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ORIGINAL ARTICLE

Effects of denosumab on bone mineral density in Japanese women with osteoporosis treated with aromatase inhibitors for breast cancer

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Abstract

Adjuvant aromatase inhibitor (AI) therapy, for hormone receptor-positive breast cancer, in postmenopausal women is associated with bone loss, leading to an increased risk of fractures. Denosumab, an antibody raised against the receptor activator of nuclear factor-κB ligand, has been proven to protect against AI-induced bone loss. Hence, we aimed to determine whether denosumab is effective in postmenopausal Japanese women with osteoporosis, treated with AI. We prospectively evaluated the bone mineral density (BMD) in the lumbar spine and the bilateral femoral neck in 102 postmenopausal women with clinical hormone receptor-positive breast cancer, stages I–IIIA, during a postoperative period of 12 months. The other inclusion criteria for this study were: women that should receive AIs as adjuvant therapy and those with evidence of osteoporosis (lumbar spine or bilateral femoral neck BMD, equivalent to T-score classification of ≤ -2.5) upon enrollment. The patients received supplemental calcium, vitamin D, and 60 mg of subcutaneous denosumab every 6 months. The BMD of the lumber spine increased by 4.9 and 6.6% at 6 and 12 months, respectively. An increase in BMD was observed at the femoral neck, bilaterally. Hypocalcemia ≥ grade 2, osteonecrosis of the jaw, and non-traumatic clinical fracture were not observed in this study. Our findings revealed that biannual treatment with denosumab is associated with a great increase of BMD in Japanese women receiving adjuvant AI therapy, irrespective of their previous history of AI therapy.

Keywords Breast cancer · Aromatase inhibitor · Denosumab · Bone mineral density · Osteoporosis

Abbreviations

AI	Aromatase inhibitor
BMD	Bone mineral density
DXA	Dual-energy X-ray absorptiometry
ONJ	Osteonecrosis of the jaw
RANKL	Receptor activator of nuclear factor κ-B ligand

Introduction

Aromatase inhibitors (AIs) are a commonly used first-line adjuvant hormone therapy in patients with postmenopausal breast cancer [1–7]. AIs prevent the conversion of androgens to estrogens by inhibiting aromatase, reducing the circulating estrogen levels to an undetectable level [8]. Though this might have a positive effect in reducing recurrence of the breast cancer, its downside is bone loss, resulting in increased risk of osteopenia and osteoporosis in patients on AI treatment, which in itself could lead to bone fracture and reduced quality of life. Therefore, efforts to prevent the decrease in bone mineral density (BMD) are needed. Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor κ-B ligand (RANKL). It suppresses differentiation, activation, and survival of osteoclasts by inhibiting the binding of RANKL to its receptor RANK [9–11].

In a 2-year, randomized, double-blind, placebo-controlled study, when compared with placebo, denosumab increased BMD at the lumber spine and other skeletal sites (T-score

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classification of − 1.0 to − 2.5) in patients with hormone receptor-positive breast cancer receiving adjuvant AI therapy who had evidence of low BMD [12]. Recently, we reported the effect of denosumab on low BMD (T-score classification of − 1.0 to − 2.5) in postmenopausal Japanese women receiving adjuvant AI for non-metastatic breast cancer [13].

Gnant et al. reported the results of the ABCSG-18 trial, which were a double-blind, placebo-controlled, phase III trial in postmenopausal patients with early stage hormone receptor-positive breast cancer who received treatment with AI (T-score classification of < − 1.0) [14]. However, to date, no prospective study has described the efficacy of denosumab in postmenopausal Japanese women with osteoporosis (T-score classification of ≤ − 2.5), treated with AI. This study is aimed to address this niche.

Materials and methods

Patients

The inclusion criteria were as follows: (1) patients diagnosed and treated for invasive breast cancer categorized as clinical stage I, II, or IIIA; (2) patients with breast cancer whose tumors were removed by an appropriate surgical procedure, such as mastectomy or breast conserving surgery; (3) estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive cancers defined by immunohistochemical staining; (4) postmenopausal status defined by one of the following conditions: (1) women > 54 years with cessation of menstruation, (2) spontaneous cessation of menstruation within the past year, (3) amenorrhea in women < 55 years, and (4) the presence of postmenopausal levels of follicle-stimulating hormone (FSH) and estradiol; (5) lumbar spine or bilateral femoral neck BMD equivalent to T-score classification of ≤ − 2.5; (6) the Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; (7) patients who have completed chemotherapy > 4 weeks prior to study entry; (8) patients who discontinued the drugs known to affect the skeleton (oral bisphosphonates, estrogen, raloxifene, calcitonin, vitamin K, and activated vitamin D) more than 4 weeks prior to the study; and (9) those who provided an informed written consent. The main exclusion criteria were as follows: (1) diagnosis of clinical or radiological distant metastasis prior to inclusion; (2) invasive bilateral breast cancer; (3) prior treatment with intravenous bisphosphonates within the past 12 months; (4) diseases that may interfere with dual-energy X-ray absorptiometry (DXA) scan, such as severe scoliosis and vertebral diseases; (5) active dental problems, including infection of the teeth or jawbone and recent (within 6 weeks) or planned dental or jaw surgery (e.g., extraction, implants); and (6) other conditions judged as inappropriate for the study by the investigator.

Study design

This non-randomized prospective study was conducted at four institutions in Japan. The patients ($n = 102$) were to receive subcutaneous denosumab 60 mg every 6 months. Daily intake of 500 mg of elemental calcium and at least 400 international units of vitamin D was highly encouraged throughout the study, with every patient participating. There was no change in AI therapy as a result of participating in this study. Approvals from appropriate research ethics committees were obtained for each participating study center. All patients provided written informed consent before participating. The study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine on January 10, 2014 and conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983. This study was registered with the UMIN Clinical Trial Registry (UMIN-CTR, UMIN000027425).

Assessment of outcomes

Denosumab was administered subcutaneously on study day 1 and at months 6 and 12, post-treatment. BMD was measured by DXA using Hologic (Hologic Inc, Bedford, MA, USA) or Lunar (General Electric Lunar Corp, Madison, WI, USA) densitometers. All DXA devices were standardized and cross-calibrated using four Bio-Imaging Bona Fide Phantoms. Lumbar spine and bilateral femoral neck BMD were measured at baseline and at months 6 and 12.

Albumin-corrected serum calcium levels were measured at baseline, as well as months 1, 6, and 12, post-treatment. Serum markers of bone turnover [tartrate-resistant acid phosphatase isoform 5b (TRAP5b) and bone alkaline phosphatase (BAP)] were measured at baseline, 6 months, and 12 months. In this study, grade 2 hypocalcemia, according to the Common Terminology Criteria for Adverse Events, was defined as serum corrected calcium levels of less than 8.0 mg/dL.

Endpoints

The primary endpoint was percentage change in lumbar spine BMD from baseline to month 12, which was further divided into assessing these changes in 6 months intervals. Changes in serum markers were also analyzed at same intervals.

Statistical analysis

Preliminary calculations showed that to obtain a power of 80% and to detect a 4% difference in percentage change in

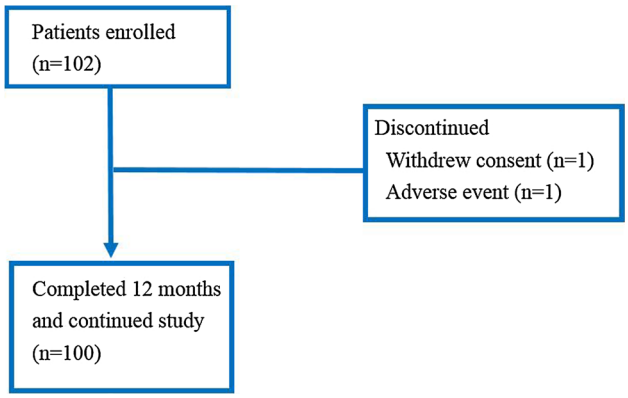

Fig. 1 Patient disposition

the lumbar spine (L1–L4) BMD from baseline to 12 months, a minimum of 74 patients should be enrolled in this study. We allowed for a 20% dropout rate, reaching a minimum number of 90. *t* tests were used to compare the two groups. *P* values were reported based on a two-sided comparison. A *P* value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the JMP software, version 12.

Results

A total of 102 patients were enrolled in this study (Fig. 1), with 98% going through the study period. Two patients withdrew from treatment; one withdrew consent, and another developed grade 2 arthralgia. The baseline characteristics are shown in Table 1. About half of the patients (58%) had started AI therapy (mean period 15 months) before the initiation of denosumab treatment. The patients which had history of fragility fracture were none.

BMD

We observed a 6.6% increase in lumbar spine BMD by the end of the study (95% CI 5.7–7.6) (Fig. 2). BMD of the right femoral neck and left femoral neck were 3.3% (95% CI 2.2–4.4) and 4.1% (95% CI 2.7–5.5), respectively, although the difference between the two sides was not significant (0.8% mean difference between right and left, $P = 0.2999$) (Fig. 3). The percentage change in BMD at the lumbar spine from baseline over 12 months before and after the initiation of denosumab was 7.0% (95% CI 5.8–8.3) and 6.0% (95% CI 4.6–7.5), respectively, with the difference being nonsignificant (1.0% mean difference between AI with denosumab and before denosumab; $P = 0.2994$) (Fig. 4). The baseline BMD of AI both with denosumab and before denosumab

Table 1 Baseline patient characteristics

Characteristics	$n = 100$
Age (years)	
Mean	68.7
Range	53–91
Initiation of aromatase inhibitor therapy (%)	
With denosumab	42
Before denosumab	58
Body mass index (kg/m^2)	
Mean	21.6
Range	17.0–27.6
Time from last menstrual period (years)	
≤ 5	6
> 5	94
Type of aromatase inhibitor therapy	
Anastrozole	48
Letrozole	36
Exemestane	16
History of fragility fracture	0

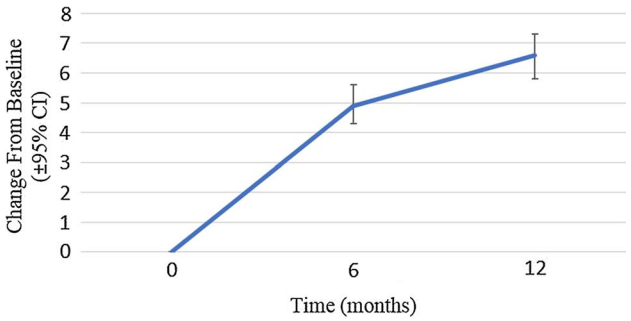

Fig. 2 Percentage change in bone mineral density (BMD) of the lumbar spine from baseline (± 95% CI) over a period of 12 months in all patients

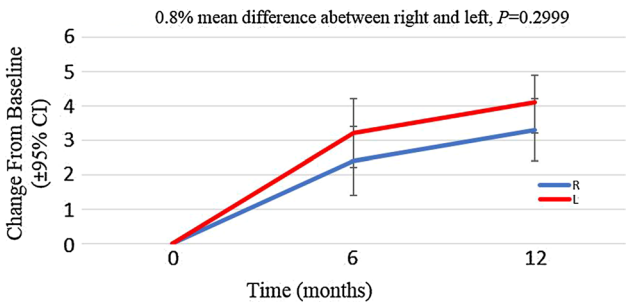

Fig. 3 Percentage change in bone mineral density (BMD) from baseline in (R) the right femoral neck and (L) the left femoral neck (± 95% CI) over 12 months in all patients

administration at the lumber spine was 0.732 g/cm^2 (95%

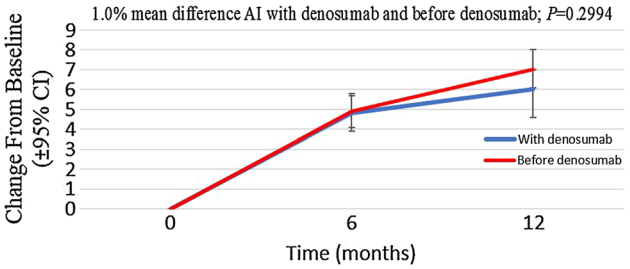

Fig. 4 Percentage change in bone mineral density (BMD) of the lumbar spine from baseline (± 95% CI) over 12 months in patients who started receiving aromatase inhibitor (AI) therapy with denosumab ("with denosumab") and those who had received AI before the initiation of denosumab therapy ("before denosumab"). *AI* aromatase inhibitors, *CI* confidence interval

CI 0.694–0.770) and 0.756 g/cm^2 (95% CI 0.723–0.789), respectively, with no significance found ($P = 0.3389$).

Fractures

At month 12, non-traumatic clinical fracture was not observed in patients receiving AI and denosumab.

Safety

Drug safety was evaluated in all 102 cases that were enrolled in this trial. The occurrence of adverse events (AEs; 5% or more) is shown in Table 2. Arthralgia occurred in around 18.6% of the cases, but almost all were of grade 1 severity, and controlled with nonsteroidal anti-inflammatory drugs (NSAIDs), although one patient withdrew from the study due to this AE. Suspicion of osteonecrosis of the jaw (ONJ) was an excluding criterion, and was not observed in any patient. Hypocalcemia ≥ grade 2 was not observed in any patient.

Table 2 Summary of adverse events

	$n = 102$	
	No. of patients	%
Adverse events		
Arthralgia	19	18.6
Extremity pain	9	8.9
Back pain	10	9.8
Hypocalcemia	9	8.8
CTC grade 3, 4, or 5 adverse events	0	0.0
Deaths	0	0.0

CTC National Cancer Institute Common Toxicity Criteria

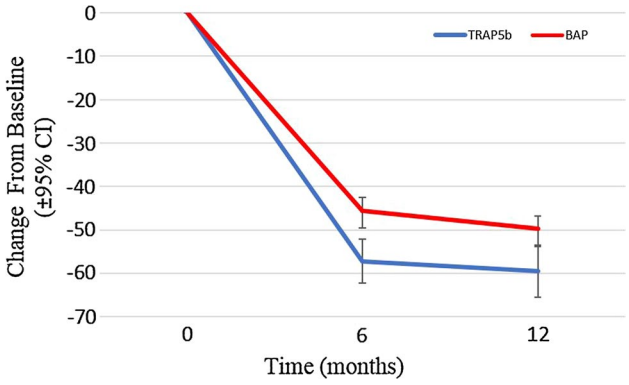

Fig. 5 Changes in serum markers of bone turnover, tartrate-resistant acid phosphatase isoform 5b (TRAP5b) and bone alkaline phosphatase (BAP) levels, between baseline and 12 months

Markers of bone remodeling

Levels of TRAP5b and BAP rapidly reduced by denosumab (Fig. 5), with a mean percentage reduction of 59.5 and 49.8%, respectively after 12 months. This extent of reduction remained constant between 6 and 12 months.

Discussion

Osteoporosis is a chronic, progressive condition that generally requires long-term management, and is also a health issue in the aging population, particularly postmenopausal women. Significant morbidity and mortality associated with osteoporotic fracture have led to the recognition of osteoporosis as an important bone health problem [15], with several longitudinal studies associating osteoporosis with increased mortality [16–19].

Adjuvant therapy with AIs has become the gold standard treatment for postmenopausal women experiencing hormone receptor-positive breast cancer, after surgery [2, 3]. AI-induced bone loss occurs at more than twice the rate of physiologic postmenopausal bone loss [20], which will in itself result in the worsening of bone health problems in these patients, reducing quality of life. It has been reported that the lower the baseline BMD, the lower the BMD, 5 years after AI treatment [21]. Therefore, we can assume that patients who had baseline T-score classification of ≤ − 2.5 before the start of AI treatment, or during AI treatment, were at a higher risk of fracture associated with osteoporosis.

Hence, this study aimed to determine the effect of denosumab on BMD (T-score classification of ≤ − 2.5) in postmenopausal women with non-metastatic breast cancer, who were receiving adjuvant AI treatment in Japan. We found that biannual treatment with denosumab increased BMD in Japanese women receiving adjuvant AI therapy, with a

rapid increase in lumber spine BMD over 12 months, and a consistent increase in BMD of the bilateral femoral neck. A 5-year adjuvant trial therapy with anastrozole in postmenopausal women with breast cancer was associated with a cumulative 6.1% decrease in lumber spine BMD [9]. Our study showed a 6.6% gain in lumbar spine BMD, after a year of denosumab therapy, irrespective of prior AI treatment.

We previously reported the effect of denosumab on osteopenia ($-1.0 <$ T-score < -2.5) [13]. Interestingly, the improvement in BMD found in this trial (6.6% at the lumber spine, 3.3% at the right femoral neck, and 4.1% at the left femoral neck) had increased more than that of osteopenia (4.7, 2.4, and 1.4%, respectively). Our previous and current trials differed in that one studied osteopenia, while the other examined osteoporosis; therefore, we are not able to directly compare these two studies. However, we did speculate that the difference in BMD improvement between these two studies might be dependent on baseline BMD.

Denosumab was generally well-tolerated and the AEs in this trial were consistent with those associated with AI therapy. Calcium data showed a decreasing trend at 1 month; however, hypocalcemia ≥ grade 2 was not observed in patients receiving calcium and vitamin D supplementation. It has been suggested that high doses of bisphosphonates and denosumab lead to higher rates of ONJ [22], which is a concern in the treatment of different types of metastatic cancer. Since ONJ negatively affects the quality of life for cancer patients, it is of special importance to determine the risk of such an event when deciding on any additional treatment in cancer patients. In our study, we did not observe any cases of ONJ as a result of denosumab therapy.

Previous studies have shown that individuals who received prior bisphosphonate therapy and transitioned to denosumab had greater BMD gains at all measured skeletal sites, compared to continuation of alendronate or initiation of ibandronate or risedronate [23–25]. Recently, a phase III randomized trial revealed that transitioning to denosumab was well-tolerated and more effective at increasing BMD at all sites measured, than transitioning to once-yearly IV bisphosphonate (zoledronic acid) in postmenopausal women with osteoporosis who were on oral bisphosphonates [26]. Furthermore, the effect of zoledronic acid (4 mg intravenously, every 6 months) among postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole was previously reported, and the improvement of BMD in lumber spine at 12 months was 2.9%, which was less than the 6.6% observed in our trial [27]. Therefore, this suggests that denosumab is more efficient for postmenopausal women with osteoporosis, compared to bisphosphonates. Ellis et al. reported the effect of denosumab on BMD in osteopenic postmenopausal women (T-score classification between -1.0 and -2.5), who received adjuvant AI therapy for non-metastatic breast cancer [12]. To the best of our knowledge, this is the first trial to determine the effects of denosumab on BMD in osteoporotic postmenopausal women (T-score classification of ≤ -2.5), who received AI therapy for non-metastatic breast cancer. Furthermore, we are currently conducting a multicenter, randomized, comparative study on the effect of denosumab on normal BMD (T-score classification of ≥ -1.0) in postmenopausal patients with adjuvant AI (ClinicalTrials.gov identifier NCT03324932).

The adjuvant use of bisphosphonates has been shown to reduce breast cancer recurrence and improve outcomes in several adjuvant breast cancer trials [28]. A recent large meta-analysis showed convincing evidence that disease-free and overall survival are improved in postmenopausal patients treated with adjuvant bisphosphonates [29]. The D-CARE trial (ClinicalTrial.gov identifier NCT01077154), which uses a higher dose of denosumab, will provide information on whether the above findings are true for the anti-RANK ligand antibody.

Our study was a non-randomized study, with limited data available. Additional data to aid our investigation could not be collected. However, we would not have been ethically permitted to conduct a placebo-controlled study because AI treatment decreases BMD. Therefore, we felt that a non-randomized prospective study was the best option. The second limitation is the small sample size of the clinical trial. A larger sample size would have provided more reliable results. The third limitation was that lateral spine X-rays (thoracic and lumber) were not taken at the baseline visit. Finally, a centralized DXA review was not performed because we felt that this was beyond the scope of this investigation. A more extensive review of the literature would provide additional data to support our findings in the future.

In summary, twice-yearly denosumab was associated with great gains in BMD among Japanese women receiving adjuvant AI therapy, irrespective of prior AI therapy or skeletal site.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine, on January 10, 2014, and the conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983. This study was registered with the UMIN Clinical Trial Registry (UMIN-CTR, UMIN000027425). Informed consent was obtained from all individual participants included in the study.

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