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Bisphosphonate-related osteonecrosis of the jaws: Cohort study of surgical treatment results in seventy-four stage II/III patients

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ABSTRACT

Introduction: Bisphosphonates are used in the treatment of osteoporosis and bone metastases. They inhibit osteoclast function, thereby decreasing bone resorption. A side effect of these drugs is bisphosphonate-related osteonecrosis of the jaw (BRONJ), which can be difficult to treat. The purpose of this study was to evaluate the surgical treatment protocol used in our hospital for BRONJ patients. The patients were retrospectively analyzed and followed-up at the Leiden University Medical Center.
Methods: All patients who were referred to our hospital with therapy-resistant BRONJ between 2003 and 2014 were seen. At first presentation, the clinical features, medical and dental history, bisphosphonate use, and the use of other medications were recorded. Patients underwent surgical intervention, performed by senior surgeons, following the principles of our previously published protocol.
Results: Seventy-four patients were followed-up for 6–96 months. Curation was successful with this surgical approach in 93.2% of the patients.
Discussion: All the patients were cured with our surgical protocol, for up to 5 years after surgery. We conclude that this treatment protocol has a high success rate in treating all stages of BRONJ.

1. Introduction

Bisphosphonates are medications used to treat osteoporosis and bone metastases. They decrease bone resorption by inhibiting the resorption function of the osteoclasts, and by causing apoptosis of the osteoblasts. In addition, they reduce pain, and resolve hypercalcemia in bone-metastasized cancer. Bisphosphonates are reported to have side effects, mainly gastrointestinal complaints. However, a rare but more severe side effect is the risk of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ). Many authors have claimed BRONJ to be difficult to treat. The first cases were reported in 2003 (Marx, 2003). Although several reports have since been published, the exact pathogenesis remains unclear. While some authors state that it has a spontaneous origin (Ruggiero et al., 2004; Badros et al., 2009; Estilo et al., 2008), others claim that it has a dental or a traumatic etiology (Bamias et al., 2005; Bedogni et al., 2008; Otto et al., 2012; Pichardo et al., 2013). Despite the difference in opinions on the etiology of BRONJ, the treatment recommendations are either, 1) non-invasive approaches (Marx et al., 2005; Ruggiero et al., 2014), which involve treatment with antibiotics, or a chlorhexidine mouth rinse, or removal of loosened sequestra, or 2) invasive approaches with sometimes aggressive surgical methods that often involve resection of large parts of the jaw with free-flap osseous reconstructions. BRONJ, if untreated at an early stage, involves worsening of the symptoms (Marx et al., 2005, 2007; Vescovi et al., 2011), with possibly serious consequences such as pathological fractures. Recently more authors (Fliefel et al., 2015; Ristow et al., 2015; Voss et al., 2012; Wilde et al., 2010; Williamson, 2010) have promoted early surgical intervention.

The initial BRONJ patients in our institution were treated with a simple surgical intervention based on the treatment of chronic suppurative osteomyelitis (CSO) of the jaws. These patients seemed to respond very well to this treatment (Alons et al., 2009; van Merkesteyn et al., 1997). This treatment was based on the treatment of chronic suppurative osteomyelitis, which has a dental cause (van Merkesteyn et al., 1997). As mentioned earlier, BRONJ seems to show a dental cause, thereby strongly suggesting a similar pathogenesis of BRONJ and CSO. We believe that early surgical

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intervention produces the best treatment results in BRONJ. Therefore, the purpose of this study was to evaluate our combined surgical and antimicrobial method of BRONJ patients. Secondary outcomes were to characterize the patients by investigating clinical features, medication use, (dental) history and (previous) treatment.

2. Material and methods

In this cohort study, consecutive patients referred from other clinics, presenting with therapy-resistant BRONJ, were treated and retrospectively analyzed. The study population consisted of all patients presenting for evaluation of BRONJ between January 2003 and December 2014 in the department of Oral & Maxillofacial Surgery of the Leiden University Medical Center. At presentation, the clinical features, medical and dental history, bisphosphonate use, and the use of other medications were noted.

The inclusion criterion for this study was a BRONJ diagnosis according to the criteria stated by the American Association of Oral and Maxillofacial Surgeons (AAOMS) (Ruggiero et al., 2009). This implies a recent use of bisphosphonates, the presence of exposed or necrotic bone in the oral cavity for more than 8 weeks, and no history of radiation therapy to the jaws. Further, a minimum bisphosphonate use of at least 12 months intravenously or 24 months orally was necessary for inclusion. The patients who used both oral and intravenous (IV) bisphosphonates were considered as IV users, for the purpose of this study.

The first aim of this study was to observe the result of our combined surgical and antimicrobial treatment.

Curation was classified as present or absent and defined as a situation with no complaints, and the presentation of a healed, closed mucosa. Additionally healing was classified as ideal if there was a closed mucosa within 2 weeks of surgery and non-ideal if a closed mucosa was reached after this amount of time or if needed an extra intervention (antibiotics or surgery). The patients were followed-up for at least 6 months: weekly in the first postoperative month; monthly, a month after; every 3 months, after 3 months post-surgery, up to a maximum of 5 years. During the follow-up the main focus was on the mucosa, and whether dehiscence or recurrence of the exposed bone had developed.

Secondary aims were to characterize the patients with BRONJ. Variables studied consisted of sex, age, bisphosphonate indication, duration of bisphosphonate use and administration manner. The duration of complaints and other medication (immunosuppressants, steroids, cytostatics) were studied. Clinical features (location and stage), dental history (luxating moment) and (previous) treatment were investigated. The collected data were statistically analyzed with SPSS.

At presentation, panoramic radiographs were taken of all the patients to localize the lesion, and to gain a first impression of the lesion. Then, a computed tomography (CT) scan was used to determine the extent of the defect. The clinical features and the radiological findings, together, defined the stage of BRONJ, based on the AAOMS classification (Ruggiero et al., 2014) (Table 1). The patients with an absence of any radiological findings on the X-ray or CT scan, but with clinical bone exposure, were categorized as stage I. Radiological findings on the CT scans such as osteolysis and sequestra in the alveolar process were categorized as stage II. Osteolysis in large parts of the jaws or pathologic fractures was categorized as stage III.

From the moment of diagnosis, surgical debridement for the patients was planned, with either local or general anesthesia, depending on the extent of the defect. After their referral, the patients did not receive any other treatment before the surgery. All the patients had either stopped their bisphosphonate use by then, or it was stopped, in consultation with their prescribing doctor, upon presentation in our hospital.

The patients underwent surgical intervention as reported before (Alons et al., 2009; Merkesteyn et al., 1997). Surgery was performed by senior surgeons. The surgical approach consisted of the removal of the sequestra, thorough surgical removal and saucerization of the non-vital bone until reaching the bleeding bone margins, and closing the defect primarily in layers (Fig. 1). This meant closing the periosteum as close to the bone as possible with mattress sutures, leaving no or as little dead-space as possible when closing the overlying mucosa in layers. During the surgery, no gastric tube was placed, culture samples were collected, and the resected bone was submitted for histopathological analysis.

The surgical treatment was supplemented by the administration of the antibiotics, penicillin G and metronidazole, intravenously for 1 week, and amoxicillin and metronidazole, orally for 3 weeks.

Panoramic radiographs were taken immediately after surgery, and every 3–6 months, for up to 1-year after the surgery, in order to monitor the condition of the bone margins and the healing of the bone. After 1-year, an annual radiographic follow-up was considered sufficient.

Overlying dentures were not allowed during the first 12 weeks in order to avoid pressure and damage to the mucosa, which could lead to dehiscence of the wound. The patients were instructed to maintain a liquid diet postoperatively for 2 weeks, and were permitted a soft diet after that period.

3. Results

Seventy-four patients were included in this retrospective cohort study. These patients were surgically treated and followed-up for 6–96 months.

3.1. Patient characteristics (Table 2)

Most patients (56.7%; n = 42) had osteoporosis as an indication for bisphosphonate use. In this group, 26 patients used bisphosphonates because of the use of steroids such as prednisolone (in cases of rheumatoid arthritis). The most common malignancies (n = 30) were breast cancer (60.0%; n = 18), prostate cancer (16.7%; n = 5), and multiple myeloma (20.2%; n = 6).

The clinical features are listed in Table 1. The ages of the female (83.8%; n = 62) and the male (16.2%; n = 12) patients varied from 26 to 91 years, with a mean of 67.9 years.

BRONJ was located in the maxilla in 11 patients, in the mandible in 58 patients, and in both the jaws in 5 patients.

Fifty-two patients were found to have stage III disease, and 22, stage II.

Oral bisphosphonates had been used in 40 cases, with a minimum of 24 months and a maximum of 120 months (mean = 68.0). Intravenous bisphosphonates had been used in 34 cases, including both oral and intravenous use (n = 6), with a minimum of 12 months and a maximum of 96 months (mean = 31.2 months). In 45 patients, steroids, such as prednisone, or methotrexate were used as co-medication.

The luxating moments of the BRONJ were mainly extractions (73.0%; n = 54), implants (13.5%; n = 10), and pressure sores due to ill-fitting dentures (5.4%; n = 4). All BRONJ were retraceable to a dental surgery/origin.

3.2. Surgical outcome

The majority of patients (n = 72) were treated under general anesthesia. After the surgery, all patients were followed-up for at least 6 months. In 69 patients (93.2%), curation was achieved by the