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LETTER TO THE EDITOR

Bisphosphonate treatment as a cause of jaw osteonecrosis

Recently, a new complication associated with the use of bisphosphonates has been described: osteonecrosis of the jaw (ONJ). ONJ was initially reported in 36 patients who developed ONJ while receiving pamidronate or zoledronate (Marx, 2003). A total of 85 patients were treated with bisphosphonates for bone metastases in our clinic and four of the 85 patients (4.7%) developed ONJ (Table 1).

These patients were being treated with monthly 4 mg zoledronate when the symptoms of ONJ began. Two patients also initially received monthly 90 mg pamidronate and later switched to zoledronate. The duration of the treatment with bisphosphonates before presentation ranged from 18 to 75 months. ONJ was unilateral and localized to the posterior mandible (case 1, 3 and 4) and maxilla (case 2). All patients presented with jaw pain. In three patients (case 1, 2 and 4) symptoms began following tooth extraction: the average time between the extraction and first evidence of ONJ was 4 months. In these patients ONJ occurred in the sites of non-healing dental extraction. Histopathological examination biopsy specimens confirmed osteonecrosis with no evidence of metastatic disease. Wound cultures grew mixed oral flora and microbiological methods did not reveal any *Actinomyces* colonies in all patients. Treatments with bisphosphonates were discontinued after the confirmation of diagnosis. Initially, all the patients were treated conservatively with antibiotics (amoxicillin or amoxicillin/clavulonate or metronidazole) and clorhexidine mouthwash. Periodic minor debridement was performed in all cases. Case 2 also received hyperbaric oxygen and the patient experienced an improvement. The minimum follow-up after development of ONJ has been 19 months (range, 19–29 months), and all the patients experienced relief of their symptoms.

The true incidence of ONJ related to the use of bisphosphonates is largely unknown. Durie *et al* (2005) performed a Web-based survey in 1203 patients with multiple myeloma (MM) and breast cancer receiving bisphosphonates and found the incidence of ONJ to be 6.8% and 4.4%, respectively. Prolonged duration of such treatment with bisphosphonate increases the risk of ONJ. Bamias *et al* (2005) found that the median time of exposure to bisphosphonates was 39.3 months for patients who developed ONJ, compared with 19 months for patients who did not ($P = 0.001$). The type of bisphosphonates may also play a role in the development of ONJ. In the study of Bamias *et al* (2005), the hazard of developing ONJ was found to be significantly higher in patients who received zoledronate ($P < 0.001$).

The exact mechanism of bisphosphonates-induced ONJ is unknown. Impaired blood supply to the jaw has been frequently implicated in the development of ONJ. The antiangiogenic effects of bisphosphonates, which were demonstrated *in vitro* and in animal studies, may contribute to the interruption of intraosseous circulation and bone blood flow (Migliorati *et al*, 2005, 2006). It has been speculated that dental extraction may be a precipitating factor for the occurrence of ONJ, which was documented in our three patients. According to the results of a recent study reported by Badros *et al* (2006), a patient with MM who has a dental extraction is nine times more likely to develop ONJ after extraction. At the time of onset of ONJ, all the patients were receiving chemotherapy for the treatment of malignant disease in our series. However, the contribution of chemotherapy in the development of ONJ remains unknown. *Actinomyces* colonies were detected in close contact with necrotic bone tissue in some cases. It can be speculated that these organisms may be involved in the chronic and non-healing inflammatory processes.

Management of patients with bisphosphonates-induced ONJ may be difficult. In our patients, we discontinued the bisphosphonates therapy after the diagnosis of ONJ. However, there is no evidence that the discontinuation of the bisphosphonates therapy contributes to improvement of osteonecrosis. Oral ampicillin/clavulonate, amoxicillin/clavulonate and metronidazole and 0.12% clorohexidine mouth rinses can control bone infection and pain. Marx *et al* (2005) did not recommend extensive surgical debridement in the treatment of ONJ because it may lead to further exposed bone, worsening of symptoms and an increase in the risk for pathological jaw fracture.

We think that a close communication and collaboration between medical oncologists and dental professionals may lead to the prevention and early detection of ONJ. In our centre, patients are now referred to an experienced dentist for oral examination before initiating bisphosphonates therapy. Regular dental examination is also performed during the therapy.

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Table 1 Patient's characteristics

Case	*Age/gender*	*Primary malignancy*	*Site of necrosis*	*Treatment duration (months)*	*Presentation*	*Treatment*
1	57/Female	Multiple myeloma	Mandible	Zoledronate 28	Site of previous tooth extraction	Debridement, antibiotics
2	56/Male	Multiple myeloma	Maxilla	Pamidronate (59) and zoledronate (16)	Site of previous tooth extraction	Debridement, hyperbaric oxygen,
3	35/Female	Breast cancer	Mandible	Zoledronate (18)	Spontaneous	Debridement, antibiotics
4	45/Female	Breast cancer	Mandible	Pamidronate (35) and zoledronate (33)	Site of previous tooth extraction	Debridement, antibiotics

References

Badros A, Weikel D, Salama A *et al*. (2006). Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* **24:** 945–952.

Bamias A, Kastritis E, Bamia C *et al*. (2005). Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* **23:** 8580–8587.

Durie BGM, Katz M, Crowley J (2005). Osteonecrosis of the jaw and bisphosphonates. *N Eng J Med* **353:** 99.

Marx RE (2003). Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* **61:** 1115–1117.

Marx RE, Sawatari Y, Fortin M, Broumand V (2005). Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* **63:** 1567–1575.

Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB (2005). Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. *J Am Dent Assoc* **136:** 1658–1668.

Migliorati CA, Siegel MA, Elting L, Schuster M (2006). Oral osteonecrosis and other long-term complications of bisphosphonate therapy. *Lancet* **7:** 508–514.