Evaluation of Pentosidine as Bone Quality Marker in Postmenopausal Breast Cancer Patients Receiving Aromatase Inhibitors

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Abstract

Background: Osteoporosis and fractures are important aromatase inhibitor (AI) related adverse events in postmenopausal women with hormone receptor positive breast cancer. An incremental increase of pentosidine is associated with a deterioration of bone quality. In this study, pentosidine was evaluated in postmenopausal breast cancer patients receiving AIs.

Methods: Fifty Japanese postmenopausal breast cancer patients receiving AIs were retrospectively evaluated. Sixteen patients were given a bone modifying agent (BMA) concomitant with AIs. Changes of pentosidine, bone turnover markers and bone mineral density (BMD) before and after 12 months of AI therapy were compared between BMA administered patients (BMA group) and a non-BMA group. These factors were assessed by BMA groups using chi-square of categorical variables and t-test for continuous variables.

Results: The median age of the subjects was 67 years, and 21, 23 and 6 subjects were classified as normal, bone loss and osteoporosis, respectively. There was no significant difference between pentosidine low and high groups in regard to age, height, weight, BMD of femoral neck and lumbar spine, and bone turnover markers including TRACP-5b and BAP. In the non-BMA group, pentosidine was increased in 18 cases (53%), and the average change of pentosidine was 21.5% (95%CI; 0.23 to 42.7%, $p=0.048$). In the BMA group, pentosidine was increased only in 2 cases (13%), and the average change of pentosidine was -16.6% (95%CI; -30.6 to -2.6%, $p=0.023$). There was a significantly lower proportion of pentosidine-increased cases ($p=0.0065$) and decrease of pentosidine ($p=0.021$) in the BMA group compared to those in the non-BMA group.

Conclusions: Pentosidine was increased with AI, however, BMA inhibits an AI-induced increase of pentosidine in postmenopausal breast cancer patients.

Background

More than 70% of early breast cancers are hormone-receptor positive, and adjuvant endocrine therapy reduces breast cancer recurrence and improves overall survival in patients with hormone receptor positive breast cancer[1]. Administration of an aromatase inhibitor (AI) for 5-10 years has become standard therapy for postmenopausal woman with hormone receptor positive breast cancer[2]. AI inhibits the peripheral conversion of androgens to estrogens, which leads to estrogen deficiency resulting in bone loss and vulnerability. Compared with tamoxifen, a selective estrogen receptor modulator, the long-term administration of AI is associated with a higher incidence of osteoporosis and bone fracture[3]. In addition to bone density, bone quality is regarded as an independent factor of bone strength[4]. Bone quality is determined by bone collagen and collagen crosslinks which determines biomechanical structures and pliability[5]. Collagen cross-links are classified into physiological cross-links and advanced glycation end products (AGEs) cross-links, and hyperplasia of AGEs reduces suppleness that results in hard and brittle bone. Pentosidine is an AGE and hyperplasia of bone pentosidine is associated with a

deterioration of bone strength without a decrement of BMD[6]. Several studies evaluated the association between osteoporotic fractures and urinary/serum level of pentosidine[7-11]. In Japanese osteoporosis patients receiving bisphosphonate treatment, a regression analysis regarding the relative risks for development of incident vertebral fracture showed that incremental increase in baseline urinary pentosidine (5 pmol/mg Cr) was a significant predictor for incidental vertebral fracture (HR 1.03, 95% CI 1.00–1.05, $p=0.039$)[9]. In a cohort study of Japanese postmenopausal women, a 1 SD increase in urinary pentosidine was a significant predictor for vertebral fracture (HR 1.18, 95% CI 1.05-1.33, $p < 0.01$) [10]. The serum pentosidine level is also associated with deteriorated bone strength and incidence of vertebral fracture[7,8]. In a cohort study of patients with prostate cancer undergoing androgen deprivation therapy, serum pentosidine was increased after endocrine therapy and denosumab inhibited the increment of serum pentosidine[11]. However, there are no reports of pentosidine in breast cancer patients receiving AI therapy and the effect of a bone modifying agent (BMA) on changes from pentosidine is uncertain.

This study was conducted with the aim of evaluating the effects of AI and BMA on pentosidine in postmenopausal breast cancer patients. Pentosidine in addition to BMD and a bone turnover marker were evaluated retrospectively in postmenopausal breast cancer patients receiving AIs with or without BMAs.

Materials And Methods

Subjects

A retrospective evaluation was done for a total of 50 consecutive postmenopausal patients that were administered AIs as adjuvant therapy for hormone receptor positive early breast cancer at Kure Medical Center and the Chugoku Cancer Center, Kure, Japan, between October 2016 and December 2019. All patients received steroidal AIs, anastrozole or letrozole, as adjuvant endocrine therapy. BMAs including bisphosphonate or denosumab were administered for 16 patients who were diagnosed as having osteoporosis or high risk for fracture based on BMD and general condition. Osteoporosis was determined as a T-score less than -2.5 at either the lumbar spine or total hip. Patients with a T-score greater than -2.5 but less than -1.0 at either the lumbar spine or total hip and with clinical risk factors for fracture were also determined high risk for fracture. Among these patients, 10 received denosumab 60 mg every six months, while six received bisphosphonate. Prescribed bisphosphonate was oral sodium risedronate hydrate in two, oral alendronate sodium hydrate in two, and intravenous zoledronic acid in two patients. Changes of pentosidine, bone turnover markers and BMD before and after 12 months of AI therapy were compared between BMA administered patients (BMA group) and a non-BMA group. Patients with a history of fracture, chronic renal failure or diabetes requiring insulin therapy were excluded from this study.

This study was approved by the Kure Medical Center ethics review board (29-70). The requirement for written informed consent from each subject was waived because this study was conducted with retrospective reviews of a prospectively maintained hospital database.

Measurement of pentosidine, bone turnover marker and BMD

Pentosidine and bone turnover markers, including TRACP-5b and BAP, were evaluated using blood samples. Fasting blood samples were collected before and 12 months after administration of AI and were stored at 4°C for measurement of BAP and -80°C for measurement of TRACP-5b and pentosidine. TRACP-5b was measured by enzyme immunoassays (Osteolinks, SB bioscience, Tokyo, Japan). Intra-assay CV was less than 15%. Bone alkaline phosphatase (BAP) was measured by chemiluminescent enzyme immunoassay (Access Ostase, Beckman Coulter, Tokyo, Japan). Intra-assay CV was 7.4%. Pentosidine was measured using enzyme-linked immunosorbent assays (FSK pentosidine, FUSHIMI, Marugame, Japan). Intra-assay CV was 5.5%. BMD was measured in the lumbar spine and femoral neck before and 12 months after administration of AI using dual-energy X-ray absorptiometry (DXA) (Horizon DXA system, HOLOGIC, Tokyo, Japan). The quality control was performed using a spine phantom. Intra-assay CV was 0.6%. Lumbar spine and femoral neck BMD, pentosidine, TRACP-5b and BAP were all statistically confirmed to showed normality of the distribution with Shapiro-Wilk W test.

Statistical analysis

Patient characteristics, BMD, and bone markers were assessed by BMA groups using chi-square of categorical variables and t-test for continuous variables. Subjects were classified into pentosidine high and low groups according to the upper limit of normal value 0.431 µg/ml, and the correlation between clinical factors and pentosidine was evaluated using chi-square of categorical variables and t-test for continuous variables. The relation between changes of pentosidine and other bone markers, including lumbar spine and femoral neck BMD, TRACP-5b and BAP, was evaluated by univariate linear regression analysis. Statistical analyses were performed using SPSS software (version 11 for Windows; 5 SAS Institute, Tokyo, Japan). A P value <0.05 was considered as statistically significant.

Results

Relationship between serum pentosidine and clinical factors

The median age of the subjects was 67 years, and 21, 23 and 6 subjects were classified as normal, bone loss and osteoporosis, respectively, according to the BMD results. All 6 subjects with osteoporosis were administered BMAs. Among 23 subjects with bone loss, 10 were administered BMAs considering risk for osteoporotic fracture. None with normal BMD was administered BMA. Table 1 shows the relationship between BMA administration and other clinical factors. BMA group showed significantly lower BMD in both lumbar spine and femoral neck, and higher BAP compared with non-BMA group. No significant correlation was found between the BMA and non-BMA group in regard to age, height, weight, TRACP-5b and Pentosidine. Table 2 shows the relationship between pentosidine and other clinical factors. There

was no significant difference between the pentosidine high and pentosidine low group in regard to age, height, weight, BMD of the lumbar spine and femoral neck and bone turnover markers including TRACP-5b and BAP. No patient experienced breast cancer recurrence, non-traumatic fractures or osteonecrosis of the jaw during this study period.

Changes in serum pentosidine according to BMA

Table 3 shows the change of pentosidine in the non-BMA and BMA group. In the non-BMA group, pentosidine increased in 18 cases (53%), and the average change of pentosidine was 21.5% (95%CI; 0.23 to 42.7%, $p=0.048$). In the BMA group, pentosidine increased in two cases (13%), and the average change of pentosidine was -16.6% (95%CI; -30.6 to -2.6%, $p=0.023$). A significantly lower proportion of pentosidine-increased cases ($p=0.0065$) and decrease of pentosidine ($p=0.021$) were recognized in the BMA group compared with the non-BMA group.

Changes in bone turnover markers and BMD according to BMA

Table 4 shows changes in bone turnover markers and BMD in the femoral neck and lumbar spine. After 12 months treatment with AIs, the mean changes of TRACP-5b (-54.4% vs. 10.9%, $p<0.001$) and BAP (-44.8% vs. 19.3%, $p<0.001$) were significantly lower in the BMA group compared with non-BMA group, respectively. In regard to BMD, the mean changes of femoral neck (3.9% vs. -1.9%, $p<0.001$) and lumbar spine (7.4% vs. -0.93%, $p<0.001$) were significantly higher after 12 months of treatment with AIs in the BMA group compared with the non-BMA group, respectively.

In univariate linear regression analysis, neither change of lumbar spine BMD ($R^2=0.016$, $p=0.37$), femoral neck BMD ($R^2=0.00015$, $p=0.93$), TRACP-5b ($R^2=0.027$, $p=0.25$) nor BAP ($R^2=0.026$, $p=0.26$) was significantly associated with change of pentosidine between baseline and 12 months after AI administration. In contrast, decrease of TRACP-5b and BAP were significantly associated with increase of lumbar spine BMD (TRACP-5b; $R^2=0.46$, $p<0.0001$, BAP; $R^2=0.36$, $p<0.0001$), femoral neck BMD (TRACP-5b; $R^2=0.42$, $p<0.0001$, BAP; $R^2=0.33$, $p<0.0001$).

Discussion

In this cohort study of postmenopausal breast cancer patients receiving AIs as adjuvant therapy, the bone quality marker pentosidine was increased by AI and reduced with BMAs. Bone turnover markers and BMD also showed significant improvement with BMAs. These results indicate that administration of BMA exerts not only an inhibition of bone loss, but also an improvement of bone quality in patients receiving AIs.

Fracture and osteoporosis are important adverse events in postmenopausal breast cancer patients receiving adjuvant AIs, and the prophylactic administration of BMA is recommended for patients with a high risk of bone-related adverse events[12,13]. Because long-term prescription of BMA can cause serious adverse events, such as osteonecrosis of the jaw and atypical femoral fracture in breast cancer, an

appropriate evaluation of the risk of AI related fracture is desirable[14,15]. Although low BMD in femoral neck or lumbar spine is regarded as an independent risk factor for fracture, a certain proportion of patients with a non-osteoporotic range of BMD experience nontraumatic fractures[16,17]. In a cohort study of postmenopausal women, more than half of osteoporotic fractures occur in cases with a non-osteoporotic range of BMD[18]. The Fracture Risk Assessment Tool (FRAX) is used to estimate the risk of osteoporotic fracture using femoral neck BMD and clinical risk factors, which include age, prior non-traumatic fracture, glucocorticoid use, low body mass index, family history of osteoporosis, smoking, and excess alcohol intake, which are also associated with incidence of fracture. However, FRAX is not designed to estimate the risk of AI-related fracture, and the estimated fracture risk by FRAX tends to be lower than that of the actual fracture incidence in breast cancer patients receiving AI[19]. Thus, the evaluation of other risk factors is warranted to determine appropriate administration of BMA to prevent AI-related fracture in postmenopausal breast cancer patients.

Independent of BMD, bone quality is regarded as an important factor of bone strength when considering the risk of osteoporotic fracture. The trabecular structure, including trabecular number, separation and homogeneity of the trabecular network, is also deteriorated with exemestane. A follow-up study of 29,407 postmenopausal women aged 50 years and older showed that patients with bone loss by BMD and a low Trabecular Bone Score (TBS) were at the same risk of fracture as those with osteoporosis by BMD and high TBS[20]. In an accompanying study of a randomized control trial evaluating exemestane, an AI, for prevention of breast cancer in healthy postmenopausal women, high-resolution peripheral quantitative CT showed a significant decrease in volumetric BMD and cortical thickness at the distal radius and distal tibia with exemestane[21]. These findings suggest that deterioration of bone quality is also an important AI-related bone adverse effect.

Serum and urine pentosidine have been investigated as bone quality markers. Pentosidine is positively correlated with deteriorated collagen crosslinks AGEs[6], and elevated pentosidine is shown as an independent risk factor of fracture in postmenopausal women[22]. In this study, we evaluated the serum change of pentosidine in postmenopausal breast cancer patients receiving adjuvant AIs with or without BMAs. First, approximately half of subjects administered adjuvant AIs without BMA had an elevation of pentosidine. AI treatment can be associated with not only a decrease of BMD, but also a deterioration of bone quality. Second, the administration of BMA significantly suppressed an AI-induced pentosidine increase and BMD decrease. Our findings are consistent with a previous study evaluating the effects of denosumab on prostate cancer patients treated with hormonal therapy. BMA therapy can maintain BMD and prevent a deterioration of bone quality in patients treated with hormonal therapy. Finally, measurement of baseline and change of pentosidine may provide additional risk assessment of osteoporotic fracture in breast cancer patients receiving AIs. In univariate linear regression analysis, there was no significant difference between the pentosidine low and high groups in regard to age, height, weight, BMD and bone turnover markers.

This study has several limitations. First, this is a cohort study with a relatively small number of cases and a short duration of follow up. A prospective study with a larger number of cases with a long-term period is

warranted to confirm our findings. Second, BMAs were essentially prescribed for patients with a high risk of osteoporotic fracture determined by low BMD and/or clinical factors in this study. The effect of BMA on preventing AI-induced bone quality deterioration is uncertain in patients with a normal range of BMD. Finally, no bone quality assessment other than pentosidine was done in this study. Imaging studies evaluating bone structure should be done in future study to confirm our findings.

In summary, this study demonstrated that serum pentosidine significantly increased with AI therapy in postmenopausal women with hormone receptor positive breast cancer, and administration of BMAs inhibit an AI-induced increase of pentosidine. A prospective long-term study is warranted to confirm the relationship between pentosidine and non-traumatic fracture during adjuvant AI therapy.

Abbreviations

AI: aromatase inhibitor; BMA: bone modifying agent; AGEs: advanced glycation end products; BMD: bone mineral density; DXA: dual-energy X-ray; S.D: Standard deviation

Declarations

Acknowledgements

None.

Authors' contributions

HS: construction of this clinical study, data collection and writing the original manuscript. TY: data collection and editing manuscript. DY: data collection and editing manuscript. SO: designing the study, and reviewing and editing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data analyzed in this study are available from the corresponding author on appropriate reason.

Ethics approval

This study was approved by the Kure Medical Center ethics review board (29-70). The requirement for written informed consent from each subject was waived because this study was conducted with retrospective reviews of a prospectively maintained hospital database.

Consent for publication

Not applicable.

Competing interests

All authors have no conflicts of interest in this study.

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Tables

Table1. Baseline clinical factors of patients according to administration of BMA

Factors	Non-BMA group (n=34)	BMA group (n=16)	p value (t test)
Age (mean±S.D.)	66.1±1.6	66.6±1.6	0.8
Height (cm, mean±S.D.)	154.3±1.0	153.2±1.4	0.5
Weight (kg, mean±S.D.)	62.5±1.8	56.5±2.6	0.06
BMD of lumbar spine (g/cm ² , mean±S.D.)	0.955±0.019	0.744±0.028	<0.0001
BMD of femoral neck (g/cm ² , mean±S.D.)	0.812±0.017	0.650±0.024	<0.0001
TRACP-5b (mU/dl, mean±S.D.)	491.5±26.9	486.1±39.2	0.9
BAP (µg/l, mean±S.D.)	14.7±1.4	20.1±2.0	0.03
Pentosidine (µg/ml, mean±S.D.)	0.054±0.003	0.061±0.005	0.3
BMA, bone modifying agent; S.D., Standard deviation; BMD, bone mineral density			

Table2. Clinical factors of patients according to pentosidine low or high group

Factors	Pentosidine low (n=11)	Pentosidine high (n=39)	p value (t test)
Age (mean±S.D.)	65.1±2.4	66.7±1.3	0.55
Height (cm, mean±S.D.)	153.3±1.7	154.2±0.9	0.65
Weight (kg, mean±S.D.)	59.2±3.2	61.0±1.7	0.63
BMD of lumbar spine (g/cm ² , mean±S.D.)	0.844±0.045	0.899±0.024	0.28
BMD of femoral neck (g/cm ² , mean±S.D.)	0.717±0.037	0.772±0.020	0.20
TRACP-5b (mU/dl, mean±S.D.)	504.5±47.2	485.6±25.1	0.72
BAP (µg/l, mean±S.D.)	15.0±2.5	16.8±1.3	0.53
S.D., Standard deviation; BMD, bone mineral density; BMA, bone modifying agent			

Table3. A. Proportion of patients with an increase or decrease of pentosidine from baseline to 12 months according to BMA administration. B. Percentage change from baseline to 12 months in pentosidine according to BMA administration.

Table 3A			
Pentosidine	Non-BMA group (n=34)	BMA group (n=16)	p value (Pearson)
Increase	18 (53%)	2 (13%)	0.0065
Decrease	16 (47%)	14 (87%)	
Table 3B			
	Change from baseline (95% CI)		p value (t test)
Non-BMA group	21.5% (0.23% to 42.7%)		0.021
BMA group	-16.6% (-30.6% to -2.6%)		
S.D., Standard deviation; BMA, bone modifying agent; CI, confidential interval			

Table 4. Percentage change from baseline to 12 months in BMD and bone turnover markers according to BMA administration

Factor	Group	Change from baseline (%, mean±S.D.)	p value (t test)
BMD of lumber spine (g/cm ² , mean±S.D.)	Non BMA	-0.93±0.76	<0.001
	BMA	7.4±1.1	
BMD of femoral neck (g/cm ² , mean±S.D.)	Non BMA	-1.9±0.60	<0.001
	BMA	3.9±0.86	
TRACP-5b (mU/dl, mean±S.D.)	Non BMA	10.9±3.3	<0.001
	BMA	-54.4±4.8	
BAP (µg/l, mean±S.D.)	Non BMA	19.3±4.6	<0.001
	BMA	-44.8±6.6	
S.D., Standard deviation; BMD, bone mineral density; BMA, bone modifying agent			