Bisphosphonate-associated osteonecrosis of the jaws: surgical treatment with ErCrYSGG-laser. Case report

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Bisphosphonates (BP) play an important role in concomitant therapy of certain types of cancer and multiple myeloma as well as in treatment of osteoporosis. The administration of BP has great therapeutic benefits, but correlates with a specific kind of osteonecrosis of the alveolar bone. The so-called bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a rare, but often severe adverse side effect of high-dosage and long-term BP therapy. Thus far, no consensus for treatment of BRONJ has been achieved. All strategies have to take into account the insecure prognosis and danger of recurrence of clinically apparent necrosis and progression of disease. At the Department of Oral Surgery and Radiology, Medical University of Graz, an ErCrYSGG laser was successfully applied in surgical treatment of BRONJ. Stable mucosal coverage could be achieved in all of 5 cases. Laser surgery can be considered as a promising technique for the effective treatment of BRONJ. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:e1-e6)**

Malignant primary or metastatic bone lesions often cause sequential skeletal complications. These may include pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy.[1] Bisphosphonates (BPs) help to reduce these cancer-related events and inhibit the growth of bone metastases related to breast, prostate, or lung cancer.[2]

The biological effect of BPs is based on the inhibition of bone resorption and of bone turnover in general that can be documented by suppression of specific serum bone resorption markers. Their structure is similar to the configuration of pyrophosphate; thus, they bind to hydroxyapatite by their phosphate groups. But in contrast to pyrophosphate, this linkage is irreversible because of the replacement of oxygen by carbon in the backbone of the molecule, which makes it resistant against hydrolysis. As a consequence, BPs have a very long half-life period and hence accumulate in bone matrix. Furthermore, their degradation in the context of bone remodeling is limited because of their toxic effect on osteoclasts. They inhibit the mevalonate pathway, cause a severe decrease of osteoclast function, and can even lead to apoptosis.[3,4] The preferred deposition of BPs in the jaws, especially in the alveolar process is a result of a high rate of local bone turnover, which is 10 times higher than for example in the tibia.[5]

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Received for publication Feb 11, 2010; returned for revision Jul 13, 2010; accepted for publication Aug 8, 2010.
1079-2104/$ - see front matter
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doi:10.1016/j.tripleo.2010.08.013

Zoledronic acid, a potent new BP, is suspected of having antiangiogenetic and antitumoral effects besides its specific inhibition bone turnover. The mechanism is supposed to result from the inhibition of vascular endothelial growth factor, which is involved in the spread of secondary lesions in neoplasia.[6]

A recent study on 1800 breast cancer patients demonstrated that zoledronic acid administered in 4-mg doses every 6 months over 3 years, showed a significantly increased disease-free survival rate of 94% in the zoledronic acid group compared with 90.8% in the control group after 4 years of follow-up.[7]

Despite its great benefits in cancer therapy, intravenous administration of BPs in particular correlates with bisphosphonate-related osteonecrosis of the jaws (BRONJ) first described in 2003.[8-10] Since then, the number of cases of this severe complication is steadily increasing. The published incidence of BRONJ ranges from 0.8% to 12.0%.[11]

Apart from the individual potency of different pharmaceuticals, the accumulated dose of bisphosphonates over the period of administration is thought to be a main risk factor. Additional risk factors have been described. BRONJ occurs with a sevenfold increased frequency after dentoalveolar surgery. Mucosal trauma attributable to dentures and also endodontic treatment have been discussed as further trigger factors. Even spontaneous occurrence has been mentioned.[12-14]

So far, no consensus for treatment of BRONJ has been achieved. Recommendations range from strictly conservative management, including antiseptic rinses and antibiotics,[15,16] to extended surgical interventions, including entire jaw resection and subsequent reconstruction.[17]

All regimens are associated with a high incidence of recurrence of clinically apparent necrosis and progression of disease. This poor prognosis causes additional psychological strain to the patients.

Recently, the success of extended jaw resection has been reported in the literature.[18] Nevertheless, regarding the fact of BP deposit in the entire jaws, the risk for development of further clinically apparent necroses at other sites should be considered. A sequel of several resections may thus lead to severe functional and esthetic restrictions that can compromise a patient's quality of life.

Lasers have been introduced to different fields of medical treatment with varying physical properties and doses of application. Soft lasers are supposed to enhance wound healing by biostimulation and to offer antiseptic effects in conservative treatment.[19-22] Hence, low level laser therapy (LLLT) has been used in the treatment of BRONJ. LLLT has led to significant reduction of reported pain, clinical size, edema, and presence of pus and fistulas.[23]

So-called hard lasers are expected to ensure safe and tissue-preserving surgical treatment and to provide antibacterial effects. Especially in bone surgery, accelerated revascularization and regeneration similar to the effects of LLLT have been described.[24,25] Therefore, hard lasers have been recently introduced for the removal of necrotic tissue[26] and bone ablation in cases of BRONJ.[27,28]

OBJECTIVE

In the following, the successful surgical application of ErCrYSGG laser is supported by a sequel of 5 cases. Before treatment, all cases presented areas of exposed necrotic bone, corresponding to Stage II BRONJ of the classification of the American Association of Oral and Maxillofacial Surgery (AAOMS).[29] The objective of the presented case series was to evaluate the effectiveness of surgical ErCrYSGG laser application regarding successful achievement of stable mucosal closure.

CASE PRESENTATION

The overall treatment regimen was based on a stage-related management. After clinical staging, routine conservative treatment was immediately started. Staging was supported by medical history and clinical diagnosis, including examination of serum bone markers (e.g., β-cross laps [normal range 0.9-0.44 ng/mL in postmenopausal women]), and advanced radiological imaging by cone beam computed tomography (CBCT).

Generally, presurgical conservative standard treatment consisted of rinsing with hydrogen peroxide 3% and application of an adhesive paste (Solcoseryl Adhäsiv-Paste, Valeant, CA, USA) on the exposed necrotic bone areas to reduce further local infection. Inflammation, presenting erythema, pain, swelling or pus, was treated by oral antibiotic therapy with amoxicillin with clavulane acid (Augmentin, GlaxoSmithKline, United Kingdom), administered at least until acute inflammation was gone. When the clinical situation had improved to BRONJ Stage I according to AAOMS, surgery was performed. The aim was to achieve a long-term stable symptom-free clinical situation by secure mucosal coverage.

Each surgical procedure was performed under local anesthesia. Oral antibiotics (amoxicillin with clavulanic acid) were administered from 1 day before surgery until sutures were removed 10 days postoperatively. Bony sequestra and adjacent superficial bone with a typical yellow pumice stone appearance were removed and bony edges were smoothed using rotating burs. The last debridement was done with the ErCrYSGG laser at a working distance of 1 mm until bleeding points could be observed. Laser settings were 2780 nm, 6 W, 30% water, 70% air, and 30 pulses per second in H mode for bone ablation and 2780 nm, 3 W, 30% water, 70% air, and 25 pps in S-mode for the soft tissue removal. Finally, periosteal releasing incisions were carried out to ensure a dense and tensionless wound closure. To provide secure mucosal coverage, double-layer sutures were used.

Postoperative regimen included the recommendation not to wear removable dentures. Follow-up examinations were performed twice a week during the first 14 postoperative days. In the case of signs of wound infection, 3% hydrogen peroxide and photodynamic therapy by low-level laser irradiation (Helbo Minilaser 2075 F dent [HELBO Photodynamic Systems, Austria], 75 mW, 680 nm, 90 s, 2-mm distance) were applied. Sutures were removed after 10 days. A summary of the 5 cases is presented in Table I.

The following representative case illustrates the standardized procedure.

In December 2006, a female patient, age 86, presented 6 months after tooth extractions with empty painful sockets 44 and 45. Because of multiple myeloma, the patient had been treated with zoledronic acid (Zometa) once a month since 2003. Conventional radiological examination displayed persistent pockets with no signs of bony regeneration. Bone biomarkers showed considerably decreased β-cross laps (CTX 0.05 ng/mL) as expected after intensified BP therapy. After a short phase of follow-up together with routine conservative treatment, there was neither evidence for acute inflammation nor signs of spontaneous regeneration. Thus, a first attempt at surgical wound closure was indicated, including superficial contouring of the alveolar ridge using rotating burs, and subsequent dense

Table I. Summary of the 5 treated cases

Patient	*Age*	*Sex*	*Disease*	*Number failed*	*BP*	*Region*	*Local risk factor*	*Laser surgery*
1	86	F	Multiple myeloma	3	Zoledronate (Zometa, Novartis, Switzerland) 4 mg IV monthly since 2003	Right mandible, canine – second premolar region	Tooth extraction 44, 45 in December 2005	January 2009
2	64	F	Breast cancer	2	Ibandronate (Bondronat, Roche, United Kingdom) 50 mg PO daily since December 2005	Left maxilla, lateral incisor – first premolar region	Tooth extraction 22, 23 in June 2007	January 2009
3	75	F	Bronchial carcinoma	0	Zoledronate (Zometa) 4 mg IV monthly since 2006	Left mandible, canine – first molar region	Tooth extraction 33, 34 in November and December 2008	March 2009
4	77	F	Multiple myeloma	0	Zoledronate (Zometa) 4 mg IV every 3 mo since April 2006	Left mandible, premolar region	Tooth extraction 34, 35 in 2007	January 2009
5	75	F	Breast cancer	0	Zoledronate (Zometa) 4 mg IV monthly since 2005	Left mandible, first premolar – first molar region	Nonfitting removable denture (pressure mark) June 2008	October 2008

BP, bisphophonate; *IV,* intravenously; *PO,* orally.
Number failed: Number of failed surgical attempts without laser application.
Laser surgery: Date of ErCrYSGG laser combined surgery.

Fig. 1. Clinical appearance.

and tensionless soft tissue closure with a vestibular mucosal flap. Perioperative antibiotic treatment was administered orally for 1 week. Seven days postoperatively, the patient showed recurrence of exposed bone, and therefore conservative treatment was resumed. The patient was educated in efficient oral hygiene and clinical follow-up took place every 2 weeks.

The disease progressed 3 times to Stage II over 18 months (Fig. 1), even though the conservative treatment regimen was not interrupted and 2 further attempts at surgical wound closure were performed. Possible malignant infiltration was ruled out by biopsies.

In October 2008, adjuvant photodynamic therapy by low-level laser was added to conservative treatment. Nevertheless, there was no improvement in the clinical situation. As a further attempt, ErCrYSGG laser combined surgery was scheduled. The preoperatively performed CBCT showed bone sequestra (Fig. 2).

The surgical procedure took place in January 2009 and included the combination of a rough debridement with a rotating bur and the subsequent contouring of the bony surface with the ErCrYSGG-Waterlase MD Laser by Biolase, Irvine, CA, USA. The settings were 6 W, 30% water, 70% air, and 30 pps in H-mode for bone ablation and 3 W, 30% water, 70% air, and 25 pps in S-mode for the removal of surrounding inflamed soft tissue (Figs. 3 and 4).

Tensionless wound closure and concomitant antibiotic therapy were contained.

Histologic examination of a collected biopsy confirmed the diagnosis of superinfected BRONJ. One week after surgery, a small dehiscence without exposure of bone was noticed, accompanied by insufficient oral hygiene. The defect healed within a month undergoing conservative treatment. Finally, safe soft tissue cover with no apparent necrotic bone could be achieved. The 12-month follow-up showed no progression of disease, and confirmed a stable mucosal coverage (Fig. 5).

DISCUSSION

The presented cases showed stable mucosal conditions 1 year after surgical therapy according to the regimen described above.

In particular, recurrent lesions could be managed successfully by the surgical use of the ErCrYSGG laser. These results are similar to those presented by Stübinger et al[27] and Vescovi et al[28] who used an Er:YAG laser for the bony debridement. In most cases,

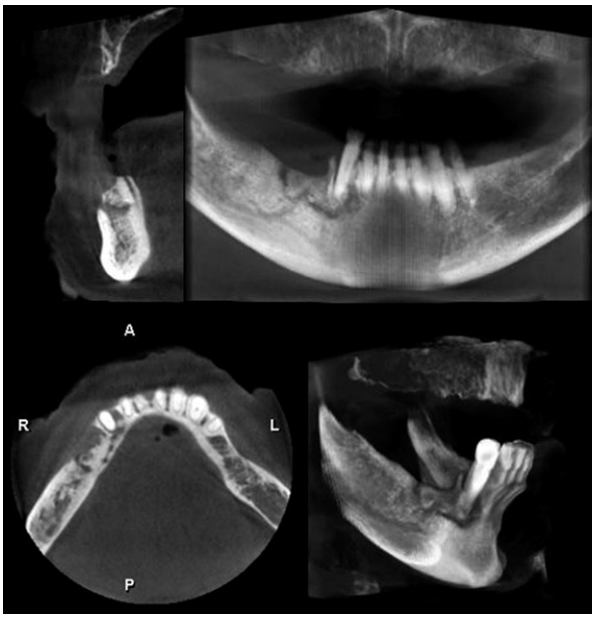

Fig. 2. Preoperative CBCT scan.

Fig. 3. Intraoperative view.

Fig. 4. Extent of bone removal.

Fig. 5. Fifteen months postoperatively.

it is not practical to only use the ErCrYSSG laser for bone ablation. Its minor performance especially concerning the speed of ablation would extend the duration of the surgical procedure considerably. Therefore, it was combined using a rotating bur. Nevertheless the physical properties of the ErCrYSGG laser are very suitable for application in bone surgery. The inorganic calcium salts and the organic matrix of bone have very high absorption for the ErCrYSGG beam. Tissue is removed by thermally induced mechanical ablation. Water vapor is produced, expands and creates pressure until microexplosions take place.[28] The laser beam provides a bactericidal and biostimulatory effect that reduces secondary infection by *Actinomyces*, *Candida* spp., and anaerobes.[24,30] In addition, more marked revascularization and quicker bone healing after surgery compared with carbide tools have been described.[31,32] The antibacterial effect of the ErCrYSGG laser and thus the sterilization of the bony surface might be the underlying principle for the success of the presented cases.[27] Therefore, the surgical application of the ErCrYSGG laser is a promising option for the treatment of BRONJ.

Other treatment regimens that follow a conservative, combined, or radical strategy are described in the literature. A strictly conservative approach relies on the assumption that patients could live with some exposed

bone without pain and with normal function. The regimen consists of the long-term or permanent administration of antibiotics and antiseptic mouth rinses to control pain and prevent progression of disease. Other attempts, like surgical debridement, aside from rounding off sharp bony projections that produce soft tissue inflammation and pain, are not recommended.[15] In this conservative approach, successful treatment is defined as absence of pain and other signs of acute inflammation. Nevertheless, a permanent improvement of symptoms, such as that achieved by antibiotic therapy, is exceptional.[33] According to the authors' experience, most patients have difficulties in dealing with areas of exposed bone, which can lead to recurrent infective inflammations and progression of disease. Therefore, therapy was directed to the achievement of mucosal coverage, which was defined as success of surgery. The AAOMS suggests a combined conservative-surgical management that is related to the stage of disease.[11] It ranges from patient education, antibacterial mouth rinse, and pain control to removing bony sequestra, superficial debridement, and resection in advanced cases.

The third possible approach is that of radical surgery recommended by Abu-Id et al,[17] who failed using local disinfecting therapy in 67% of cases and who made use of limited surgical debridement in 33% of cases. A high success rate of 91.6% of extended jaw resections has been reported recently by Carlson and Basile.[34] Nevertheless, there is also a possible worsening of symptoms[33] and recurrence of exposed bone after extended resection and even an enhanced risk of pathologic fracture.[27] It can cause a severe impairment of function and esthetics and can compromise the patient's quality of life. Moreover, regarding the fact that BPs deposit in the entire jaws, the development of further necroses is possible.

The key factors for successful treatment have not been clearly identified yet. There are several aspects that are likely to influence the success of surgery and can cause progression of disease. Before surgery, a regression of the bacterial burden and inflammation by conservative means to reduce bacterial contamination and support wound healing after surgery should be attempted. The role of photodynamic therapy in supporting tissue regeneration has to be evaluated. A further factor is the extension of the debridement that provides best outcome prognosis. Despite signs of possible radiological necrosis, such as sequestra, osteolysis, osteosclerosis, and periosteal reaction in CT or CBCT scans, the definite extent is difficult to define. Scintigraphy may be an early indicator for the development of BRONJ[35] and is helpful to distinguish metastases from necrosis but cannot display the exact localization. Furthermore, superinfection and consequent inflammation often shows detention. However, the typical macroscopic yellow pumice stone appearance of the necrotic bone may indicate extension of necrosis. Another possibility might be a fluorescence-guided debridement after administration of doxycycline using a certified medical lamp emitting exciting light at 400 to 460 nm.[36] Possible trigger factors of progression or recurrence of clinically evident necrosis include local traumas. Therefore, elective oral surgery and pressure marks attributable to dental prosthetics should be avoided.

Not least, oral hygiene plays an important role in reducing future bacterial burden and preserving stable conditions involving permanent soft tissue covering of the former defect. Thus, detailed patient education, a strict follow-up, and eventually professional dental hygiene to achieve periodontal health are essential. In any case, routine checkups are essential because patients who show BRONJ once are likely to develop a progression of disease in another region.

CONCLUSIONS

In case of BRONJ, mucosal coverage should be achieved to prevent secondary infection and progression of disease. Although the surgical application of the erCrYSGG in 5 cases led to successful achievement of mucosal coverage, this treatment regimen needs further evaluation by clinical trials.

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