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Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a metanalysis

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Abstract To estimate the cumulative randomized evidence for the overall incidence of bisphosphonates induced jaw osteonecrosis in adjuvant treatment of breast cancer. Systematic review and meta-analysis of randomized clinical trials. Trials were located through PubMed, ISI, Cochrane Library, and major cancer scientific meetings searches. We identified 15 studies reporting data on osteonecrosis of the jaw. A total of 10,694 randomized women were included, of whom 5,312 received bisphosphonates and 5,382 received either placebo or no treatment. Osteonecrosis of the jaw was a rare event, occurring in 13 (0.24%) of the 5,312 patients receiving bisphosphonates, and in one of the 5,382 patients in the control group. All the 13 events of osteonecrosis of the

jaw reported among bisphosphonates arms occur in patients undergoing treatment with zoledronic acid (13/3,987, 0.33%). No events of osteonecrosis of the jaw were reported among patients randomized to receive clodronate ($n = 669$), pamidronate ($n = 460$), risedronate ($n = 171$), and ibandronate ($n = 25$); however, these samples were too small to be able to rule out the condition. Treatment with zoledronic acid was significantly associated to the occurrence of osteonecrosis of the jaw (OR = 3.23, 95% CI = 1.7–8) compared with no use. No significant between-study heterogeneity was observed. Despite use of zoledronic acid is associated to a higher number of events compared with no use, the osteonecrosis of the jaw during the adjuvant treatment of breast cancer is a rare event. At current dosage, adjuvant use of bisphosphonates in breast cancer treatment is safe.

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Zoledronic acid

Introduction

Improvements in early detection of breast cancer have resulted in an increase in the number of patients diagnosed and treated in the early stages of the disease.

Female patients receiving adjuvant treatment for early breast cancer are at significant risk of cancer treatment-induced bone loss (CTIBL) due to cytotoxic chemotherapy-induced menopause, and hormonal therapies with aromatase inhibitors [1–4]. Patients with CTIBL, are at high risk for bone fractures and may complain for chronic pain, loss of mobility, and even shorter survival [5, 6].

Evidence from clinical trials suggests that use of bisphosphonates in adjuvant setting may be effective in the treatment and prevention of CTIBL [7–10].

Furthermore, data from preclinical studies demonstrate that bisphosphonates may have antitumor activity by preventing tumor cell adhesion to bone [11–13], by inducing tumor cell apoptosis [14], by antagonising of growth factors [15], and by antiangiogenic effects [16]. In addition, a recent clinical trial evidenced that use of zoledronic acid in adjuvant treatment of early breast cancer setting may prolong disease free survival when compared with non use [17].

Anyhow, osteonecrosis of the jaw is an uncommon but serious side effect of bisphosphonates use and its incidence vary with length of exposure, being 5% among patients treated for 4–12 months, and rising to 7.7% after treatment for 37–48 months [18]. Therefore, considering the long life expectancy of patient with primary breast cancer, jaw osteonecrosis complication may jeopardize the quality of life of these patients for all their life. Fortunately, dose intensity of bisphosphonates regimens used in the treatment of primary breast cancer, is notably lower than those used for metastatic disease, but no study to date was powered enough to estimate the incidence of this complication in adjuvant breast cancer setting.

We therefore plan a meta-analysis, in order to estimate the cumulative randomized evidence for the overall incidence of bisphosphonates induced jaw osteonecrosis in primary breast cancer setting. Secondary outcome was the subgroup analysis by the use of each bisphosphonate agent.

Materials and method

Search strategy

We conducted a systematic review of all English and non-English articles using MEDLINE, the Cochrane Controlled Trials Register, and ISI Web of Knowledge. We set no year or country restriction. The searching algorithm used in electronic database search was: (early OR adjuvant) AND (breast OR mammary) AND (tumor OR malign* OR carcinom* OR cancer) AND (biphosphonates OR bisphosphonates OR clodronate OR pamidronate OR zoledronic acid OR ibandronate). The latest search was done on January, 2009.

The reference lists of all studies included in the meta-analysis were examined for other relevant articles missed by the electronic searches. Abstracts from scientific meetings of the last few years were electronically searched (American Society of Clinical Oncology annual Meeting, San Antonio Breast Cancer Symposium, the European Cancer Conference).

Study selection

Eligibility and exclusion criteria were prespecified. We collected all randomized controlled trials which investigated the use of bisphosphonates in breast cancer patients in adjuvant setting, with a control group receiving no treatment or placebo. From those trials, we included only trials which clearly stated the number of patients with osteonecrosis of the jaw either in published article or meeting abstract. In any other case, we contacted authors of the original trials. Trials which met the above criteria were eligible with no restriction in sample size, in type of bisphosphonate and in any dosage that was used. Non-randomized studies were excluded.

Whenever multiple reports pertained to overlapping groups of patients, we retained only the report with the longest follow-up (the largest number of events) for the meta-analysis calculations to avoid duplication of information. The rarity of the events rendered a survival/longitudinal analysis impractical.

Data extraction

We recorded the following information about each eligible trial: authors' names, journal and year of publication, country of origin, inclusive dates of patient enrollment, number of centers involved, and study design items (including whether there was a description of the mode of randomization, allocation concealment, number of withdrawals per arm, blinding, and whether any planned or unplanned interim analyses had been performed). We recorded the following items for both arms of each eligible trial: the number of patients randomly assigned to treatment and analyzed per arm, the baseline characteristics of the patients, the type, the dose and duration of bisphosphonate therapy, and any additional breast cancer treatment given in both arms.

Outcomes

Primary outcome of our study was to estimate and compare the incidence of patients with osteonecrosis of the jaw in patients with breast cancer receiving adjuvant bisphosphonates compared with those without adjuvant bisphosphonates.

Secondary outcome was the subgroup analysis of primary outcome according to the kind of bisphosphonate agent used.

Data extraction was conducted independently by two authors (A.V. and M.D.), and consensus was achieved for all data. In case consensus was not achieved a third investigator (N.P.P.) revised the data to reach consensus.

Statistical analysis

The number of patients with osteonecrosis of the jaw in treated and control groups were retrieved from each primary study and 2×2 tables were constructed. Because of the large number of empty cells found and the fact that the control arm had a total of one event, this problem presents itself as extremely sparse. The effect of such dataset is to render the effect of any kind of continuity correction or in general any compensation for the failure of the various approximations (e.g., normality assumption) used to compute estimates and variances relatively large.

We thereafter performed a meta-analytical approach for rare events. Sweeting approach was used for the analysis of sparse data [19]. We discarded inverse variance methods and fixed effect simple Bayesian methods, since they are very likely to be biased, unstable or both for this type of data [19]. Since the studies analyzed were very well balanced, Mantel-Haenszel (M-H) pooled odds ratio using a small continuity correction and Peto's should be the least biased, and were therefore used in the analyses [19–21]. Multiple approaches were used to provide a sensitivity analysis, i.e., to give a better idea of how the results depend upon the estimation method chosen. Q statistic was used to evaluate test heterogeneity.

Results

A flow chart indicating the identification of RCTs for inclusion in the meta-analysis is reported in Fig. 1. We identified 21 different trials that were potentially eligible for our study [7–10, 17, 22–37]. Of these trials, six were excluded since data regarding the osteonecrosis of the jaw could not be retrieved. Finally, 15 trials were included in the meta-analysis [7, 8, 10, 17, 22–32].

A total of 10,694 randomized women were included, of whom 5,312 received bisphosphonates and 5,382 received either placebo or no treatment.

Trials characteristics

Table 1 presents the characteristics of the 15 trials that met our eligibility criteria. Nine studies (7,990 patients) used the bisphosphonate zoledronic acid [7, 8, 17, 22, 24–26, 28, 32], two trials (1,351 patients) used clodronate [29, 31], two trials (350 patients) used risedronate [23, 27], one pamidronate (953 patients) [30] and one ibandronate (50 patients) [10].

Four of the trials were double-blinded [10, 23, 27, 31]. Randomization model, allocation concealment, and withdrawal description were evaluated in only eight eligible trials

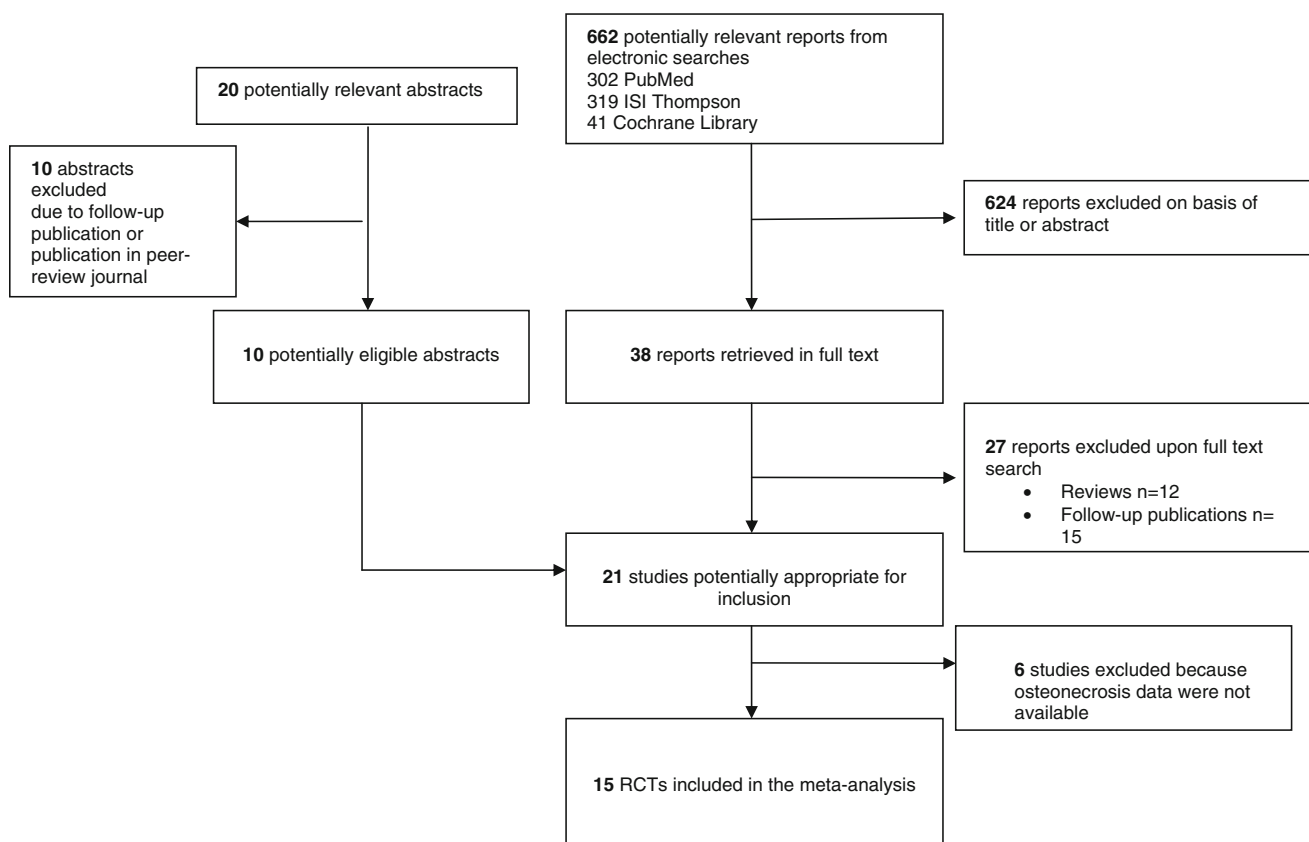


Fig. 1 Flowchart diagram of study selection

Table 1 Characteristics of eligible trials

Author (Study) [ref]	Year	Intervention	Dosage of treatment	Duration (yr)	Number of patients	Follow-up (mo)
Brufsky A (Z-FAST) [7]	2007	Upfront zoledronic acid	4 mg IV every 6 months	5	300	36
		Delayed zoledronic acid			300	
De Boer R (ZO-FAST) [8]	2007	Upfront zoledronic acid	4 mg IV every 6 months	5	532	24
		Delayed zoledronic acid			533	
Lester JE (ARIBON) [10]	2008	Ibandronate	150 mg orally monthly	2	25	24
		Placebo			25	
Gnant M (ABCSG-12) [17]	2009	Zoledronic acid	4 mg IV every 6 months	3	873	47.8
		No treatment			871	
Mincey BA (N03CC) [22]	2008	Zoledronic acid	4 mg IV every 6 months	5	197	12
		No treatment			198	
Van Poznak C (SABRE) [23]	2008	Risedronate	35 mg/week orally	2	65	24
		Placebo			73	
Schenk N (EZO-FAST) [24]	2007	Upfront zoledronic acid	4 mg IV every 6 months	5	252	12
		Delayed zoledronic acid			270	
Shapiro CL (CALGB-79809) [25]	2008	Zoledronic acid	4 mg IV every 3 months	NA	81	12
		No treatment			85	
Hershman DL et al. [26]	2008	Zoledronic acid	4 mg every 6 months	1	50	12
		Placebo			53	
Hines SL (N02C1) [27]	2008	Risedronate	35 mg weekly	1	106	12
		Placebo			106	
Tevaarwerk A et al. [28]	2007	Zoledronic acid	4 mg IV every 12 weeks	1	26	12
		No treatment			23	
Saarto T [29]	2004	Clodronate	1,600 mg orally daily	3	139	120
		Placebo			143	
Kristensen B [30]	2008	Pamidronate	150 mg orally twice daily	4	460	NA
		No treatment			493	
Powles T et al. [31]	2006	Clodronate	1,600 mg orally daily	2	530	66
		Placebo			539	
Coleman R (AZURE) [32]	2006	Zoledronic acid	4 mg IV monthly for 6 months, then every 3 months for 8 doses and then every 6 months for 5 doses	5	1,681	Within 6 months from randomization
					1,678	
					No treatment	

ref Reference, yr year, No number, mo months, IV intravenous, NA not assessable

published in full text. Two trials [26, 31] described in detail the mode of randomization and the mode of allocation concealment. Withdrawals were described in detail in all eight trials published in full text [7, 8, 10, 17, 26, 29–31].

Descriptive results

Overall, osteonecrosis of the jaw was a rare event, occurring in 13 (0.24%) of the 5,312 patients receiving bisphosphonates, and in one of the 5,382 patients in the control group.

All the 13 events of osteonecrosis of the jaw reported among bisphosphonates arms occur in patients undergoing treatment with zoledronic acid (13/3,987, 0.33%).

No events of osteonecrosis of the jaw were reported among patients randomized to receive clodronate ($n = 669$), pamidronate ($n = 460$), risedronate ($n = 171$), and ibandronate ($n = 25$).

Due to the absence of events among patients randomized to receive treatment other than zoledronic acid, these studies were excluded from analysis since they provide no information concerning the odds ratio of developing

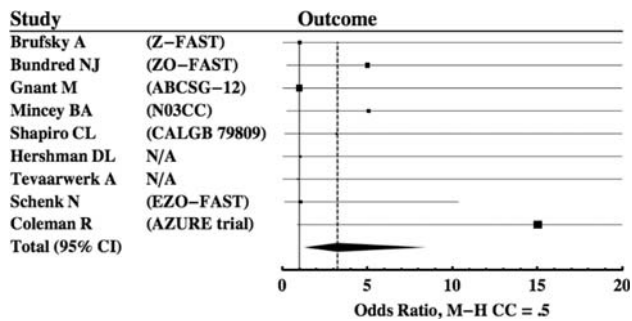


Fig. 2 Meta-analysis plots comparing the risk of osteonecrosis of the jaw between zoledronic acid and control group. Mantel-Haenszel (M-H) statistics. *Squares* represent odds ratios (ORs) and size of *squares* is proportional to the size of the trials. *Error bars* represent 95% confidence intervals (CIs). Values higher than one indicate that use of zoledronic acid increases the rate of osteonecrosis of the jaw. ORs and their CIs are computed using a continuity correction of .5—see text. Forrest Plot is truncated at OR = 20

Table 2 Sensitivity analysis

Method	Estimate	CI	<i>Q</i>	Chi ² for <i>Q</i>
M-H, CC = 0	13.6	1.74–105	NA	NA
M-H, CC = .5	3.23	1.23–8.47	2.99	.96
M-H, IOA CC = 1	12.5	1.74–89.9	3.21	.96
M-H, NN, CC = .5	4.50	1.42–14.6	1.90	.86
M-H, NN, CC = .01	12.96	1.75–96.2	3.20	.67
M-H, NN, EC, CC = .1	9.37	1.66–52.8	2.90	.71
Peto, CC = 0	5.64	1.97–16.1	NA	NA

See Sweeting et al. [19] for details about the methods

Q statistic, *CC* continuity correction, *M-H* Mantel-Haenszel, *IOA* inverse of opposite arm weight, *NN* no null studies (with no events), *EC* empirical correction

osteonecrosis of the jaw. All they can tell us is that it is a rare or relatively rare event for both arms.

Meta-analysis

Figure 2 shows the pooled data from the nine randomized controlled trials evaluating the number of osteonecrosis of the jaw in breast cancer patients receiving adjuvant treatment with zoledronic acid versus no use.

If the cells of the studies are all summed together as if they were a single trial, the difference in risk is statistically significant with a CI of (.1–.5%), and the risk estimated for the control arm is .02.

When meta-analysis was performed, using M-H pooled odds ratio with a continuity correction of .5, we found that treatment with zoledronic acid was significantly associated to the occurrence of osteonecrosis of the jaw (OR = 3.23, 95% CI = 1.7–8) compared with no use. This means that in the worst case the probability of ONJ occurrence in

treated patients may have eight times the odds of the event to happen.

Multi-tests sensitivity analyses are reported in Table 2. No significant between-study heterogeneity was observed.

Discussion

Our study indicates that the occurrence of osteonecrosis of the jaw during the adjuvant treatment of breast cancer is a rare event. Indeed data from pooled-randomized evidences indicated that it occurred in only 13 of the 5,312 patients receiving bisphosphonates (0.24%). The observed incidence of the phenomenon was up to 20 times lower than those observed in patient treated for metastatic disease or multiple myeloma [18]. This could be explained by the dose intensity of bisphosphonates regimens used in the treatment of primary breast cancer, that are remarkably lower than those used in metastatic disease.

Furthermore, the occurrence of osteonecrosis of the jaw appeared to be lower among patient receiving bisphosphonates different than zoledronic acid since no event was reported. This might be largely attributed to the low number of patients included in investigational arms, especially if pamidronate ($n = 460$), risedronate ($n = 171$), and ibandronate ($n = 25$) are considered (the number of expected events, considering the estimated incidence of .24%, is about one or smaller for these trials and still smaller than two even for clodronate). Another explanation could be found in the greater potency of zoledronic acid as demonstrated by its larger reductions in collagen type-I degradation products (*N*-telopeptide) [38]. However, the data currently available do not allow us to address this question.

Our meta-analysis provides substantial evidence that use of zoledronic acid in the adjuvant setting among women with breast cancer statistically increase the number of events of osteonecrosis of the jaw. Even with this increment, the phenomenon remains rare with a maximum estimated risk (upper bound of risk CI) of .5%.

Several limitations do exist in our meta-analysis. None of the eligible trials was prospectively designed or was powered enough to measure the risk of osteonecrosis of the jaw as primary outcome. Analyses were based on rare events, thereafter sensitivity analysis was needed to confirm the results. Finally, we excluded six trials due to lack of data on jaw osteonecrosis events. Nonetheless, these studies were unlikely to change significantly our results, since they were either small or with short follow-up.

Allowing for these caveats, our study provides substantial evidence suggesting that osteonecrosis of the jaw is a rare event in breast cancer patient treated with adjuvant use of bisphosphonates. Despite use of zoledronic acid is

associated to a higher number of events compared with non use, the overall occurrence of the phenomenon continue to be low. Thereafter, at current dosage, adjuvant use of bisphosphonates is relatively safe in adjuvant treatment of breast cancer, even if the risks are not entirely negligible.

Author contributions Antonis Valachis, Davide Mauri and Nikolaos P. Polyzos, Ilias P. Polyzos participated in the design of the study; Antonis Valachis and Davide Mauri participated in data extraction;

Lorenzo L. Pesce performed the statistical analyses; Lorenzo Pesce, Davide Mauri, Konstantinos Kamposioras, and Nikolaos P. Polyzos interpreted the results.

Davide Mauri, Antonis Valachis, and Ilias P. Polyzos wrote the manuscript.

Nikolaos P. Polyzos and Konstantinos Kamposioras review and commented final manuscript.

Conflict of interest statement There is no conflict of interest.

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