

Experience with the treatment of bisphosphonate-related osteonecrosis of the jaw

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Aim. This article covers the authors' experience with the treatment of bisphosphonate-related osteonecrosis of the jaw in 11 individuals.

Methods. A retrospective study of patients diagnosed and treated for bisphosphonate-related osteonecrosis of the jaw at the Department of Dentistry, University Hospital Hradec Králové during the period January 2006 to October 2012. The treatment protocol consisted of antimicrobial mouth rinses and systemic antibiotic administration according to the stage of the disease. Additional surgical debridement and sequestrectomy in combination with antimicrobial therapy was performed in two cases.

Results. Complete healing was achieved in six patients. In two cases, satisfactory healing was noted. Stage of the disease was lowered and only a small area of asymptomatic necrotic bone of up to five mm in diameter persisted. Two patients developed a stable disease without progression. In one patient, the disease progressed to the third stage with osteonecrosis involving all quadrants of both jaws.

Conclusion. From these data it was concluded that conservative approach in the treatment of bisphosphonate-related osteonecrosis of the jaw led to symptom regression but was not curative. Surgical intervention, however, bears the risk of further progression of the osteonecrosis and must be carefully planned with respect to the patient's general health status and life expectancy. The treatment of bisphosphonate-related osteonecrosis of the jaw is generally difficult. For this reason, prevention plays a predominant role in the management of the disease.

Key words: BRONJ, bisphosphonates, osteonecrosis, jaw, treatment

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INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a condition first described by Marx in 2003 (ref.¹). Since then, BRONJ has become a growing epidemic with several thousands of cases reported. Bisphosphonates have been used in human medicine in the treatment of both malignant and non-malignant bone lesions in various diseases, frequently osteoporosis, metastatic bone disease and bone involvement in multiple myeloma. By inhibiting bone resorption, they prevent loss of bone mass, pathologic fractures, pain and hypercalcaemia caused by the underlying disease resulting in significantly positive effect on the quality of life of the affected patients^{2,3}. Even though the clinical benefit of bisphosphonate therapy is huge, patients are at risk of developing osteonecrosis as a serious adverse effect. The incidence has been reported to be less than ten percent in various studies⁴. Incidence data for BRONJ vary considerably due to different definitions of the disease. This aside, mild cases of asymptomatic denuded bone very likely remain unidentified⁵. Most incidences of BRONJ have been reported as a result of intravenous administration of high doses of aminobisphosphonates indicated mostly in oncologic patients⁶. The association of BRONJ

and non-nitrogen bisphosphonates is very rare⁷. The risk of BRONJ development in patients receiving low doses of bisphosphonates orally mainly for the treatment of postmenopausal osteoporosis is relatively low^{6,8}.

According to the American Association of Oral and Maxillofacial Surgeons, the disease is defined as the presence of an area of exposed necrotic bone in the maxillofacial region lasting for more than eight weeks in a patient who was receiving bisphosphonate and had not received radiation therapy to the craniofacial region⁹. This definition does not include so-called, non-exposed variant, where no denuded necrotic bone is exposed but symptoms and signs such as bone pain, swelling, sinus tract or radiographic abnormality are present. In the pathogenesis defective bone remodelling caused by weakened synergism among the key cells that interact during bone remodeling plays a main role. Disruption of the bone remodelling may be caused by the combination of the underlying disease and the effects of bisphosphonate medication at the lesion site¹⁰. Minor dentoalveolar surgery such as tooth extraction or chronic trauma of the oral mucosa caused by poorly fitting dentures are common triggering factors of bone exposure. However spontaneous development has also been reported^{11,12}.

MATERIALS AND METHODS

We performed a retrospective study of all patients diagnosed and treated for bisphosphonate-related osteonecrosis of the jaw at the Department of Dentistry at the University Hospital in Hradec Králové during six years (January 2006 to October 2012). The diagnostic procedure was based on the results of clinical examination. Each patient also underwent radiological examination – panoramic radiography or cone-beam computed tomography to establish the final diagnosis (Fig. 1). The definition and staging system published by the American Association of Oral and Maxillofacial Surgeons was used to determine the stage of the disease⁹ (Table 1). We assigned the patients to the first to the fourth stage of the disease according to the presence or absence of the following symptoms and signs: exposed necrotic bone,

pain and evidence of infection, intraoral or extraoral fistula, oro-antral or oro-nasal communication, osteolysis extending to the inferior border of mandible or sinus floor, pathologic fracture (Fig. 2). The treatment protocol included conservative therapy consisting of daily oral antimicrobial rinses (chlorhexidine 0.12%, hexetidine, benzydamin-hydrochlorid) and analgesics. Systemic antibiotic therapy was indicated when signs of infection were present. Antibiotics were administered orally in mild cases of infection. Patients in whom BRONJ manifested with inflammation of deep head and neck spaces were admitted to bed ward for intravenous antibiotic administration. Duration of antibiotic therapy was at least 14 days and always continuing until all signs of infection subsided. Lincosamide antibiotics (clindamycin, lincomycin) and broad-spectrum penicillin antibiotics (amoxicillin) were used. In cases of severe inflammation of deep head and

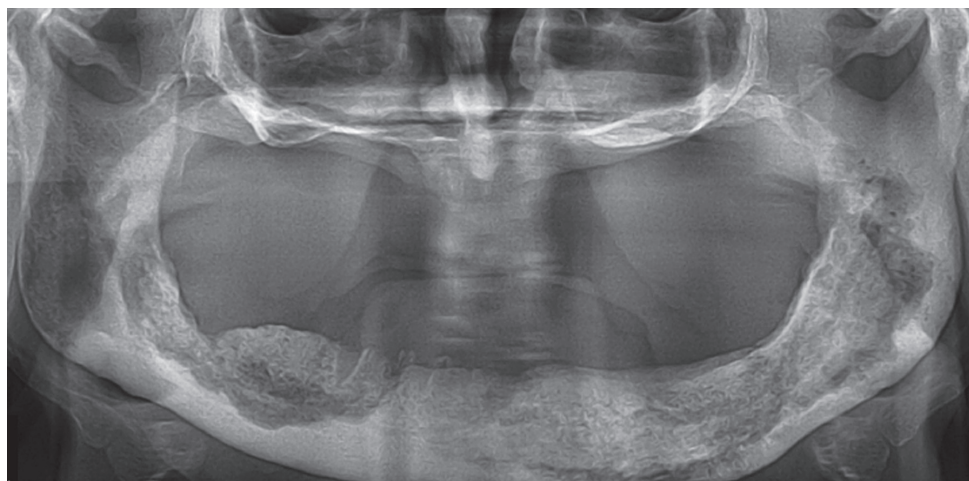


Fig. 1. Orthopantomograph of a patient with significant pathologic bone changes in BRONJ.



Fig. 2. Exposed necrotic alveolar bone in the oral cavity.

Table 1. Staging and recommended treatment of BRONJ according to AAOMS.

Stage	Bone exposure	Recommended treatment
0	No bone exposed, but presence of symptoms and signs as jaw bone pain, bone enlargement, gingival swelling, sinus tracts, radiological abnormalities	Analgesics Systemic antibiotics
I	Exposed bone, no symptoms and signs of infection	Antibacterial mouth rinses
II	Exposed bone, pain, signs of infection	Antibacterial mouth rinses Systemic antibiotics Analgesics
III	Exposed bone extending beyond the region of alveolar bone, cutaneous fistula, oro-antral or oro-nasal fistula, pathologic fracture	Antibacterial mouth rinses Systemic antibiotics Analgesics Surgical therapy (optional)

Table 2. Patient data.

Patient	Age/Gender	Diagnosis	Bisphosphonate	Site of necrosis	Triggering cause
1	65/M	Renal cancer	Zolendronate	Maxilla, mandible	Tooth extraction
2	58/F	Breast cancer	Zolendronate	Mandible	Tooth extraction
3	84/F	Breast cancer	Zolendronate, Ibandronate	Maxilla, mandible	Tooth extraction
4	66/M	Multiple myeloma	Clodronate, Ibandronate	Mandible	Denture trauma
5	59/F	Osteoporosis	Ibandronate	Mandible (bilateral)	Denture trauma
6	85/F	Osteoporosis	Alendronate	Maxilla, mandible	Tooth extraction
7	77/F	Osteoporosis	Ibandronate	Mandible	Tooth extraction
8	70/F	Osteoporosis	Ibandronate	Mandible	Spontaneous
9	60/F	Osteoporosis	Risendronate	Mandible	Spontaneous
10	65/F	Osteoporosis	Ibandronate	Mandible (bilateral)	Tooth extraction
11	65/F	Osteoporosis	Ibandronate	Maxilla	Tooth extraction

Table 3. Results of the treatment.

Patient number	Type of therapy	Results	Antibiotics (Length of administration in weeks)	Follow-up (months)
1	Conservative	Satisfactory healing	Lincosamides (6)	23
2	Surgical – sequestrectomy	Complete healing	Amoxicillin (5) Lincosamides (5)	22
3	Conservative	Progression	Amoxicillin(15) Ciprofloxacin (4) Lincosamides (41)	82
4	Conservative	Stable disease	Lincosamides (5)	7
5	Conservative	Complete healing	Ciprofloxacin(3) Lincosamides (7)	30
6	Conservative	Stable disease	Lincosamides (13)	5
7	Conservative	Satisfactory healing	Lincosamides (7)	30
8	Conservative	Complete healing	Amoxicillin (3) Lincosamides (6)	5
9	Conservative	Complete healing	Amoxicillin (3)	43
10	Surgical - debridement	Complete healing	Amoxicillin (4) Lincosamides (10)	32
11	Conservative	Complete healing	Lincosamides (6)	3

neck spaces and in patients non-responsive to the previous treatment, ciprofloxacin was used (Table 3). In all cases, equalisation of sharp bony edges was performed whenever necessary to prevent further trauma of the soft tissue. Surgical therapy consisting of sequestrectomy or minor debridement of the necrotic tissue with primary wound closure in combination with systemic antibiotic therapy was performed in two cases.

RESULTS

From January 2006 to October 2012, we diagnosed 11 patients with BRONJ. The patient age ranged from 58 to 85 years with a mean age 68.5 years. The male-female ratio was 2:9. Postmenopausal osteoporosis was the indication of bisphosphonate administration in seven patients, while four patients received bisphosphonates for one of the following oncologic diseases: prostate cancer (one case), breast cancer (two cases), multiple myeloma (one case). Three oncologic patients were exposed to zoledronate as the most potent bisphosphonate, one patient received oral ibandronate for the treatment of multiple myeloma and the rest were administered oral bisphosphonates, ibandronate (six patients), alendronate (one patient), risendronate (one patient) for the treatment of osteoporosis. The putative cause of BRONJ development was tooth extraction in eight cases, while in two cases it was a spontaneous occurrence and chronic denture trauma was the presumable triggering factor in one case (Table 2). Complete healing defined as the absence of any mucosal breaches and exposed necrotic bone, absence of any signs of inflammation and absence of subjective complaints was achieved in six patients. One of these patients underwent surgical intervention, sequestrectomy with curettage of necrotic bone with primary wound closure supported by systemic antimicrobial therapy and daily oral antimicrobial rinses. Satisfactory healing was achieved in two patients. In these patients a small area of asymptomatic exposed necrotic bone up to five millimeters in diameter persisted. In one oncologic patient, rapid progression with the development of necrotic bone in all quadrants with severe complaints and slow sequestration process was noted. Spontaneous sequestration continued over a period of 5 years. Complete mucosal healing was achieved in the upper jaw but bilateral oroantral communication occurred. In the lower jaw, necrotic bone was persisting. Resective surgery was not indicated in this case due to extensive jaw bone involvement and patient's morbidity. In two cases conservative therapy led to stabilisation of the disease with a minimum or no subjective complaints present (Table 3).

DISCUSSION

Osteonecrosis as an adverse effect of bisphosphonate therapy is a relatively rare complication but may negatively influence patients' oral health. Especially oncologic patients receiving high doses of intravenous bisphosphonates

have high risk of developing osteonecrosis. Patients receiving lower doses of oral bisphosphonates as in the treatment of postmenopausal osteoporosis are at low risk. Management of the disease is a complicated task since no ideal treatment strategy has been suggested so far. Complete healing is rarely achieved. Most authors agree on conservative treatment strategy which leads to symptom reduction and decrease in the frequency of infectious complications¹³⁻¹⁵. In addition to antimicrobial mouth rinses combined with systemic antibiotic treatment, minor surgical procedures are often performed as a part of the conservative treatment protocol. These include sequestrectomy of mobile bone fragments and equalisation of prominent bony edges. Surgical treatment approach with wide bone resection is controversial since bisphosphonates affect the whole jaw and surgical trauma to the bone could trigger progression of the osteonecrosis. Moreover, visualisation of vital bone margins during the surgery is difficult¹⁶. For these reasons, the results are not easily predictable. Nevertheless, several reports on resective surgical therapy of BRONJ with positive results have been published so far. These suggest that carefully planned segmental bone resection with pre- and postoperatively administered antibiotics can result in complete resolution¹⁷⁻¹⁹. Fluorescence-guided bone resection can aid in the visualisation of vital bone margins during the surgery according to several studies²⁰. Yet, careful indication of resective surgery as well as accurate diagnostic procedure and preoperative assessment are necessary. The patient's morbidity and life expectancy should be taken into account when planning surgical intervention. BRONJ seems to be a preventable complication to a certain degree since osteonecrosis is a result of tooth extraction. Less often it may develop spontaneously or as a result of chronic trauma to the oral mucosa, often caused by ill-fitting dentures²¹. Adverse effects and possible risks should be explained to the patient by the prescribing physician before the therapy onset and dental preventive measures should be taken²². Patients in whom intravenous administration of high doses of bisphosphonates is planned are at higher risk of BRONJ development. Therefore dental examination and treatment of all dental diseases is highly recommended prior to drug administration^{23,24}. This requires close cooperation between the patient, the dentist and the physician. Lack of communication could increase the risk of BRONJ development²⁵.

Prevention of BRONJ also includes dental care of asymptomatic patients who are already receiving bisphosphonates. The main goal of dental care is to maintain good oral hygiene and to prevent diseases that may lead to the need for invasive osseous procedures, since BRONJ is most frequently a result of dentoalveolar surgery. Elective dentoalveolar surgery does not seem to be contraindicated in patients taking bisphosphonates orally according to AAOMS. In contrast, in high risk patients receiving high doses of intravenous bisphosphonates invasive procedures leading to bone injury should be avoided whenever possible. Less invasive treatment methods should be considered instead⁹. In situations when surgical procedures leading to bone injury cannot be avoided, certain precau-

tions should be taken to minimise the risk of BRONJ development. Teeth should be extracted using the least traumatic technique, preferably one tooth at a time, or by a sextant-by-sextant approach. Wounds should be closed primarily where possible to reduce the time for ingress of oral microorganisms. Many authors suggest the use of perioperative antibiotics and a chlorhexidine mouthwash to reduce the risk of BRONJ development. Antimicrobial prophylaxis should be continued until mucosal seal over the wound is present²⁶.

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