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A New Strategy for Surgical Intervention of Bisphosphonate-Related Osteonecrosis of the Jaw : A retrospective study.

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Bisphosphonates (BPs) are now widely used to treat various skeletal complications. Although the number of reported cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) is rapidly increasing worldwide, therapeutic strategies remain controversial. Conservative treatments including antibacterial mouth rinses, the systemic administration of antibiotics, and superficial debridement in stage II BRONJ have been recommended by the American Association of Oral and Maxillofacial Surgeons position paper. However, these treatments are only partially successful. We performed a surgical intervention that consisted of osteotomy and primary wound closure in patients with stages II and III BRONJ. Forty-three out of 44 cases were treated effectively by this strategy, leading to improvements in quality of life. All BRONJ patients treated with oral BPs were treated successfully by the surgical intervention. We also proposed a surgical intervention for patients with stage II BRONJ.

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Key words: bisphosphonate-related osteonecrosis of jaws (BRONJ), surgical intervention, bisphosphonate, conservative treatment.

Introduction

Bisphosphonates (BPs) are now widely used to treat various skeletal complications because they effectively inhibit bone resorption. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was initially identified by Marx[1)] and Migliorati[2)] in 2003 as a serious adverse event of the long-term administration of BPs. Most cases of BRONJ in these studies were attributed to the use of intravenous BPs to treat hypercalcemia in patients with multiple myeloma and metastatic breast cancer[1,2)]. The number of reported cases of BRONJ has since rapidly increased worldwide. The first nationwide survey was performed in Japan in 2006, and 28 patients were confirmed to have BRONJ[3)]. Of these patients, 60.7% had received intravenous BPs while 32.1% had received oral BPs[3)]. Another nationwide survey was performed in 2008[3)], and identified 568 cases of BRONJ, including suspected cases. Of these, 263 cases met the working definition of BRONJ proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[4)]. Among the 263 cases confirmed to have BRONJ, 57.8% had received intravenous BPs while 39.5% had received oral BPs[3)]. The number of BRONJ patients in Japan has increasing rapidly since the first nationwide survey. One of the characteristics of BRONJ patients in Japan is that the relative proportion of oral BP-related BRONJ cases is greater than that in other

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countries[5-8].

The therapeutic strategies used to treat patients with BRONJ remain controversial. According to the former position paper reported by the AAOMS, therapeutic strategies for BRONJ should eliminate pain, control infection, and prevent the progression or occurrence of bone necrosis[9]. Conservative treatments including antibacterial mouth rinses, the systemic administration of antibiotics, and superficial debridement in stage II BRONJ have been recommended[9]. The radical removal of necrotic bone is limited to severe cases such as those with stage III BRONJ[9]. In the modified position paper by AAOMS in 2014, debridement to relieve soft tissue irritation has been recommended from "superficial debridement"[10] Therapeutic strategies used in Japan are based on the position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons, in a stage-dependent manner similar to the AAOMS position paper[9,10]. However, these treatments have only been partially successful, with mucosal closure only being reported in 50% of cases[12-17]. Many cases do not respond to these conservative treatments and infection and bone destruction are progressive in stages II and III BRONJ. In contrast, surgical management has achieved superior results with success rates exceeding 80%[18-21]. However, surgical protocols remain controversial. In the present study, we assessed the effectiveness of a surgical protocol in the treatment of stage II BRONJ.

Patients and Methods

This retrospective analysis involved a review of patients with a clinical and radiographical diagnosis of BRONJ. The definition of BRONJ was described according to the AAOMS[4,9]. BRONJ was diagnosed by the following three characteristics: 1. Current or previous treatment with a BP. 2. Exposed bone in the maxillofacial region that persisted for more than 8 weeks. 3. No history of radiation therapy to the jaws. Many patients that participated in this study had discontinued their bisphosphonate medication on their own accord or had been recommended to discontinue it by the referring doctor. The treatment strategy used for BRONJ in our department was in a stage-dependent manner according to the AAOMS[4,9]. However, the symptoms of some patients with stage II BRONJ who were treated conservatively were aggravated and disease progression was also observed. Therefore, we selected a surgical intervention for stage II BRONJ in order to improve the quality of life of our patients. All patients underwent an imaging examination with a panoramic radiograph and computed tomography scan. All mandibular and maxillary resections were performed under general anesthesia. The standardized terminology to describe jaw resections was used in this study. Osteotomies referred to the removal of the affected bone with an abnormal color until confirming sufficient bleeding from the surrounding bone surfaces (Fig. 1 and 2). Thereafter, the sharp edges of the bone were removed to avoid damage to the soft tissues(Fig. 3). Primary wound closure of the mucoperiosteal flaps had to be performed without tension. If this was not possible, openings were filled with gauze incorporating antibiotic ointments. Mandibular resection referred to segmental resection in which mandibular continuity was broken and reconstructed with a reconstruction plate and marginal resection in which the alveolus was resected without the loss of mandibular continuity. Segmental resection was performed when extensive necrotic bone was present in the mandible and approached or involved the mandibular inferior border or an orocutaneous fistula was present. Marginal resection was performed when clinical and radiographical examinations revealed that necrotic bone was isolated to the alveolus of the mandible. In the case of the maxilla, partial maxillectomy was performed. The prophylactic antibiotics were administrated intravenously with 1mg cephem antibiotics. Postoperatively, we administrated intravenously 2g/day of cephem antibiotics. Intravenous antibiotics were continued to 5 days postoperatively. Then oral antibiotics with 300mg/day of cepem antibiotics continued to 5 days. To improve and keep the oral hygiene of the patients, we guided the methods of oral health care to the patients. Although any of the patients including this study had discontinued their BPs medication on their own accord, or had been recommended to discontinue it by the referring doctor, no recommendation for preoperative or postoperative BPs medication discontinuation were made by authors. The use of BPs medication was of benefit to the patients from the standpoint of their cancer and related skeletal complications or osteoporosis such that discontinuation was not considered to be prudent. A recommendation for discontinuation of BPs medication was not made, therefore, because of the identification of multiple possible risk factors in the development of the osteonecrosis, as well as the known benefit of the BPs medication to the patients.

Follow-up examinations were carried out regularly after patients were discharged. The former operation area was checked for intactness of the mucosal layer and panoramic

radiography examinations were performed. The outcome criteria was defined as follows: resolution of the disease was defined as maintenance of the mucosal closure without signs of residual infection or exposed bone at the time of the evaluation, remission was defined as down-staging such as exposed bone without symptoms, and persistent and progressive disease were defined as no changes and an increase in the severity of symptoms, respectively.

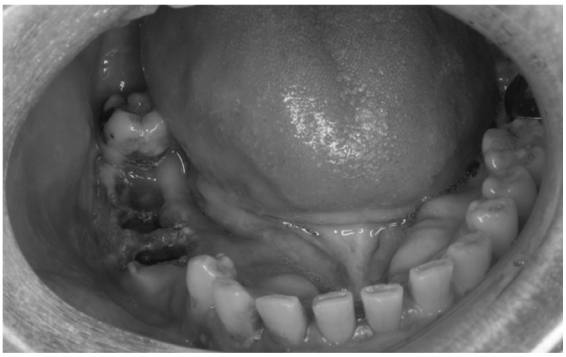

Fig. 1 Preoperative view of a stage II BRONJ patient.
The necrotic bone was exposed in the right lower molar region in which pain and the discharge of pus were noted.

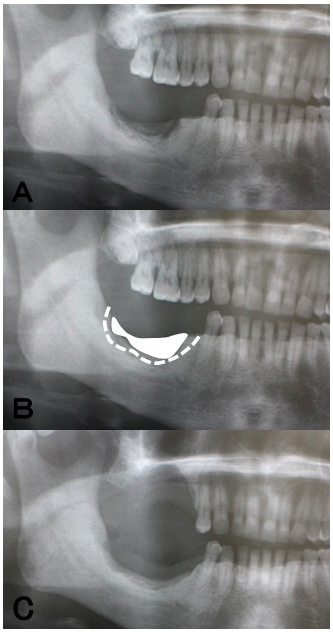

Fig. 2 Panoramic X –ray pictures showing the bone resection area.
A: Preoperating findings showing the necrotic lesion at right lower molar region.
B: A shame of the bone resection area. Broken line shows resection line.
C: Postoperating findings after bone resection.

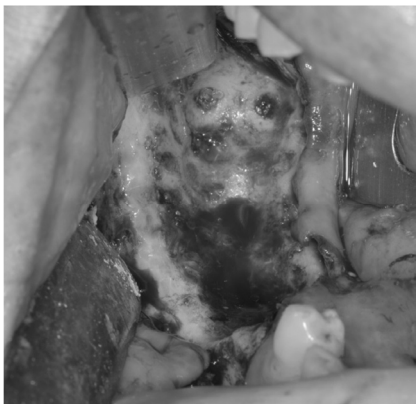

Fig. 3 Intraoral view of the surgical intervention for BROJ.
Affected bone with an altered color with sufficient bleeding from the surrounding bone surfaces as well as sharp edges were aggressively removed to avoid damage to the soft tissues were performed.

Results

In a retrospective review, 55 patients were clinically diagnosed with stages II and III BRONJ, and surgical intervention for BRONJ was indicated for 44 of these patients. A total of 44 patients, 15 male and 29 female, with a mean age of 75.5 years old (range 51 to 88) at presentation, were treated (Table 1). Of these patients, 25 received oral BPs and 19 p intravenous BPs. Of the patients administered oral BPs, 19 were given alendronate. 5 risedronate, and 1 minodronate. All patients treated with intravenous BPs were administrated zoledronate. The average period of the administration of zoedronate was 40 months (range 3 to 60 months). In oral BP cases, the affected sites of the jaw were 21 mandibles, 2 of maxillae, and 2 of both jaws. In the intravenous BP cases, the affected sites of the jaw were 10 mandibles and 9 maxillae. The stages resected in oral BPs were 1 patient with stage I, 20 with stage II, and 4 with stage III, while those resected in intravenous BPs were 15 with stage II and 4 with stage III.

After informed consent was obtained and a medical evaluation was conducted, all patients agreed to the treatment and were medically stable for surgical intervention. Of the 44 patients, 39 were treated with osteotomy, while 2 of the remaining 5 patients underwent segmental resection and partial maxillectomy, respectively, and 1 underwent marginal resection. The outcome of the surgical intervention in patients administered oral BPs was resolution of the disease was achieved in all cases with an average follow-up period of 11.9 months (range 1 to 28) (Table 2 and Fig. 4). No recurrence was noted during the follow-up period. In patients

administered intravenous BPs, resolution of the disease was achieved in 11 and remission of the disease in 11, respectively. However, persistent disease was only observed in 1 case. Forty-three out of 44 patients who underwent a surgical intervention were treated effectively, leading to improvements in the quality of life.

Table 1 The characteristics of the BRONJ patients

	No. of Patients
Male	15
Female	29
Bisphosphonate medication	
Patients taking oral bisphosphonates	
Alendronate	19
Risedronate	5
Minodronate	1
Patients taking intravenous bisphosphonates	
Zoledronate	19
No. of sites of osteonecrosis diagnosed	
Mandible	
Oral bisphosphonates	21
Intravenous bisphosphonates	10
Maxilla	
Oral bisphosphonates	2
Intravenous bisphosphonates	9
Mandible and Maxilla	
Oral bisphosphonates	2
Intravenous bisphosphonates	0
Stage resected in oral bisphosphonates	
Stage I	1
Stage II	20
Stage III	4
Stage resected in intravenous bisphosphonates	
Stage I	0
Stage II	15
Stage III	4

Table 2 The outcomes of the surgical intervention of BRONJ

outcome	Oral bisphosphonates	Intravenous bisphosphonates
Resolution	24	11
Remission	0	7
Persistent	0	1
Total	24	19

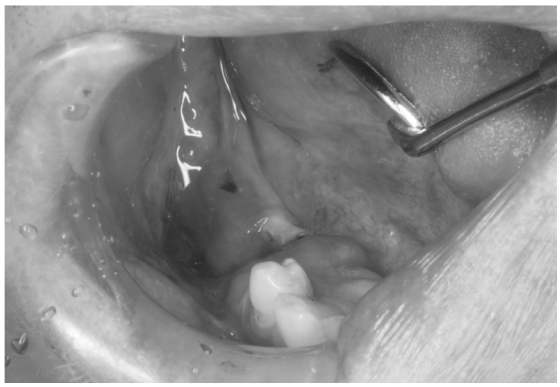

Fig. 4 Intraoral view 8 months after surgery
Complete mucosal closure with no symptoms was noted 8 months after surgery.

Discussion

The number of patients being administrated BPs is rapidly increasing in Japan; therefore, the number of patients with BRONJ has also been increasing[3]. A nationwide survey for BRONJ was conducted in Japan in 2006 and 2008[3]. The relative ratio of BRONJ related to the use of oral BPs was found to be greater in Japan than in the United States and European Union[3]. The number of cases of oral BP-related BRONJ was attributed to differences in the approval times and number of prescriptions issued for intravenous and oral BPs between Japan and the United States and Europe[3]. Since the prevalence of osteoporotic fractures is greater in Japanese women than in Caucasian women older than 50 years, the preventive administration of oral BPs to patients with osteoporosis has been increasing[22]. Additionally, poorer oral hygiene practices in the elderly in Japan than in other developed countries may also have contributed to the differences observed between these countries. However, the absolute incidence of BRONJ remains unclear, and further studies are needed to confirm the relationship between oral and intravenous BPs and BRONJ.

Therapeutic strategies for BRONJ are controversial. According to the AAOMS position paper[9,10], therapeutic strategies for BRONJ in Japan include stage-dependent surgery. Conservative treatments are recommended for patients with stage II BRONJ. Most studies have supported the use of conservative treatments for BRONJ, with minor surgical debridement only being performed in the more recalcitrant cases. However, many patients do not respond to conservative treatments and infection and bone destruction are progressive. According to the findings of the nationwide survey conducted in Japan, surgical treatments were found to con-

tribute to the remission of BRONJ, whereas conservative treatments, concurrent anticancer drugs, poor oral hygiene, and intravenous BPs did not[3]. Therefore, surgical protocols need to be developed for recalcitrant cases and surgical indications need to be defined for BRONJ. Good oral hygiene is also essential to good treatment outcomes in BRONJ patients. Kademani et al[23]. performed surgical management using local vascularized pedicle flaps and a buccal pad, and concluded that a primary surgical treatment may be beneficial for selected patients with BRONJ. In a retrospective review of 90 multiple myeloma patients, Badros et al[24]. concluded that although surgery was potentially curative when performed by experienced surgeons, postoperative complications were significant and, in many cases, resulted in the further exposure of bone. Williamson et al. described 40 cases of BRONJ in which surgical debridement of all necrotic bone and tension-free primary closure were performed, and all 40 cases healed uneventfully with no wound breakdown during the follow-up period[25]. Carlson et al. concluded that healing was particularly predictable after resection of the maxilla and mandible in patients treated with oral BPs, as well as after resection of the maxilla in patients with parental or oral BPs[19]. Stockmann et al. proposed a surgical procedure that consisted of osteotomy of the affected jaw bone that showed an abnormal color until there was sufficient bleeding from the surrounding surfaces, the removal of sharpened edges of the bone to avoid damage to the soft tissue, and primary wound closure of the mucoperiosteal flaps without tension[20]. They concluded that stage-independent osteotomy and primary closure with antibiotics was a viable treatment option for patients with BRONJ[21]. In our study, 43 out of 44 cases that underwent a surgical intervention were treated effectively, leading to improvements in their quality of life with relief from the uncomfortable symptoms. All BRONJ patients treated with oral BPs were treated successfully by the surgical intervention. Because oral BPs are mainly administrated to osteoporosis patients, the stage – independent surgical intervention is suggested to bring good prognosis to these patents. Due to the difference of the half-life of BPs metabolism between oral and intravenous BPs, the BRONJ patients treated with intravenous BPs might be poorer outcomes than patients with oral BPs. A systematic review of the therapeutical approaches in BRONJ revealed that a surgical approach to BRONJ lesion seems to be the more effective overall and in every disease stage[26]. Our results also support stage-independent surgical intervention. It is important and often difficult to obtain a surgical margin with a viable bleeding bone. This aspect represented one of the major problems associated with previous surgical approaches. In our study, osteotomy was performed until bone with an altered color was completely removed and bleeding could be identified from the surrounding bony surface. Pautke et al. adapted tetracycline fluorescence-guided bone resection in the surgical management of BRONJ and reported good treatment outcomes and utilities for discriminating between viable and necrotic bone intraoperatively[27,28]. This method may be useful to determine the area of the bone resection clearly. However, randomized clinical trials are needed to investigate the efficacy of this method.

Conclusion

We performed a surgical intervention that consisted of osteotomy and primary wound closure in patients with stages II and III BRONJ. Forty-three out of 44 cases that underwent the surgical intervention according to our protocol were treated effectively, leading to improvements in their quality of life. All BRONJ patients treated with oral BPs were treated successfully by the surgical intervention. We also proposed a stage-independent surgical intervention in patients with stage II BRONJ.

Conflict of interest

None.

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