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ORIGINAL ARTICLE

Predictive factors for the efficacy of denosumab in postmenopausal Japanese women with non-metastatic breast cancer receiving adjuvant aromatase inhibitors: a combined analysis of two prospective clinical trials

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Abstract
Aromatase inhibitors (AIs) are the gold standard therapy for breast cancer in postmenopausal women. AI suppresses the conversion of androgens to estrogens; however, this results in osteopenia, osteoporosis, and bone fracture, thus reducing the patient's quality of life. The use of adjuvant denosumab reduces the risk of clinical fractures in postmenopausal patients with breast cancer receiving AI. However, the efficacy of denosumab in the treatment of AI-associated bone loss has not been prospectively evaluated in Japan. In this study, we aimed to investigate the predictive factors for the efficacy of denosumab in postmenopausal patients with breast cancer treated with AI by analyzing the results of two prospective trials. The patients received 60 mg denosumab subcutaneously every 6 months. The primary endpoint was percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12 in lumbar spine. Post hoc analysis and *T* tests were performed. A total of 205 patients were enrolled. At 12 and 24 months, the lumbar spine BMD increased by 5.6% [95% confidence interval (CI) 4.9–6.3] and 8.3% (95% CI 7.5–9.1), respectively. Subgroup analysis was conducted according to the time of AI therapy initiation, type of AI therapy, age, time since menopause, baseline body mass index, and BMD. The results showed that baseline lumbar and left femoral BMD was significantly associated with a percentage change in these sites, respectively. In addition, baseline left femoral BMD was also associated with a change in lumbar BMD. In conclusion, the baseline BMD in the lumbar spine was a predictive indicator for the efficacy of denosumab in this site and the baseline BMD in left femoral neck was a predictive indicator in lumbar spine and left femur.

Keywords Breast cancer · Aromatase inhibitor · Denosumab · Predictive factor

Introduction

Female osteoporosis is mainly caused by postmenopausal osteoporosis. The profound morbidity associated with osteoporotic fractures has led to the classification of osteoporosis as an important public bone health concern [1]. Several longitudinal studies have also suggested that osteoporosis is associated with increased mortality [2–10].

The use of aromatase inhibitors (AI) as adjuvant therapy is known to increase the risk of bone loss and fracture in patients with breast cancer. Therefore, the International Osteoporosis Foundation recommended antiresorptive therapy for any patient receiving AI therapy with a *T* score lower than −2.0, irrespective of the presence of other risk factors [11].

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In Japan, more than 8 million women have osteoporosis. Our previous analysis of a 12-month and 24-month, non-randomized prospective study showed that denosumab, a fully human monoclonal antibody against receptor activator of nuclear-factor kappa-B ligand, increased the BMD at the lumbar spine and femoral neck in patients with hormone receptor-positive breast cancer who were receiving adjuvant AI therapy and showing signs of osteoporosis and osteopenia [12–15]. These trials were the first clinical prospective studies in Japan that we analyzed to investigate the effect of denosumab for patients with breast cancer with osteopenia (T score -1.0 to -2.5) and osteoporosis (T score ≤ -2.5) receiving AI therapy. We think that the next step should be to evaluate the effects of denosumab via subgroup analysis to identify patients who will and will not yield optimal benefit from denosumab. Thus, this study aimed to analyze the effect of denosumab at 24 months to determine the predictive factors for its efficacy in patients with breast cancer receiving AI therapy.

Materials and methods

Patients

The complete inclusion and exclusion criteria have been described previously [12, 13]. Briefly, postmenopausal women with early stage, histologically confirmed, hormone receptor-positive invasive breast cancer who were scheduled to receive AIs as adjuvant endocrine therapy or were receiving AI adjuvant therapy were included for analysis. The other inclusion criteria were (1) completion of the chemotherapy regimen ≥ 4 weeks before study entry, (2) evidence of low bone mass (BMD corresponding to a T score < -1.0 in at least one of the following sites: lumbar spine, right femoral neck, and left femoral neck), and (3) absence of prior vertebral diseases and current active dental problems including infection of the teeth or jawbone. The exclusion criterion was normal BMD (T score ≥ -1.0) in all three sites (lumbar and bilateral femoral necks).

Study design

This non-randomized prospective study was conducted at 3 institutions in Japan, namely Kyoto Prefectural University of Medicine, Nara City Hospital, and Saiseikai Kyoto Hospital. The two studies analyzed were approved by the Institutional Review Board of Kyoto Prefectural University of Medicine on August 2, 2013 and on January 10, 2014 and were registered with the UMIN Clinical Trial Registry (UMIN-CTR, UMIN 000013863 and 000027425). Patients were to receive 60 mg of denosumab subcutaneously every 6 months. Daily supplements containing 500 mg of elemental calcium and at least 400 IU of vitamin D were highly recommended throughout the study. No changes in AI therapy were mandated by the study protocol. This study was approved by the research ethics committees of each participating study center. Informed consent was obtained from all individual participants of the study.

Assessment of outcomes

Denosumab was administered subcutaneously on day 1 of the study and then after 6, 12, 18, and 24 months. BMD was measured via dual-energy DXA using the Hologic (Hologic Inc, Bedford, MA, USA) or Lunar (General Electric Lunar Corp, Madison, WI, USA) densitometer. All DXA devices were standardized and cross-calibrated using 4 Bio-Imaging Bona Fide Phantoms. Lumbar spine and bilateral femoral neck BMDs were measured at baseline and after 6, 12, 18, and 24 months.

Subgroup analyses

An analysis of the percent change in baseline BMD at the lumbar spine and bilateral femoral neck at 24 months post-treatment was conducted in the following patient subgroups according to the following categories: time of AI therapy initiation (concurrently with denosumab or prior to denosumab), type of AI therapy (steroidal or non-steroidal), age (< 65 or ≥ 65 years), time since menopause (≤ 5 or > 5 years), baseline body mass index (BMI < 20 or ≥ 20 kg/m^2), and BMD (T score ≤ -2.5, $-2.5 < T$ score < -1.0, $-1.0 \leq T$ score). Subgroup analysis was conducted using post hoc analysis. Multiplicity adjustment was used for these analyses.

End points

The primary endpoint was percentage change from baseline to month 12 in lumbar spine (L1–L4) BMD. The secondary endpoints were (1) percentage change in lumbar spine (L1–L4) BMD from baseline to 24 months after denosumab treatment; (2) percentage change in bilateral femoral neck BMD from baseline to 24 months after denosumab treatment; and (3) subgroup analysis of the therapeutic effects of denosumab at 24 months in the lumbar spine and bilateral femoral neck BMD.

Statistical analysis

According to preliminary calculations, a sample size of 74 patients was required to obtain a power of 80% and detect a 4% difference in percentage change in lumbar spine (L1–L4) BMD from baseline to 12 months. To allow for a 20% drop-out rate, at least 90 patients were required. T tests were used

for comparisons between the groups. Multivariate analysis using logistic regression analysis was performed to examine the factors that influenced BMD. All p values reported are based on a two-sided comparison, and $p < 0.05$ was considered significant. All statistical analyses were performed using the JMP software, version 12.

Results

Patients

A total of 205 patients were enrolled (Fig. 1); of these, 25 (12%) dropped out and thus 180 (88%) completed the study. Of the 25 who dropped out, six patients withdrew consent, two developed grade 2 arthralgia, sixteen had missing DXA data, and one was eliminated because of disease progression (bone metastasis). The baseline characteristics of the patients are shown in Table 1. The majority of patients (65.6%) received AI therapy (mean period: 24 months) before the initiation of denosumab treatment.

Bmd

At 12 months, the lumbar spine BMD increased by 5.6% (95% CI 4.9–6.3) (Fig. 2), and the right femoral neck and left femoral neck BMD increased by 2.8% (95% CI 2.0–3.6) and 2.7% (95% CI 1.9–3.5), respectively (Fig. 3). At 24 months, the lumbar spine BMD increased by 8.3% (95% CI 7.5–9.1) (Fig. 2), and the right femoral neck and left femoral neck BMD increased by 4.0% (95% CI 3.1–4.8) and 4.3% (95% CI 3.5–5.1), respectively (Fig. 3). The results of subgroup analysis using univariate analysis of the therapeutic effects of denosumab at 24 months are shown in Table 2. Baseline BMD of lumbar spine and left femoral neck (T score < -2.5) was significantly associated with the percentage change of

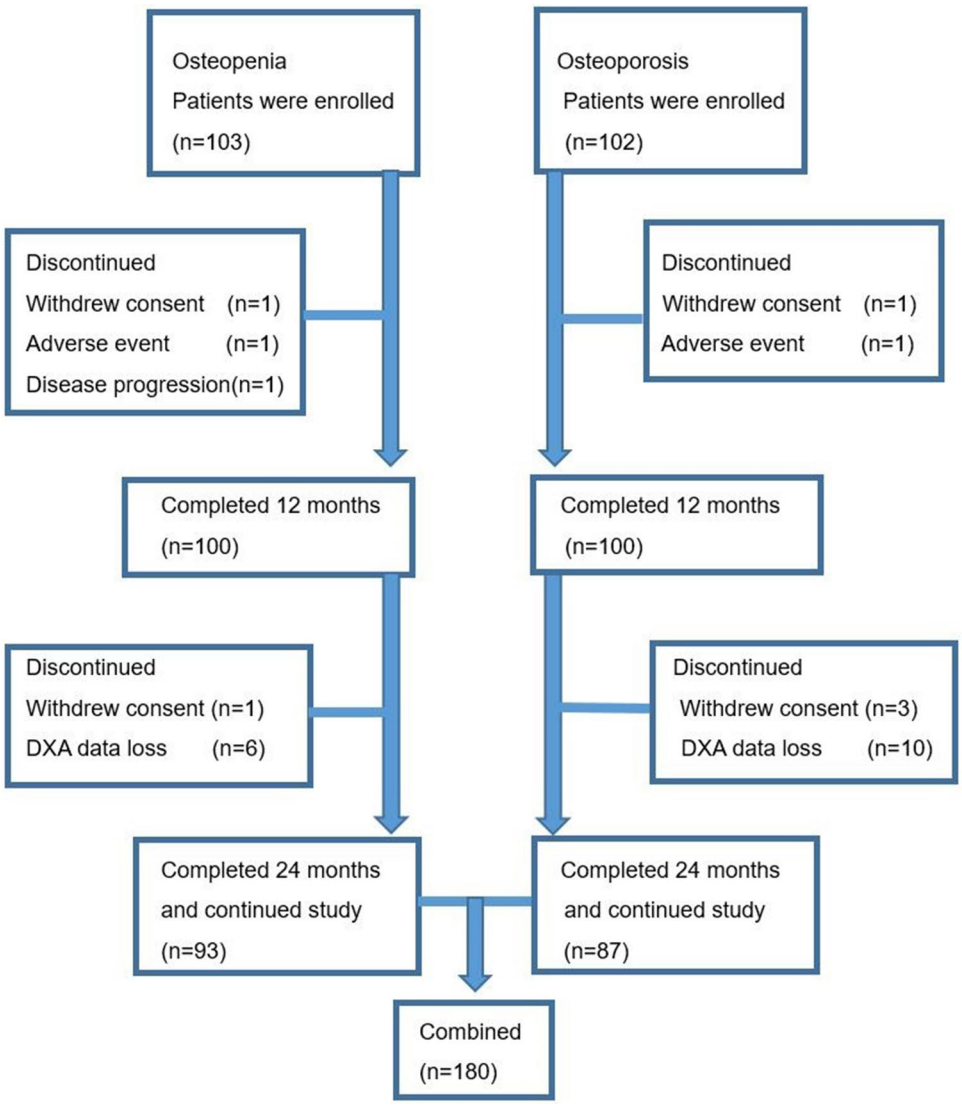

Fig. 1 Patient selection

Table 1 Summary of baseline variables

	Number of patients, (%)
Start of AI therapy, *n*	
Concurrent with denosumab	62, (34.4)
Before denosumab	118, (65.6)
Type of AI therapy, *n*	
Non-steroidal	156, (86.7)
Steroidal	24, (13.3)
Age, *n* (%)	
< 65 years	80, (44.4)
≥ 65 years	100, (55.6)
Time since last menstrual cycle, *n*	
≤ 5 years	12, (6.7)
> 5 years	168, (93.3)
Body mass index (kg/m^2), *n*	
< 25	144, (80.0)
≥ 25	36, (20.0)
Lumbar spine BMD *T* score, *n*	
< − 2.5	37, (20.6)
− 2.5 ≤ *T* score ≤ − 1.0	82, (45.6)
> − 1.0	61, (33.8)
Right femoral neck BMD *T* score, *n*	
< − 2.5	40, (22.2)
− 2.5 ≤ *T* score ≤ − 1.0	101, (56.1)
> − 1.0	39, (21.7)
Left femoral neck BMD *T* score, *n*	
< − 2.5	43, (23.9)
− 2.5 ≤ *T* score ≤ − 1.0	98, (54.4)
> − 1.0	39, (21.7)

AI aromatase inhibitors, *BMD* bone mineral density

BMD in these sites, respectively ($p < 0.0001$ and $p < 0.04$, respectively). The results of multivariate analysis of the predictive factors for the efficacy of denosumab in the lumbar spine and left femoral neck are shown in Table 3. *T* score < − 2.5 in lumbar spine and left femoral neck was significantly associated with the percentage change of BMD in these sites, respectively ($p < 0.0001$ and $p < 0.011$, respectively).

Baseline BMD (*T* score < − 2.5) in the lumbar spine was not associated with the percentage change in left femoral neck ($p = 0.4073$), but the baseline BMD (*T* score < − 2.5) in the left femoral neck was significantly associated with the lumbar spine ($p = 0.0145$).

Fractures

At month 24, no non-traumatic clinical fractures occurred in the patients receiving AI and denosumab.

Discussion

The two major randomized trials of denosumab for the prevention of AI-related bone loss in postmenopausal women with breast cancer are the adjuvant denosumab in breast cancer trial (ABCSG-18) and hormone ablation bone loss trial breast cancer (HALT-BC) [16, 17]. The ABCSG-18 did not include the baseline BMD in the inclusion criteria, while the HALT-BC specified a *T* score classification of − 1.0 to − 2.5 for eligibility to the trial. However, no prospective trial of denosumab has been conducted specifically for postmenopausal patients with breast cancer receiving adjuvant AI with a baseline *T* score of ≤ − 2.5. Only one prospective clinical study that included patients with osteoporosis such as *T* score ≤ − 2.5 has been conducted [13].

No subset analysis has been conducted in ABCSG-18, [16], while subset analysis in HALT-BC showed that treatment with denosumab was associated with larger BMD gains than placebo, regardless of duration and type of AI,

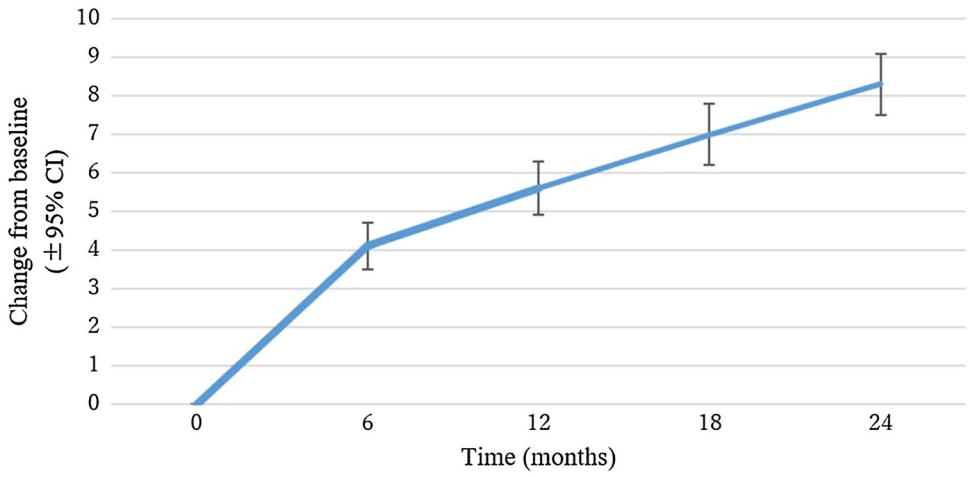

Fig. 2 Percentage change in bone mineral density (BMD) of the lumbar spine from baseline (± 95% CI) to over 24 months for all patients

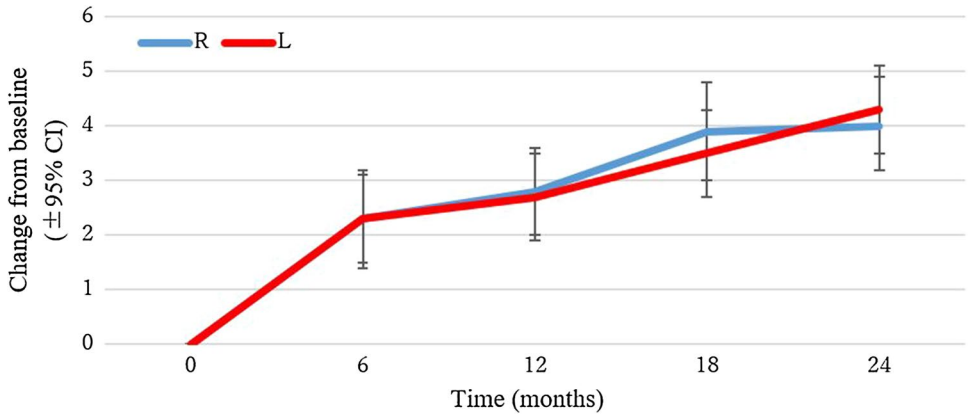

Fig. 3 Percentage change in bone mineral density (BMD) of the right (R) femoral neck and the left (L) femoral neck from baseline (±95% CI) to over 24 months for all patients

Table 2 Subgroup analysis of the therapeutic effects of denosumab at 24 months

	Lumbar spine	Right femoral neck	Left femoral neck
Start of AI therapy			
Concurrent with denosumab ($n=62$)	7.8 (6.5, 9.1)	3.0 (1.6, 4.4)	4.2 (2.8, 5.5)
Before denosumab ($n=118$)	8.5 (7.6, 9.5)	4.5 (3.5, 5.5)	4.3 (3.3, 5.3)
p	0.38	0.08	0.85
Type of AI therapy			
Non-steroidal ($n=156$)	8.4 (7.5, 9.2)	3.8 (2.9, 4.7)	4.0 (3.2, 4.9)
Steroidal ($n=24$)	7.8 (5.7, 10.0)	5.1 (2.9, 7.4)	5.9 (3.6, 8.1)
p	0.64	0.26	0.13
Age			
<65 years ($n=80$)	8.0 (6.8, 9.1)	4.5 (3.3, 5.8)	4.9 (3.7, 6.1)
≥65 years ($n=100$)	8.6 (7.5, 9.6)	3.5 (2.4, 4.6)	3.8 (2.7, 4.9)
p	0.45	0.22	0.20
Time since menopause			
≤5 years ($n=12$)	8.2 (5.2, 11.3)	4.7 (1.5, 7.9)	6.8 (3.6, 9.9)
>5 years ($n=168$)	8.3 (7.5, 9.1)	3.9 (3.1, 4.8)	4.1 (3.3, 4.9)
p	0.97	0.65	0.11
Body mass index (kg/m^2)			
<25 ($n=144$)	8.5 (7.6, 9.3)	4.3 (3.3, 5.2)	4.2 (3.3, 5.1)
≥25 ($n=36$)	7.6 (5.9, 9.4)	2.8 (1.0, 4.6)	4.5 (2.7, 6.3)
p	0.40	0.16	0.77
T score			
<-2.5	12.1(10.4,13.7)*	4.3 (2.6, 6.0)	6.1 (4.5, 7.8)*
$-2.5 \leq T$ score ≤ -1.0	7.7 (6.6, 8.8)*	4.2 (3.1, 5.3)	3.7 (2.6, 4.8)*
>-1.0	6.8 (5.5, 8.0)*	3.1 (1.3, 4.9)	3.7 (1.9, 5.4)*
p	<0.0001	0.56	0.04

Data are shown as the least squares mean percent difference (95% confidence interval)

*$p<0.05$

tamoxifen use, age, time since menopause, body mass index, T score, or skeletal sites [17]. However, the inclusion criterion of BMD in HALT-BC was only osteopenia (T score -1.0 to -2.5) and did not include osteoporosis (T score ≤ -2.5). Therefore, it has been a critical issue whether the effect of denosumab is similar between those with and without osteoporosis. As such, we combined our two prospective trials that included patients with osteoporosis and osteopenia, and we revealed that baseline BMD (T score ≤ -2.5) is associated with large BMD gains. These results indicate that baseline BMD might be used as a predictive factor for the efficacy of denosumab for postmenopausal women receiving AI. of denosumab for postmenopausal women receiving AI. We found no reason for denosumab being more efective in those with low baseline BMD than in those with high baseline BMD at the lumbar spine and

Table 3 Multivariate analysis of the predictive factors for the efficacy of denosumab in the lumbar spine and left femoral neck

Factors	Multivariate analysis			
	Lumbar spine		Left femoral neck	
	Relative risk	*p* value	Relative risk	*p* value
Start of AI therapy				
Concurrent with D-mab, before D-mab	1.40	0.16	0.12	0.78
Type of AI therapy				
Non-steroidal, steroidal	−0.64	0.53	1.02	0.09
Age				
< 65 years, ≥ 65 years	−0.15	0.88	0.69	0.12
Time since menopause				
≤ 5 years, > 5 years	0.17	0.86	1.15	0.19
Body mass index (kg/m^2)				
< 25, ≥ 25	0.21	0.83	−0.21	0.68
T score				
< −2.5	6.4	< 0.0001*	2.0	0.011*
−2.5 ≤ *T* score ≤ −1.0				
> −1.0				

D-mab Denosumab

*$p < 0.05$

left femoral neck. However, we speculate that the lower the baseline BMD, the more porous the bone, and denosumab circulates freely into the porosities and can inhibit remodeling rapidly. Zebaze et al. reported that denosumab reduced porosity more than alendronate [18–21]. These findings should be verified using additional BMD data from patient administered denosumab and in randomized control trials comparing low and high baseline BMD.

Moreover, we found no reason for lower baseline BMD being significantly associated with the better BMD increase at the left femoral neck and not the right side. However, we speculate that the different effects of denosumab at the right and left femoral neck depend on the different pressers used. We previously reported that baseline BMD was not associated with the efficacy of denosumab in osteopenia patients receiving AI [14]. The difference between this trial and the previous trial is that this trial included osteoporosis patients, while the previous trial did not.

Our study had some limitations. First, this was a subset analysis of two combined non-randomized prospective trials. Second, the sample size was small. A larger sample size would have provided more reliable results. Lastly, a centralized DXA data review was not performed, as we felt that this was beyond the scope of this investigation. In future studies, a more extensive review of the literature could provide additional data to support our findings. In conclusion, the baseline BMD in the lumbar spine and left femoral neck was a predictive indicator for the efficacy of denosumab in these sites and the baseline BMD in left femoral neck was a predictive indicator in lumbar spine and left femur.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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