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Efficacy and Safety of Monthly Minodronate Therapy in Postmenopausal Breast Cancer Patients Receiving Aromatase Inhibitors

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Abstract. *Background/Aim: Post-menopausal breast cancer (BC) patients who receive adjuvant aromatase inhibitor (AI) therapy may be at increased risk of bone loss, osteoporosis, and bone fracture. We aimed to evaluate the efficacy and safety of oral bisphosphonate minodronate in preventing bone loss complications. Patients and Methods: Patients receiving AI and 80% of those with suboptimal bone mineral density (BMD) were prescribed monthly oral minodronate 50 mg every 4 weeks for 72 weeks. BMD, bone metabolism markers, incidence of bone fractures, medication compliance, and other adverse events (AE) were examined every 24 weeks following administration. Results: Fifty postmenopausal BC patients with a median age of 64.0 years were enrolled. The mean value of lumbar spine BMD was higher than that of the value before the minodronate administration at each observation point. Before and after the treatment, the median serum values of Tartrate-resistant Acid Phosphatase 5b (TRACP-5b) (mU/dl) and serum type I collagen cross-linked N-telopeptide (NTX) (nmolBCE/l) were decreased from 535.7 and 18.5 to 230.1 and 11.9, respectively. No adverse grade 2 or higher event was observed throughout this study. Conclusion: The combined administration of minodronate and AIs was safe and effective in preventing bone loss complications in postmenopausal BC patients.*

Hormone receptor (HR) positive, post-menopausal breast cancer (BC) patients are recommended to receive hormone therapy for 10 years for prevention of BC recurrence. Third-generation aromatase inhibitors (AIs) strongly suppress the peripheral conversion of androgen to estrogen, resulting in significant estrogen deficiency. This accelerates loss of bone mineral density (BMD) and increases the risk of bone fracture (1). Additionally, the post-menopausal biological status accelerates the development of osteoporosis and related adverse events (2). Therefore, the guidelines of Japanese Breast Cancer Clinical Practice (JBCS) 2018 (3) recommends bisphosphonates and denosumab for the prevention and treatment of osteoporosis in BC patients using AIs, and a number of randomized controlled trials have already shown the efficacy of this combination therapy. Since its launch in 2011, the efficacy and safety of monthly oral doses of 50 mg minodronate have been shown to be noninferior to daily 1 mg oral doses in osteoporotic patients, and monthly dose has become widely used (4).

This study aimed to determine whether a monthly oral dose of 50 mg minodronate is safe and effective as a daily 1 mg oral dose, even in BC patients undergoing AI therapy. The second aim was to identify a clinical factor that affects BMD recovery in BC patients while administrating minodronate.

Patients and Methods

Target cases. From 2012 to 2016, fifty hormone receptor-positive BC patients who were post-menopausal, had osteoporosis, and were undergoing treatment with AIs were enrolled in this study. After obtaining informed consent, oral minodronate (50 mg) was prescribed every 4 weeks for 72 weeks. Since BMD was predicted to decrease when combined with AI, less than 80% of the young adult mean (YAM) patients were targeted, regardless of the presence or absence of fragility fractures.

Exclusion criteria. The patients who were treated with post-menopausal hormonal replacement therapy, active vitamin D3, vitamin K, calcitonin, glucocorticoids, parathyroid hormone (PTH) drugs, bisphosphonates, denosumab, or selective estrogen receptor modulators were excluded from the study.

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Evaluation of items. Medical records corresponding to the patients included in the study were collected and information on patients' age, height, weight, body mass index (BMI), tumour stage of BC, and types of AIs, and Dual-energy X-ray absorptiometry values, was extracted.

Dual-energy X-ray absorptiometry. Dual-energy X-ray absorptiometry was used to examine the lumbar spine (L2-L4) and total hip (left and right proximal femurs) at baseline and at 4, 24, 48, and 72 weeks after minodronate treatment.

Bone resorption markers. The bone resorption markers, serum type I collagen cross-linked N-telopeptide (NTX), and serum values of tartrate-resistant acid phosphatase 5b (TRACP-5b), were measured as bone metabolism markers, together with bone fracture, medication compliance, and adverse events at every outpatient visit.

Analysis of factors predicting the reactivity of bisphosphonates. Serum assays were performed in 21 patients using baseline frozen serum samples and PTH, calcitonin, 25-hydroxyvitamin D (25(OH)D), and dehydroepiandrosterone sulphate (DHEA-S).

Comparative analysis of categorical variables was used to calculate p-values. Patients with unknown or missing data were excluded from statistical comparisons. Univariate models were used in logistic regression analyses to determine the relationship between each variable and improvements in BMD. Variables used for univariate models included subtype (luminal *versus* luminal HER2), chemotherapy (with *versus* without), and radiation therapy (with *versus* without). Statistical significance was set at $p<0.05$. A *t*-test or chi-squared test was used. The factors that contributed to BMD improvement were evaluated using multivariate analysis. All statistical analyses were performed using JMP statistical software (version 16.0; SAS Institute Inc., Cary, NC, USA).

Ethical issues. This study was approved by the institutional review board of our hospital. Prior to the study's commencement, written informed consent was obtained from all patients after they were provided with sufficient information about the study and related matters. This study considered the rights, safety, and well-being of the participants, consistent with the ethical principles laid down in the Declaration of Helsinki.

Table I. *Baseline characteristics*.

	No. of patients (n=50)	
	Median	Range
Age (years)	64	47-83
Height (cm)	154	139-168
Body weight (kg)	52	37-65
Body mass index	21.8	16.2-28.1

Table II. *Breast cancer stage and subtype and treatment choices*.

	No.	(%)
Stage		
0	2	4
I	29	58
IIA	9	18
IIB	4	8
IIIA	2	4
IIIB	3	6
IV	1	2
Subtype		
Luminal	35	70
Luminal-HER	15	30
Hormonal therapy		
ANA	28	56
LET	19	38
EXE	1	2
TAM	2	4
Adjuvant Chemotherapy		
FEC/EC only	6	12
FEC/EC + DTX/PTX	8	16
TC only	5	10
Others	3	6

ANA: Anastrozole; DTX: docetaxel; EC: epirubicin/cyclophosphamide; EXE: exemestane; FEC: fluorouracil/epirubicin/cyclophosphamide; LET: letrozole; PTX: paclitaxel; TC: paclitaxel/carboplatin.

Results

The patients' median age was 64.0 years and BMI was 21.6 kg/m^2 (Table I). The adjuvant hormonal therapy used was anastrozole (ANA) in 27 patients, letrozole (LET) in 20 patients, and exemestane (EXE) in one patient. Two patients received tamoxifen (TAM) because of their extremely low BMD levels. BC stages and other characteristics are listed in Table II. Of the 50 patients, 49 were in the early stage, and treatment was adjuvant hormonal therapy. One case had post-operative recurrence and received multiple chemotherapy regimens and then continued maintenance hormonal therapy during the study period. Twenty-six patients received radiation therapy. Two cases discontinued treatment because of death and exacerbation of other malignancies.

As shown in Figure 1, both lumbar spine BMD and total hip BMD continuously improved after minodronate administration. The mean BMD (%) of these increased by 3.0 and 2.4 at 24 weeks, 3.8 and 2.6 at 48 weeks, and 4.7 and 3.0 at 72 weeks, respectively. However, the serum levels of TRACP-5b (mU/dl) and NTX (nmolBCE/l) dropped from 535.7 to 230.1 and from 18.5 to 11.9 in the first 24 weeks, respectively. After that, both values remained constant throughout the observation periods (Figure 2).

In order to identify factors that may contribute to BMD improvement during minodronate administration, patients were divided into the decreased BMD group (≤0) and increased BMD group, and clinicopathologic factors were compared.

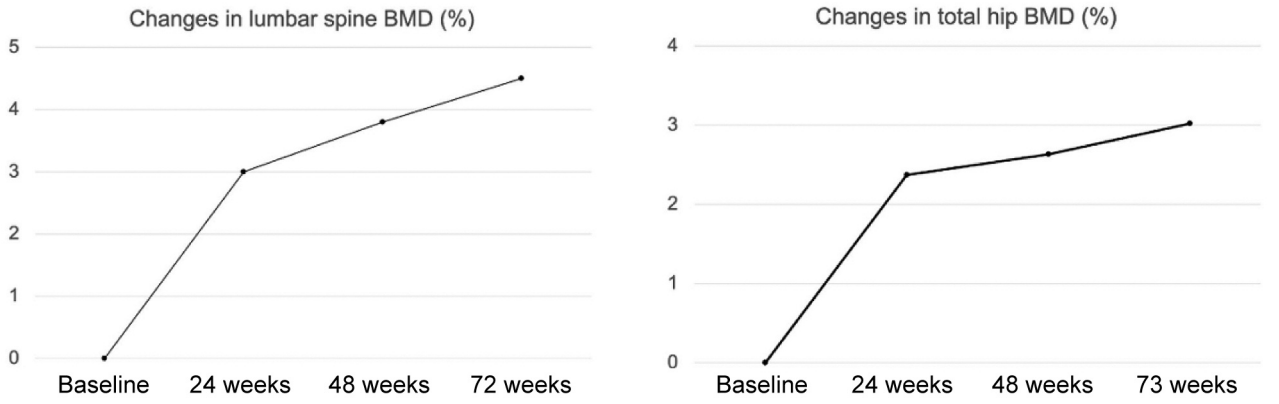
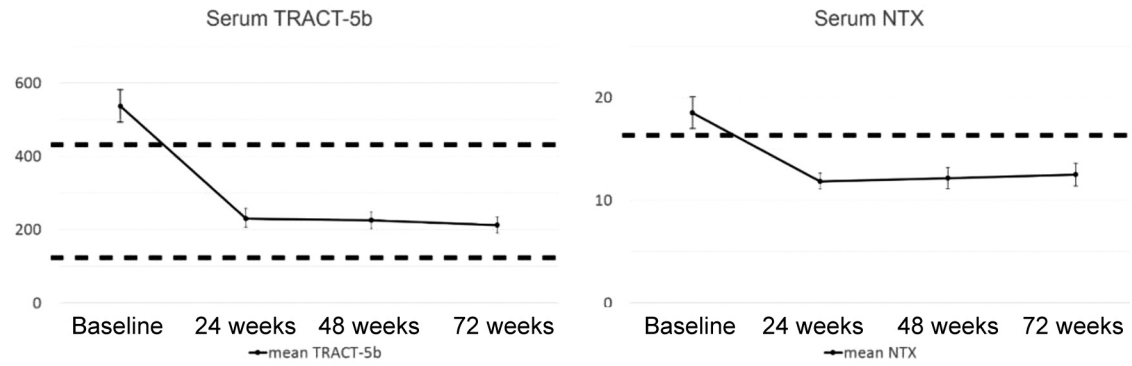


Figure 1. *Change in lumbar spine and total hip BMD. Mean BMD (%) of lumber spine and total hip increased by 3.0 and 2.4 at 24 weeks, 3.8 and 2.6 at 48 weeks, and 4.7 and 3.0 at 72 weeks, respectively. BMD: Bone mineral density.*



Mean	535.67	230.13	226.11	211.96	18.52	11.85	12.15	12.49
Average 95% upper limit	581.08	255.19	248.56	230.23	20.06	12.64	13.18	13.56
Average 95% lower limit	490.26	205.07	203.67	193.68	16.98	11.05	11.12	11.44

Figure 2. *Change in serum bone resorption markers. TRACT-5b: Tartrate-resistant acid phosphatase 5b (normal level: under 16.5) (mU/dl). NTX: typeIcollagen cross-linked N-telopeptide (normal level: 120-420) (nmolBCE/l). Mean baseline levels of TRACP-5b and NTX were 535.7 and 18.5, respectively; both decreased to 230.1 and 11.9, 226.1 and 12.2, and 212.0 and 12.5 each week, respectively.*

Table III. *Association of each factor with change in bone mineral density (BMD).*

	Number of patients	Lumbar BMD	Odds ratio (95%CI)	Total hip BMD	Odds ratio (95%CI)
Subtype					
Luminal	35	p=0.76	1.45	p=0.95	1.04
HER2	15		(0.14-15.21)		(0.29-3.35)
Chemo					
With	22	p=0.89	0.87	p=0.75	0.83
Without	28		(0.11-6.75)		(0.26-2.69)
Radiation					
With	26	p=0.24	3.79	p=0.09	2.82
Without	24		(0.36-39.41)		(0.84-9.51)

We divided patients into the decreased BMD group (≤0) and increased BMD group and analyzed them; however, none of the items were associated with improvements in BMD.

However, none of the following items, subtype, chemotherapy, and radiation therapy, were associated with improvements in BMD (Table III).

There were no fractures during the registration period, and likewise grade 2 or higher adverse events. The association between the BMD change rates and baseline serum levels of DHEA-S, 25(OH)Vit.D, PTH, and calcitonin was also analyzed; however, no correlation was found.

Discussion

Third-generation AIs, ANA, LET, and EXE, have been used as alternatives to TAM for adjuvant therapy among estrogen hormone receptor positive post-menopausal BC patients (5-7). Because this replacement and the extending recommended hormonal therapy period increase the risk of fractures, bisphosphonates are recommended for the prevention and treatment of osteoporosis in BC patients using AIs. While it is an effective treatment, adverse effects such as osteonecrosis of the jaw have been noted (8, 9). In this study, we chose monthly oral minodronate 50 mg treatment because of few reports on side effects and ease in administration.

In post-menopausal Japanese women, a randomized placebo-controlled trial revealed that daily 1 mg minodronate reduced vertebral fractures by 59% (10). Another randomized, double-blinded, multicenter study showed that monthly minodronate at 30 or 50 mg had similar efficacy as 1 mg daily in terms of changes in BMD and bone turnover markers, with similar safety profiles (11). Our results indicate that the combination therapy of minodronate and AI is safe, effective, and easy to administer, even after 72 weeks. We divided groups with BMD change rates higher or lower than average and examined whether there were any factors related to the treatment effect. No significant association was found between age, BMI, pre-treatment BMD, and bone metabolism markers. Several clinical trials have shown that fracture risk in Asians is lower than that in Caucasians (12), which might be related to estrogen receptor gene polymorphisms (13). Despite racial differences, more than one-fourth of women in their 70s experience at least one osteoporotic vertebral fracture (14); therefore, attention should be paid in the prevention of unnecessary fractures in post-menopausal BC patients.

According to the American Society of Clinical Oncology (ASCO)- Ontario Health [OH; Cancer Care Ontario (CCO)] guideline update 2022 (15), adjuvant bisphosphonate therapy should be discussed early with all post-menopausal patients (natural or therapy-induced) with primary BC, who are candidates to receive adjuvant systemic therapy. This benefit will vary depending on the underlying risk of recurrence and is associated with a modest improvement in overall survival (OS). The therapeutic options with the strongest supporting data include oral clodronate, oral ibandronate, and zoledronic acid for 2-3 years. If similar results are shown for monthly oral minodronate, it would benefit BC patients even more.

Because some patients are refractory to osteoporosis treatment, we sought to identify blood biomarkers that could predict treatment responsiveness. PTH promotes the activation of vitamin D in the proximal tube and calcium reabsorption in the distal tube of the kidney; it induces bone metabolism by activating both bone formation and bone resorption. Therefore, if the PTH level is continuously high due to hyperparathyroidism, the cortical BMD decreases. In our study, only two patients' PTH levels were above the normal range (10-65 pg/ml). Therefore, we compared these two patients with the others for BMD changes; however, no correlation was found.

Calcitonin is a calcium metabolism-regulating hormone whose secretion decreases with age. As a therapeutic agent, it suppresses the action of osteoclasts—bone resorption, and promotes bone formation to increase BMD. In our study, only one patient showed a normal range (≤6.4 pg/ml); the calcitonin levels in the remaining patients were less than 0.50 pg/ml and could not be examined.

Vitamin D promotes bone metabolism and calcium absorption in the small intestine and suppresses PTH production. 25(OH)vitamin D deficiency was observed in all cases; however, there are reports that 90% of Japanese women have vitamin D deficiency. Therefore, we compared the baseline lumbar BMD and treatment response rate between the upper and lower groups on average but found no correlation.

DHEA-S, an adrenal androgen that decreases in the peak 20s, is partially converted to estrogen in peripheral tissues and shows anti-osteoporotic action by acting on estrogen and androgens. DHEA replacement therapy can increase BMD. Because osteoblasts express aromatase, which converts androgen to estrogen, DHEA may protect against osteoporosis. The DHEA-S values were within the normal range in all patients in our study. We compared the upper and lower groups on an average but found no correlation in BMD changes.

None of the four baseline biomarker concentrations correlated with treatment response. This may be due to the small number of cases. It is also possible that the cryopreservation periods were as long as 3 years or more, and the concentrations may have changed. These data suggest that the combination of minodronate with AI therapy might be safe and effective in preventing osteoporosis and fracture in BC patients undergoing adjuvant hormonal therapy.

Conflicts of Interest

None of the Authors have any potential conflicts of interest relevant to this study.

Authors' Contributions

Study concept and design, analysis, and interpretation of data, and drafting and revising of the article: Ogata N, Toh U, Ogata S, Sudo

T, and Akagi Y. All Authors contributed to medical care and data collection and approved the final manuscript.

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