Current Problems in Cancer xxx (xxxx) xxx

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials

Mei Mei[a], Zijian Xiang[b], Jinghua Yang[b], Ruolan Xiang[c,*]

[a] *First Clinical Division, Peking University School and Hospital of Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Laboratory for Digital and Material Technology of Stomatology & Beijing Key Laboratory of Digital Stomatology, Beijing, China*
[b] *Beijing Zhiyun Data Technology Co Ltd, Beijing, China*
[c] *Department of Physiology and Pathophysiology, Peking University School of Basic Medical Sciences, Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education, and Beijing Key Laboratory of Cardiovascular Receptors Research, Beijing, China*

ABSTRACT

Early-stage breast cancer (BC) patients receiving adjuvant therapy suffer from bone loss and increased fracture risk. Zoledronic acid (ZA) has been confirmed to inhibit bone metastasis and improve survival outcomes in early BC postmenopausal patients receiving adjuvant therapy. However, the efficacy of ZA for prevention of adjuvant therapy-induced bone loss from 2 different early BC groups, namely premenopausal and postmenopausal patients, still remain unclear. To obtain detailed characteristics, we performed this meta-analysis. PubMed, EMBASE, and Cochrane were searched. In premenopausal BC patients and postmenopausal BC patients, to assess bone loss, we calculated the weighted mean differences with 95% confidence intervals (CI) to evaluate lumbar spine (LS) bone mineral density (BMD), total hip (TH) BMD, and femoral neck (FN) BMD in ZA and non-ZA group with follow-up of 12 months. Thirteen randomized controlled trials (RCTs) encompassing 7375 patients were included. In a mixed population of early BC patients receiving adjuvant therapy, ZA significantly increased LS BMD ($P < 0.00001$), TH BMD ($P < 0.00001$), and FN BMD ($P = 0.01$) compared with non-ZA group. In premenopausal patient subgroup, LS BMD was greatly

☆ Funding: This work was supported by the National Natural Science Foundation of China (grant numbers 81700993, 81570993); and the Beijing Natural Science Foundation (grant number 7162100).

☆☆ Declaration of Competing Interest: Mei Mei, Zijian Xiang, Jinghua Yang, and Ruolan Xiang declare that they have no conflict of interest.

* Correspondence to: Ruolan Xiang, Department of Physiology and Pathophysiology, Peking University School of Basic Medical Sciences, Beijing, China

E-mail address: xiangrl@bjmu.edu.cn (R. Xiang).

https://doi.org/10.1016/j.currproblcancer.2019.100507

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

higher in patients with ZA compared to controls (0.06 g/cm^2; 95% CI: 0.05-0.08), whereas there were no differences in TH BMD and FN BMD between patients with ZA and controls. In postmenopausal patient subgroup, both LS BMD (0.06 g/cm^2; 95% CI: 0.05-0.07) and TH BMD (0.04 g/cm^2; 95% CI: 0.03-0.04) were significantly higher in patients with ZA compared to controls, but there was no difference in FN BMD between patients with ZA and controls. To sum up, ZA prevents bone loss in early-stage BC patients receiving adjuvant therapy at different skeletal sites. In premenopausal patients, effectiveness of ZA in prevention of bone loss is confirmed at LS site, but not at TH and FN site. In postmenopausal patients, ZA has a satisfying efficacy for prevention of bone loss at LS and TH site, but not at FN site.

ARTICLE INFO

Keywords: Zoledronic acid; Bone mineral density; Early-stage breast cancer; Adjuvant therapy; Meta-analysis; Randomized controlled trials

Introduction

Breast cancer (BC) is the most common malignant tumor in women. In current days, adjuvant therapy is conventionally performed in patients with hormone-responsive early-stage BC.[1] Adjuvant therapy, which includes adjuvant chemotherapy and endocrine therapy, can effectively help preventing tumor recurrence and improving patient survival after surgical excision.[2] However, adjuvant therapy drugs can disrupt estrogen signaling and induce ovarian failure or premature menopause as well as deleterious effects on bone health, resulting in rapid bone loss and increased fracture risk.[3-6] As BC patients survive for longer periods of time after adjuvant therapy,[7,8] maintaining skeletal health is an important consideration.

Zoledronic acid (ZA), a potent nitrogen-containing third-generation bisphosphonate, is recognized as an effective treatment for patients with multiple myeloma,[9] bone metastasis in solid tumors such as lung cancer[10] and early BC.[11] ZA improves disease-free survival (DFS) in postmenopausal women with early BC,[12] reduces the development of bone metastases in patients with early BC,[13] and decreases the skeletal-related events and bone pain in BC patients with bone metastases.[14] Recently, the use of ZA has become an important component of treatments for adjuvant therapy-associated bone loss in early BC.[15,16] Bone mineral density (BMD) is a key contributor to assess bone loss and predict fracture risk as a surrogate endpoint, and the most used BMD values are from lumbar spine (LS), total hip (TH), and femoral neck (FN) sites. Aromatase inhibitors (AIs)-associated reduction of BMD can be prevented by concurrent ZA (4 mg intravenously every 6 months) for postmenopausal patients with early BC.[17] Adding ZA to adjuvant therapy improves BMD in premenopausal women with early BC receiving adjuvant chemotherapy and/or endocrine therapy.[18] To clarify the effect of ZA on BMD more precisely and comprehensively in early BC patients receiving adjuvant therapy, we performed current meta-analysis to assess the efficacy of ZA at different skeletal sites in premenopausal and postmenopausal patients respectively.

Methods

Literature search

We performed a literature search before September 2018 in PubMed, EMBASE, and Cochrane with no restrictions for data and language, following the PRISMA guideline.[19] The search terms included breast neoplasms, BC, breast tumor, ZA, and zoledronate.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

Inclusion and exclusion criteria

From an initial list of 2086 abstracts identified, all records were downloaded and duplicate records were removed. About 1944 articles were selected, screened from title and abstract, and then 168 full-text related articles were assessed for eligibility. We included studies that met the following criteria: (1) the analysis included controlled trials that randomized early BC patients receiving adjuvant endocrine therapy and/or chemotherapy to undergo intravenous ZA treatment (upfront ZA or ZA) or non-ZA treatment (delayed ZA or placebo or no treatment), (2) the dosage of ZA was 4 mg every several months and the most common period is every 6 months, (3) the trials defined bone loss by assessing BMD at LS, and/or TH, and/or FN with dual-energy x-ray absorptiometry devices, (4) early BC patients in trials were premenopausal or postmenopausal. Exclusion criteria included the following: (1) study was performed on cell line. (2) study design was nonrandomized. (3) The focus of the study was pathologic analysis, survival outcomes, dosing frequency or cost-effectiveness. (4) The post type of the study was review, conference abstract, editorial, letter, case report, or expert opinion. The flow chart of searches was shown in Fig. 1.

Data extraction and quality assessment

Two reviewers (MM and Xiang RL) independently screened and checked the articles to determine the final inclusions according to the inclusion and exclusion criteria. Then 2 reviewers (Xiang ZJ and Yang JH) independently extracted data from each potential study using predefined extraction forms with the following variables: (1) The first author; (2) year of publication; (3) sample size of the intervention group; (3.1) mean value and standard deviation of baseline BMD; (3.2) mean value and standard deviation of final BMD; (4) sample size of the control group; (4.1) mean value and standard deviation of baseline BMD; (4.2) mean value and standard deviation of final BMD. The Cochrane Risk of Bias Tool for assessing risk of bias was used to assess the quality of randomized controlled trials (RCTs). Any discrepancies were addressed by a joint evaluation of the original article.

Statistical analysis

The data were summarized by the final values of BMD (g/cm^2) from follow-up of 12 months. The data were presented as mean difference with 95% confidence interval (CI), and our analysis was presented as a forest plot, with heterogeneity assessed using the *I*-squared statistic. The random-effects model was used to pool the data if heterogeneity (*I*-squared value >50%) was found; Otherwise, the fixed-effects model was selected.

Subgroup analysis was performed for LS BMD, TH BMD, and FN BMD in premenopausal and postmenopausal patients respectively. The adverse events were analyzed by Pearson chi-square test in SPSS 22, and other statistical analyses were performed in RevMan 5.3 software. All *P* values less than 0.05 were considered statistically significantly.

Results

Search results

There were 2086 potentially relevant references. After screening the titles and abstracts of all studies, 47 full-text articles met the general inclusion criteria and were reviewed for strict inclusion or exclusion criteria. Thirteen RCTs were finally included in the meta-analysis.[15,16,18,20-29] Figure 1 showed the search process and study selection.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

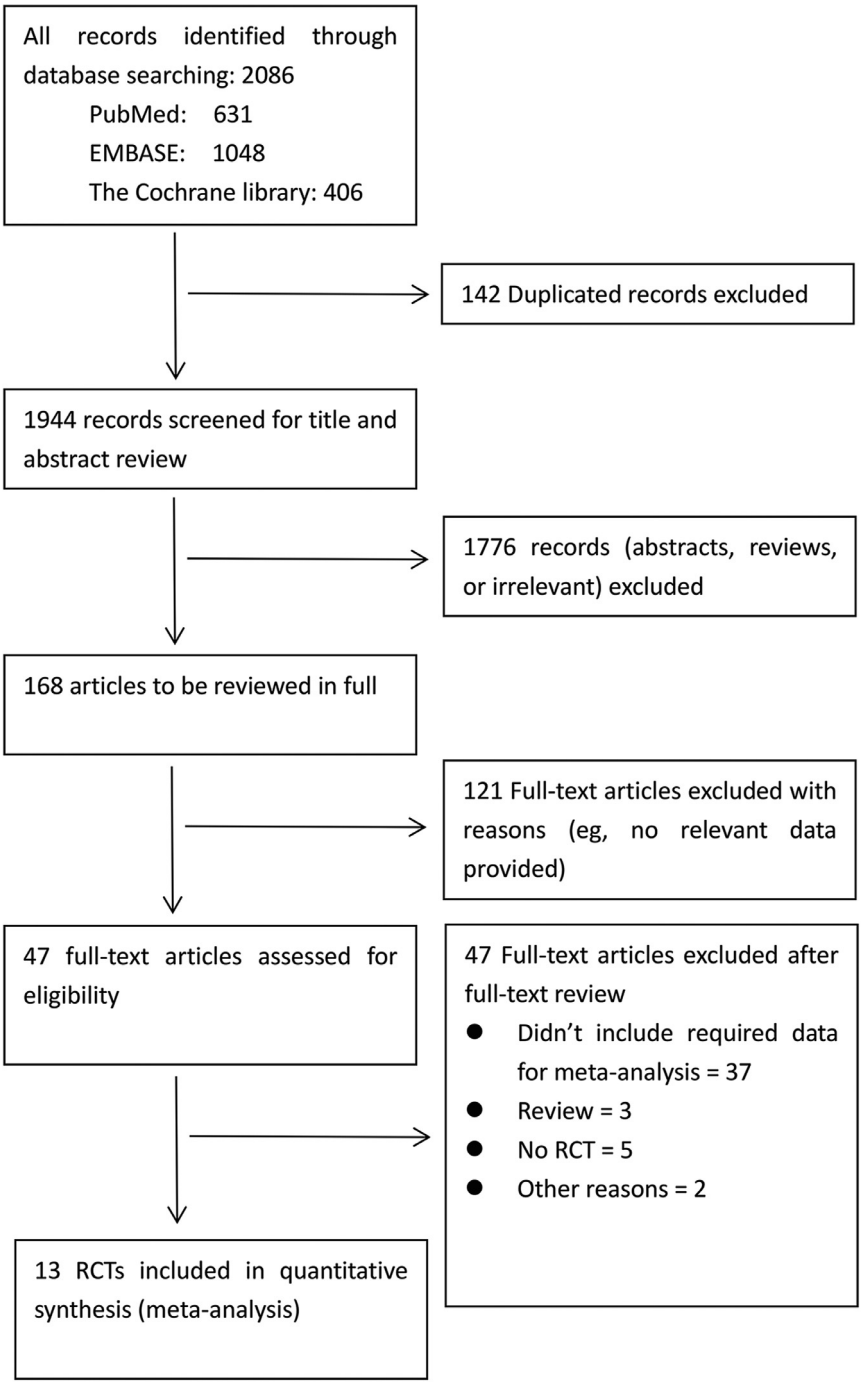

Fig. 1. Flowcharts of study selection and search.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

Sample characteristics

Table 1 presents the characteristics of the 13 trials that met the eligibility criteria for this study. Eight studies were performed on postmenopausal patients, and the rest 5 studies were performed on premenopausal patients. Control groups of 7 studies were delayed-start ZA groups, which received ZA when LS or TH T score decreased to less than −2.0 or when a nontraumatic fracture occurred, and the rest 6 studies were using placebo or no treatment as controls. Among all trials, 2 studies were double blinded.

Risk of Bias Assessment

The risk of bias was assessed including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting. All trials were randomized, but only 1 article claimed the specific method of randomization.[30] For allocation concealment, all trials did not mention. For blinding, 2 studies used double-blinding method,[18,26] the other 11 studies did not give information on blinding. One trial did not report the BMD value of 12-month follow-up, so we extracted BMD of 24-month follow-up.[18] Therefore, the risk of bias of included studies was moderate, indicating some lack of power to ensure the therapeutic effect. More details of the trials were presented in Fig 2.

Effect of ZA on LS, TH, and FN BMD in a mixed population of patients

All 13 articles had compared the final values of LS BMD for early BC patients receiving adjuvant therapy with ZA vs non-ZA. We observed a significantly increased LS BMD in those with ZA compared with non-ZA group, and the mean difference between groups was 0.06 g/cm^2 (95% CI: 0.05-0.07, $P < 0.00001$) (Fig 3a)

Eleven trials included TH BMD investigation. Results showed that ZA significantly improved the TH BMD compared with non-ZA group, and the mean difference between groups was 0.03 g/cm^2 (95% CI: 0.03-0.04, $P < 0.00001$) (Fig 3b).

Five trials explored FN BMD. Results showed that ZA greatly increased FN BMD compared with non-ZA group, and the mean difference was 0.03 g/cm^2 for LS (95% CI: 0.01-0.06, $P = 0.01$) (Fig 3c).

Effect of ZA on LS, TH, and FN BMD in premenopausal subgroup

There were 5 trials investigated LS BMD in premenopausal patients with early BC receiving adjuvant therapy. The results demonstrated a significantly increased LS BMD in premenopausal patients with ZA compared with non-ZA, and the mean difference between groups was 0.06 g/cm^2 (95% CI: 0.05-0.08, $P < 0.00001$) (Fig 4a).

Three trials included TH BMD investigation in premenopausal patients. There was no significant difference in TH BMD between ZA group and non-ZA group (0.02 g/cm^2; 95% CI: −0.00 to 0.05, $P = 0.05$) (Fig 4b).

Three trials explored FN BMD in premenopausal patients. There was no significant difference in FN BMD between ZA group and non-ZA group (0.03 g/cm^2; 95% CI: −0.00 to 0.06, $P = 0.05$) (Fig 4c).

Effect of ZA on LS, TH, and FN BMD in postmenopausal subgroup

Eight articles included had explored the effect of ZA on LS BMD in postmenopausal patients with early BC receiving adjuvant therapy. Each included article had originally reported a

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

Table 1
Characteristics of included trials.

Study	Year	Intervention	Dosage of treatment	Duration (y)	Numbers of patients	Population	Follow-up (mo)
Brufsky, et al	2008	Upfront ZA; Delayed ZA	4 mg IV every 6 months	5	833; 834	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	12
Brufsky, et al	2007	Upfront ZA; Delayed ZA	4 mg IV every 6 months	5	301; 301	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	12
Brufsky, et al	2009	Upfront ZA; Delayed ZA	4 mg IV every 6 months	5	301; 301	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	36
Brufsky, et al	2012	Upfront ZA Delayed ZA	4 mg IV every 6 months	5	301; 301	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	61
Bundred, et al	2008	Upfront ZA; Delayed ZA	4 mg IV every 6 months	5	532; 533	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	12
Leal, et al	2010	ZA; no treatment	4 mg IV every 3 months	1	36; 32	Postmenopausal women with early BC receiving adjuvant endocrine therapy (the majority received tamoxifen)	12
Sun, et al	2016	ZA; no treatment	4 mg IV every 6 months	1	60; 60	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	12
Takahashi, et al	2012	Upfront ZA; Delayed ZA	4 mg IV every 6 months	1	94; 95	Postmenopausal women with early BC receiving adjuvant endocrine therapy (letrozole)	12
Gnant, et al	2008	ZA; no treatment	8 mg IV every 6 months, then amended to 4 mg IV every 6 months	3	899; 904	Premenopausal women with early BC receiving adjuvant endocrine therapy (goserelin and anastrozole or goserelin and tamoxifen)	60
Gnant, et al	2007	ZA; no treatment	8 mg IV every 6 months, then amended to 4 mg IV every 6 months	3	204; 197	Premenopausal women with early BC receiving adjuvant endocrine therapy (goserelin and anastrozole or goserelin and tamoxifen)	36
Hadji, et al	2014	ZA; placebo	4 mg IV every 3 months	2	34; 36	Premenopausal women with early BC receiving adjuvant chemotherapy and/or endocrine therapy	24
Kim, et al	2011	Upfront ZA; Delayed ZA	4 mg IV every 6 months	1	57; 59	Premenopausal women with early BC receiving adjuvant chemotherapy	12
Kyvernitakis, et al	2018	ZA; placebo	4 mg IV every 3 months	2	34; 36	Premenopausal women with early BC receiving adjuvant chemotherapy and/or endocrine therapy	60

IV, intravenous injection; BC, breast cancer; ZA, zoledronic acid.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

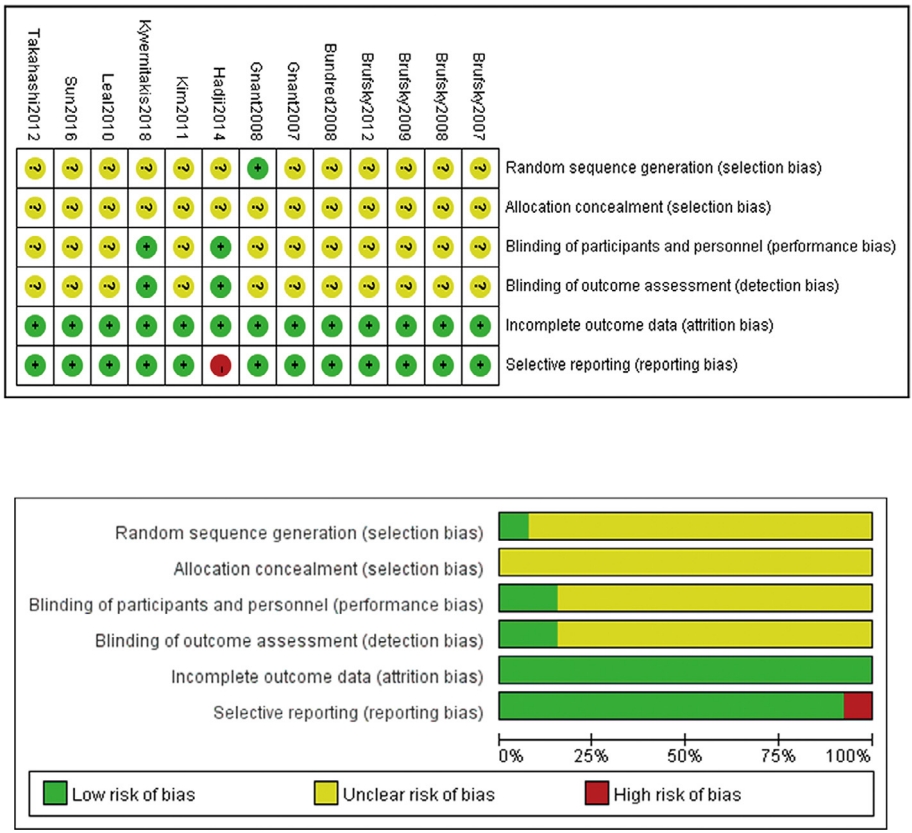

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study (a). Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies (b).

significantly increased LS BMD in postmenopausal patients with ZA compared with non-ZA, our meta-analysis demonstrated that the mean difference between groups was 0.06 g/cm^2 (95% CI: 0.05-0.07, $P < 0.00001$) (Fig 4d).

Eight trials included had reported the effect of ZA on TH BMD in postmenopausal patients. Results showed that ZA significantly improved TH BMD in postmenopausal patients with ZA compared with non-ZA. Our meta-analysis revealed that the mean difference in TH BMD between groups was 0.04 g/cm^2 (95% CI: 0.03-0.04, $P < 0.00001$) (Fig 4e).

There were 2 trials explored the effect of ZA on FN BMD in postmenopausal patients. The results indicated that there was no significant difference in FN BMD between ZA group and non-ZA group (0.04 g/cm^2; 95% CI: −0.01 to 0.08, $P = 0.1$) (Fig 4f).

Adverse events

Eight trials[16,18,20-23,26,29] mentioned the adverse events during the follow-up in ZA group vs non-ZA group as showed by Table 2, and the analysis revealed that in contrast to control group, ZA significantly increased the occurrence rate of pyrexia, bone pain, chills, fever,

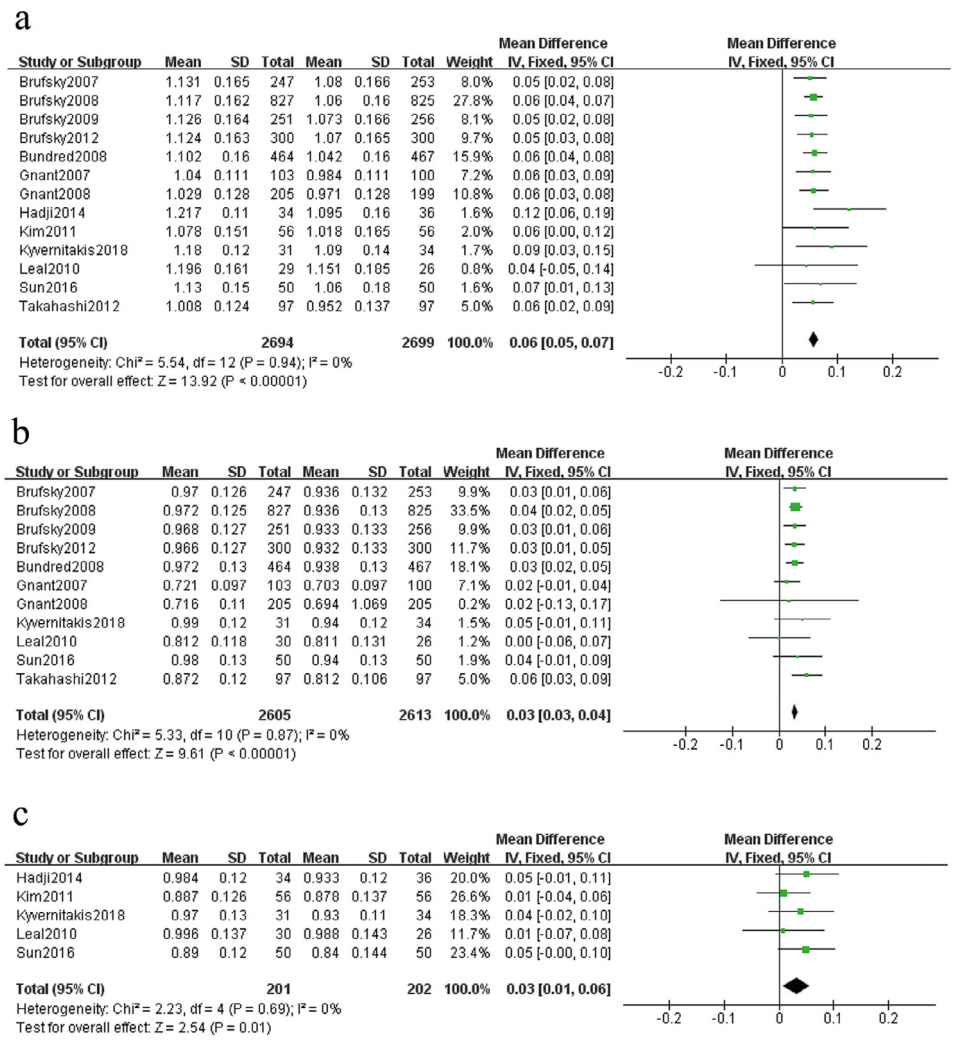

Fig. 3. Meta-analysis comparing the LS BMD (a), TH BMD (b), and FN BMD (c) in a mixed population of early BC patients receiving adjuvant therapy with ZA versus non-ZA.

headache, influenza-like illness, and myalgia in early BC patients receiving adjuvant therapy, while ZA greatly decreased the occurrence rate of cough, depression, and sleep disorders. Out of the 8 trials, only 1 trial reported a case of osteonecrosis of the jaw (ONJ) in ZA group. No fracture and other severe adverse events were reported.

Discussion

In this meta-analysis of RCTs, we investigated the efficacy of ZA for prevention of bone loss at different skeletal sites in premenopausal and postmenopausal patients with early BC receiving adjuvant therapy respectively. The follow-up of included data was from 12 months. Here, we showed that ZA was associated with increased LS BMD in both premenopausal and postmenopausal patients by 0.06 g/cm^2 compared to controls. In postmenopausal patients, TH BMD

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

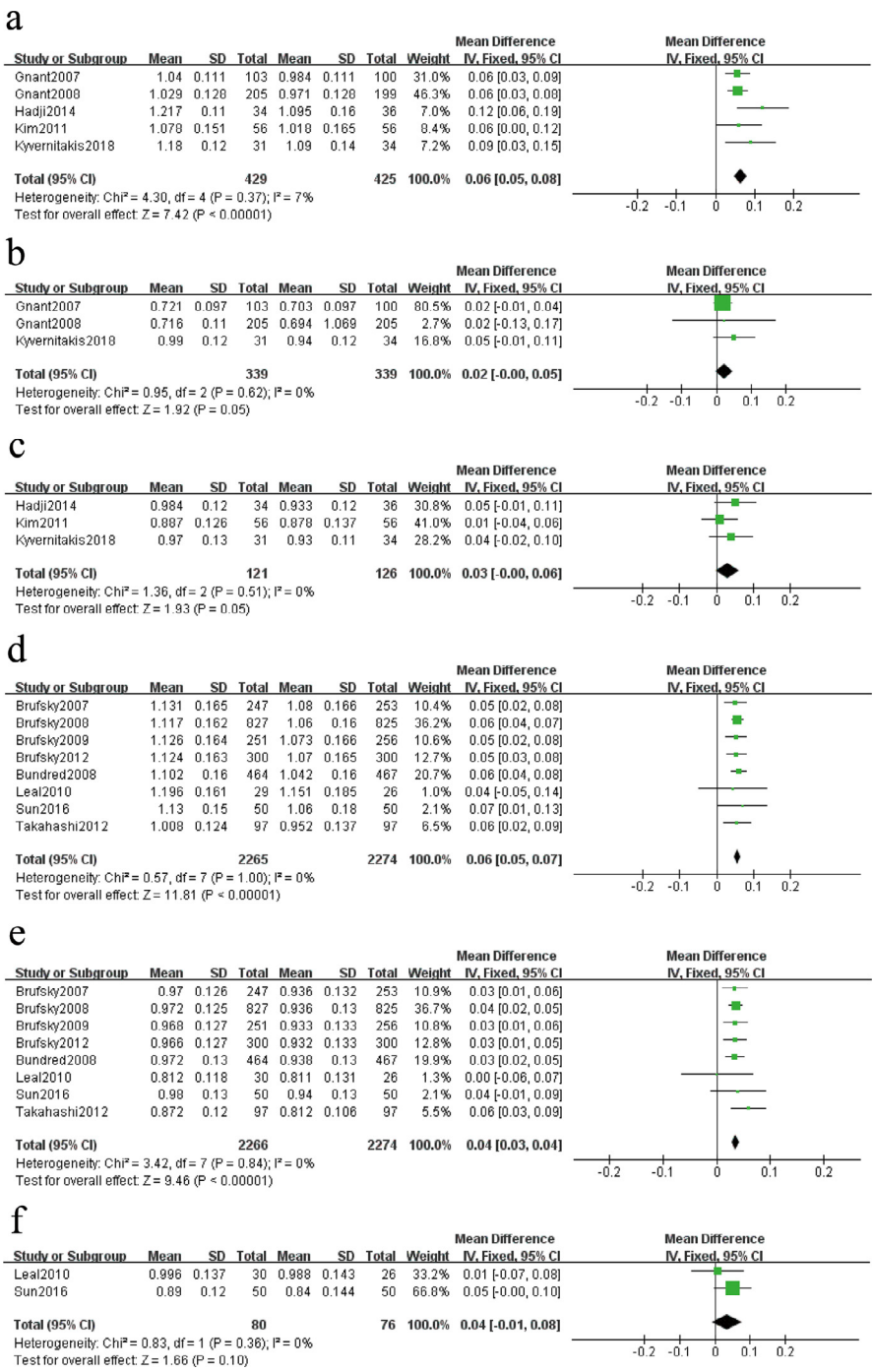

Fig. 4. Meta-analysis comparing the LS BMD (a), TH BMD (b), and FN BMD (c) in premenopausal early BC patients receiving adjuvant therapy with ZA versus non-ZA, and meta-analysis comparing the LS BMD (d), TH BMD (e), and FN BMD (f) in postmenopausal early BC patients receiving adjuvant therapy with ZA versus non-ZA.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

Table 2
Adverse events of ZA group vs non-ZA group in early-stage BC patients with adjuvant therapy.

Adverse event	Overall rates in ZA group	Overall rates in non-ZA group	Pearson chi-square
Anxiety	4.67% (14/300)	6.00% (18/300)	0.467
Diarrhea	7.33% (44/600)	8.17% (49/600)	0.589
Dizziness	5.00% (15/300)	5.67% (17/300)	0.716
Fatigue	17.45% (410/2349)	16.11% (378/2347)	0.216
Insomnia	7.70% (133/1727)	6.20% (107/1725)	0.084
Pyrexia	12.33% (204/1654)	1.03% (17/1650)	0.000
Sweating	5.26% (5/95)	3.09% (3/97)	0.452
Arthralgia	35.37% (855/2417)	33.57% (812/2419)	0.186
Back pain	7.49% (174/2322)	8.35% (194/2322)	0.277
Bone pain	13.31% (309/2322)	7.11% (165/2322)	0.000
Chills	20.59% (14/68)	2.78% (2/72)	0.001
Constipation	6.67% (20/300)	6.33% (19/300)	0.868
Cough	7.17% (43/600)	10.83% (65/600)	0.026
Depression	5.55% (125/2254)	8.31% (187/2250)	0.000
Dyspnea	6.00% (18/300)	4.33% (13/300)	0.356
Extremity pain	10.12% (114/1127)	12.78% (95/1125)	0.172
Fever	23.16% (22/95)	2.06% (2/97)	0.000
Headache	10.21% (237/2322)	7.54% (175/2322)	0.001
Hot flush	27.22% (658/2417)	28.03% (678/2419)	0.532
Hypertension	10.33% (31/300)	8.00% (24/300)	0.322
Influenza-like illness	32.35% (22/68)	11.11% (8/72)	0.002
Lymphedema	10.33% (38/368)	14.78% (55/372)	0.067
Menopausal symptoms	47.06% (32/68)	38.89% (28/72)	0.329
Musculoskeletal pain	9.00% (54/600)	6.33% (38/600)	0.083
Myalgia	12.77% (300/2349)	10.40% (244/2347)	0.011
Nausea	8.81% (213/2417)	7.40% (179/2419)	0.072
Osteonecrosis of the jaw	2.94% (1/34)	0% (0/36)	0.300
Paresthesia	11.76% (8/68)	16.67% (12/72)	0.407
Peripheral edema	7.63% (86/1127)	6.67% (75/1125)	0.375
Pruritus	5.26% (5/95)	3.09% (3/97)	0.452
Rash	5.32% (21/395)	4.28% (17/397)	0.496
Sleep disorders	5.88% (4/68)	19.44% (14/72)	0.017
Weight increase	5.88% (31/527)	5.33% (28/525)	0.699

was increased by 0.03 g/cm^2 with ZA compared to controls. However, TH BMD and FN BMD in premenopausal patients, and FN BMD in postmenopausal patients, were not significantly different between the groups. To sum up, we demonstrated that ZA played an important role in preventing bone loss at LS site from both premenopausal and postmenopausal patients with early BC receiving adjuvant therapy. Moreover, ZA might be more effective for prevention of bone loss at TH site from postmenopausal patients, rather than from premenopausal patients.

In recent years, the clinical treatment modalities for early-stage BC have undergone a fundamental change. Numerous studies show that expanded surgery range does not have a decisive impact on the prognosis for BC, while adjuvant chemotherapy or endocrine therapy is able to improve BC patients DFS and overall survival.[31] However, these therapies result in bone loss and fractures, either due to the direct effect on the balance of bone formation by osteoblasts and bone resorption by osteoclasts or due to therapies-induced ovarian failure and low estrogen concentration. Estrogen is essential for the maintenance of bone mass for women, and the decrease in estrogen levels results in increased bone turnover and loss. Therefore, early BC patients who receive chemotherapy or endocrine treatment are at increased risk of osteopenia, osteoporosis, and bone fracture. Oral calcium and vitamin D has minimal effects and cannot even maintain bone mass in these patients,[32,33] and the estrogen therapy, which is useful in preventing bone loss for postmenopausal individuals,[34] is advised to be avoid, due to the presence of estrogen and progesterone receptors in the majority of these malignancies.

Bisphosphonates have profound effects on osteoclasts and T-cell function. They induce osteoclast apoptosis, leading to decreased bone turnover, this and the increasing secondary

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

mineralization contribute to a moderate BMD increase.[35] In postmenopausal women, bisphosphonates have been utilized for the treatment of osteoporosis in normal postmenopausal women. At present, bisphosphonate therapy is increasingly used in clinical with early BC patients receiving adjuvant chemotherapy or endocrine therapy, and newly American Society of Clinical Oncology Clinical Practice Guideline recommends that usage of ZA (4 mg intravenously every 6 months), a third-generation bisphosphonate, is considered as adjuvant therapy for postmenopausal patients with BC to prevent bone recurrence, improve survival, and maintain bone mass.[36] Our meta-analysis included 13 RCTs involving 7375 participants including both premenopausal and postmenopausal patients, which reported the efficacy of ZA for prevention of bone loss in early BC patients receiving adjuvant therapy. Results showed that ZA significantly increased BMD at LS, TH, and FN sites, indicating the preventive function of ZA in bone loss from a mixed population of women. To some extent, the BMD results, as surrogate endpoints for predicting risk of fractures, were consistent with the fracture results from a previous meta-analysis, in which results have shown that the 5-year fracture rate is reduced from 5.9% (95% CI: 4.8%-7.1%) to 3.8% (95% CI: 2.9%-4.7%) with ZA.[37] However, the effect of ZA on maintaining bone mass in premenopausal and postmenopausal patients differs due to different ovarian function and estrogen concentrations. In premenopausal patients, the bone protective effects of ZA have been initially investigated,[26] while the role of ZA in preventing bone loss is still vague. In postmenopausal patients, present articles have demonstrated the effectiveness of ZA for prevention of bone loss, but the specific bone mass change at different skeletal sites induced by ZA remains unclear. Next we made meta-analysis in premenopausal and postmenopausal subgroups.

In premenopausal patients with early BC receiving adjuvant chemotherapy, it has been reported that BMD decreases with chemotherapy-induced amenorrhea, with declines ranging from 4% to 8% at the LS and 2% to 4% at the hip.[38] A phase III trial of the Korean Cancer Study Group (KCSG-BR06-01) demonstrated that chemotherapy induced significant bone loss at 12 months, upfront ZA treatment effectively prevented bone loss at LS and FN site, and the differences in percent change of BMD between upfront ZA and controls were 6.4% for LS, and 3.6% for FN.[25] Adjuvant endocrine therapy is routinely used for premenopausal patients with the hormone receptor positive early BC, including ovarian suppression using a luteinizing hormone-releasing hormone agonist such as goserelin and combination with tamoxifen, and in this way, rates of BMD loss are even higher.[15] The Austrian Breast and Colorectal Cancer Study Group trial-12 showed that endocrine therapy greatly decreased BMD with 11.3% at LS and 7.3% at trochanter, and concomitant ZA effectively prevented bone loss at LS and trochanter.[15] Five RCTs involving 2460 participants were included in our meta-analysis assessing the efficacy of ZA for prevention of bone loss in premenopausal patients with early BC receiving adjuvant therapy, in which 2 RCTs were receiving adjuvant endocrine therapy,[15,24] 2 RCTs were receiving endocrine and/or chemotherapy,[18,26] and the rest 1 RCT was receiving chemotherapy.[25] Results showed that concomitant ZA treatment was associated with increased LS BMD by 0.06 g/cm^2 compared to controls, but there were no significant differences in TH BMD and FN BMD between ZA and controls, suggesting that ZA played an important role in preventing bone loss at LS site from follow-up of 12 months, but not at TH and FN sites. BMD decreases more rapidly at LS site than other skeletal sites in premenopausal women undergoing adjuvant therapy,[15,38] and this might partially contribute to significant higher BMD at LS induced by ZA compare to controls, but not at TH and FN site.

In postmenopausal patients with hormone receptor positive BC, adjuvant endocrine therapy is routinely administered by AIs alone or sequentially after tamoxifen.[39] AIs results in a longer DFS interval and produces fewer endometrial and thromboembolic adverse events than tamoxifen, consequently, more postmenopausal patients are receiving AIs as first-line adjuvant therapy.[40,41] Bone loss in postmenopausal BC patients using long-term AIs is 2 times more than that of normal postmenopausal women of the same age.[22,42] In a meta-analysis of 7 clinical trials evaluating adjuvant endocrine therapy in postmenopausal women with BC (N = 30,023), long-term AIs increase the relative risk of bone fractures by 47% compared with tamoxifen.[43] Therefore, efforts to prevent bone loss and fractures are necessary. One trial in postmenopausal

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

Chinese population with early BC receiving AI demonstrated that ZA significantly increased BMD at LS, TH, and FN site for follow-up of 12 months.[28] Leal et al reported that ZA significantly increased BMD at LS, but there was no difference in FN BMD between groups in postmenopausal patients with early BC receiving tamoxifen.[27] In our meta-analysis of postmenopausal subgroups, 8 RCTs were included (included 4915 participants), in which 7 RCTs were receiving AI therapy (letrozole), and the rest 1 RCT was receiving tamoxifen for the majority participants. Results showed that concomitant ZA treatment was associated with increased LS BMD by 0.06 g/cm^2 and increased TH BMD by 0.03 g/cm^2 compared to controls, but there was no significant difference in FN BMD between groups, indicating that ZA played an important role in preventing bone loss at LS and TH site from follow-up of 12 months, but not at FN site in postmenopausal patients. For postmenopausal individuals, a previous study focusing on determining the effect of hormone replacement therapy on preventing bone loss, reported that hormone replacement therapy achieved greater benefit at LS site rather than FN site,[44] indicating that LS may be a more sensitive bone metabolic site than FN, this helps explain why FN BMD value was not affected by ZA in postmenopausal BC patients. The observed greater benefit at TH site in postmenopausal patients, but not in premenopausal patients, suggests that ZA may be a more effective means of preventing bone loss and reducing fracture risk in postmenopausal patients. Postmenopausal patients usually experience lower initial bone mass than premenopausal patients for reduced ovarian function and estrogen concentrations, which probably contributes to the significantly increased BMD at TH in postmenopausal patients but not premenopausal ones. From the molecular mechanism, in postmenopausal women, an increased receptor activator of nuclear factor-kappa b ligand to osteoprotegerin ratio promotes osteoclastogenesis and accelerates bone turnover,[45] this may be another reason which could explain why ZA was more effective in postmenopausal women. In addition, in 4915 postmenopausal patients enrolled, most of the patients (4727 individuals) were randomized into upfront ZA group (initiated simultaneously with adjuvant therapy) and delayed ZA group (initiated with a decrease in T score <-2 or occurrence of clinical nontraumatic fracture), so the significantly elevated BMD also suggests that upfront ZA is the preferred treatment strategy in preventing bone loss compared with delayed ZA administration in postmenopausal patients with early BC receiving adjuvant therapy.

Considering the adverse events, ZA can exert toxic effects such as nephrotoxicity and ONJ, which are potential unsafe factors for its clinical use. In our meta-analysis of assessing the efficacy of ZA for preventing bone loss, the included RCTs also reported the adverse events during the follow-up. Results showed that ZA treatment significantly increased the occurrence rate of pyrexia, bone pain, chills, fever, headache, influenza-like illness, and myalgia compared to controls, and there was no nephrotoxicity and fracture observed and only 1 case of ONJ in ZA group. A previous meta-analysis (47 studies including 20,607 patients) from our team focusing on adverse events in patients treated with bisphosphonate therapy for BC recently reported that bisphosphonates were significantly associated with influenza-like illness, fatigue, fever, dyspepsia, anorexia, and urinary tract infection, and the pooled probability of ONJ toxicity in bisphosphonates group was 2%.[46] Our observations for adverse events of ZA basically agreed with the bisphosphonates results.

There are several limitations in our study. First, we included 4 trials from the same author,[16,20-22] and suspected that some participants may be the same ones in different articles. Second, only 2 trials were double-blinded, this can lead to increased risk of performance bias or detection bias. Third, the number of participants evaluated the FN BMD were small, so the analysis results of FN BMD should be interpreted with caution and more clinical trials should be conducted in future to help exploring.

Conclusions

In this meta-analysis, we demonstrated that ZA prevented bone loss at LS site in both premenopausal and postmenopausal patients with early BC receiving adjuvant therapy. Moreover,

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

ZA prevented bone loss at TH site in postmenopausal but not in premenopausal patients, indicating that ZA was a more effective means for prevention of bone loss in postmenopausal patients with early BC receiving adjuvant therapy. Furthermore, there was no significant difference in FN BMD between ZA and controls in premenopausal or postmenopausal patients, suggesting that ZA was not involved in prevention of bone loss at FN from follow-up of 12 months.

References

1. Moo TA, Sanford R, Dang C, Morrow M. Overview of Breast Cancer Therapy. *PET Clin*. 2018;13:339–354.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
3. Vehmanen LK, Elomaa I, Blomqvist CP, Saarto T. The effect of ovarian dysfunction on bone mineral density in breast cancer patients 10 years after adjuvant chemotherapy. *Acta Oncol*. 2014;53:75–79.
4. Eastell R, Hannon RA, Cuzick J, et al. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res*. 2006;21:1215–1223.
5. Geisler J, Lønning PE, Krag LE, et al. Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: a randomised, placebo-controlled study. *Eur J Cancer*. 2006;42:2968–2975.
6. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med*. 1995;333:1437–1443.
7. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med*. 2015;13:195.
8. Wazir U, Mokbel L, Wazir A, Mokbel K. Optimizing adjuvant endocrine therapy for early ER+ breast cancer: an update for surgeons. *Am J Surg*. 2019;217:152–155.
9. Sanfilippo KM, Gage B, Luo S, et al. Comparative effectiveness on survival of zoledronic acid versus pamidronate in multiple myeloma. *Leuk Lymphoma*. 2015;56:615–621.
10. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. *Oncologist*. 2002;7:481–491.
11. Singh T, Kaur V, Kumar M, Kaur P, Murthy RS, Rawal RK. The critical role of bisphosphonates to target bone cancer metastasis: an overview. *J Drug Targe*. 2015;23:1–15.
12. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. 2015;386:1353–1361.
13. Coleman R, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol*. 2014;15:997–1006.
14. Chiang PH, Wang HC, Lai YL, et al. Zoledronic acid treatment for cancerous bone metastases: a phase IV study in Taiwan. *J Cancer Res Ther*. 2013;9:653–659.
15. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol*. 2008;9:840–849.
16. 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;118:1192–1201.
17. Sun S, Wang F, Dou H, Zhang L, Li J. Preventive effect of zoledronic acid on aromatase inhibitor-associated bone loss for postmenopausal breast cancer patients receiving adjuvant letrozole. *Onco Targets Ther*. 2016;9:6029–6036.
18. Hadji P, Kauka A, Ziller M, et al. Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: the ProBONE II study. *Osteoporos Int*. 2014;25:1369–1378.
19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
20. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol*. 2007;25:829–836.
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;13:503–514.
22. 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;9:77–85.
23. 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;112:1001–1010.
24. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol*. 2007;25(7):820–828.
25. 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;125:99–106.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507

26. Kyvernitakis I, Kann PH, Thomasius F, Hars O, Hadji P. Prevention of breast cancer treatment-induced bone loss in premenopausal women treated with zoledronic acid: Final 5-year results from the randomized, double-blind, placebo-controlled ProBONE II trial. *Bone*. 2018;114:109–115.
27. Leal T, Tevaarwerk A, Love R, et al. Randomized trial of adjuvant zoledronic acid in postmenopausal women with high-risk breast cancer. *Clin Breast Cancer*. 2010;10:471–476.
28. Sun S, Wang F, Dou H, Zhang L, Li J. Preventive effect of zoledronic acid on aromatase inhibitor-associated bone loss for postmenopausal breast cancer patients receiving adjuvant letrozole. *Onco Targets Ther*. 2016;9:6029–6036.
29. Takahashi S, Iwase T, Kohno N, et al. Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 12-month results. *Breast Cancer Res Treat*. 2012;133:685–693.
30. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103–115.
31. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol*. 2017;7:1–12.
32. Bijelic R, Milicevic S, Balaban J. Correlation of osteoporosis and calcium urolithiasis in adult population. *Med Arch*. 2016;70:66–68.
33. 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;27:367–376.
34. Kim HJ, Oh YK, Lee JS, Lee DY, Choi D, Yoon BK. Effect of transdermal estrogen therapy on bone mineral density in postmenopausal korean women. *J Menopausal Med*. 2014;20:111–117.
35. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer. *Clin Oncol*. 2013;25:135–145.
36. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2017;35:2062–2081.
37. Wilson C, Bell R, Hinsley S, et al. Adjuvant zoledronic acid reduces fractures in breast cancer patients; an AZURE (BIG 01/04) study. *Eur J Cancer*. 2018;94:70–78.
38. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol*. 2001;19:3306–3311.
39. Mouridsen H, Giobbie-Hurder A, et al.BIG 1-98 Collaborative Group Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*. 2009;361:766–776.
40. Jakesz R, Jonat W, Gnant 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;366:455–462.
41. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet*. 2007;369:559–570.
42. Llombart A, Frassoldati A, Paija 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;12:40–48.
43. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103:1299–1309.
44. Duan Y, Tabensky A, DeLuca V, Seeman E. The benefit of hormone replacement therapy on bone mass is greater at the vertebral body than posterior processes or proximal femur. *Bone*. 1997;21:447–451.
45. Hadji P, Coleman R, Gnant M, Green J. The impact of menopause on bone, zoledronic acid, and implications for breast cancer growth and metastasis. *Ann Oncol*. 2012;23:2782–2790.
46. Yang YL, Xiang ZJ, Yang JH, Wang WJ, Xiang RL. The incidence and relative risk of adverse events in patients treated with bisphosphonate therapy for breast cancer: a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2019;11.

Please cite this article as: M. Mei, Z. Xiang and J. Yang et al., Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials, Current Problems in Cancer, https://doi.org/10.1016/j.currproblcancer.2019.100507