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Bisphosphonate-related osteonecrosis of the jaw in randomized clinical trials

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One should read with great interest the paper of Mauri et al. [1] in the Online First section of Breast Cancer Research and Treatment. The paper presents a meta-analysis of the existing randomized clinical trials (RCTs) for the overall incidence of bisphosphonates-induced jaw osteonecrosis (ONJ) in adjuvant treatment of breast cancer. This is a well-conducted meta-analysis, which is definitely going to be cited several times in the near future.

However, important information may be missing from the discussion. In their introduction, Mauri et al. characterize ONJ uncommon, with a reported incidence of 5–7.7%. In their discussion, the authors report that ONJ during the adjuvant treatment of breast cancer is a rare event with an incidence of 0.24%. The authors attribute this difference in incidence to the dose intensity of bisphosphonates regimens used in the treatment of primary breast cancer. The low ONJ incidence reported by this meta-analysis of RCTs could be attributable to the following:

1. The trials had increased dosing intervals, as the authors report.
2. The RCT protocols may have failed to detect cases of ONJ. During December 2008, Edwards et al. [2] published a comprehensive review regarding the pharmacovigilance and reporting of ONJ related to bisphosphonates. Edwards et al. [2] point out that the first cases of ONJ have been reported only 9 months after zoledronate FDA approval for the treatment of cancer-related skeletal events. Their data reported the incidence of ONJ to be 0.016% for pamidronate and 0.116% for zoledronate when data from manufacturer-sponsored clinical

trials were utilized. On the contrary, the incidence of ONJ was reported to be as high as 7.7% when prospective case series at cancer centers were taken into consideration. They concluded that prospective epidemiological efforts, such as those made by academic researchers, are probably the most reliable source of information regarding ONJ incidence [2]. Thus, Mauri et al. [1] may report on a low incidence of ONJ in those patients receiving bisphosphonates as adjuvant treatment of breast cancer, simply because the RCTs at study have not been able to detect ONJ cases, similarly to the previous experience with RCTs and ONJ [2].

3. Mauri et al. [1] do not comment on whether the included RCT protocols integrated a clinical dental evaluation. It appears that integration of clinical dental evaluation in the study protocol is critical to accurately detect ONJ cases, while scrutinizing dental records may be insufficient [3]. This argument further suggests that RCTs may have failed in detecting every ONJ case. Mauri et al. [1] discuss that the eligible trials were neither prospectively designed nor adequately powered to measure the risk of ONJ as a primary outcome.
4. Reading Table 1 [1], one can easily understand that over half the patients included in the meta-analysis by Mauri et al. received only up to five bisphosphonate doses. Since bisphosphonates are known to have long bone clearance times [4], increasing bisphosphonate accumulation in the skeleton with time may lead to ONJ development. Incidentally, the majority of ONJ cases are reported to occur after administration of over six bisphosphonate doses [5].

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Mauri et al. [1] discuss that the occurrence of ONJ appeared to be lower among patients receiving

bisphosphonates different than zoledronate. It is noteworthy that the authors managed through a well-conducted meta-analysis to detect this outcome in a population with a very low incidence rate. In a recently published prospective epidemiological study from Northern Greece, in which ONJ is the primary outcome, the incidence of ONJ is reported to be elevated in those patients receiving zoledronate when compared to patients receiving pamidronate and especially ibandronate [5]. The authors concluded that future RCTs should verify this outcome [5], and the meta-analysis by Mauri et al. supports this argument.

Administered at the doses reported by Mauri et al. [1], bisphosphonates may be relatively safe in adjuvant treatment of breast cancer. Future, prospective epidemiological efforts from academic researchers will support or reject the latter argument. Until then, caution should be paid to the preventive measures suggested by various organizations [4] for every patient receiving bisphosphonates.

References

- Mauri D, Valachis A, Polyzos IP, Polyzos NP, Kamposioras K, Pesce LL (2009) Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a meta-analysis. *Breast Cancer Res Treat*. doi:[10.1007/s10549-009-0432-z](https://doi.org/10.1007/s10549-009-0432-z)
- Edwards BJ, Gounder M, McKoy JM, Boyd I, Farrugia M, Migliorati C, Marx R, Ruggiero S, Dimopoulos M, Raisch DW, Singhal S, Carson K, Obadina E, Trifilio S, West D, Mehta J, Bennett CL (2008) Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. *Lancet Oncol* 9(12):1166–1172
- Walter C, Al-Nawas B, Grotz KA, Thomas C, Thuroff JW, Zinser V, Gamm H, Beck J, Wagner W (2008) Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. *Eur Urol* 54(5):1066–1072
- Kyrgidis A, Triaridis S, Vahtsevanos K, Antoniadis K (2009) Osteonecrosis of the jaw and bisphosphonate use in breast cancer patients. *Expert Review of Anticancer Therapy*. doi:[10.1586/ERA.09.74](https://doi.org/10.1586/ERA.09.74)
- Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis C, Boukovinas I, Koloutsos G, Teleioudis Z, Kitikidou K, Paraskevopoulos P, Zervas K, Antoniadis K (2009) Bisphosphonate related osteonecrosis of the jaws: a longitudinal cohort study of risk factors in cancer patients. *J Clin Oncol*. doi:[10.1200/JCO.2009.21.9584](https://doi.org/10.1200/JCO.2009.21.9584)