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The prognostic impact of zoledronic acid in patients with early breast cancer: systematic assessment

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Summary

Objective: The aim of this study was to assess the effectiveness of zoledronic acid in patients with early breast cancer. *Materials and Methods:* All randomized controlled trials (RCTs) on zoledronic acid for patients with early breast cancer were retrieved from databases including Cochrane Library, MEDLINE, EMBASE, CBMdisc, VIP, and Wanfang databases. RCTs meeting inclusive criteria were included, the data were extracted, quality was evaluated, and cross-checked by two reviewers independently according to Cochrane Handbook for Systematic Reviews of Interventions, and then meta-analyses were conducted using RevMan 5.1 software. A total of eight eligible studies met the search criteria and were evaluated. *Results:* With respect to follow-up time of five or more years, compared with the control arm, zoledronic acid could significantly improve overall survival rate (odds ratio (OR) = 1.19, 95% confidence interval (CI) 1.02-1.40, $p = 0.03$); zoledronic acid therapy also had a clear effect on frature events (OR, 0.72, 95% CI, 0.57 to 0.92, $p = 0.01$); Low level estrogen subgroup analysis indicated that zoledronic acid therapy showed a great beneficial effect on disease recurrence and bone metastasis (OR = 0.66, 95%CI (0.52, 0.84), $p = 0.0009$, OR = 0.79, 95%CI (0.63, 0.98), $p = 0.03$, respectively). *Conclusion:* Compared with the control arm, zoledronic acid significantly improve overall survival. Its clinical benefit is likely to be comprehensive results from reducing the rate of fracture and antitumor effect; zoledronic acid can decrease the recurrence rate and bone metastasis rate at low levels of estrogen; low estrogen is a key factor of the anti-tumor effects. This conclusion should be further proved by conducting more high-quality, large-scale RCTs.

Key words: Zoledronic acid; Early breast cancer; Overall survival; Recurrence rate; Bone metastasis; Meta-analysis.

Introduction

Breast cancer is one of the common female malignancy [1], In 2010 there were an estimated 1.5 million cases of breast cancer diagnosed, representing nearly a quarter of all cancer diagnoses in women [2]. With the continuous improvement of medical technology, the prognosis of breast cancer patients has been significantly improved [3], however, breast cancer remains a complex disease process affecting millions worldwide [4], Zoledronic acid (ZOL) is a third-generation bisphosphonate that has been widely used with bone metastases in patients with advanced cancer [5]. Present study confirms that ZOL post-menopausal bone adverse events in patients with endocrine therapy early breast cancer (EBC) caused a significant role in the prevention and improvement [6], but also found that there is a potential anti-tumor effects, such as ZO-FAST [7], AZURE [8], and ABCSG-12 [9], and clinical trial results are suggesting that it may have anti-cancer effects. However, the recent results of the evaluation system was incompatible with the above studies; the control group (non-user) or extended use ZOL) were compared and ZOL did not improve overall survival and disease-free survival in breast cancer patients and did not reduce the incidence of bone metastases. In EBC in post-menopausal patients, ZOL can improve disease-free survival and lower recurrence rate which may be related to low estrogen levels after menopause [10]. In the same year, Huang *et al.* with their meta-analysis results support ZOL to extend overall survival; however, a subgroup analysis found that ZOL can reduce the EBC relapse rate in patients but also increase the relapse rate in patients with advanced breast cancer. To some extent this finding contrasts ZOL's anti-tumoral effect [11]. 2013 Valachis *et al*. [12] extended the study to 15 randomized controlled trials, and meta-analysis found that ZOL can improve overall survival in breast cancer patients, but the recurrence and bone metastasis rates were not valid. The present authors also found that none of these three systems included a subgroup analysis of follow-up time, but the general outcome measures with different follow-up times may lead to bias in the results of the meta-analysis. In addition, according to the subgroup findings of AZURE [8] and ABCSG-12 [9] (AZURE: EBC patients for more than five years of adjuvant chemotherapy in post menopausal ZOL when added into the group can improve disease-free survival and reduce the risk of death), ZOL can reduce the risk of EBC recurrence in patients with age of 40 years or above, suggesting that ZOL low estrogen levels in breast cancer patients may lead to greater survival benefit and low estrogen levels could be a key factor in ZOL treatment EBC; therefore it is necessary to assess this ZOL subgroup to fur-

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Table 1. — *Included in the study of basic situation.*

Author	Follow-up time (month)	Cases (n) ZOL control		Overall survival ZOL control		Disease-free survival ZOL control		Recurrence rate ZOL control		Transfer rate ZOL control		Fracture rate ZOL control	
		900	903	870	860	824	793	59	86	21	32	10	15
Coleman 2011 [3]	59	1681	1678	1438	1402	1304	1303	333	331	108	122	60	92
		519*	522*	437*	408*	NR	NR	NR	NR	NR	NR	NR	NR
Eidtmann 2010 [4]#	36	532	532	521	514	506	489	22	40	9	17	24	36
Coleman 2013 [13]#	60	532	533	506	497	490	471	37	59	14	24	NR	NR
Brufsky 2012 [9]	36	300	300	296	298	289	283	7	15	1	2	NR	NR
	61	300	300	293	296	277	275	16	21	3	7	28	33
Coleman 2009 [10]	36	263	264	254	262	NR	NR	NR	NR	NR	NR	NR	NR
Aft 2010 [11]	61	60	59	46	46	NR	NR	NR	NR	NR	NR	NR	NR
Leal 2010 [12]	96	36	32	31	27	NR	NR	NR	NR	NR	NR	NR	NR

*Postmenopausal patients; #References 4 and 13, respectively, describe three- and five-year follow-up results of ZO-FAST test; NR: no report.

ther clarify the mechanism of action. Given the aforementioned, the present authors once again assess the prognosis of systematic reviews of ZOL with EBC patients, in order to provide clinical decision-making for such patients.

Materials and Methods

Study design was an EBC randomized controlled trial including ZOL published domestically and experimental groups adding ZOL to standard cure. Control group did not use or delay use of ZOL on the basis of standard care. The languages of research were limited to Chinese and English.

Overall survival, disease-free survival, recurrence rate, bone metastasis rate, and fracture rate were all assessed.

Terminology utilized in this study included: early, breast, mammary, tumor, malign, carcinoma, bisphosphonates, zoledronic acid, azole phosphate, double phosphate, breast cancer, breast malignant tumor. Computer retrieval of information included platforms such as Cochrane Library, PubMed, and EMBASE. Chinese biomedical literature database, including Wanfang database included standard research. Indexed time cut-off was established to commence from March of 2013 onwards.

Two evaluators extracted the incorporated research documents independently, including test design method, periodical's name, first author, publication year, country, follow-up visit time, overall survival and other evaluation index, then cross-checked the results through discussion or/and negotiating with third evaluator to decide the difficulty to confirm conflicting incorporated research. Quality evaluation of documents was performed by using Cochrane Handbook method.

Meta-analysis was performed by using RevMan 5.0 software supplied by Cochrane collaboration network. The heterogeneity analysis was performed, with the chi-square test (test level $\alpha = 0.10$). The random-effects model and fixed-effects model were applied for data with heterogeneity ($p < 0.10$) and without heterogeneity ($p > 0.10$), respectively. If the heterogeneity was too large, the descriptive analysis was conducted.

Results

The included study initial survey included 1,251 articles, including abstracts and full text, and after exclusion criteria resulted in 48 articles, and after further analysis of the latter full texts led to eight research articles. The countries represented included Austria [13], England [8, 14, 15], Germany [7], and America [16-18]. One study [13] compared a group using goserelin combined with tamoxifen or anastrozole and a test group that added ZOL (4 mg/six month, period is three years). Another study [8] compared a group using neoadjuvant chemotherapy and a test group that added ZOL (4 mg/one month of first half year, one time per three months in afterwards two years, one time per six months in final 2.5 years, five years total). Other studies [7, 14, 16] assessed whether ZOL has protective function to bone loss and fracture risk caused by letrozole used in EBC patient. The test group added ZOL (4 mg/six months, five years in total) on letrozole and compared group according to the incidence of osteoporosis or bone fractures and other adverse events as ZOL. Aft *et al.* [17] compared the neoadjuvant chemotherapy group against the test group adding ZOL (4 mg/three weeks, one year in total) on the basis of compared group. In the literature [12], the control group received standard treatment, and ZOL (4 mg/12 weeks, in total 48 weeks) was added to the experimental group. In detection of estrogen level, the subjects in literatures [8, 19] were pre-menopause or post-menopausal patients, and those in literatures [7, 14, 16, 18] were post-menopause patients. The other characteristics of included subjects are shown in Table 1.

The methodological quality evaluation of included studies was as follows: all included studies were open multicenter randomized-controlled trials. Only literature [13] mentioned the single-blinding to the detectors. Literatures [7, 16, 18] did not mention random grouping method or allocation concealment (Table 2).

In three years follow-up visit, compared with ZOL group and control group, overall survival rate was not different. ZOL obviously showed a higher in disease-free survival rate (OR = 1.67, 95%CI (1.10, 2.55), $p = 0.02$). Comparing recurrence rate and bone transport rate, there was no difference. Follow-up visit ≥ five years, ZOL group was

Table 2. — *Included in the study of methodological quality evaluation.*

Study	Random method	Allocation concealment	Blind method	Intentional analysis	Report selectively	Incomplete Results	Other bias
Gnant 2011 [2]	Computer randomization	Yes	outcome blinded	Yes	No	No	No
Coleman 2011 [3]	Computer randomization	Yes	No	Yes	No	No	No
Eidtmann 2010 [4]	Not mentioned	Not mentioned	No	Yes	No	No	No
Brufsky 2012 [9]	Not mentioned	Not mentioned	No	Yes	No	No	No
Coleman 2009 [10]	Computer randomization	Yes	No	Yes	No	No	No
Aft 2010 [11]	Computer randomization	Yes	No	Yes	No	No	No
Leal 2010 [12]	Not mentioned	Not mentioned	No	Yes	No	No	No

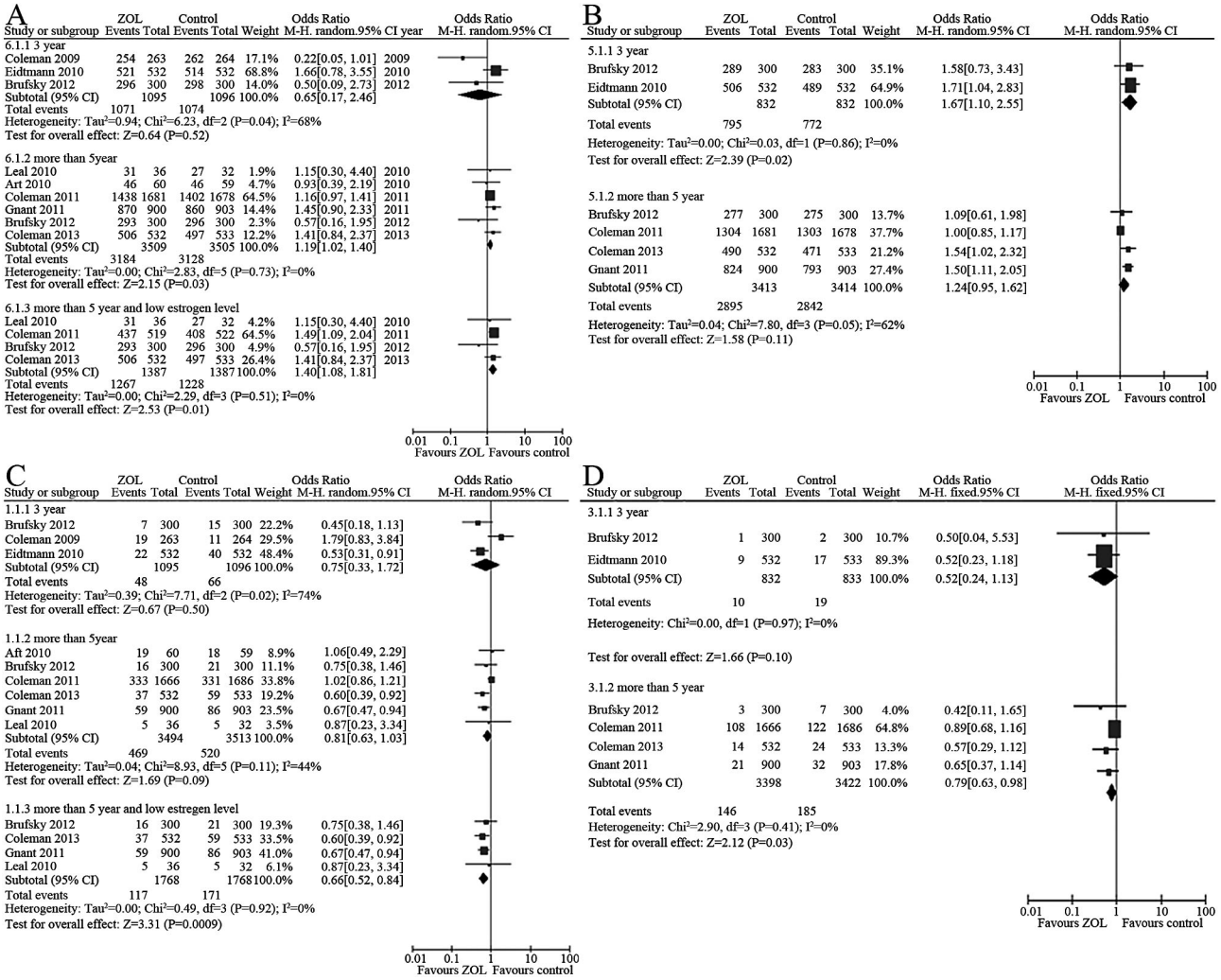

Figure 1. — Forest map of overall survival (A), disease-free survival (B), recurrence rate (C), and transfer rate (D) between ZOL and control groups.

higher in overall survival rate (OR = 1.19, 95%CI (1.02, 1.40), $p = 0.03$). Disease free survival rate and recurrence rate were also not different. Bone fractures were lower than control group compared with ZOL group (OR = 0.72, 95%CI (0.57, 0.92), $p = 0.01$). With low estrogen levels, five-year follow-up visit showed that ZOL could increase disease free survival rate (OR = 1.40, 95%CI (1.08, 1.81), $p = 0.01$), reduce recurrence rate (OR = 0.66, 95%CI (0.52, 0.84), $p = 0.0009$), reduce bone transport rate (OR = 0.79, 95%CI (0.63, 0.98, $p = 0.03$) (Figure 1).

Discussion

Although the current comprehensive cure has improved prognosis of breast cancer, its recurrence and transport rate are still one of problems that plague clinicians [19]. Most middle and advanced stage breast cancer patients all have bone transport [20]. After cancer cell seeding into bone, it will release many soluble growth factors like transforming growth factor β, etc., which can irritate osteoclasts to grow, and lead to soluble bony destruction [21]. Soluble bony absorption process secrete kinds of cell factors to irritate tumor cell proliferation, like interleukin-6, etc., causing a bony destructive vicious circle [22]. ZOL is the strongest pharmacological activity diphosphonate medicine, mainly through restrain osteoclast grow and induces its apoptosis to restrain bone absorption [23]. Because of its effective treatment and little side-effects, it is commonly used by clinicians. Accompanied with opening clinical test, ZOL potential anti-tumor effect is also greatly affected. For example, ABCSG-12 test result showed that ZOL could reduce the progressing risk of breast cancer patient, and profit survival in two years after completing the cure. AZURE test result discovered in post-menopause EBC patients, ZOL and cytotoxic drugs have a synergistic effect [8], which can reduce the mortality risk. ZO-FAST showed that ZOL can increase disease-free survival of post-menopause EBC patients [7, 15]. In vitro results also showed that ZOL could induce breast cancer cell apoptosis and autophagy, restrain cancer cell increase, prevent cancer cell to affect and adhere bone, restrain angiogenesis, and have immunomodulatory effects [24, 25]. Although there are encouraging results as the aforementioned, further meta-analysis results are not the same and the reasons may include: study had some differences, general combination of the results in different periods, or the relation between low estrogen level and ZOL treatment result were not assessed; hence further meta-analyses are warranted.

In this study, the subgroup analyses of overall survival rate, three RCT (Z-FAST, ZO-FAST, E-ZO-FAST) were included and the follow-up time was three years, and the subjects in the study were postmenopausal patients with early breast cancer. Only in ZO-FAST, three-year overall survival rate of ZOL group was higher than that in control group. After the inclusion of meta-analysis, the three-year overall survival rate showed no difference between ZOL and control groups. In a subgroup analysis after follow-up of five years, the present authors enrolled six RCT (including ZO-FAST, Z-FAST, AZURE, ABCSG-12, six trials). The five-year overall survival rate of ZOL group was higher than control group. The overall survival rate of subgroup analysis at a low level of estrogen and follow-up time ≥ five years, showed that ZOL can improve five-year overall survival rate in the low estrogen level patients with EBC; however there is some consistency between this result and results of AZURE and ABCSG-12 trails. It is possible that ZOL may have anti-tumor effect. However, previous studies found that osteoporotic fractures can increase 5-10 year mortality of women over the age of 60 and ZOL's bone inhibiting absorption effect can reduce the incidence of osteoporotic fracture. The results of this study showed that ZOL can reduce the incidence of fractures in patients with EBC in five years, indirectly increased five-year overall survival rate in patients with EBC, and caused some confusion regarding its anti-tumor effects. Therefore, it must be assessed to whether ZOL can reduce the recurrence rate of the patients with EBC. The present authors found in the recurrence rate no differences between ZOL group and control group after three years and ≥ five years follow-up time. subgroup Analysis of low estrogen level after five years follow-up, the present authors found that the recurrence rate of ZOL group was significantly lower than the control group. At low estrogen level after five years follow-up, showed that ZOL can reduce the incidence of bone metastasis in patients with EBC according to subgroup analyses of the rate of bone metastasis. From these results, the present authors speculate that ZOL can improve five-year overall survival rate of patients with EBC; the clinical benefit may be from two aspects: the first is the anti-tumor effects in low estrogen level, which can significantly reduce the rate of recurrence and bone metastasis and the second is the inhibition effect of bone resorption, which can significantly reduce the rate of fracture and indirectly improves overall survival rate. Which one is more important remains to be further studied. Regarding whether ZOL can reduce other body tissue (exclude bone) metastasis, still needs to be assessed due to limited literature data, but previous meta-analysis did not show that ZOL had this effect. Presumably the ZOL target is mainly the osteoclast, so its antitumor effect is limited. Regarding the adverse reaction of ZOL, the present authors did not perform meta-analysis due to limited data collection. Combining the research literature included in this study and previous data [26], the present authors believe that ZOL has less side effects including a lower incidence of serious adverse reactions, renal failure, and osteonecrosis of the jaw.

Limitations of this study include: 1) lack collecting of unpublished papers and reports and the results in bias; 2) meta-analysis itself has certain limitations and the reliability of results depends on the quality of the included studies. Although the present authors strictly selected the literature, however the research object of the trails are still not identical to a certain extent, and this may also have affected the accuracy of result; 3) meta-analysis based on the previous studies and not on the control, renders it difficult to ensure the reliability of information. Therefore, randomized controlled trials with a strict design and larger sample need to be carried out to clinically assess the curative effect in the future.

ZOL can improve five-year overall survival rate of patients with EBC, may have an anti-tumoral effect, and in-

hibit bone destruction. At low estrogen levels, ZOL may be significantly have an anti-tumor effect and can reduce the recurrence rate and the rate of bone metastasis of patients with EBC. In addition, ZOL has slight side effects and good clinical tolerance. In the future it may be routinely recommended in the treatment of patients with EBC, but its mechanism of action, the optimal dose, and course of treatment need to be further studied.

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