosis and BMI showed that previous exposure to oral bisphosphonates was significantly associated with reduced incidence of bone metastases: HR = 0.04 (95%CI 0.004–0.403, $p < 0.006$) (Table 2). This association remained significant after adjustment for tumor stage: HR = 0.032 (95%CI 0.004–0.451, $p < 0.009$) (Table 3) as well as after adjustment for treatment: HR = 0.040 (95%CI 0.002–0.834, $p < 0.038$) (Table 4).

Discussion

In this cohort of post-menopausal osteoporotic early breast cancer

patients, we found a significant negative association between prior exposure to oral bisphosphonates, mostly alendronate, and the incidence of bone metastases. The evidence that bisphosphonate treatment is beneficial to preserve bone mass in breast cancer patients is already well established [30], and the possibility of preventing skeletal events with an available, safe and non-expensive oral agent is very encouraging. The high-dose and highly potent antiresorptive agents which are usually used in the oncologic setting have potential serious side effects. The use of oral agents could reduce the incidence of osteonecrosis of the jaw (ONJ), a side effect more frequently seen with zoledronic acid or denosumab [31,32].

Our cohort is small, yet it has some strengths: unlike previous reports all study subjects 1) were post-menopausal women; 2) were diagnosed with osteoporosis; and 3) had BP exposure preceding the diagnosis of breast cancer, which limits the possibility of confounding by indication. Our study also has limitations. The data on exposure was limited to the kind of agent prescribed in the medical files, and we completed the data on exposure duration only partially by telephonic interviews. Data on adherence and persistence was not available. We did not collect data on BP exposure after the cancer diagnosis, and some subjects may have discontinued the treatment. BP are commonly prescribed to treat AI-associated bone loss so we may assume that most of the subjects continue to receive BP after being diagnosed. Moreover, BP accumulate in the bones and usually have a prolonged effect even after discontinuation, especially alendronate.

The mean follow up was similar for the BP-treated and non-treated groups (6.3 ± 4.5 versus 6.4 ± 3.4 years), so our results are relevant to disease recurrence within 5 years from diagnosis. Longer studies are needed to evaluate long-term recurrence and outcome.

This is an observational study and results interpretation is complicated by the influence of confounding variables. Clinico-pathological factors related to the development of bone metastases in breast cancer patients are not well established [33]. Still, our results remained significant after adjustment for age, tumor size, lymph nodes involvement, and therapy. Missing data for variables like BMI, HRT, tumor grade and other possible confounders were taken into account in the statistical analysis, and demand precaution in the interpretation of our results. Although significant, our results are based on a small number of events and more extensive studies are obviously needed to confirm our findings.

Conclusions

In line with previous studies, our data show that exposure to Alendronate, the most widely prescribed oral bisphosphonate for the treatment of osteoporosis, is associated with a lower likelihood of bone metastases in post-menopausal women with early breast cancer. Oral BP treatment could be sufficient for reducing the risk of bone metastases, while possibly reducing the risk of intravenous high dose BP which are more frequent in oncologic patients. Women at risk of recurrence may benefit from the prompt initiation of oral bisphosphonate treatment.

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Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2018.07.011.

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