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Long-term success of surgery in bisphosphonate-related osteonecrosis of the jaws (BRONJs) ☆

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SUMMARY

Objectives: Bisphosphonates are associated with osteonecrosis of the jaw. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) may be treated conservatively or by surgery.
Patients and methods: 108 patients underwent surgery and 88 patients were followed for a mean period of 337 days.

Age, gender, dental procedures, underlying disease, and the role of bisphosphonate treatment in the success of surgery were evaluated retrospectively.
Results: Surgical treatment improved the stage distribution from 19% stage I, 56% stage II and 25% stage III to 59% intact mucosa, 19% stage I and 13% stage II and 8% stage III. The improvement in the stage of disease achieved by surgery was statistically significant.

Further relevant parameters that favor a positive outcome of surgery were the event triggering the outbreak of BRONJ ($p = 0.05$) and the underlying disease ($p = 0.05$). BRONJ in the maxilla necessitated repeat surgery significantly earlier than did BRONJ in the mandible ($p = 0.03$).
Conclusion: Effective surgery might improve the outcome of BRONJ, although prevention still is the most important aspect of this condition.

Introduction

Bisphosphonates are very potent inhibitors of osteoclastic activity and are widely used to treat medical conditions associated with increased bone absorption, such as bone metastases or osteoporosis. From 2003 on, osteonecrosis of the jaw is being observed in patients treated with bisphosphonates.[1–14]

Despite the severity of disease, little is known about the reasons and mechanisms by which bisphosphonates affect the jawbone. Treatment with bisphosphonates is known to significantly reduce the number and size of remodeling sites in bone. The effect on bone remodeling varies by skeletal site. Healthy bone is constantly subject to microscopic damage. Bisphosphonate-induced suppression of remodeling favors the accumulation of microscopic damage in bone. The quantity of accumulated microdamage varies from site to site; it is more pronounced in trabecular than in cortical bone.[15]

Marx et al. presumed that, due to the rich vascularization of the jaws, bisphosphonates tend to accumulate in the jawbone. They induce apoptosis in osteoclasts and trigger anti-angiogenic as well as toxic effects in the epithelium.[1] Anti-angiogenic effects have been reported by several authors.[16–18] Bisphosphonates are also known to modulate the immune response of various types of cells.[19–21] It has been postulated that the acidity of local tissue (reduction of Ph) is altered by changes in the oral mucosa, periodontal disease, ill-fitting prostheses, or dental surgery, thus intensifying the release of acidic bisphosphonates and causing bisphosphonates to rise to potentially toxic levels.[19,22–24] These effects are believed to depress bone remodeling of the jaws and thus impair healing or cause spontaneous fractures after dental surgery or extraction.

Several national organizations have published guidelines and treatment algorithms for BRONJ.[25–28] The guidelines recommend palliative treatment of pain and infection,[10,13,28–30] and state that any kind of surgery should be deferred as long as possible. If surgery cannot be avoided, it should be limited to the removal of necrotic bone and osteosynthesis of fractures by means of reconstruction plates.[28]

Surgery for this condition still is a debated issue, but according to some authors[5,31–34] surgery has been successful in some settings: Carlson et al. achieved cure rates of 91.6%.[34]

☆ This study was approved by the Ethics Committee of the Medical University of Vienna, Austria, Approval No. 831/2009. Written informed consent was obtained from all patients included in the study.

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Wutzl et al. published a case series of 58 patients[5] reporting curing rates of 58.5. These good results encouraged us to continue treat BRONJ surgically.

We now can now report our experience in 108 patients, who were followed up for more than 2 years after surgical treatment. We also investigated the frequency of repeat surgery.

The aim of this study was to analyze the outcome of surgery in respect of potential factors that may influence the success of surgery. We also investigated the frequency of repeat surgery and factors that influence the necessity of repeat surgery.

Patients and methods

Study design

Between July 2004 and October 2010, 108 patients with BRONJ were included in a prospective cohort study at the department of oral and maxillofacial surgery, Medical University of Vienna. Out of the 108 patients, 88 patients were eligible for the retrospective analysis. Eligibility criteria were the following: (1) patients with exposed necrotic bone in the maxillofacial region that had persisted for more than eight weeks after or during bisphosphonate therapy; (2) necrosis confirmed by biopsy; (3) typical bone morphology on computed tomography; (4) no history of radiation therapy to the jaws; (5) surgical treatment.

The study design was approved by the ethics committee of the Medical University of Vienna (MUV).

Treatment algorithm

After BRONJ had been confirmed, the disease was staged according to the guidelines of the American Association of Oral and Maxillofacial Surgeons (AAOMS).[25,28] Depending on the stage of disease, patients were treated in accordance with our treatment algorithm.

Stage reduction was achieved by means conservative treatment with antibiotics and mouth rinsing for 1–3 weeks, or in case of an abscess or a fracture, additional symptomatic surgery was performed, e.g. drainage of the abscess. Intact oral mucosa was achieved by surgical procedures. Standardized surgical procedure was sequestrectomy, decortication and safe – if possible – 2 layer soft tissue closure with local flap procedures like e.g. an inverse mucoperiostal flap.

A detailed description of the treatment algorithm has been published earlier by Wutzl et al.[35] An overview is shown in Fig. 1.

Any alterations in treatment strategies according to recently published case series, guidelines, or drug manufacturers' guidelines[2,8,10,11,34,35] were discussed and decided upon by senior surgeons of the Council of Oral and Maxillofacial Surgeons at the clinic of oral and maxillofacial surgery, Medical University of Vienna.

Patients

Outcome variables were defined according to the stage of disease published by Ruggiero in a position paper on bisphosphonate-related osteonecrosis of the jaws by the American.

Association of Oral and Maxillofacial Surgeons (AAOMS), published in 2006[29] and updated in 2007 and May 2009.[25,28] Clinical findings were recorded after a predefined period of time. The following aspects were registered retrospectively and analyzed: age, gender, the underlying disease, the site of necrosis in the jawbone (maxilla or mandible), the type of bisphosphonate application, continuation of bisphosphonate therapy after surgery, the presence of actinomyces in biopsy, the clinical stage of disease at the first visit and 25 weeks after surgery, events triggering the outbreak of BRONJ, and repeat surgery.

We observed 108 patients that were scheduled for surgery with oral complications after or during bisphosphonate therapy between December 2004 and October 2010. In 14 patients follow up period was too short, or patients were lost to follow up. Six patients underwent surgery but refused to participate in this study. 88 patients could be included in this study. Patients were investigated with regard to the development of BRONJ and the success of surgery.

Patient characteristics are shown in Table 1.

Statistics

Descriptive statistics were calculated for patient demographics, follow-up period, and prosthetic rehabilitation. To evaluate the effect of surgical treatment, the preoperative and postoperative stage of disease were compared using a paired Wilcoxon's signed rank test with continuity correction. To compensate for different follow-up intervals, the time-dependent influence of various factors (underlying disease: benign vs. malignant; postoperative stage 0–3; drug holiday: yes vs. no; jaw: maxilla vs. mandible vs. both) were tested in multiple log-rank tests.

After a mean period of 202 days post-surgery, the patients' oral cavity was examined and staged according to the AAOMS[25,28] guidelines. The need for repeat surgery at the same location was assessed retrospectively, and the time between the first out-patient visit, primary and second surgery was recorded.

Results

The present study consisted of twice the number of patients investigated in previously published studies, and the patients were followed for a two-fold longer period of time. We investigated the likelihood of disease relapse and the success of a second surgical procedure by means of Kaplan–Meier analysis. The mean duration of follow-up was 337 days (±318 days; range, 25–1856 days) after the patients had first reported to our clinic, and 202 days (±224 days; range, 4–1562 days) after surgery had been performed.

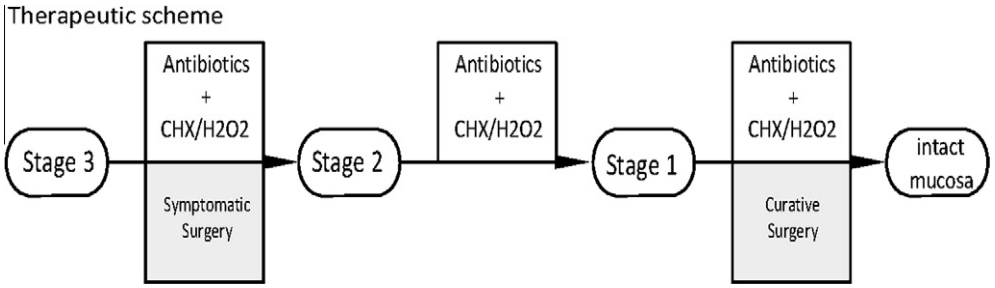

Figure 1 Clinical stage in relation to the treatment algorithm.