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Research Paper

Increased risk of SSEs in bone-only metastatic breast cancer patients treated with zoledronic acid

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ABSTRACT

Background: Bone represents one of the most common sites to which breast cancer cells metastasize. Patients experience skeletal related adverse events (pathological fractures, spinal cord compressions, and irradiation for deteriorated pain on bone) even during treatment with zoledronic acid (ZA). Therefore, we conducted a retrospective cohort study to investigate the predictive factors for symptomatic skeletal events (SSEs) in bone-metastasized breast cancer (b-MBC) patients.

Methods: We retrospectively collected data on b-MBC patients treated with ZA. Patient characteristics, including age, subtype, the presence of non-bone lesions, the presence of multiple bone metastases at the commencement of ZA therapy, duration of ZA therapy, the time interval between breast cancer diagnosis and the initiation of ZA therapy, and type of systemic therapy, presence of previous SSE were analyzed using multivariable logistic regression analysis.

Results: The medical records of 183 patients were reviewed and 176 eligible patients were analyzed. The median age was 59 (range, 30–87) years. Eighty-seven patients were aged ≥60 years and 89 patients were aged < 60 years. The proportions of patients with estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2-positive disease were 81.8%, 63.1%, and 17.6%, respectively. Fifty-three patients had bone-only MBC at the commencement of ZA therapy. SSEs were observed in 42 patients. In the multivariable logistic regression analysis, bone-only MBC but not a breast cancer subtype was an independent risk factor for an SSE during ZA therapy (odds ratio: 3.878, 95% confidence interval: 1.647–9.481; p = 0.002).

Conclusions: Bone-only MBC patients are more likely to experience an SSE even after treatment with ZA.

1. Introduction

Bone represents one of the most common sites to which breast cancer cells metastasize. Patients with bone involvement account for approximately up to 80% of those with metastatic breast cancer (MBC) [1]. The ramifications of skeletal related adverse events (SREs) (e.g., pathological fractures, spinal cord compressions, and irradiation for deteriorated pain on bone) are potentially a threat to the wellbeing of patients with bone-metastasized breast cancer (b-MBC) and could impair their quality of life throughout their clinical course. Therefore, the prevention of SREs in patients with b-MBC is a relevant strategy that is especially the case in patients with tumors that frequently metastasize to the bone (e.g., breast cancer, prostate cancer, and lung cancer).

Bisphosphonates (BPs) are a key component of therapy for the prevention of unwarranted SREs and for maintaining the quality of life of patients with bone metastases. BPs accumulates in bone on

Abbreviations: b-MBC, bone-metastasized breast cancer; BP, bisphosphonate; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; OR, odds ratio; PgR, progesterone receptor; SRE, skeletal related adverse event; SSE, symptomatic skeletal event; TN, triple-negative; ZA, zoledronic acid

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administration and osteoclast cells consume BPs through bone absorption, leading to apoptosis of osteoclast cells via abrogation of the Ras/MEK/ERK pathway [2].

The BPs zoledronic acid (ZA) and ibandronate are clinically proven to reduce SREs in patients with bone metastases from a wide variety of tumors. ZA compared with placebo reduced the rate of SREs by 39% and delayed the time to the first SRE [3]. However, there are still patients with b-MBC who experience SREs even during treatment with ZA. According to a previous study [4], N-telopeptide of type 1 collagen is a predictive factor for SREs in patients with b-MBC during treatment with BP therapy. In another study [5], the authors also reported that age, pain score, a prior history of a SRE, predominant lesion type, elevated levels of bone-specific alkaline phosphatase, and lactate dehydrogenase were predictive factors for the first SRE. Meanwhile, there are no reports evaluating the prognostic significance of breast cancer subtypes, as defined by ER, PgR, and HER2 expression, in b-MBC patients treated with ZA. Therefore, it may be postulated that the efficacy of ZA and the propensity towards SREs could vary among patients with different subtypes of b-MBC. In the present study, we hypothesize that clinical characteristics, including breast cancer subtype, the number of bone metastases, and involvement of other organs, are of relevance in predicting the occurrence of SREs in b-MBC patients treated with ZA. In order to test this hypothesis, it is necessary that we conduct a comparative study of ZA versus placebo in patients with bone metastases. However, it is no longer ethical to conduct such a study in a clinical setting. Therefore, we performed a retrospective cohort study to investigate the predictive values of breast cancer subtype, the number of bone metastases, and the involvement of other organs, in patients with b-MBC.

2. Material and methods

We retrospectively collected clinical datasets from the medical records of 183 patients with b-MBC who underwent treatment with ZA therapy at Kindai University Hospital (Osaka, Japan) and the Hyogo Cancer Center (Hyogo, Japan) between January 2007 and December 2011. Seven patients (3.8%) who were treated with ZA therapy for other purposes (e.g., hypercalcemia) were excluded from our analysis.

Univariable and multivariable analyses were conducted to elucidate the risk factors for a SRE using patient characteristics, including age, subtype, the presence of non-bone lesions, the presence of multiple bone metastases at the commencement of ZA therapy, treatment duration of ZA therapy, the time interval between breast cancer diagnosis and the initiation of ZA therapy, type of systemic therapy and presence of previous SSE. Tumors with immunohistochemical staining of $> 1\%$ for ER and/or PgR were considered hormone receptor (HR)-positive. HER2 was considered positive if the HercepTest™ score was 3+ or fluorescent in situ hybridization was positive. Fluorescent in situ hybridization analysis was performed on all specimens with a HercepTest™ score of $\geq 2+$. Patients with HR-positive and HER2-negative, HER2-positive, and HR-negative and HER2-negative tumors were classified into the HR-positive, HER2-positive, and triple-negative (TN) groups, respectively.

A symptomatic skeletal event (SSE) was defined as a pathological fracture, radiation therapy/surgery to the bone, or a spinal cord compression.

3. Statistical analysis

A multivariable logistic regression analysis was applied to estimate the odds ratio (OR) and 95% confidence intervals (CIs) of various factors on the incidence of a SSE. All statistical analyses were conducted using JMP software, version 9 (SAS Institute Inc., Cary, NC, USA). A $p < 0.05$ was considered statistically significant.

Table 1
Baseline characteristics.

	n = 176	%
Median age (y)	59 (30–87)[1]	
≧ 60	87	49.4
< 60	89	50.6
ER status		
positive	144	81.8
negative	32	18.2
PgR status		
positive	111	63.1
negative	65	36.9
HER2 status		
positive	31	17.6
negative	145	82.4
Metastases		
Bone only	53	30.1
Presence of other metastases	123	69.9
Bone metastases		
Localized	54	30.7
Multiple	122	69.3
Prior therapy		
Hormonal therapy		
yes	27	15.3
no	149	84.7
Chemotherapy		
yes	27	15.3
no	149	84.7
Combined therapy		
Hormonal therapy		
yes	127	72.2
no	49	27.8
Chemotherapy		
yes	137	77.8
no	39	22.2
The median period from diagnosis of BC to the start of ZA therapy (month)	55.5 (0–349)[2]	
Prior to SSE		
yes	27	15.3
no	149	84.7
The median period of ZA therapy (month)	15.5 (0.4–56.1)[2]	

Abbreviations: ER estrogen receptor; PgR progesterone receptor; HER2 human epidermal growth factor 2 receptor, BC breast cancer, ZA zoledronic acid.
[1] mean (range).
[2] median(range).

4. Results

4.1. Patient characteristics

Data were analyzed from 176 eligible patients. A summary of the patients' baseline characteristics is presented in Table 1. The median age was 59 (range, 30–87) years. Eighty-seven patients (49.4%) were aged ≥ 60 years and 89 patients (50.6%) were aged < 60 years. One hundred and forty-four patients (81.8%) were ER-positive, 111 patients (63.1%) were PgR-positive, and 31 patients (17.6%) were HER2-positive. Twenty-seven patients (15.3%) were receiving hormone therapy prior to ZA therapy and 27 patients (15.3%) were receiving chemotherapy prior to ZA therapy. Twenty-seven patients (15.3%) had presence of previous SSE prior to ZA therapy. Patients were categorized based on the evaluation of HR and HER2 status. The HR-positive group contained 125 patients (71.0%), the HER2-positive group contained 31 patients (17.6%), and the TN group contained 20 patients (11.4%). The characteristics of 53 patients (30.1%) with disease remaining confined to the bone and 123 patients (69.9%) who subsequently developed metastases at non-osseous sites are presented in Table 1. Details of the 123 patients (69.9%) with metastases at non-osseous sites are summarized in Table 2.

Patients were also stratified into two groups according to the number and distribution of bone metastases: those with single bone metastasis ($n = 54$, 30.7%) and those with multiple bone metastases (n

Table 2
The detail of metastases site.

	n	%
Metastases site		
Bone only	53	30.1
Lung	45	25.6
Liver	33	18.8
Lymph node	89	50.6
(Regional lymph nodes[1])	(25)	
Other	29	16.5
Site of bone metastases		
Cervical	25	
Thoracic	70	
Lumbar	72	
Sacral	42	
Rib	70	
Ilium	43	
Sternum	42	
Scapula	24	
Femur	24	
Other	19	

[1] Shows the patients metastasized regional lymph nodes.

= 122, 69.3%) (Table 1). Table 2 lists the occurrence sites of bone metastasis in the 176 eligible patients in this study. The median time interval between the diagnosis of breast cancer and the initiation of ZA therapy was 55.5 (range, 0–349) months and the median duration of ZA therapy was 15.5 (range, 0.4–56.1) months (Table 1). One hundred and twenty seven patients (72.2%) received hormone therapy in combination with ZA therapy and 137 patients (77.8%) received chemotherapy in combination with ZA therapy.

4.2. Symptomatic skeletal events

Forty-two patients (23.9%) developed a SSE during ZA therapy. Thirty patients (17.1%) were included in the HR-positive group, 8 patients (4.6%) in the HER2-positive group, and 4 patients (2.3%) in the TN group, respectively (Table 3). Of the 42 patients with a SSE, 12 patients (28.6%) developed pathological fractures, 4 patients (9.5%) developed a spinal cord compression, and 6 patients (14.3%) underwent surgery for a bone fracture or spinal cord compression. Radiation was delivered to the bone in 25 patients (59.5%; Table 4). None of the patients developed an atypical femoral fracture. In > 70% of patients, a SSE during ZA therapy occurred at existing bone metastatic sites: radiation therapy was 72.0%, fracture surgery was 81.8%, spinal cord compression was 100%, surgery was 83.3%. The incidence rates of each subtype were 24.0%, 25.8%, and 20.0% for the HR-positive group, HER2-positive group, and TN group, respectively.

4.3. Multivariable analysis

A multivariable logistic regression analysis revealed that breast cancer subtype was not associated with the incidence of a SSE during ZA therapy (TN/HR-positive groups [OR: 1.016, 95% CI: 0.206–4.427; p = 0.983] and HER2/HR-positive groups [OR: 1.158, 95% CI: 0.405–3.118; p = 0.777]). Conversely, the risk of developing a SSE was significantly greater in the group of patients whose disease was confined to the bone at the commencement of ZA therapy (OR: 3.878, 95% CI: 1.647–9.481; p = 0.002) compared to the group of patients who developed metastases at non-osseous sites. Moreover, the risk of developing a SSE was significantly greater in the group of patients who treated chemotherapy with ZA therapy (OR: 3.116, 95% CI: 1.052–10.682; p = 0.040) compared to the group of patients without chemotherapy (Table 5).

Table 3
The incidence rate of 1st SSE during ZA therapy in each subtypes.

	Characteristics N = 176 (%)	patients with a SRE N = 42 (% of patients with a SRE)
the HR positive group	125(71.0%)	30(71.4%)
the TN group	20(11.4%)	4(9.5%)
the HER2 positive group	31(17.6%)	8(19.1%)

Abbreviations: HR hormone receptor; TN triple negative; HER2 human epidermal growth factor 2 receptor; SSE symptomatic skeletal events.

Table 4
The detail of 1st SSE.

	N 42	**% 23.9**	**Time to SSE[a] (m) 11.9**
Radiation therapy	25	14.2	15.2
Lumbar	8		
Thoracic	6		
Cervical	2		
Sacral	2		
Ilium	2		
Other	5		
Fracture	12	6.8	6.3
Lumbar	4		
Thoracic	3		
Femur	3		
Other	2		
Spinal cord compression	4	2.3	13.6
Surgery	6	3.4	9.2
Spinal cord	3[b]		
Femur	2[b]		
Lumbar	1		

[a] Time to SSE; time between initiation of ZA and 1st SSE.
[b] We considered 5 patients who had surgery as multiple SSEs.

5. Discussion

Intravenous BP therapy is the standard of care for the prevention of skeletal-related complications in patients with b-MBC in the observation period. The American Society of Clinical Oncology recommends initiating treatment with intravenous BP therapy in breast cancer

Table 5
Multivariable analysis of predictive factors for occurrence of SSE.

	Odds ratio	**95% CI**	**p value**
age[a]	1.013	0.978–1.050	0.458
TN / HR positive	1.016	0.206–4.427	0.983
HER2 positive / HR positive	1.158	0.405–3.118	0.777
Presence of metastases Bone only / Other	3.878	1.647–9.481	0.002
Bone metastases Multiple / Local	2.454	0.985–6.792	0.054
Hormonal therapy prior to ZA Yes / No	1.794	0.547–5.635	0.327
Chemotherapy prior to ZA Yes / No	1.128	0.322–3.704	0.845
Hormonal therapy with ZA Yes / No	1.746	0.641–5.225	0.282
Chemotherapy with ZA Yes / No	3.116	1.052–10.682	0.040
The period from diagnosis of BC to the start of ZA[a]	1.022	0.949–1.113	0.577
The period of ZA[a]	1.000	1.000–1.002	0.074
SSE prior to ZA	2.041	0.743–5.460	0.163

Abbreviations: HR hormone receptor; TN triple negative; HER2 human epidermal growth factor 2 receptor, BC breast cancer,
ZA zoledronic acid.
[a] Continuous variable.

patients with evidence of bone destruction on plain radiographs [6]. However, there are still patients who experience SREs during treatment with ZA. HR and HER2 status is an important factor in selecting the most appropriate therapy. Furthermore, treatment selection by breast cancer subtype (e.g., TN, luminal, or HER2) has been shown to influence survival. Thus, we hypothesized that the efficacy of ZA could be dependent on subtype since breast cancer is a heterogeneous disease in terms of its biology. In this study, the incidence rates of SSEs were comparable across the three different subtypes: 24.0% for the HR-positive group, 25.8% for the HER2-positive group, and 20.0% for the TN group (not significant). These findings suggested that the incidence rates of SSEs in breast cancer patients treated with ZA were unrelated to subtype. In several studies [7,8] investigating the relationship between the incidence of bone metastasis and breast cancer subtype, bone relapse patients were observed most frequently in the luminal group, suggesting that HR-positive patients may be more prone to SREs than patients with other subtypes. In the univariate analysis, a correlation between breast cancer subtype and the duration of ZA therapy demonstrated that patients in the TN group had a significantly shorter treatment duration ($p = 0.045$), indicating the aggressive nature of the TN subtype in terms of disease progression and survival. Although the duration of ZA therapy in the TN group was short, there were no differences in the incidence rates of SSEs in the different subtypes.

Recent studies [9] suggested that the tumor recurrence and mortality rates in women with HR-positive breast cancer were reduced significantly by the use of 10 years of adjuvant tamoxifen in both the presence and absence of chemotherapy. Aromatase inhibitors are recommended as adjuvant treatment for post-menopausal women with HR-positive early-stage breast cancer. Aromatase inhibitors inhibit estrogen production in post-menopausal women, resulting in bone loss by reducing the levels of endogenous estrogen [10]. Therefore, it is important to investigate whether or not endocrine therapy influences the incidence of SREs in the population. In a multivariable logistic regression analysis, endocrine therapy was not observed to increase the incidence of SSEs during ZA therapy in this study.

Patients with disease confined to the skeleton experience SSEs during ZA therapy significantly more frequently ($p < 0.05$) compared to those patients who develop metastases at non-osseous sites. Plunkett et al. [11] reported that patients with MBC confined to the skeleton were most likely to develop a pathological fracture in four groups: the bone-only, bone and soft tissue, bone and pleuropulmonary, and bone and liver disease groups, respectively. Patients with bone-only disease were most likely to require radiotherapy to the site of painful bone metastasis and most rapidly developed spinal cord compression [11]. Our findings were consistent with this report. Conversely, Coleman et al. [12] reported that patients with bone-only disease have a longer median survival than patients who develop metastases at non-osseous sites. Therefore, we speculate that survival time may influence the incidence of SREs during ZA therapy since patients who have a longer survival time may be at a greater risk of developing SREs. Unfortunately, we do not have data OS to address this issue.

In this study, the patients treated chemotherapy with ZA had a significantly higher risk for SSE than non-treatment chemotherapy with ZA. The finding may imply that the tumors with aggressive nature and rapid pace on progression could also cause SREs in shorter time frame than indolent types as Tanaka et al. reported in their study [13].

Although not significant, a trend was observed towards a greater number of SSEs in patients with multiple bone metastases ($p = 0.054$) compared to patients with localized bone metastasis. Moreover, according to our results of the observed rate of SSEs during ZA therapy, we found that SSEs occurred at sites of pre-existing bone metastases rather than newly diagnosed sites of bone metastases in the majority of patients. These findings suggested that patients with bone-only disease and/or patients with multiple bone metastases are more likely to experience a SSE even after treatment with ZA. Therefore, patients categorized as having bone-only disease or multiple bone metastases should be carefully monitored during ZA therapy.

Previously, other bone-oriented factors, such as N-telopeptide of type 1 collagen and bone-specific alkaline phosphatase, were studied to determine their significance in relation to the efficacy of ZA therapy [5]. However, we were unable to evaluate these factors as predictors in the current study, owing to the limited number of tests performed during the study period at our institutions. Further investigation is warranted to test the efficacy of ZA therapy in bone-only MBC patients.

Denosumab is a fully humanized monoclonal antibody that specifically binds to human RANK ligand to inhibit osteoclast activity, which leads to a reduction in bone resorption, tumor-induced bone destruction, and SREs. Denosumab is superior to ZA for delaying or preventing SREs in patients with bone metastases from a variety of tumors and is generally well tolerated [14,15]. The disadvantage is that there is a risk of developing hypocalcemia, and administration of a calcium preparation is recommended to prevent this side effect. In most instances, BMAs are administered concomitantly with chemotherapy. Denosumab is administered every 4 weeks, whilst ZA is administered every 3 or 4 weeks. ZA administration every 12 weeks was reported [16] to be non-inferior to a 4-week schedule in b-MBC patients who had previously completed 12 months of treatment with a 3- or 4-week schedule of ZA therapy to reduce the SREs Thus, the convenience of ZA therapy is more advantageous than that of denosumab.

In conclusion, the patients with bone-only disease, but not any of breast cancer subtypes experienced significantly more SSEs after commencement of ZA.

Compliance with ethical standards

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Conflicts of interest

The authors declare that they have no conflict of interest.

Research involving human participants

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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