

LETTER

Bisphosphonate-Related Osteonecrosis of the Jaw in Cancer Patients and Hyperbaric Oxygen Therapy

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Dear Sir:

In the March issue of JOP. Journal of the Pancreas, Smith *et al.* provide the first report of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in a patient with pancreatic adenocarcinoma [1]. As to the greater recognition of the relationship between the use of bisphosphonates and oral osteonecrosis, new cases with different malignancies have been diagnosed as suffering from BRONJ. The case presented by Smith *et al.* reminds us to be alert against this serious complication of bisphosphonates. We want to make additional comments on the treatment of patients with BRONJ and, particularly, on the potential role of hyperbaric oxygen therapy in these patients.

Bisphosphonates are potent inhibitors of osteoclastic bone resorption and one of the most frequently prescribed drugs. They are widely used in the treatment of osteoporosis, skeletal lesions of multiple myeloma and bone metastasis of solid tumors. After the paper by Marx *et al.* which described the first cases of BRONJ, awareness increased in the medical community [2]. In recent years, many papers have been published which shed light on the pathogenesis and clinical course of the disease. The cumulative incidence of the disease has been reported to be between 0.8 to 12% in patients using intravenous bisphosphonates [3]. However, an increase in the reported incidence of BRONJ is expected with a wider recognition of the disease and

the close follow-up of the patients using bisphosphonates. Given the widespread use of bisphosphonates in clinical practice, even a very low incidence of oral osteonecrosis in bisphosphonate users should be considered a public emergency. According to the diagnostic criteria defined by the American Association of Oral and Maxillofacial Surgeons, BRONJ is diagnosed in patients with a history of current or previous treatment with a bisphosphonate, with an exposed bone in the maxillofacial region which has continued for more than eight weeks, and with no history of radiation therapy to the jaw [3].

There is no definitive treatment for BRONJ at this time. The management of BRONJ remains an important clinical challenge in cancer patients and requires a multidisciplinary approach involving dentists, medical oncologists, oral and maxillofacial surgeons and others, if necessary [4]. Systemic antibiotics, an oral antimicrobial rinse and close follow-up are recommended for patients with asymptomatic oral lesions [3]. Since bisphosphonates remain in the bone for very long periods and some patients cannot survive without bisphosphonates, cessation of bisphosphonate treatment is not carried out in every patient. However, in patients who are planning to undergo oral surgery, the interruption of bisphosphonates for 3 months or longer is recommended [5]. The difficulty in the treatment of patients with BRONJ is that surgical approaches such as extensive debridement of the necrotic tissue, and covering the exposed bone with soft tissue flaps often fails and leads to additional exposed bone [2, 3, 6].

Hyperbaric oxygen therapy is a way of treatment which increases the oxygen content of the blood and, consequently, the amount of oxygen delivered to tissues. Hyperbaric oxygen therapy has been used in the treatment and prevention of osteoradionecrosis of the jaw for more than 30 years [7]. Adjunctive hyperbaric oxygen therapy has also been suggested in the treatment of BRONJ. A number of papers have

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Abbreviations BRONJ: bisphosphonate-related osteonecrosis of the jaw

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been published which describe the successful use of hyperbaric oxygen therapy in the management of BRONJ [8, 9, 10, 11]. The proposed rationale behind the beneficial effects of hyperbaric oxygen therapy in BRONJ is increased wound healing, reduction of edema and inflammation, stem cell mobilization and moderation of the suppression of bone turnover by bisphosphonates [12]. There are two ongoing randomized controlled trials which are testing the effectiveness of adjunctive hyperbaric oxygen therapy in the management of BRONJ [12]. Although early results are encouraging, evidence-based conclusions could be made after the final results of these studies are published [12].

It is a concern for some physicians that hyperbaric oxygen may have a cancer-promoting effect or may lead to metastatic growth [13]. However, Feldmeier *et al.* reviewed all available data and concluded that there is no evidence to support the idea that hyperbaric oxygen therapy may enhance tumor growth or metastases in cancer patients [14].

Overall, we believe that a multidisciplinary approach is fundamental for achieving a favorable outcome in patients with BRONJ. As everybody knows, an ounce of prevention is worth a pound of cure; patients who are planning to receive bisphosphonate treatment should consult with a dentist in order to address potential problems before starting bisphosphonate treatment. Currently, there is no definitive treatment of BRONJ. Hyperbaric oxygen therapy may hold some promise; however, its role in the management of BRONJ should be further confirmed in randomized controlled trials.

Conflict of interest The authors have no potential conflicts of interest

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