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ORIGINAL ARTICLE

Retrospective analysis of 27 cases of bisphosphonate-related osteonecrosis of the jaw treated surgically or nonsurgically

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Abstract *Background/purpose:* Bisphosphonate-related osteonecrosis of the jaw (BRONJ) appears to be refractory to conventional treatment approaches. We offer our experiences and treatment strategies regarding the successful resolution of BRONJ.
Materials and methods: Thirty sites of BRONJ in 27 patients were clinicopathologically proven. The mandible was more commonly affected than the maxilla (67% versus 33%). The appearance of 23 (77%) BRONJ sites was preceded by a tooth extraction, dental infection, or oral trauma, and the remaining sites occurred spontaneously. There was a female predilection with a ratio of 3.5:1, and 22 (81%) patients were oral bisphosphonate (BPh) users. The treatment strategies included: (1) nonsurgical treatment using antimicrobial rinses; (2) removal of necrotic bone followed by insertion of Gelfoam impregnated with tetracycline; or (3) filling with alloplastic bone substitute plus tetracycline as the procedure of guided bone regeneration (GBR); and (4) radical resection of all necrotic bone and immediate reconstruction.
Results: In 25 (93%) patients with 27 (90%) sites, BRONJ was successfully treated. The three treatment failures were all in two intravenous BPh users. There was no significant dependence of the treatment results on the severity of BRONJ. However, there was a significant dependence of the treatment result on the route of BPh administration.

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Conclusion: Our study demonstrates a high success rate of conservative and surgical treatment of BRONJ. This is the first reported use of GBR to successfully treat oral BPh-related osteonecrosis of the jaw. Irrigation with antimicrobial rinses may result in pain reduction, and regression or even resolution of BRONJ.

Introduction

Bisphosphonates (BPhs) have been widely prescribed for the treatment of diseases characterized by intense bone resorption such as osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, multiple myeloma, and carcinoma metastasizing to the skeleton. These drugs have also been associated with a serious side effect, osteonecrosis of the jaw.[1,2] Because of a greater awareness of BPh-related osteonecrosis of the jaw (BRONJ) among physicians, oncologists, and the dental community, the number of reported cases has increased dramatically since the first report by Marx in 2003.[1–3] Patients with skeletal events associated with metastatic neoplasms or multiple myeloma who are receiving intravenous (i.v.) BPh have represented 94% of published cases to date.[1]

It is important to make a distinction between osteonecrosis of the jaw induced by oral BPh versus that induced by i.v. BPh. Oral BPh-induced osteonecrosis appears to be less frequent, less severe, more responsive to discontinuation of the drug, and curable with surgical debridement.[1] However, the risk and severity of BRONJ are likely to increase with a longer duration of oral BPh therapy (i.e., 3 years or more).[4]

The pathogenesis of BRONJ can be summarized as follows: BPhs are powerful inhibitors of osteoclastic activity and promoters of osteoclast apoptosis. Therefore, they cause decreased bone resorption and bone formation through the uncoupling of the functional osteoclast/osteoblast balance. The antiangiogenic properties of BPhs cause reduced osseous vascularity, which contributes to impaired physiologic remodeling and wound healing in the jawbone. Furthermore, BPhs have a strong affinity for hydroxyapatite crystals and are incorporated into the skeleton, without degradation, persisting in the skeleton as active drugs. The estimated half-life for alendronate is up to 12 years, and for zoledronate up to 10 years.[1,4–7] As a result, the bone turnover is oversuppressed, and self-healing capacity is reduced.

Based on current understandings in the field, BRONJ appears to be limited to the jaws. This is conceivable because the jawbones are sites of high physiologic bone turnover and increased circulation, which lead to high concentrations of BPhs within the bone. Furthermore, there is potential communication between the oral flora and the bone through the teeth and periodontal tissues, and the thin mucosa covering the jawbones. It has been observed that lesions are more common in the mandible than the maxilla (a 2:1 ratio), and 60% of the cases are preceded by a dental surgical procedure.[1,4] However, a number of edentulous or dentate patients have developed BRONJ spontaneously.[4,8] The phenomenon of spontaneous appearance of BRONJ may be explained by the fact that, once "metabolically damaged" by the BPh therapy, the jawbones remain susceptible even to minor causative factors such as injuries of the mucosa, occlusion, or prosthetic trauma.[7] In addition to local and drug-related risk factors, a variety of systemic risk factors such as advanced age, radiation, smoking, alcohol abuse, diabetes, glucocorticoid treatment, and immunosuppressive chemotherapy must also be considered as possible cofactors.[1,4]

BRONJ remains a difficult condition to treat. There are few reported studies of the successful treatment of BRONJ, and the most effective management of BRONJ remains controversial. Numerous retrospective studies have reported that pharmacologic and surgical therapies are not able to cure this complication. There are no data that favor one therapeutic choice over another, and surgery appears to worsen the course of the disease.[7,9] We therefore present a retrospective case series study of BRONJ in southern Taiwan treated with varied treatment strategies.

Materials and methods

Twenty-seven patients (21 females and 6 males, aged from 59 years to 99 years, with a mean age 76 years) with a total of 30 sites of BRONJ (20 in the mandible and 10 in the maxilla) diagnosed at the Oral Pathology and Family Dentistry Department of Kaohsiung Chang Gung Memorial Hospital during the study period were all included in a retrospective case series analysis. The observation period for the study started in February 2008 and ended in February 2012. Operations were performed from February 2008 to December 2010. Median follow-up was 82 weeks (ranging from 48 weeks to 126 weeks). Patients' characteristics and treatment results are listed in Tables 1 and 2. Depending on the severity of the BRONJ, every site was grouped according to the clinical staging system published by Wilde et al (Table 3).[10] All patients were informed that the therapy should be regarded as an individual attempt at healing, and consented. The following treatment procedure was applied in all patients with consideration of the stage and severity of BRONJ and the patient's general health status: (1) conservative treatment with a daily antimicrobial rinse, using 0.1% or 0.2% chlorhexidine, was started after the first appointment for all patients. Patients and their families were taught how to perform the oral irrigation by themselves if patients could not visit the clinic every week. In patients with symptoms of acute infection, oral antibiotics (amoxicillin or clindamycin in cases of allergy to beta-lactam antibiotics) were