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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