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Value of nonsurgical therapeutic management of stage I bisphosphonate-related osteonecrosis of the jaw

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ABSTRACT

There is still controversy about the best treatment strategy for patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) stage I. Therefore, the aim of the present study was to analyse the effect of a nonsurgical treatment protocol in patients with BRONJ stage I.

During the study period we included 17 patients (11 male; 6 female) who presented with a total of 24 separate areas of BRONJ, stage I. All patients were exclusively treated with a monthly intravenous regime of zoledronic acid due to an underlying malignant disease. All patients were treated using a standardized nonsurgical protocol consisting of antimicrobial mouth rinsing with chlorhexidine (CHX) (0.12%) three times a day, and daily CHX gel application.

In 11 patients (45.8%) the surface area of the exposed jawbone was completely healed by nonsurgical treatment. In seven patients (29.2%), nonsurgical treatment reduced the size of the exposed bone area by a mean of 64.7% (range 20.0–96.8%). None of the patients showed an increase in size of the area of exposed jawbone, or a worsening of the BRONJ from stage I to stages II or III. However, the duration of nonsurgical treatment or the duration of intravenous bisphosphonate therapy did not significantly influence the treatment outcome ($p = 0.6628$, $p = 0.6077$, respectively).

The results of the present study support the beneficial role of nonsurgical treatment in patients presenting with BRONJ stage I. Surgical therapy of BRONJ should be restricted to patients with advanced stages with clinical symptoms and local signs of infection.

1. Introduction

For nearly four decades bisphosphonates (BPs) have been widely used as potent inhibitors of bone resorption in various diseases (Rogers et al., 1997). In multiple myeloma, BPs reduce metastasis-dependent hypercalcemia (Berenson, 1997), and their use was increased in other bone metastatic diseases including breast and prostatic cancer to avoid skeletal-related complications (Lipton, 1997; McKeage et al., 2008; Saad and Hotte, 2010). But their application is not limited to the oncologic field, as BPs are used prophylactically in the management of osteoporosis or metabolic diseases such as osteogenesis imperfecta (Delmas, 2005; McClung, 2003).

On the molecular level, BPs negatively influence bone remodelling by inhibition of the osteoclasts' function and additionally by reducing the number of osteoclasts (Russell et al., 2007). Furthermore, there is evidence, that BP therapy has a direct influence not only on the bone cells but also on the soft tissue of the mucosa, by inhibiting the growth of epithelial cells, which leads to an attenuated healing capacity of the mucosa (Cornish et al., 2011). Finally, intravenous BP therapy, especially with zoledronic acid might reduce the level of vascular endothelial growth factor leading to anti-angiogenic and antineoplastic effects (Santini et al., 2003).

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) was first described by Marx in 2003 who suggested a relationship between the development of avascular necrosis of the jaw and therapy with intravenous BPs in 36 patients (Marx, 2003).

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After more than a decade there is much evidence supporting a clear association between BRONJ and BP therapy, however, the exact molecular mechanism underlying the development of BRONJ remains unclear (Khosla et al., 2007). One of the main inducing factors might be the generally reduced bone turnover of the jaw by direct osteoclast inhibition (Marx et al., 2005).

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), BRONJ is defined as an area of exposed bone in the maxillofacial region for more than 8 weeks, that is present in patients with BP therapy who are not undergoing radiotherapy of the head and neck (Ruggiero et al., 2009). Recently, AAOMS has updated the guidelines and recommended the term medication-related osteonecrosis of the jaw (MRONJ) with respect to the growing number of cases of osteonecrosis associated with other antiresorptive and antiangiogenic therapies (Ruggiero et al., 2014).

According to the severity of the clinical appearance and symptoms of BRONJ, AAOMS established a staging system, which classifies four stages of BRONJ. Based on that staging system a therapeutic algorithm can be deduced with a stage-dependent therapeutic recommendation (Ruggiero et al., 2009).

According to AAOMS the current concept for the therapy of BRONJ stage I, consists of a conservative, non-surgical approach with antimicrobial rinsing and close clinical control intervals. On the other hand, several studies have reported the successful treatment of BRONJ stage I by surgical therapy.

As the non-surgical treatment strategy of BRONJ stage I is still the subject of controversy, we evaluated a non-surgical treatment protocol in patients with BRONJ stage I, who were all treated with zoledronic acid due to an underlying malignant disease.

2. Materials and methods

This study was approved by the local Ethics Committee (Ethics number S-420/2012) and was carried out according to the Declaration of Helsinki. Written informed consent was obtained from all patients. The study was designed as a monocentric cohort study. We evaluated the value of a nonsurgical therapeutic approach in patients with BRONJ stage I according to the AAOMS criteria, who were treated in our department between January 2010 and December 2013. In order to create a homogenous study population we only included patients who were treated with an intravenous application of 4 mg of zoledronic acid monthly due to an underlying malignant disease. Additional inclusion criteria were no radiation therapy in the medical history and no prior surgical treatment of the BRONJ.

All patients were treated using a standardized nonsurgical protocol consisting of antimicrobial mouth rinsing with chlorhexidine (CHX) (0.12%) three times a day, and daily CHX gel application. It was a strictly local conservative therapeutic concept without the use of antibiotics. In the follow-up period, all patients were examined every four weeks in our outpatient department, including a thorough oral inspection. According to the AAOMS staging system, BRONJ stage I is characterized by exposed jawbone combined with a lack of symptoms. At the beginning of the therapy and at every recall appointment the surface area of exposed bone was measured in mm^2. If a patient showed more than one area of exposed bone, these were measured separately. The investigation was conducted by three different, experienced examiners.

The therapeutic success of the nonsurgical regimen was defined as complete if the area of exposed jawbone was completely healed and covered by mucosa; and as relative if the size of the exposed bone area was reduced during therapy. If the surface area of the exposed bone increased or if the BRONJ worsened to stage II or III, this was defined as treatment failure.

Furthermore, the influence of the duration of intravenous BP therapy, the duration of the nonsurgical treatment, age, sex, drug holiday and localization of BRONJ was analysed.

The statistical analysis is of an exploratory nature. Median, first and third quartiles, minima and maxima, and relative and absolute frequencies were calculated for exploratory analysis. A multiple logistic regression analysis was performed to identify the independent variables which are associated with therapeutic success. In addition univariate analyses (chi-square test) were performed.

Statistical analyses were conducted using SPSS version 19.0.0 (IBM SPSS Statistics; SPSS Inc., Chicago, IL). Due to the exploratory nature of the study, no adjustment was made for multiple testing, and test results surpassing a 5% confidence level were interpreted as statistically significant.

3. Results

During the study period we included 17 patients (11 male; 6 female) who presented with a total of 24 areas of BRONJ stage I. BRONJ stage I was defined as exposed jawbone lacking signs of infection according to the AAOMS staging criteria. Patient characteristics are summarized in Table 1. The mean age was 63.6 years (range, 41–85). All patients had been treated with an intravenous regime of 4 mg zoledronic acid monthly, due to an underlying malignant disease. Four patients had breast cancer, six had prostate cancer, three had multiple myeloma, and two had renal cancer. In two patients the malignant diseases was not further specified. The mean duration of BP therapy was 43.1 months (range, 7–108). Ten patients (58.8%) had paused their BP therapy, while seven patients (41.2%) continued to receive BPs during the study period. Concerning the localization of the BRONJ sites, 21 were located in the mandible (87.5%), while only three were in the maxilla (12.5%). Analysis of the risk factors showed that most patients had previous surgical intervention in the jaw, such as tooth extraction (12 patients, 70.0%).

All patients in this study were exclusively treated with nonsurgical therapy consisting of antimicrobial mouth rinsing with chlorhexidine (CHX) (0.12%) three times a day, and daily CHX gel application. The nonsurgical therapy was continued in all patients until the end of the observation period. The mean duration of nonsurgical treatment was 10.8 months (range, 2–36). At the beginning of the therapy and at every recall appointment the surface area of the exposed bone was measured in mm^2.

During the study period, we did not detect any increase in the area of exposed jawbone, or a worsening of the BRONJ from stage I to stage II or III (indicating an infection of the exposed bone). Individual patients have reported a spontaneous sequestration of bone, however, we were not able to evaluate this as a reliable clinical parameter as we only examined our patients every four weeks.

In 11 patients (45.8%) the surface area of exposed jawbone was completely reduced and covered by mucosa after a median duration of nonsurgical treatment of 8 months (range, 2–36) (Fig. 1). In seven patients (29.2%), nonsurgical treatment with a median duration of 6 months (range, 2–36) reduced the size of the exposed bone area by a mean of 64.7% (range, 20.0–96.8%). In six patients (25.0%) the size of the exposed bone area was not changed by nonsurgical treatment with a median duration of 4 months (range, 2–24). However, statistical analysis did not reveal any significance between the different treatment outcomes concerning the duration of nonsurgical treatment (Fig. 2) ($p = 0.6628$). In addition, the duration of intravenous BP therapy did not significantly influence the treatment outcome (Fig. 3) ($p = 0.6077$). This was confirmed in the multivariate analysis (Table 2).