

# Preventive effect of zoledronic acid on aromatase inhibitor-associated bone loss for postmenopausal breast cancer patients receiving adjuvant letrozole

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**Background:** This study aims to compare the efficacy and safety between zoledronic acid combined with calcium and calcium alone to prevent aromatase inhibitor-associated bone loss for postmenopausal breast cancer patients receiving adjuvant letrozole.

**Methods:** One hundred twenty patients were randomly divided into two groups, A and B. Patients in group A (n=60) received modified radical mastectomy or breast-conserving surgery + four cycles of AC followed by T regimen (optional) + radiotherapy (optional) + letrozole 2.5 mg daily + calcium 500 mg twice daily + vitamin D 400 international units daily +4 mg of zoledronic acid every 6 months, while patients in group B (n=60) were not given zoledronic acid and the rest of the treatments of group B were the same as group A. All the patients were followed up for 1 year. The primary endpoint was the inpatient percentage change in lumbar spine (LS) bone mineral density (BMD) from baseline to month 12. Secondary endpoints included the percentage change in total hip (TH) and femoral neck (FN) BMD, the incidence of osteoporosis, the incidence of a clinically meaningful 5% decline in BMD at 1 year, change of serum N-telopeptide of type 1 collagen (NTX) and bone-specific alkaline phosphatase (BSAP) concentrations.

**Results:** Patients in group A had a statistically significant higher average change and average percent change in LS, FN, and TH than group B. Group A had a statistically significant lower incidence of a clinically meaningful loss of bone density at the LS, FN, or TH than Group B. The incidence of osteoporosis in group A was significantly lower than group B. The decreases in NTX and BSAP concentrations from baseline to month 12 in patients of group A were significant; in contrast, patients in group B were found to have increases in NTX and BSAP concentrations from baseline. The most common adverse reactions in patients are flu-like symptoms (38%), bone pain (28%), and joint pain (20%).

**Conclusion:** AI-associated bone loss can be prevented by concurrent zoledronic acid for postmenopausal breast cancer patients.

**Keywords:** zoledronic acid, breast cancer, postmenopausal osteoporosis, letrozole

## Introduction

Breast cancer is the most commonly diagnosed malignancy and the third leading cause of cancer death among women worldwide.<sup>1</sup> Several large clinical trials, such as Breast International Group 1-98,<sup>2</sup> Austrian Breast and Colorectal Cancer Study Group trial 8<sup>3</sup> and Arimidex–Nolvadex 95,<sup>3</sup> showed that compared with tamoxifen, the third-generation aromatase inhibitors (AIs) administered either alone or sequentially after 2 to 3 years of tamoxifen for postmenopausal women with hormone receptor-positive breast cancer, resulted in a longer disease-free survival (DFS) and fewer endometrial and thromboembolic adverse events. Therefore, AIs are widely used by patients with postmenopausal

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breast cancer (PBC) as first-line adjuvant hormonal therapy or following tamoxifen therapy. AIs prevent the conversion of androgens to estrogens by inhibiting aromatase, resulting in a significant decline in circulating estrogen levels, or even leading to an undetectable level. Estrogen is essential for the maintenance of bone mass for women, and the decrease in estrogen levels results in increased bone turnover and loss. Several studies have shown that bone mass loss in PBC patients using long-term AIs is two times more than that of normal postmenopausal women of the same age.<sup>4-6</sup> Therefore, PBC patients who receive AI treatment are at increased risk of osteopenia, osteoporosis, and bone fracture, which bring great suffering to patients and reduce their quality of life. Efforts to prevent fractures are needed.

Previously, oral calcium supplements were used to prevent osteoporosis-related complications, but several reports showed that it had little effect.<sup>7,8</sup> Bisphosphonates have profound effects on osteoclasts, affect T-cell function, and increase bone mineral density (BMD) in normal postmenopausal women and have been utilized for the treatment of osteoporosis in normal postmenopausal women. In addition, bisphosphonates have no known interaction with estrogen or progesterone receptors, and therefore could also be effective as adjuvant treatments for the management of bone lesions in women with advanced breast cancer.<sup>9,10</sup> Zoledronic acid is a kind of nitrogen-containing bisphosphonates and can inhibit osteoclast-mediated bone resorption. Recent data have also indicated that compared to placebo, zoledronic acid can increase BMD by 4%–5% at the lumbar spine (LS) and 3%–4% at the femoral neck (FN) in normal postmenopausal women.<sup>11</sup> Hines et al confirmed upfront that zoledronic acid prevents bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen by clinical trial N03CC.<sup>11</sup> However, there has been no research on the efficacy and safety of zoledronic acid infusion to prevent osteoporosis for PBC patients after surgery. Therefore, we conducted this randomized controlled study to compare the efficacy and safety between zoledronic acid combined with calcium and calcium alone to prevent AI-associated bone loss for PBC patients receiving adjuvant letrozole.

## Patients and methods

### Patients

This study was approved by the Ethics Committee of Yidu Central Hospital of Weifang. All study participants provided written informed consent before participation. Written informed consent was also obtained from the patients for the publication of this report and any accompanying images. This clinical trial was a prospective open-label, randomly

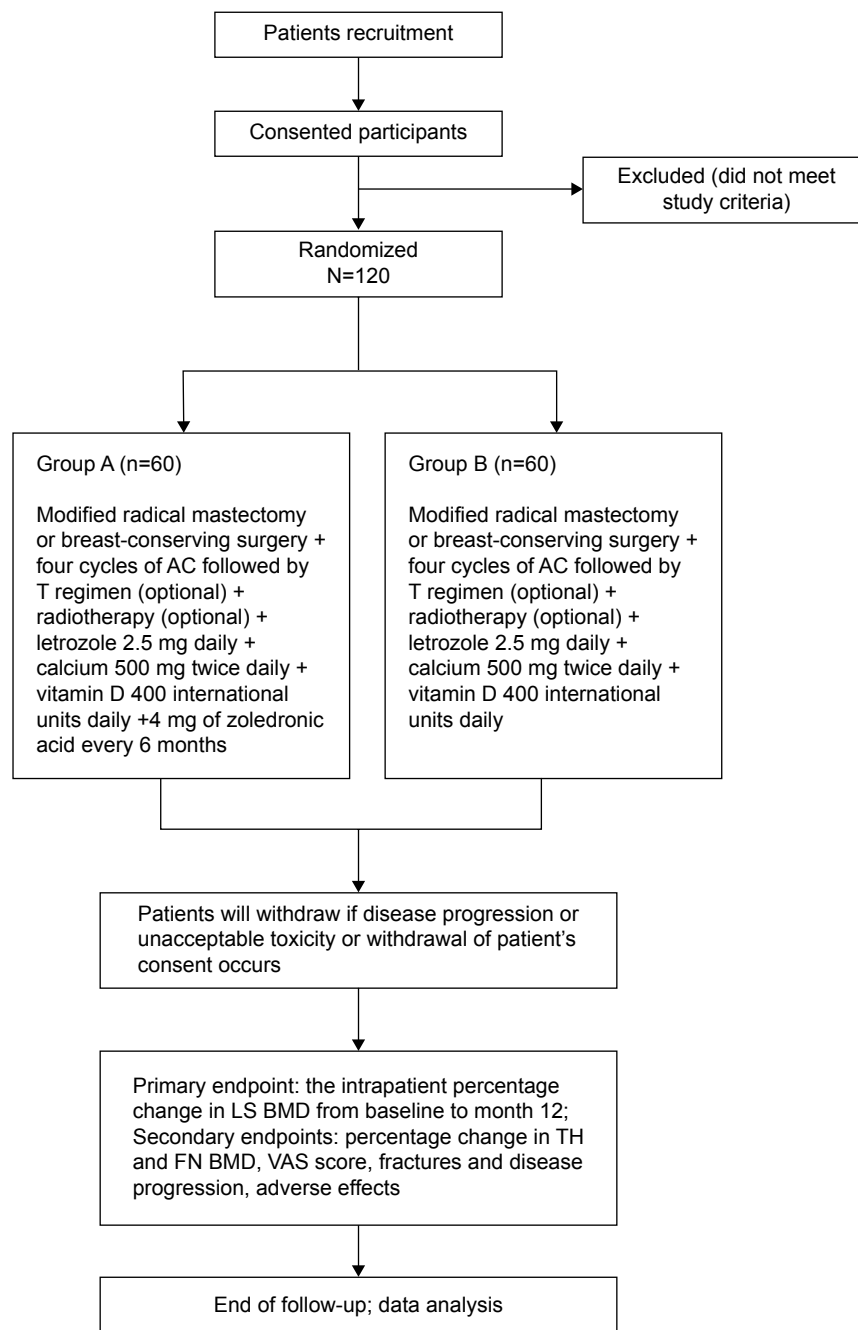
controlled trial to assess the efficacy and safety of prophylactic use of bisphosphonates combined with calcium to prevent osteoporosis in PBC patients. The flow chart of this study is shown in Figure 1. Patients were included by strictly following the inclusion and exclusion criteria.

The inclusion criteria were as follows: 1) women >60 years with cessation of menses, women ≤60 years with spontaneous cessation of menses >12 months, women with bilateral oophorectomy, or women ≤60 years, with no spontaneous menses for <1 year but with postmenopausal estradiol levels; 2) histopathological or cytological diagnosis as invasive breast cancer; 3) stage I, II, or IIIA breast cancer; 4) estrogen and/or progesterone receptor positive; 5) no evidence of recurrent or metastatic disease; 6) life expectancy of ≥5 years; 7) an Eastern Cooperative Oncology Group performance status of 0–2; 8) the baseline total LS or FN BMD T-score must have been <–2.0; 9) hematology, liver, and kidney function are normal; and 10) good understanding and compliance by patients with the pilot program and provision of informed consent.

The exclusion criteria were as follows: 1) patients with clinical or radiological evidence of distant metastases; 2) patients with existing LS or total hip (TH) fracture, or a history of nontraumatic fractures or osteoporosis; 3) patients who received recent treatment with any drugs known to affect the skeleton, prior treatment with intravenous bisphosphonates or AIs, prior exposure (within the past 6 months) to anabolic steroids or growth hormone; 4) patients with diseases known to influence bone metabolism, other malignancy within 5 years (except adequately treated basal or squamous cell carcinoma of the skin and in situ carcinoma of the cervix), renal dysfunction, uncontrolled infections, diabetes mellitus, thyroid dysfunction, seizure disorders associated with falls, HIV, malabsorption syndrome, or mental illnesses; 5) patients with a known hypersensitivity to zoledronic acid, other bisphosphonates, letrozole, calcium, or vitamin D; and 6) patients contraindicated for the dual X-ray absorptiometry.

### Treatment

Research began in January 2013, while the deadline for follow-up was December 2015. All patients received modified radical mastectomy or breast-conserving surgery. Patients with one or more pathological risk factors (eg, positive nodes, positive surgical margin) were administered four cycles of adjuvant chemotherapy followed by the T regimen, which included adriamycin (Pfizer Pharmaceuticals Ltd, Wuxi, People's Republic of China) 60 mg/m<sup>2</sup> on day 1 and cyclophosphamide (Hengrui Medicine Co., Ltd., Jiangsu, People's Republic of China) 600 mg/m<sup>2</sup> on day 1 for four cycles, followed by paclitaxel (Sinochem United Pharmaceutical



**Figure 1** The trial flow chart.

**Abbreviations:** BMD, bone mineral density; FN, femoral neck; LS, lumbar spine; TH, total hip; VAS, visual assessment scale.

Industry Co., Ltd, Hainan, People's Republic of China) 175 mg/m<sup>2</sup> on day 1 for four cycles with 14 days per cycle. According to indications for postoperative radiotherapy, the patients started radiotherapy 2–4 weeks after completion of chemotherapy. The total planned dose was 50 Gy/25 fractions to ipsilateral breast ± lymphatic drainage area and 10–16 Gy was added to the tumor bed. Endocrine therapy was started after completion of chemotherapy. All patients were assigned to take letrozole 2.5 mg daily for 5 years or until onset of disease recurrence. All patients were instructed

to take calcium 500 mg twice daily and vitamin D 400 international units. Patients were randomly assigned in a 1:1 ratio to either group A (intervention group) or B (control group). Apart from the above treatments, patients in group A were given zoledronic acid treatment for the first time at the beginning of chemotherapy. All doses of zoledronic acid (Zometa, Novartis Pharma Stein AG, LTD, Switzerland) were administered intravenously over 30 minutes at a dosage of 4 mg. The dose of zoledronic acid was adjusted for a creatinine clearance <60 mL/minute. Doses were given every 6 months

until breast cancer recurrence. Patients who discontinued letrozole or zoledronic acid were withdrawn from the study. Prohibited concomitant therapy included any other bisphosphonates, calcitonin, sodium fluoride, parathyroid hormone, mithramycin, gallium nitrate, or tibolone.

## Endpoint

The primary endpoint of this analysis was the inpatient percentage change in LS (L1–L5) BMD from baseline to month 12. Secondary endpoints were the percentage change in TH and FN BMD. The incidence of osteoporosis on each treatment regimen was calculated. Osteoporosis was defined as a standardized BMD score of at least 2.5 standard deviations below the normal BMD for a young healthy woman. Since a 5% difference in inpatient BMD scores from baseline was defined as clinically significant and indicative of an important loss of bone density, the incidence of this event in each treatment arm was calculated.

BMD was measured using Norland (Norland, Fort Atkinson, WI, USA) dual-energy X-ray absorptiometry (DEXA) devices. Each DEXA device was cross-calibrated at baseline using four Bio-Imaging Bona Fide Phantoms (Bio-Imaging Technologies, Inc., Newtown, PA, USA); the stability of the DEXA devices was monitored quarterly. T scores, defined as the difference in the number of standard deviations between an individual's BMD and mean BMD for a group of young, healthy females, were calculated using manufacturer-specific T-score databases.

Serum N-telopeptide of type 1 collagen (NTX) and bone-specific alkaline phosphatase (BSAP) concentrations were evaluated for all patients by a central laboratory (Center Laboratory Weifang Medical College, Shandong, People's Republic of China) at baseline and every 3 months during follow-up. The samples were obtained in the morning while the patients were fasting. The frequency and severity of toxicity reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events was calculated. Disease progression was assessed at each patient visit. Any patient diagnosed with disease progression was removed from the study.

Data were analyzed only for the 1-year study period. After 1 year, the researchers were free to change to other bisphosphonates drug for patients in group A or to add bisphosphonates drug for patients in group B according to their symptoms.

## Statistical analysis

Statistical Package for Social Scientists (SPSS, version 18.0, SPSS Inc., Chicago, IL, USA) was used for all analyses. The comparison of the inpatient percentage change in LS (L1–L5) BMD from baseline to month 12 was assessed using *t*-test for

paired data. Comparison for categorical variables was completed by chi-squared test or Fisher's exact test. An independent sample *t*-test was used for continuous variables between groups. A *P*-value of <0.05 was considered statistically significant.

## Results

### Patient characteristics

Between January 2011 and February 2012, 120 patients meeting the inclusion and exclusion criteria were enrolled and assigned in a 1:1 ratio to groups A (intervention group, *n*=60) and B (control group, *n*=60). Two patients in group A were lost to follow-up (they moved to other cities and were unable to keep in touch). Eighteen patients dropped off from the study for reasons which included patient refusal and adverse events, of which eight patients were from group A and ten were from group B. Data for the remaining 100 patients, 50 in each group, were available for the final analysis. The distribution of baseline factors by the treatment arm is outlined in Table 1. Age, age at onset of menopause, Eastern Cooperative Oncology Group performance score, stage of breast cancer, number of patients receiving chemotherapy, number of patients receiving radiotherapy, and baseline T score of LS did not significantly differ between the two treatment groups (all *P*>0.05).

### Bone mineral density

As we can see in Table 2, patients in group A had a statistically significant higher average change (mean 0.04 vs -0.02, *P*<0.05) and average percent change (mean 3.67%

**Table 1** Baseline patient characteristics

| Characteristics   | Group A<br>( <i>n</i> =50) | Group B<br>( <i>n</i> =50) | $\chi^2/t$         | <i>P</i> -value |
|---|----------------------------|----------------------------|--------------------|-----------------|
| Age (median, range)                                       | 58, 35–83                  | 56, 33–79                  | 1.041 <sup>b</sup> | >0.05           |
| Age at onset of menopause <sup>a</sup><br>(median, range) | 49, 28–61                  | 50, 26–63                  | 1.225 <sup>b</sup> | >0.05           |
| ECOG performance score                                    |                            |                            | 0.712              | 0.700           |
| 0   | 45                         | 43                         |                    |                 |
| 1   | 2                          | 4                          |                    |                 |
| 2   | 3                          | 3                          |                    |                 |
| Stage of breast cancer                                    |                            |                            | 1.535              | 0.464           |
| I   | 15                         | 13                         |                    |                 |
| II  | 25                         | 24                         |                    |                 |
| IIIa  | 10                         | 13                         |                    |                 |
| Number of patients<br>receiving chemotherapy              | 43                         | 45                         | 0.379              | 0.538           |
| Number of patients<br>receiving radiotherapy              | 39                         | 41                         | 0.250              | 0.617           |
| Baseline T score of LS                                    | 1.09±0.15                  | 1.08±0.18                  | 1.725 <sup>b</sup> | >0.05           |

**Notes:** <sup>a</sup>Defined as women aged >60 years with cessation of menses, women aged ≤60 years with spontaneous cessation of menses >12 months, women with bilateral oophorectomy, or women aged ≤60 years, with no spontaneous menses for <1 year but with postmenopausal estradiol levels; <sup>b</sup>*t*-value.

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; LS, lumbar spine.

**Table 2** LS, FN, and TH BMD changes at 1 year for the two groups (mean)

| Variable (g/cm <sup>2</sup> ) | Group A (n=50) | Group B (n=50) | P-value |
|-------------------------------|----------------|----------------|---------|
| Baseline LS                   | 1.09           | 1.08           | >0.05   |
| 1-year LS                     | 1.13           | 1.06           | <0.05   |
| LS change at 1 year           | 0.04           | -0.02          | <0.05   |
| LS % change at 1 year         | 3.67%          | -1.85%         | <0.05   |
| Baseline FN                   | 0.85           | 0.87           | <0.05   |
| 1-year FN                     | 0.89           | 0.84           | <0.05   |
| FN change at 1 year           | 0.04           | -0.03          | <0.05   |
| FN % change at 1 year         | 4.71%          | -3.45%         | <0.05   |
| Baseline TH                   | 0.96           | 0.95           | <0.05   |
| 1-year TH                     | 0.98           | 0.94           | <0.05   |
| TH change at 1 year           | 0.02           | -0.01          | <0.05   |
| TH % change at 1 year         | 2.08%          | -1.05%         | <0.05   |

**Abbreviations:** FN, femoral neck; LS, lumbar spine; TH BMD, total hip bone mineral density.

vs -1.85%,  $P < 0.05$ ) in LS than group B. At the FN, patients in group A had significantly higher values for both change and percent change than group B (mean 0.04 vs -0.03,  $P < 0.05$ ; mean 4.71% vs -3.45%,  $P < 0.05$ ). The average change in TH BMD and percent change at 1 year were also significantly higher in group A than group B (mean 0.02 vs -0.01,  $P < 0.05$ ; mean 2.08% vs -1.05%,  $P < 0.05$ ).

A 5% inpatient decline in BMD at 1 year was defined as a clinically meaningful loss of bone density. Group A had a statistically significant lower incidence of a clinically meaningful loss of bone density at the LS, FN, or TH than group B (LS: 4% vs 20%,  $P = 0.014$ ; FN: 8% vs 24%,  $P = 0.029$ ; TH: 6% vs 22%,  $P = 0.021$ ) (Table 3). The incidence of osteoporosis (LS T score  $< -2.5$ ) in group A was significantly lower than that in group B (0 vs 4,  $P = 0.041$ ).

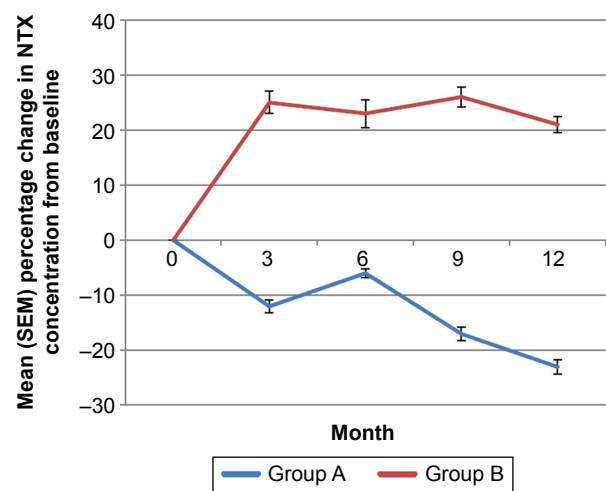
## Markers of bone turnover

The decreases in NTX and BSAP concentrations from baseline to month 12 in patients of group A were significant

**Table 3** Incidence of a clinically meaningful 5% decline in BMD at 1 year for the two groups

| Characters | Group A (n=50) | Group B (n=50) | $\chi^2$ | P-value |
|------------|----------------|----------------|----------|---------|
| LS         |                |                | 6.061    | 0.014   |
| Yes        | 2 (4%)         | 10 (20%)       |          |         |
| No         | 48 (96%)       | 40 (80%)       |          |         |
| FN         |                |                | 4.762    | 0.029   |
| Yes        | 4 (8%)         | 12 (24%)       |          |         |
| No         | 46 (92%)       | 38 (76%)       |          |         |
| TH         |                |                | 5.316    | 0.021   |
| Yes        | 3 (6%)         | 11 (22%)       |          |         |
| No         | 47 (94%)       | 39 (78%)       |          |         |

**Abbreviations:** FN, femoral neck; LS, lumbar spine; TH, total hip.

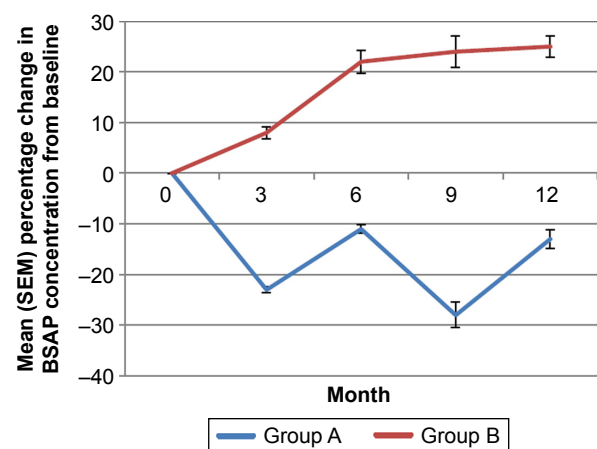
**Figure 2** Mean (SEM) percentage change in NTX concentration from baseline in patients of group A compared with those of group B.

**Abbreviations:** NTX, N-telopeptide of type I collagen; SEM, standard error of the mean; Group A, intervention group; Group B, control group.

(NTX, -23.2%; BSAP, -13.4%;  $P < 0.05$  for both) (Figures 2 and 3); in contrast, patients in group B were found to have increases in NTX and BSAP concentrations from baseline (NTX: 21.7%;  $P < 0.05$ ; BSAP: 25.3%;  $P < 0.05$ ) (Figures 2 and 3). Between the two groups, the differences in percentage change for both NTX (range, 29.7%–46.9%;  $P < 0.05$ ) and BSAP (range, 31.6%–52.5%;  $P < 0.05$ ) concentrations were statistically significant at all time points.

## Fractures and disease progression

During follow-up, two patients in group A experienced significant pain of waist and back. The orthopedic X-ray examination revealed wedging of thoracic and lumbar

**Figure 3** Mean (SEM) percentage change in BSAP concentrations from baseline in patients of group A compared with those of group B.

**Abbreviations:** BASP, bone-specific alkaline phosphatase; SEM, standard error of the mean; Group A, intervention group; Group B, control group.

vertebral body, and MRI examination confirmed the diagnosis as vertebral compression fracture induced by osteoporosis (fracture incidence 4.0%). Eight cases in group B experienced severe back and lumbar pain during follow-up. X-ray examination of these patients revealed wedging of the thoracic and lumbar vertebral body, but only three patients were confirmed to have the diagnosis of osteoporotic vertebral body compression fracture (6.0%). No participants in both groups experienced disease progression within the first year of therapy.

## Adverse effects

No adverse reactions were related to zoledronic acid for patients in group B who received only calcium. In general, zoledronic acid was well tolerated by patients in group A. The main adverse reactions included flu-like symptoms (38%), bone pain (28%), joint pain (20%), fatigue (12%), headache (10%), and fever (6%), all of which is because some patients experienced acute-phase reaction after zoledronic acid infusion. Bone pain of mild-to-moderate degree occurred 2–3 days after infusion of zoledronic acid, which can be alleviated by nonsteroidal anti-inflammatory drugs. Flu-like symptoms occurred within 5 days of infusion of zoledronic acid. Three cases (6%) experienced fever, with the highest temperature of 39.5°C, and body temperature returned back to normal within 24 hours following symptomatic treatment.

One patient in group A developed grade 2 renal impairment, which was believed to be related to the study drug; zoledronic acid was permanently discontinued in this patient. Serious adverse reactions were observed in four (8%) patients, leading to study drug discontinuation in only 2%. No confirmed cases of osteonecrosis of the jaw (ONJ) were reported.

## Discussion

In recent years, the clinical treatment modalities for breast cancer have undergone a fundamental change. Numerous studies show that expanded surgery range does not have a decisive impact on the prognosis for breast cancer, while chemotherapy combined with endocrine therapy was able to improve breast cancer DFS and overall survival. However, chemotherapy drugs directly affect bone metabolism in breast cancer patients, manifesting as increased bone resorption and loss.<sup>12</sup> Endocrine therapy represented by AI, can greatly reduce estrogen levels in patients with PBC, leading to reduced bone mass and density.<sup>13</sup> Secondary factors of

chemotherapy combined with endocrine therapy make PBC patients at high risk of primary osteoporosis to be susceptible of severe osteoporosis, which significantly impact their quality of life. However, the widely administered treatment of calcium and vitamin D in such patients has minimal effects and cannot even maintain their bone mass. In this study, the 1-year LS, FN, and TH BMD of patients in group B who only received the widely administered treatment of calcium and vitamin D were significantly reduced. This also confirmed the above views. Estrogen therapy (with or without progesterone) has been shown to prevent bone loss and reduce the risk of hip and vertebral fractures for PBC patients. However, women with breast cancer are commonly advised to avoid this therapy, due to the presence of estrogen and progesterone receptors in the majority of these malignancies.

Bisphosphonates are an attractive solution for the prevention of cancer treatment-associated bone loss in PBC patients. Zoledronic acid is the only compound that has been extensively studied and has proven efficacy for AI-associated bone loss. Another advantage of intravenous administration of zoledronic acid is that it can bypass the potential disadvantages of the oral route used by other bisphosphonates, which may include poor bioavailability, gastrointestinal intolerance, and inadequate compliance. Literatures recommend 4 mg every 6 months as the optimum dose selection to prevent bone loss for PBC patients.<sup>14–16</sup>

This randomized clinical trial demonstrated that zoledronic acid could prevent bone loss in postmenopausal women with breast cancer treated with letrozole. The patients who did not receive zoledronic acid lost a mean 1.85% bone density at the LS at 1 year. However, zoledronic acid did not only prevent this bone loss but was associated with an increase in bone density of 3.67% at the LS at 1 year. This 5.52% difference in BMD at 1 year between the two treatment arms is considered clinically meaningful, since it is reported that a loss of 10% BMD may double the fracture risk.<sup>17,18</sup> Although comparison of the fracture rates was a secondary endpoint of this study, the number of fractures in either group was insufficient to provide a clinically reliable statistical analysis. However, all other endpoints used in this trial produced consistent results regarding the finding that zoledronic acid provides a statistically significant improvement in BMD at 1 year. Notably, patients in group B who did not receive zoledronic acid were three to five times more likely to experience a clinically meaningful loss (not <5%) of bone density compared to patients in group A treated with zoledronic acid. The changes in bone marker measurements

suggested that the effect of zoledronic acid on bone turnover is both rapid and sustained over at least the first year. The mean of percentage change from baseline in BSAP and NTX significantly decreased in group A but significantly increased in group B.

The results from this study are consistent with previously published reports that bone density declines in postmenopausal women who begin AI therapy.<sup>19,20</sup> This happens because AI suppresses the anti-absorptive effect of estrogen on osteoclasts. This effect can be overcome by inhibition of osteoclast activity with zoledronic acid. The results from this study also supported this view. The prevention of bone loss with zoledronic acid therapy is also consistent with the results from the Zometa–Femara Adjuvant Synergy trial, which found that BMD in the LS was 4.4% higher at 1 year in PBC patients treated with upfront zoledronic acid compared with controls.<sup>21,22</sup>

Zoledronic acid was generally well tolerated. In this study, the most common adverse reactions in patients after administration of zoledronic acid were flu-like symptoms (38%), bone pain (28%), and joint pain (20%), all of which are generally mild and can be alleviated by nonsteroidal anti-inflammatory drugs or soon relieve on their own. We conclude that strict monitoring of renal function and serum calcium, adequate hydration during the process of treatment and close monitoring of symptoms, and timely measures guarantee a minimum incidence of adverse reactions. It is reported that ONJ is a potential complication from chronic intravenous or high-dose of zoledronic acid and is most commonly observed in patients who have undergone dental procedures and/or received chemotherapy and/or corticosteroid therapy.<sup>23</sup> In this study, no confirmed cases of ONJ were reported. For patients at high risk of ONJ, zoledronic acid should be used carefully.

In conclusion, therapy with AI has been shown to improve DFS in women with hormone-responsive breast cancer but it is also associated with worsening bone loss and increased fracture rates. This study demonstrates AI-associated bone loss can be prevented by concurrent zoledronic acid (4 mg intravenously every 6 months) for PBC patients.

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## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2013;62(1):10–29.
2. Regan MM, Price KN, Giobbie-Hurder A, Thürlimann B, Gelber RD; Interpreting Breast international group (BIG) 1-98: a randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer. *Breast Cancer Res*. 2011;13(3):209.
3. Jakesz R, Jonat W, Gnani M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005;366(9484):455–462.
4. Llombart A, Frassoldati A, Pajja O, et al. Immediate administration of Zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. *Clin Breast Cancer*. 2012;12(1):40–48.
5. Brufsky A, Harker G, Beck J, et al. The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: the Z-FAST Study 5-Year final follow-Up. *Cancer Res*. 2010;69(24 Suppl):4083–4083.
6. Brufsky AM, Bosserman LD, Caradonna RR, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. *Clin Breast Cancer*. 2009;9(2):77–85.
7. Bijelic R, Milicevic S, Balaban J. Correlation of osteoporosis and calcium urolithiasis in adult population. *Med Arch*. 2016;70(1):66–68.
8. Weaver CM, Alexander DD, Boushey CJ, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int*. 2016;27(1):367–376.
9. Yu T, Witten PE, Huysseune A, Buettner A, To TT, Winkler C. Live imaging of osteoclast inhibition by bisphosphonates in a medaka osteoporosis model. *Dis Model Mech*. 2015;9(2):155–163.
10. Coleman R, Powles T, Paterson A, et al; Group E B C T C G. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. 2015;386(10001):1353–1361.
11. Hines SL, Mincey B, Dentchev T, et al. Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. *Breast Cancer Res Treat*. 2009;117(3):603–609.
12. Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. *Ann Oncol*. 2009;20(9):1489–1498.
13. Guisado AM, Muñoz AS, Garrido MDLCL, et al. Initialization of adjuvant hormonal treatment for breast cancer. *Adv Ther*. 2011;28(Suppl 6):66–84.
14. Wagner-Johnston ND, Sloan JA, Liu H, et al. 5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (Alliance) trial. *Cancer*. 2015;121(15):2537–2543.
15. Amir E, Ocaña A, Seruga B, Josse R, Clemons M. Medical oncology: zoledronic acid for breast cancer therapy-induced bone loss. *Nat Rev Clin Oncol*. 2010;7(4):187–188.
16. Kim JE, Ahn JH, Jung KH, et al. Zoledronic acid prevents bone loss in premenopausal women with early breast cancer undergoing adjuvant chemotherapy: a phase III trial of the Korean Cancer Study Group (KCSG-BR06-01). *Breast Cancer Res Treat*. 2011;125(1):99–106.
17. Bucur RC, Panjwani DD, Turner L, Rader T, West SL, Jamal SA. Low bone mineral density and fractures in stages 3–5 CKD: an updated systematic review and meta-analysis. *Osteoporos Int*. 2015;26(2):449–458.

18. Biver E, Salliot C, Combescure C, et al. Influence of adipokines and ghrelin on bone mineral density and fracture risk: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2011;96(9):2703–2713.
19. Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST study results. *Cancer.* 2008;112(5):1001–1010.
20. Majithia N, Atherton PJ, Lafky JM, et al. Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy: a 5-year follow-up. *Support Care Cancer.* 2016;24(3):1219–1226.
21. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist.* 2008;13(5):503–514.
22. Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer.* 2012;118(5):1192–1201.
23. Aguirre JI, Akhter MP, Kimmel DB, et al. Oncologic doses of zoledronic acid induce osteonecrosis of the jaw-like lesions in rice rats (*Oryzomys palustris*) with periodontitis. *J Bone Miner Res.* 2012;27(10):2130–2143.

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