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Osteonecrosis of the jaw and bevacizumab therapy

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Osteonecrosis of the jaw (ONJ) initially came to attention through case reporting. It appears to occur in 1–18% of patients with metastatic bone disease treated with bisphosphonate therapy [1,2] and is seen less frequently in patients treated with bisphosphonates for osteoporosis or Paget's Disease of Bone [3]. ONJ is seen uncommonly in patients with early stage breast cancer treated with bisphosphonates as was demonstrated in the recent metaanalysis of breast cancer adjuvant bisphosphonate studies where the incidence of ONJ was 0.24% [4]. ONJ may be uncommon, but it is clinically significant to the patient, medical, and dental communities [5]. Risk factors for developing ONJ appear to be bisphosphonate exposure, cancer and its therapies (possibly including antiangiogenesis therapies), bone invasive dental procedures, lifestyle, and behaviors [6,7]. There are many potential mechanisms of ONJ (Table 1). The etiology of ONJ is presently unknown.

Osteonecrosis of the jaw appears to occur most frequently in patients cancer treated with high potency nitrogen-containing bisphosphonates [6], and many of the leading hypotheses for the mechanism behind ONJ relate to potential affects of the bisphosphonates. The main effect of bisphosphonate therapy is osteoclast inhibition, and over suppression of bone metabolism has been proposed as a mechanism involved in the development of ONJ [6]. There are evolving data demonstrating that the bisphosphonates may have additional affects including altering cell migration, invasion, adhesion, apoptosis, and synergizing with antitumor cytotoxic drugs, as well as decreasing angiogenesis [8]. The antiangiogenic effects of bisphosphonates are of particular interest in regard to ONJ due to the importance of neo-vascularization in wound healing. Dental extraction is a risk factor for ONJ, and healing after bone invasive surgeries or mucosal trauma requires revascularization. It is possible that interrupting the normal healing process increases the risk for ONJ. In line with the hypothesis that ONJ is of vascular origin is that avascular necrosis of the hip and osteoradionecrosis are both conditions of necrotic bone associated with vascular disruption [9]. Angiogenesis and ONJ have been linked by the case reports of ONJ occurring in patients treated with antitumor therapies targeting vascular endothelial growth factor. Guarneri et al. [10] provide an excellent presentation of the ONJ case reports involving patients treated with bevacizumab or sunitinib and the rationale for performing their analysis of bevacizumab in patients with locally recurrent or metastatic breast cancer (LR/MBC).

Guarneri et al. investigated the databases of three clinical trials, AVADO, RIBBON-1, and ATHENA, where bevacizumab was studied in LR/MBC. Analysis was performed comparing the incidence of ONJ in patients receiving bevacizumab versus placebo and in patients with and without bisphosphonate exposure. A thorough analysis was performed of the data available; however, there are limitations to the research. As acknowledged by the authors, the case report forms for these three clinical trials did not include detailed assessment of oral health and were limited to the NCI CTCAE 3.0 toxicity assessments. The limitations of assessing ONJ using data from pharmacovigilance reporting and the contrasts between

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pharmacovigilance data and prospective epidemiologic research have been highlighted in the recent literature [11,12]. Rare toxicities are likely to be underreported using techniques similar to those used by Guarneri et al., given that the clinical trials analyzed were not specifically designed to address these events.

The data from the review of ONJ adverse events in the 3,560 patients treated with bevacizumab in AVADO, RIBBON-1 and ATHENA are reassuring in that the incidence of ONJ does not appear to be greater then expected for the population of patients with MBC receiving systemic antitumor therapy. ONJ in this population is often estimated at 0.8–12% [13] and a recent longitudinal cohort study in patients with breast cancer demonstrated the crude incidence of ONJ to be 3.1% [14]. The overall incidence of ONJ in patients treated with bevacizumab in AVADO, RIBBON-1 and ATHENA was 0.3–0.4% [10]. In those patients receiving bevacizumab and bisphosphonate therapy the incidence was slightly higher at 0.9–2.4%. The incidence of ONJ was not statistically different in patients receiving bevacizumab and chemotherapy for LR/MBC compared to those receiving chemotherapy alone, with or without concurrent bisphosphonate therapy. These data are consistent with the Memorial Sloan-Kettering Cancer Center retrospective analysis of 1,711 patients with cancer where the incidence of ONJ was 0% in patients treated with bevacizumab without bisphosphonate and 2% in those treated with bevacizumab and bisphosphonate [15]. This frequency of ONJ is consistent with recent reports from two Phase III randomized, placebo controlled, clinical trials comparing zoledronic acid to denosumab in the management of metastatic bone disease where the incidence of ONJ was 1–2% and with both zoledronic acid and denosumab [16,17]. The true incidence of ONJ is unknown.

To prospectively define the incidence of ONJ in patient with metastatic bone disease receiving zoledronic acid, the Southwest Oncology Group registry study S0702, NCT00874211, will assess the cumulative incidence of ONJ at 3 years. Secondary objectives of S0702 are to prospectively gather data on the clinical presentation, natural history, and risk factors for developing ONJ, as well as define patient-related outcomes and explore potential mechanisms of ONJ through the development of a specimen and imaging bank for correlative studies. The Cancer and Leukemia Group B study of patients with metastatic bone disease receiving zoledronic acid dosed either monthly or every 3 months will also generate data on ONJ (CALGB-70604; NCT00869206), along with other studies (NCT00434447, NCT00601068, NCT00869206). Preclinical studies are ongoing to aid in defining the pathogenesis of ONJ. These include investigating angiogenesis and its relationship to ONJ by assessing the vasculature in the oral mucosa of a rat model treated with zoledronic acid in the setting of tooth extraction and in assessing alterations of vasculature reconstitution in the setting of suppression of angiogenesis and hypoxia-related gene expression [18].

Osteonecrosis of the jaw is an uncommon problem that is not well understood. However, in the past few years the field has progressed, primarily through case reports, epidemiologic studies, and the evolving preclinical models. The data generated by Guarneri et al. are clinically relevant and will aid in ONJ risk assessment in both the medical and dental offices. It is reassuring to see the bevacizumab does not appear to significantly increase the risk of ONJ in patients with LR/MBC treated with chemotherapy, with or without bisphosphonates. However, caution must be exercised until additional data are generated. In caring for patients with metastatic breast cancer, the clinician is faced with the need to manage patients in advance of adequate data and a complete understanding of ONJ. Ongoing clinical and basic science studies will add to the understanding of the mechanism, risks, and therapy for ONJ. In the interim, although disruption of angiogenesis could be a factor in the pathogenesis of ONJ, bevacizumab therapy does not appear to be a strong risk factor in the development of ONJ.

References

1. Reid IR. Osteonecrosis of the jaw—who gets it, and why? Bone 2009;44(1):4–10. [PubMed: 18948230]
2. Aragon-Ching JB, Ning YM, Chen CC, Latham L, Guadagnini JP, Gulley JL, Arlen PM, Wright JJ, Parnes H, Figg WD, Dahut WL. Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. Cancer Investig 2009;27:221–226. [PubMed: 19235596]
3. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling P, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo S-B, Shane E. Bisphosphonate-associated osteonecrosis of the jaw: report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007:1479–1491. [PubMed: 17663640]
4. Mauri D, Valachis A, Polyzos IP, Polyzos NP, Kamposioras K, Pesce LL. Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a metaanalysis. Breast Cancer Res Treat 2009;116:433–439. [PubMed: 19521766]
5. Kolata, G. Drug for bones is newly linked to jaw disease. The New York Times; Jun 2. 2006
6. Almazrooa SA, Woo SB. Bisphosphonate and nonbisphosphonate-associated osteonecrosis of the jaw: a review. J Am Dent Assoc 2009;140(7):864–867. [PubMed: 19571050]
7. Gliklich R, Wilson J. Epidemiology of bisphosphonate-related osteonecrosis of the jaws: the utility of a national registry. J Oral Maxillofac Surg 2009;67(5, Suppl):71–74. [PubMed: 19371817]
8. Winter MC, Holen I, Coleman RE. Exploring the antitumour activity of bisphosphonates in early breast cancer. Cancer Treat Rev Aug;2008 34(5):453–475. [PubMed: 18423992]
9. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. J Oral Maxillofac Surg 2009;67(5, Suppl):61–70. [PubMed: 19371816]
10. Guarneri V, Miles D, Robert N, Diéras V, Glaspy J, Smith I, Thomssen C, Biganzoli L, Taran T, Conte P. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat. 2010 doi:10.1007/s10549-010-0866-3.
11. 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. Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. Lancet Oncol 2008;9(12):1166–1172. [PubMed: 19038763]
12. Kyrgidis A. Bisphosphonate-related osteonecrosis of the jaw in randomized clinical trials. Breast Cancer Res Treat 2010;119:253–254. [PubMed: 19585235]
13. American Association of Oral and Maxillofacial Surgeons. Position paper on bisphosphonate-related osteonecrosis of the jaw. J Oral Maxillofac Surg 2007;65:369–376. [PubMed: 17307580]
14. Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis C, Boukovinas I, Koloutsos G, Teleioudis Z, Kitikidou K, Paraskevopoulos P, Zervas K, Antoniades K. Bisphosphonate related osteonecrosis of the jaws: a longitudinal cohort study of risk factors in cancer patients. J Clin Oncol 2009;27(32):5356–5362. [PubMed: 19805682]
15. McArthur HL, Estilo C, Huryn J, Williams T, Fornier M, Traina TA, Howard J, Hudis CA, Dickler MN. Osteonecrosis of the jaw (ONJ) among intravenous (IV) bisphosphonate- and/or bevacizumab-treated patients (pts) at Memorial Sloan-Kettering Cancer Center (MSKCC). J Clin Oncol 2008;26:9588.
16. Stopeck A, Body JJ, Fujiwara Y, Lipton A, Steger GG, Viniegra M, Fan M, Braun A, Dansey R, Jun S. Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase 3 study. Eur J Cancer Suppl 2009;7(3):2. abstract 2LBA.
17. Henry D, von Moos R, Vadhan-Raj S, Hungria V, Spencer A, Hirsh V, Wang J, Jun S, Yeh H, Dansey R. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Eur J Cancer Suppl 2009;7(3):11. abstract 20LBA.
18. National Institute of Health Research Portfolio Online Reporting Tools. [Accessed 15 Apr 2010]. http://projectreporter.nih.gov/reporter.cfm 1R03DE0196 84-01A1.

19. Van Poznak C. The phenomenon of osteonecrosis of the jaw in patients with metastatic breast cancer. Cancer Investig 2006;24:110–112. [PubMed: 16467002]

Table 1

Potential mechanisms of ONJ [19]

Inhibition of bone remodeling	Compromised bone microenvironment functioning affecting bone remodeling and repair
Vascular	Antiangiogenic affects delaying wound healing and/or affecting micro-infarction in bone and/or soft tissues
Infection and inflammation	Microorganisms of the oral cavity promoting cell death in the bone and/or oral soft tissues
Genetic predisposition	Genetic polymorphisms affecting drug metabolism, excretion, or drug targets within pathways of bone metabolism and/or wound healing
Drug interactions	Drug interactions between chemotherapy and bisphosphonate selectively promoting cell death