Adjuvant Therapy With Zoledronic Acid in Patients With Breast Cancer: A Systematic Review and Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Zoledronic acid • Adjuvant • Breast cancer • Bisphosphonates

ABSTRACT

Background. The purpose of the study was to estimate the impact on survival and fracture rates of the use of zoledronic acid versus no use (or delayed use) in the adjuvant treatment of patients with early-stage (stages I–III) breast cancer.

Materials and Methods. We performed a systematic review and meta-analysis of randomized clinical trials. Trials were located through PubMed, ISI, Cochrane Library, and major cancer scientific meeting searches. All trials that randomized patients with primary breast cancer to undergo adjuvant treatment with zoledronic acid versus nonuse, placebo, or delayed use of zoledronic acid as treatment to individuals who develop osteoporosis were considered eligible. Standard meta-analytic procedures were used to analyze the study outcomes.

Results. Fifteen studies were considered eligible and were further analyzed. The use of zoledronic acid resulted in a statistically significant better overall survival outcome (five studies, 6,414 patients; hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70–0.94). No significant differences were found for the disease-free survival outcome (seven studies, 7,541 patients; HR, 0.86; 95% CI, 0.70–1.06) or incidence of bone metastases (seven studies, 7,543 patients; odds ratio [OR], 0.94; 95% CI, 0.64–1.37). Treatment with zoledronic acid led to a significantly lower overall fracture rate (OR, 0.78; 95% CI, 0.63–0.96). Finally, the rate of osteonecrosis of the jaw was 0.52%.

Conclusion. Zoledronic acid as adjuvant therapy in breast cancer patients appears to not only reduce the fracture risk but also offer a survival benefit over placebo or no treatment. *The Oncologist* 2013;18:353–361

Implications for Practice: Zoledronic acid appears to have a role in adjuvant therapy in patients with breast cancer because it reduces the fracture rate and seems to offer survival benefits. The need for additional research is essential to determine if its effect is enhanced in low-estrogen environments and to reveal the magnitude of interaction between estrogen levels and zoledronic acid. Meanwhile, in patients with signs of bone loss (osteopenia or osteoporosis) during adjuvant endocrine therapy when the initiation of bisphosphonates is indicated, zoledronic acid might be preferred over other therapies due to its beneficial effect on survival.

INTRODUCTION

Bisphosphonates are antiresorptive agents that inhibit osteoclast function, and they are widely used in the treatment of benign and malignant bone diseases [1]. Bisphosphonates have an established role as preventive and therapeutic agents for osteoporosis [2] and as preventive therapy against skeletal-related events among cancer patients with bone metastases, including breast, prostate, and lung malignancies [3].

Recently, a growing body of evidence from preclinical studies in breast cancer models suggests that the use of bisphosphonates may improve survival outcomes in certain cancer patients because of their documented antitumor activity, including prevention of tumor cell adhesion to bone

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[4, 5], induction of tumor cell apoptosis [6], and inhibition of angiogenesis [7].

Given all the above evidence, it was hypothesized that the beneficial effects of bisphosphonate use in the metastatic setting (palliative care) could possibly be extended to use in the adjuvant setting (potentially healthy individuals) for specific categories of cancer patients. However, in spite of initial promising results, especially in breast cancer patients, more recent data seriously question the beneficial effect of bisphosphonate use in the adjuvant setting [8, 9]. Indeed, although bisphosphonates successfully maintained bone mineral density (BMD) when administered in the adjuvant treatment of breast cancer patients [10–13], their use did not appear to positively affect either the frequency of fractures [9] or survival outcomes [8]. Thus, the crucial question is why do the clinical data in the adjuvant setting not conform to the initial preclinical results and the benefits observed in the metastatic setting?

From a preclinical model view, the differences existing among bisphosphonate categories might be an answer to this question. Zoledronic acid's unique pharmacologic profile has been associated not only with a higher binding affinity to bone and a higher antiresorptive potential [14, 15] but also with

Although bisphosphonates successfully maintained bone mineral density when administered in the adjuvant treatment of breast cancer patients, their use did not appear to positively affect either the frequency of fractures or survival outcomes. Thus, the crucial question is why do the clinical data in the adjuvant setting not conform to the initial preclinical results and the benefits observed in the metastatic setting?

more potent antitumoral activity [4, 16], compared with other less potent or non-nitrogen containing bisphosphonates.

Although a previous meta-analysis showed that bisphosphonates considered as a single therapeutic intervention did not lower breast cancer recurrence in the adjuvant setting, a statistically significant lower risk for breast cancer recurrence was observed among patients receiving zoledronic acid [8]. Is the observed superior efficacy of zoledronic acid over other bisphosphonates enough to consider its use as a new standard of care in the adjuvant treatment of breast cancer patients?

Taking into account the entire above-mentioned body of evidence, we set out to estimate the impact on survival outcomes and fracture rates of the use of zoledronic acid, versus no use, in the adjuvant treatment of patients with early-stage (stages I–III) breast cancer. A systematic review of the literature was performed, and pooled estimates from the cumulative available randomized evidence were analyzed.

MATERIALS AND METHODS

Search Strategy

Two independent investigators searched MEDLINE and the Cochrane Controlled Trials Register, without language or year restriction, through December 2011. The following search strategy was used (early OR adjuvant) AND (breast OR mam-

mary) AND (tumor OR malign* OR carcinom* OR cancer) AND (bisphosphonates OR zoledronic acid).

In addition, abstract books from major scientific meetings (the American Society of Clinical Oncology Annual Meeting, the San Antonio Breast Cancer Symposium, and the European Cancer Conference) were also hand-searched in duplicate. Discrepancies between investigators were solved through discussion.

Finally, the reference lists of all eligible studies were also scrutinized to identify relevant articles missed by the electronic searches.

Selection Criteria

Only randomized controlled trials in which patients with primary breast cancer were allocated to a zoledronic acid or a no treatment or placebo group in the adjuvant setting were eligible. This was irrespective of the type of study (phase II or phase III), the study sample size, and the dosage or duration of zoledronic acid therapy. Trials in which patients were randomized to upfront zoledronic acid treatment in the adjuvant setting, versus the delayed use of zoledronic acid as treatment for individuals who developed osteoporosis, were also included in the analysis.

Finally, whenever multiple records were related to the same study, endpoint data were extracted from the report with the longest follow-up (largest number of events) to avoid duplication of information in the meta-analysis calculations.

Data Extraction

Data extraction was conducted independently by two authors (A.V. and N.P.P.). In cases of discrepancy, a third author (D.M.) was consulted. If data on the outcome were not available from a trial, we contacted the primary investigator of the eligible trial.

From each eligible trial, we extracted the following data from a prespecified database: author names, journal name and year of publication, country of origin, inclusive dates of patient enrollment, and number of centers involved. Additionally, we recorded the following items for both arms of each eligible trial: number of patients randomly assigned to treatment and analyzed per arm, age, menopausal status, schedule and dosing scheme of zoledronic acid, and any additional breast cancer treatment given. Primary and secondary outcome measures, as described below, were recorded. Study design items such as randomization mode, allocation concealment, and withdrawal descriptions were further recorded.

Risk of Bias and Publication Bias Assessment

Cochrane's risk of bias tool was used to assess the individual risk of bias of each study [17]. The criteria used for quality assessment were sequence generation of allocation; allocation concealment; masking of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Two authors (A.V., N.P.P.) independently assessed the risk of bias in each eligible trial.

Publication bias was assessed with the construction of contour-enhanced funnel plots.

Outcome Measures

The primary outcome of this study was the overall survival (OS) time difference between the zoledronic acid and control arms. Secondary outcomes included the disease-free survival

Figure 1. Flowchart diagram of study selection.

(DFS) interval, incidence of bone metastasis, disease recurrence (locoregional or distant) rate, and overall fracture rate.

Finally, the rate of osteonecrosis of the jaw (ONJ), a well-documented side effect of zoledronic acid [18], was also recorded.

Statistical Analysis

For meta-analyses of the time-to-event outcomes (OS and DFS times), the most appropriate statistic is the hazard ratio (HR). If provided in a trial report, the HR and associated variances were used directly in the meta-analysis. Alternatively, HRs were calculated based on other summary statistics (number of events in each arm, log-rank *p* value) according to the datasheet developed by Tierney et al. [19]. HRs and 95% confidence intervals (CIs) were pooled according to the inverse of variance method. An HR < 1 favored zoledronic acid use.

The number of events (bone metastases, locoregional metastases, distant metastases, fractures) and the number of nonevents in the treated and control groups were retrieved from each primary study and 2 × 2 tables were constructed. Odds ratios (ORs) of events for treated with respect to nontreated patients and their 95% CIs were calculated. Studies with zero events in both groups (treated and nontreated) were excluded from the analysis.

The χ^2 test of heterogeneity and the I^2 statistic of inconsistency were used to assess heterogeneity among studies. Statistically significant heterogeneity was defined as a χ^2 *p* value < .1 or an I^2 statistic > 50%. In the absence of heterogeneity, pooled estimates of ORs or HRs with their 95% CIs were calculated using the Mantel-Haenszel method. In the

presence of heterogeneity, the DerSimonian and Laird random effects method was used to pool primary study estimates.

Prespecified subgroup analyses were performed for primary and secondary outcomes based on whether delayed administration of zoledronic acid was allowed in the control arm or not. We explored our findings further by two additional sensitivity analyses. To assess the potential impact of the quality of studies on outcomes, we performed a sensitivity analysis with the exclusion of low-quality studies. Furthermore, we conducted a sensitivity analysis by excluding studies with a shorter length of zoledronic acid administration (< 3 years).

All statistical analyses were performed using the Review Manager software (version 5.0. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008).

RESULTS

Study Selection and Characteristics

The electronic search yielded 505 reports. Of these, 473 were excluded on the basis of the abstract or title, leading to 32 potentially eligible trials. After scrutiny, 13 randomized controlled trials were considered eligible according to the inclusion criteria, whereas hand searches in major meeting abstract books resulted in two additional trials. In total, 15 trials [12, 13, 20–32] were considered eligible and further analyzed (Fig. 1).

Baseline characteristics of the eligible trials are presented in Table 1. Five studies [21–25, 27] allowed the delayed use of

Table 1. Characteristics of eligible trials

Study	Intervention	Zoledronic acid administration	Duration (yrs)	n of patients	Follow-up (mos)	n of recurrences	n of deaths
AZURE trial (2011) [20]	Zoledronic acid	4 mg every 4 wks $\times$ 6 $\geq$ every 3 mos $\times$ 8 $\geq$ every 6 mos $\times$ 5	5	1,681	59.3	377	243
	Observation			1,678	58.6	375	276
ABCSG-12 trial (2011) [21]	Zoledronic acid	4 mg every 6 mos	3	900	84	98	33
	Observation			903	84	132	49
ZO-FAST (2011) [22]	Upfront zoledronic acid	4 mg every 6 mos	5	532	54	34	26
	Delayed zoledronic acid			533	54	53	36
Z-FAST trial (2011) [23]	Upfront zoledronic acid	4 mg every 6 mos	5	300	61 ^a	16	7
	Delayed zoledronic acid			300	61 ^a	21	4
N03CC trial (2009) [24]	Upfront zoledronic acid	4 mg every 6 mos	5	274	24 ^a	NR	NR
	Delayed zoledronic acid			277	24 ^a		
EZO-FAST (2009) [25]	Upfront zoledronic acid	4 mg every 6 mos	5	263	36 ^a	18	9
	Delayed zoledronic acid			264	36 ^a	11	2
HOBEO trial (2011) [26]	Zoledronic acid	4 mg every 6 mos	5	154	NR	NR	NR
	Observation			305			
Takahashi et al. (2011) [27]	Upfront zoledronic acid	4 mg every 6 mos	5	97	12 ^a	1	NR
	Delayed zoledronic acid			97	12 ^a	0	
Aft et al. (2010) [28]	Zoledronic acid	4 mg every 3 wks	1	60	61.9	19	14
	Observation			59	61.9	18	13
KCSG-BR06-01 trial (2011) [12]	Zoledronic acid	4 mg every 6 mos	1	57	NR	NR	NR
	Observation			59			
Hershman et al. (2010) [13]	Zoledronic acid	4 mg every 3 mos	1	50	24 ^a	NR	NR
	Placebo			53	24 ^a		
Safra et al. (2011) [29]	Zoledronic acid	4 mg every 6 mos	2	47	41.4	NR	NR
	Observation			43	41.4		
ProBone trial (2011) [30]	Zoledronic acid	4 mg every 3 mos	2	40	NR	NR	NR
	Placebo			41			
Leal et al. (2010) [31]	Zoledronic acid	4 mg every 3 mos	1	36	96	5	5
	Observation			32	96	5	5
Swenson et al. (2010) [32]	Zoledronic acid	4 mg every 3 mos	15 mos	33	12 ^a	NR	NR
	Physical activity			29	12 ^a		

^aAnalysis when all patients reached this certain follow-up time.

Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; EZO-FAST, Zometa/Femar Adjuvant Synergy Trial; HOBEO, Hormonal Adjuvant Treatment Bone Effects; KCSG, Korean Cancer Study Group; NR, not reported; Z-FAST, Zometa Adjuvant Synergy Trial; ZO-FAST, Zometa–Femara Adjuvant Synergy Trial.

zoledronic acid in the control group for individuals who developed osteoporosis. Eight of the eligible trials [12, 13, 24, 26, 27, 29, 30, 32] were designed to only address the role of zoledronic acid in preventing BMD loss. Those studies did not provide any data regarding survival whereas some reported data on fractures. Only seven studies [20–23, 25, 28, 31] were planned to report survival data as either a primary or secondary outcome. However, all studies included data on ONJ.

In two cases [33, 34], we used data derived from updated study reports with longer follow-up but presented only at scientific meetings.

In five studies [12, 13, 21, 30, 32], only pre- or perimenopausal women were considered eligible, whereas seven studies [22–25, 27, 29, 31] included only postmenopausal women. Three studies [20, 25, 28] allowed inclusion of both pre- and postmenopausal women.

Primary Outcome: OS Duration

The primary outcome was assessed in seven studies (7,541 patients). However, only five studies (6,414 patients) either re-

ported HRs or provided data that allowed the calculation of HRs. As shown in Figure 2, zoledronic acid resulted in a statistically significant better OS outcome (HR, 0.81; 95% CI, 0.70–0.94; *p* value = .007). No between-study heterogeneity was observed (Q statistic *p* value = .63; *I*² = 0%). A subgroup analysis including only trials with an observation arm as the comparator (four studies; 5,349 patients) showed that the results remained statistically significant (HR, 0.82; 95% CI, 0.70–0.96) (Fig. 2). In addition, a sensitivity analysis with the exclusion of studies with a shorter length of zoledronic acid administration did not alter the statistically significant benefit (HR, 0.81; 95% CI, 0.69–0.94).

Secondary Outcomes

The number of overall recurrences was reported in nine studies (7,838 patients). However, DFS intervals or data to calculate HRs regarding the DFS interval were provided in seven studies, with a total of 7,541 patients. The pooled HR for the DFS outcome did not show a significant advantage for the use of zoledronic acid versus no use (HR, 0.86; 95% CI, 0.70–1.06; *p* value = .15) (Fig. 3). In all but two studies [28, 31], the defi-

Figure 2. Forest plot for overall survival outcome. Squares represent hazard ratios and size of squares is proportional to the size of the trials. Error bars represent 95% CIs. For all figures, values <1 indicate that zoledronic acid use has a beneficial effect on outcome.

Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; CI, confidence interval; SE, standard error; ZO-FAST, Zometa–Femara Adjuvant Synergy Trial.

Figure 3. Forest plot for disease-free survival outcome. Squares represent hazard ratios and size of squares is proportional to the size of the trials. Error bars represent 95% CIs. For all figures, values <1 indicate that zoledronic acid use has a beneficial effect on outcome.

Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; CI, confidence interval; EZO-FAST, Zometa–Femara Adjuvant Synergy Trial; SE, standard error; Z-FAST, Zometa Adjuvant Synergy Trial; ZO-FAST, Zometa–Femara Adjuvant Synergy Trial.

nition of the DFS time included not only disease recurrences but also death resulting from any cause.

Furthermore, recurrence rates and incidences of bone metastases did not differ between the zoledronic acid and control groups. The OR for locoregional recurrence was 0.81 (95% CI, 0.50–1.30; p value = .38) (six studies; 7422 patients) for the comparison of zoledronic acid use versus no use. The OR for distant recurrence was 0.88 (95% CI, 0.70–1.10; p value = .27) (six studies; 7422 patients) and the OR for bone metastasis was 0.94 (95% CI, 0.64–1.37; p value = .74) (seven studies; 7,543 patients).

Data regarding fractures were available for 11 studies (8,473 patients). Of those, four studies had zero events in both arms and were excluded from the analysis. In total, seven studies (7,967 patients) were included in a meta-analysis of

the fracture rate. Treatment with zoledronic acid led to a significantly lower overall fracture rate (OR, 0.78; 95% CI, 0.63–0.96; p value = .02) (Fig. 4). A sensitivity analysis with the inclusion of studies with a longer duration of zoledronic acid administration revealed a comparable lower risk for fracture (OR, 0.78; 95% CI, 0.63–0.97).

Finally, the cumulative ONJ rate among patients receiving zoledronic acid was calculated. We used the number of patients who received at least one dose of zoledronic acid as the denominator. ONJ occurred in 25 of 4,774 patients (0.52%) who received zoledronic acid and in none of the patients in the control arm.

Risk of Bias and Publication Bias Assessment

We used Cochrane's risk of bias tool to assess the methodological quality of the trials. The assessment was performed

Figure 4. Forest plot for fracture rates. Squares represent odds ratios and size of squares is proportional to the size of the trials. Error bars represent 95% CIs. For all figures, values <1 indicate that zoledronic acid use has a beneficial effect on outcome.

Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; CI, confidence interval; EZO-FAST, Zometa–Femara Adjuvant Synergy Trial; Z-FAST, Zometa Adjuvant Synergy Trial; ZO-FAST, Zometa–Femara Adjuvant Synergy Trial.

for 13 eligible studies [12, 13, 20–24, 26–29, 31, 32] that were published in full text. Among the eligible studies, eight [13, 20–23, 28, 31, 32] reported an adequate randomization mode, three [20, 21, 28] used an adequate mode of allocation concealment, whereas five [21–23, 28] clearly reported blinding of outcome assessment.

In all meta-analyses, the funnel plots were symmetrical, indicating that publication bias was unlikely to have had a major influence in the analyses (plots not shown).

DISCUSSION

Our meta-analysis provides evidence in favor of zoledronic acid use in the adjuvant breast cancer setting. Zoledronic acid not only has a protective effect for fractures, with a 21% lower risk, it also reduces the risk of death by 19%. Thus, taking into account this substantial benefit, along with the acceptable toxicity regarding ONJ, with an incidence rate of 0.52%, it appears that the use of zoledronic acid in adjuvant breast cancer treatment should be considered.

A potential explanation for the beneficial role of zoledronic acid should be attributed first of all to its antitumoral activity from preclinical evidence through preventing tumor cell adhesion to bone [4, 5], inducing tumor cell apoptosis [6], inhibiting angiogenesis, and inhibiting interactions with mesenchymal stem cells [35]. In addition, zoledronic acid has been shown, in clinical studies, to eliminate micrometastatic tumor cells from the bone marrow, which could lead to a better survival outcome [28]. It is therefore likely that several of these zoledronic acid-mediated effects on the metastatic process could combine to produce the clinical benefits observed in our study. However, one may argue that the potential benefit of zoledronic acid to the natural history of breast cancer is limited, given that no differences in the DFS time or disease recurrence rate were observed in our meta-analysis.

A potential explanation for this inconsistency could be the fact that zoledronic acid has a preventative impact on the overall fracture rate and the mortality related to this. Previous trials have shown that all types of osteoporotic fractures increase the risk of death [36]. Consequently, it is likely that the significantly lower risk for fracture resulting from zoledronic acid might be extrapolated as a cumulative beneficial effect on the OS rate. This is in total alignment with the results of the large Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE)

A potential explanation for the beneficial role of zoledronic acid should be attributed first of all to its antitumoral activity from preclinical evidence through preventing tumor cell adhesion to bone, inducing tumor cell apoptosis, inhibiting angiogenesis, and inhibiting interactions with mesenchymal stem cells. In addition, zoledronic acid has been shown, in clinical studies, to eliminate micrometastatic tumor cells from the bone marrow, which could lead to a better survival outcome.

trial that demonstrated a lower risk for fracture in patients treated with zoledronic acid [20] as well as with the results of other randomized studies [10–13] demonstrating the beneficial effect of zoledronic acid on the prevention of BMD loss related to breast cancer therapy.

A key question, however, is why does zoledronic acid manage to improve both the fracture rates and survival rates whereas other bisphosphonates have shown either little or no benefit at all [8, 9]? This discrepancy might be attributed to the diverse pharmacological profile and the more potent activity

of zoledronic acid [4, 14–16]. The diversity between different bisphosphonate agents has been proven by several large randomized trials and meta-analyses in patients with metastatic cancer [37, 38], multiple myeloma [39], and osteoporosis [2]. Therefore, it may be likely that the potency of the drug may be a determinant of its success among breast cancer patients. In addition, zoledronic acid was shown to have a more potent antitumor activity than other bisphosphonates in preclinical studies [4, 16].

An interesting finding from the largest study on this topic, the AZURE trial [20], comes from a prespecified subgroup analysis based on age and menopausal status. Patients who had undergone menopause >5 years before their breast cancer diagnosis had statistically significant better DFS and OS outcomes with zoledronic acid than with placebo, whereas there was no benefit at all among premenopausal, perimenopausal, or unknown menopausal status patients. These data are consistent with those from the Zometa–Femara Adjuvant Synergy Trial [34] and the Austrian Breast and Colorectal Cancer Study Group 12 trial [33], in which significant survival benefits were observed in patients >5 years from menopause or >40 years old and with low estrogen levels resulting from gonadotropin-releasing hormone use, respectively. These findings suggest that zoledronic acid might have the greatest potential for anticancer benefits in a low-estrogen environment. The underlying mechanism for this observation is unclear; nonetheless, it has been suggested that estrogen's effects on the bone microenvironment may play a key role in determining who may benefit most from adjuvant zoledronic acid therapy.

Although a subgroup analysis according to menopausal status could have been of value in our meta-analysis, such an attempt would be prone to serious biases, mainly because of heterogeneity in the definition of postmenopausal status and the fact that the majority of the subgroup analyses were unplanned, making comparisons unreliable. However, it is essential to outline a potential enhanced effect of zoledronic acid in patients with a low-estrogen environment.

These results are in complete contrast with a recent meta-analysis focusing on the same research question [40]. Although Yan et al. [40] could not find any statistically significant differences in favor of zoledronic acid in their meta-analysis, this should be attributed to the parameters used in the methodology rather than a lack of efficacy of the drug itself. First, the inclusion criteria of our meta-analysis were broader, allowing inclusion of all randomized trials irrespective of the type of study (phase II or phase III randomized controlled trial). Given that the inclusion of all randomized evidence is of paramount importance to ensure the fundamental concept and practice that a meta-analysis should be systematically inclusive [41], our inclusion criteria yielded 10 more randomized trials. These additional trials may have contributed to a divergent outcome. In addition, we point to the inclusion of updated data with longer follow-up from three trials [21–23] and the publication of a new trial in full text [20] as reasons for the discrepancy between our analysis and that of Yan et al. [40].

We have to acknowledge, however, that several limitations exist in our meta-analysis. First of all, our analysis is

based on published or presented data and not on individual patient data. Individual patient data meta-analysis is considered more reliable [42]. As a result, an individual patient data meta-analysis would be of great interest to give a definitive answer to our questions about the role of zoledronic acid in adjuvant breast cancer treatment. Second, some of the included studies [21–25, 27] were designed with a control group of delayed zoledronic acid. Consequently, a number of patients in the control group received zoledronic acid during follow-up. Therefore, a potential underestimation of the effect of zoledronic acid on the outcomes cannot be excluded. A subgroup analysis with the exclusion of these studies did not alter the statistically significant results in favor of zoledronic acid. In addition, most of the studies were not designed to reveal differences in survival outcomes or fracture rates; nonetheless, the major advantage of a meta-analysis is exactly this ability to increase the statistical power of the study by increasing the overall sample size. Furthermore, we cannot overlook the differences in the duration and schedule of zoledronic acid in the different patient groups (regarding menopausal status and endocrine treatment), which may have resulted in inflated or deflated outcomes. However, even when including only trials with a treatment duration >3 years, the benefit in favor of zoledronic acid remained statistically significant. Moreover, in the meta-analysis of the fracture rate, we decided to exclude four trials with zero events in both arms because they make no contribution to the magnitude of the treatment effect. We have to acknowledge, however, that addressing this statistical issue is a grey zone, and some researchers propose the addition of zero event trials in analyses [43]. Finally, we have to acknowledge that several of the trials demonstrated an unclear or high risk of bias; although a previous meta-analysis showed that the inclusion of trials with a high risk of bias may have resulted in inflated results [44], trial quality is not always determinant of the final outcome [45]. Thus, future trials in the field should focus on more adequate methodological quality reporting.

In conclusion, our meta-analysis summarizes the current randomized evidence on the role of zoledronic acid as an adjuvant therapy for breast cancer patients. Zoledronic acid not only reduces the fracture risk but also appears to offer a substantial survival benefit over placebo and over no treatment. This survival benefit and the lower fracture risk along with the acceptable drug-specific toxicity create a positive risk-benefit profile and render zoledronic acid an attractive option for adjuvant breast cancer therapy. Although our results show a clear benefit of zoledronic acid in the adjuvant setting, further research is essential to confirm our findings and potentially identify specific subgroups that may experience an even more substantial benefit from the administration of zoledronic acid as an antitumor agent in the adjuvant setting.

AUTHOR CONTRIBUTIONS

Conception/Design: Antonis Valachis, Nikolaos P. Polyzos, Davide Mauri
Provision of study material or patients: Antonis Valachis, Robert E. Coleman, Michael Gnant, Holger Eidtmann, Adam M. Brufsky, Rebecca Aft, Amye J. Tevaarwerk, Karen Swenson

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DISCLOSURES

Robert E. Coleman: Other: Expert Testimony: Novartis; **Michael Gnant:** Novartis (C/A); Novartis, Amgen, AstraZeneca, Roche, Sanofi-Aventis, Pfizer, Genomic Health (H); Novartis, Roche, Amgen, Sanofi-Aventis (RF); **Adam M. Brufsky:** Novartis (C/A).
 The other authors indicated no financial relationships.
 (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- Rodan GA, Fleisch HA. Bisphosphonates: Mechanisms of action. *J Clin Invest* 1996;97:2692–2696.
- Jansen JP, Bergman GJ, Huels J et al. The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-nonhip fractures in osteoporosis: A network meta-analysis. *Semin Arthritis Rheum* 2011;40:275–284.e1–e2.
- Machado M, Cruz LS, Tannus G et al. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: A meta-analysis of randomized clinical trials. *Clin Ther* 2009;31:962–979.
- Daubiné F, Le Gall C, Gasser J et al. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J Natl Cancer Inst* 2007;99:322–330.
- van der Pluijm G, Vloedgraven H, van Beek E et al. Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. *J Clin Invest* 1996;98:698–705.
- Senaratne SG, Pirianov G, Mansi JL et al. Bisphosphonates induce apoptosis in human breast cancer cell lines. *Br J Cancer* 2000;82:1459–1468.
- Fournier P, Boissier S, Filleul S et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 2002;62:6538–6544.
- Mauri D, Valachis A, Polyzos NP et al. Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. *J Natl Compr Canc Netw* 2010;8:279–286.
- Valachis A, Polyzos NP, Georgoulas V et al. Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: A meta-analysis. *Gynecol Oncol* 2010;117:139–145.
- 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.
- Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al.; Austrian Breast and Colorectal Cancer Study Group (ABCSCG). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSCG-12 bone-mineral density substudy. *Lancet Oncol* 2008;9:840–849.
- 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.
- Hershman DL, McMahon DJ, Crew KD et al. Prevention of bone loss by zoledronic acid in premenopausal women undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment. *J Clin Endocrinol Metab* 2010;95:559–566.
- Nancollas GH, Tang R, Phipps RJ et al. Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite. *Bone* 2006;38:617–627.
- Russell RGG. Determinants of structure–function relationships among bisphosphonates. *Bone* 2007;40:S21–S25.
- Verdijk R, Franke HR, Wolbers F et al. Differential effects of bisphosphonates on breast cancer cell lines. *Cancer Lett* 2007;246:308–312.
- Higgins JP, Altman DG, Gzysche PC et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Mauri D, Valachis A, Polyzos IP et al. Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: A meta-analysis. *Breast Cancer Res Treat* 2009;116:433–439.
- Tierney JF, Stewart LA, Ghersi D et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
- Coleman RE, Marshall H, Cameron D et al.; AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med* 2011;365:1396–1405.
- Gnant M, Mlineritsch B, Stoeger H et al.; Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSCG-12 randomised trial. *Lancet Oncol* 2011;12:631–641.
- Eidtmann H, de Boer R, Bundred N et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST study. *Ann Oncol* 2010;21:2188–2194.
- 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.
- 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;117:603–609.
- Coleman R, Bundred N, de Boer R et al. Impact of Zoledronic Acid in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole: Z-FAST, ZO-FAST, and E-ZO-FAST. *Cancer Res* 2009;69(24 suppl):4082.
- Rossi E, Morabito A, Di Rella F et al. Endocrine effects of adjuvant letrozole compared with tamoxifen in hormone-responsive postmenopausal patients with early breast cancer: The HOBEO trial. *J Clin Oncol* 2009;27:3192–3197.
- 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.
- Aft R, Naughton M, Trinkaus K et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: An open label, randomised, phase 2 trial. *Lancet Oncol* 2010;11:421–428.
- Safra T, Bernstein-Molho R, Greenberg J et al. The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: A prospective, randomized, phase II trial. *Oncology* 2011;81:298–305.
- Hadji P, Kauka A, Bauer T et al. Influence of zoledronic acid on BMD in premenopausal women with breast cancer and neoadjuvant or adjuvant chemotherapy and/or endocrine treatment – the ProBone studies. *Cancer Res* 2011;71(24 suppl):P2–19-03.
- 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.
- Swenson KK, Nissen MJ, Anderson E, Shapiro A, Schousboe J, Leach J. Effects of exercise vs bisphosphonates on bone mineral density in breast cancer patients receiving chemotherapy. *J Support Oncol* 2009;7:101–107.
- Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al. Long-term follow-up in ABCSCG-12: Significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine-receptor-positive early breast cancer. *Cancer Res* 2011;71(24 suppl):S1–S2.
- de Boer R, Bundred N, Eidtmann H et al. Long-term survival outcomes among postmenopausal women with hormone receptor-positive early breast cancer receiving adjuvant letrozole and zoledronic acid: 5-year follow-up of ZO-FAST. *Cancer Res* 2011;71(24 suppl):S1–S3.
- Gallo M, De Luca A, Lamura L et al. Zoledronic acid blocks the interaction between mesenchymal stem cells and breast cancer cells: Implications for adjuvant therapy of breast cancer. *Ann Oncol* 2012;23:597–604.
- Bliu D, Nguyen ND, Milch VE et al. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301:513–521.
- Rosen LS, Gordon DH, Dugan W Jr et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36–43.
- Rosen LS, Gordon D, Kaminski M et al. Long-

term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: A randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;98:1735–1744.

39. Morgan GJ, Davies FE, Gregory WM et al.; National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): A randomised controlled trial. *Lancet* 2010;376:1989–1999.

40. Yan T, Yin W, Zhou Q et al. The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials. *Eur J Cancer* 2012;48:187–195.

41. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: One answer is not always enough. *Lancet* 1998;351:123–127.

42. Jones AP, Riley RD, Williamson PR et al. Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. *Clin Trials* 2009;6:16–27.

43. Friedrich JO, Adhikari NK, Beyene J. Inclusion

of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol* 2007;7:5.

44. Polyzos NP, Polyzos IP, Zavos A et al. Obstetric outcomes after treatment of periodontal disease during pregnancy: Systematic review and meta-analysis. *BMJ* 2010;341:c7017.

45. Balk EM, Bonis PA, Moskowitz H et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002;287:2973–2982.