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 Marx1) and Migliorati2) 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 cancer1,2). 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 BRONJ3). Of these patients, 60.7% had received intravenous BPs while 32.1% had received oral BPs3). Another nationwide survey was performed in 20083), and 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 Surgeons4). Among the 263 cases confirmed to have BRONJ, 57.8% had received intravenous BPs while 39.5% had received oral BPs3). The number of BRONJ patients in Japan has increased 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

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 Marx1) and Migliorati2) 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 cancer1-2). 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 BRONJ3). Of these patients, 60.7% had received intravenous BPs while 32.1% had received oral BPs3). Another nationwide survey was performed in 20083), 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 BPs3). The number of BRONJ patients in Japan has increased 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
countries. 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. Conservative treatments including antibacterial mouth rinses, the systemic administration of antibiotics, and superficial debridement in stage II BRONJ have been recommended. The radical removal of necrotic bone is limited to severe cases such as those with stage III BRONJ. In the modified position paper by AAOMS in 2014, debridement to relieve soft tissue irritation has been recommended from “superficial debridement.” 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. However, these treatments have only been partially successful, with mucosal closure only being reported in 50% of cases. 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%. 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. 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. 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.

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 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 zoledronate 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

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

**Table 2** The outcomes of the surgical intervention of BRONJ

<table>
<thead>
<tr>
<th>outcome</th>
<th>Oral bisphosphonates</th>
<th>Intravenous bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Remission</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Persistent</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>19</td>
</tr>
</tbody>
</table>

**Discussion**

The number of patients being administrated BPs is rapidly increasing in Japan; therefore, the number of patients with BRONJ has also been increasing3). A nationwide survey for BRONJ was conducted in Japan in 2006 and 20083). 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 Union3). 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 Europe3). 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 increasing22). 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 paper9,10), 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 not3. 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 pa-
tients. 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 benefi-
cial for selected patients with BRONJ. In a retrospective re-
view of 90 multiple myeloma patients, Badros et al.24) con-
cluded that although surgery was potentially curative when
performed by experienced surgeons, postoperative compli-
cations 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 ne-
ocrotic bone and tension-free primary closure were performed,
and all 40 cases healed uneventfully with no wound break-
down during the follow-up period33). 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 pa-
rental or oral BPs19). Stockmann et al. proposed a surgical
procedure that consisted of osteotomy of the affected jaw
bone that showed an abnormal color until there was suffi-
cient bleeding from the surrounding surfaces, the removal of
sharpened edges of the bone to avoid damage to the soft tis-
sue, and primary wound closure of the mucoperiosteal flaps
without tension20). They concluded that stage-independent
osteotomy and primary closure with antibiotics was a viable
treatment option for patients with BRONJ19). In our study, 43
out of 44 cases that underwent a surgical intervention were
treated effectively, leading to improvements in their quality
of life. All BRONJ patients treated with oral BPs were treat-
ed successfully by the surgical intervention. We also pro-
posed a stage-independent surgical intervention in patients
with stage II BRONJ.

Conclusion

We performed a surgical intervention that consisted of os-
teotomy 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 treat-
ed successfully by the surgical intervention. We also pro-
posed a stage-independent surgical intervention in patients
with stage II BRONJ.

Conflict of interest

None.

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