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Clinical Report

Bisphosphonate-related Osteonecrosis of Jaw (BRONJ) in Japanese Population: A Case Series of 13 Patients at Our Clinic

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Abstract

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) affects quality of life and is an important problem for dentists. A Japanese position paper on BRONJ was published in 2010. The purpose of this study was to review clinical data on the treatment of BRONJ obtained at the Clinic of Oral and Maxillofacial Surgery, Tokyo Dental College, Chiba Hospital to further our understanding of this disease. A total of 13 patients (6 men and 7 women) were included. All the patients included in this study had received Bisphosphonate (BP) therapy and had BRONJ. Five of them (38.5%) had received oral BP therapy for osteoporosis, while the remaining 8 (61.5%) had received parenteral BP therapy for bone metastases from breast or prostate cancer. Osteoporosis patients were treated with risedronate or alendronate. Breast or prostate cancer patients were treated with zoledronate. Two patients with rheumatoid arthritis were treated with corticosteroid. Three patients had diabetes mellitus. Eleven patients were treated with antibiotics, while 5 underwent surgical treatment. Discontinuation of BP was recorded in 7 patients during dental treatment. Sequestration was observed in 6 patients during an 11-month follow-up. Eventually, healing and improvement of the oral mucosa were observed in 3 patients. The current standard treatment for BRONJ does not always provide good results. It is necessary to accumulate further clinical data to establish more effective treatment strategies for BRONJ.

Key words: Bisphosphonate-related osteonecrosis of jaw (BRONJ) —
Bisphosphonate (BP) — Osteoporosis — Bone metastasis — Cancer

Introduction

Bisphosphonates (BPs) are widely used in the treatment of metabolic or malignant bone

disease. The use of oral BPs has been approved in the treatment of metabolic diseases such as osteoporosis and Paget's disease^{3,4}. Intravenous BPs are used in the treatment of bone

metastases from malignant diseases such as breast or prostate cancer or multiple myeloma^{2,13,18}. Marx was the first to report osteonecrosis of the jaw due to administration of BP in 2003¹⁵, and many studies since then have confirmed BPS-related osteonecrosis of the jaw (BRONJ) as an adverse side effect of BP therapy. Moreover, many studies worldwide have reported an association between a range of serious dental diseases and BP. In 2007, the American Association of Oral and Maxillofacial Surgeons (AAOMS) published a position paper on BRONJ to inform practitioners, patients and other interested parties¹. In Japan, the Allied Task Force Committee of the 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 published a position paper on BRONJ in 2010¹⁹. Although these guidelines are adhered to at this hospital, the prognosis of BRONJ patients remains unclear. The purpose of this study was to review clinical data on the treatment of BRONJ obtained at the Clinic of Oral and Maxillofacial Surgery, Tokyo Dental College, Chiba Hospital to further our understanding of this condition.

Cases

The AAOMS stipulated that a diagnosis of BRONJ must meet the following three conditions¹.

1. The patient is currently receiving or has previously been treated with BP.
2. The patient has had exposed necrotic bone in the maxillofacial area for longer than 8 consecutive weeks.
3. The patient has no medical history of radiation therapy for the jawbones.

A total of 13 patients (6 men and 7 women) were included in the study, all of whom had received BP therapy and had BRONJ. Comorbidities were noted in some. All patients had undergone treatment for BRONJ at the Clinic of Oral and Maxillofacial Surgery, Tokyo Den-

tal College, Chiba Hospital between 2005 and 2012. The mean age was 71.2 years (range, 46–84 years). The diagnosis of BRONJ in these patients was based on the guidelines provided by the above-cited position paper. This study was approved by the Ethics Committee of Tokyo Dental College (Approval no. 396).

1. Clinical features and medical history

(Table 1)

A total of 13 patients with BRONJ were observed. Five of these patients (38.5%) had received oral BP therapy for osteoporosis, while 8 (61.5%) had received parenteral BP therapy for bone metastases from breast or prostate cancer.

1) Symptoms

Initial symptoms were pus discharge in 6 patients (46.2%), pain in 6 (46.2%), swelling in 4 (30.8%), intraoral fistula in 3 (23.1%), foul odor in 1 (7.7%) and itching in 1 (7.7%), while a combination of these symptoms was also observed. The mandible was affected by BRONJ in 11 patients (84.6%) and the maxilla in 2 (15.4%).

2) Trigger event

The trigger event was tooth extraction in 5 patients (38.5%), minor surgery in 2 (15.4%), dental implant in 2 (15.4%) and a poorly-fitting denture in 2 (15.4%).

3) Staging of BRONJ

The Japanese position paper classified BRONJ cases into 4 groups. Stage 0: no apparent necrotic/exposed bone, Vincent's symptom, intraoral fistula, deep periodontal pocket or small osteolytic lesions on radiographs; stage 1: necrotic/exposed bone, asymptomatic and/or no infection; stage 2: necrotic/exposed bone, infection (pain, erythema) and/or purulent discharge; and stage 3: stage 2 plus extended necrotic/exposed bone, pathologic fractures, extraoral fistula, oral antral/oral nasal communication and/or extending osteolysis. In this study, 4 patients were stage 1, 8 were stage 2 and 1 was stage 3.

4) BP therapy and Co-medication

Among osteoporosis patients, 3 of 5 (60%) were treated with oral risedronate (weekly

Table 1 Clinical features and medical history of patients with BRONJ

Case No.	Age	Sex	Disease	Chief complaint	Location	Trigger event	Stage	BP therapy	Dose	Duration BP therapy (m)	Comorbid disease	Co-medication
1	76	F	Osteoporosis	Swelling	Mandible	Minor surgery	2	Risedronate	2.5 mg/weekly	48	Diabetes mellitus, Hypertention	Voglibose, Amlodipine
2	72	F	Osteoporosis	Itching sensation	Mandible	Minor surgery	1	Risedronate	2.5 mg/weekly	6	—	—
3	72	F	Osteoporosis	Intraoral fistula	Maxilla	Extraction	1	Risedronate	2.5 mg/weekly	9	Rheumatoid arthritis	Prednisolone
4	81	F	Osteoporosis	Swelling, Pus discharge	Mandible	Implant	2	Alendronate	35 mg/weekly	69	Diabetes mellitus, Rheumatoid arthritis	Insulin, Prednisolone
5	84	F	Osteoporosis	Swelling, Intraoral fistula	Mandible	—	1	Alendronate	35 mg/weekly	24	Diabetes mellitus	Glubenzamide
6	46	F	Breast cancer	Intraoral fistula	Maxilla	Implant	1	Zoledronate	4 mg/monthly	12	—	—
7	55	F	Breast cancer	Pain, Pus discharge	Mandible	Extraction	2	Zoledronate	4 mg/monthly	57	—	—
8	71	M	Prostate cancer	Pain, Pus discharge, Foul odor	Mandible	Extraction	2	Zoledronate	4 mg/monthly	36	—	—
9	71	M	Prostate cancer	Pain, Pus discharge	Mandible	—	2	Zoledronate	4 mg/monthly	24	—	—
10	73	M	Prostate cancer	Pain	Mandible	Poorly-fitting denture	2	Zoledronate	4 mg/monthly	50	—	—
11	75	M	Prostate cancer	Pain, Pus discharge	Mandible	Extraction	2	Zoledronate	4 mg/monthly	6	—	—
12	79	M	Prostate cancer	Swelling, Pain	Mandible	Poorly-fitting denture	3	Zoledronate	4 mg/monthly	24	—	Dexamethasone, Docetaxel
13	80	M	Prostate cancer	Pus discharge	Mandible	Extraction	2	Zoledronate	4 mg/monthly	21	Hypertention	—

Stage of BRONJ is as follows; Stage 0 is observed no apparent necrotic/exposed bone, Vincent's symptom, intraoral fistula, deep periodontal pocket or small osteolytic lesions on radiograph. Stage 1 is observed necrotic/exposed bone, asymptomatic or/and no infection. Stage 2 is observed necrotic/exposed bone, infection (pain, erythema) and/or purulent discharge. Stage 3 is observed stage 2 plus extending necrotic/exposed bone, pathological fractures, extraoral fistula, oral antral/oral nasal communication and/or extending osteolysis.

dose of 2.5 mg), while the remaining 2 (40%) were given oral alendronate (weekly dose of 35 mg). The mean duration of oral BP therapy was 31.2 months (range 6–69 months). In particular, 2 of these 5 patients (40%) were affected by rheumatoid arthritis, and another 2 (40%) were treated with corticosteroid (prednisolone). Three of the 13 patients (23.1%) were also affected by diabetes mellitus. Among breast or prostate cancer patients, 8 (100%) were treated with intravenous zoledronate (monthly dose of 4 mg). The mean duration of parenteral BP therapy was 28.8 months (range 6–57 months).

2. Treatment and outcome for BRONJ

(Table 2)

1) Surgical treatment

A history of surgical treatment at the site affected by BRONJ was observed in 5 patients (38.5%). In particular, 4 of these patients

underwent sequestrectomy. One of the 5 cases involved curettage. Healing of the oral mucosa was observed in 2 of these 5 patients (40%). Furthermore, 1 patient underwent sequestrectomy with particulate cancellous bone and marrow (PCBM) graft. However, no change was recorded in 1 of the 5 patients (20%). Progression of BRONJ from stage 2 to stage 3 (case 4: extraoral fistula; case 8: pathological fracture) was observed in 2 of the 5 patients (40%).

2) Antibiotics

Eleven of the patients (84.6%) were treated with antibiotics, 6 of whom (54.5%) were prescribed oral clarithromycin (daily dose of 400 mg), with a tendency toward long-term administration. On the other hand, 4 of these 11 patients (36.4%) were treated with oral amoxicillin (daily dose of 750 mg). Acute blastic crisis was observed in 1 of the 11 patients (9.1%), who was subsequently treated

Table 2 Treatment and outcome for BRONJ

Case No.	Surgical treatment	Antibiotics	Follow up (m)	BP discontinuation	Sequestration	Outcome	Pathologic report
1	Sequestrectomy with PCBM graft, Extraction	Clarithromycin 400 mg/day	14	Yes	Yes	Healed mucosa	Sequester with bacterial infection
2	Sequestrectomy	Clarithromycin 400 mg/day	75	No	Yes	No change	Sequester with bacterial infection
3	Sequestrectomy	Amoxicillin 750 mg/day	11	Yes	Yes	Healed mucosa	Sequester with bacterial infection
4	Curettage	Amoxicillin 750 mg/day	24	No	Yes	Extraoral fistula	No
5	—	Ampicillin 2 g/day	8	Yes	No	Extraoral fistula	No
6	—	Amoxicillin 750 mg/day	9	No	No	Pus discharge	No
7	—	Amoxicillin 750 mg/day	21	No	Yes	Death	No
8	Sequestrectomy	Clarithromycin 400 mg/day	12	No	Yes	Pathological fracture	Sequester with bacterial infection
9	—	Clarithromycin 400 mg/day	3	Yes	No	No change	No
10	—	—	4	Yes	No	Loss of follow-up	No
11	—	—	2	Yes	No	No change	No
12	—	Clarithromycin 400 mg/day	5	No	No	Healed mucosa	No
13	—	Clarithromycin 400 mg/day	22	Yes	Yes	No change	No

with intravenous ampicillin (daily dose of 2 g) at a hospital.

3) Follow-up and outcome

It is the policy of our clinic to re-examine each patient once a week for the first month, twice a month for the second-third months, and then once a month for the next 2 months. After that, the patient is recalled every 3 months in accordance with the guidelines given in the position paper cited above. Therefore, the mean follow-up period was 16.2 months (2–75 months). Systemic condition and local site characteristics (extension of lesion, presence or recurrence of infection, pain, quality of life, and patient compliance) were analyzed in collaboration with the prescribing physicians. A surgical approach was considered after 3 months of termination of

BP therapy. As a result, discontinuation of BP was recorded in 7 patients (53.8%). Sequestration was recorded in all patients after 11 months of follow-up. Healing of the oral mucosa was observed in 3 patients (23.1%). However, no change was observed in 4 patients (30.8%) and progression of BRONJ with an extraoral fistula was noted in 2 (15.4%). One patient died during dental treatment and 1 was lost during follow-up. Sequestration and bacterial infection were observed in all the present cases.

Discussion

According to the AAOMS, the annual incidence of oral BP-treated BRONJ cases is

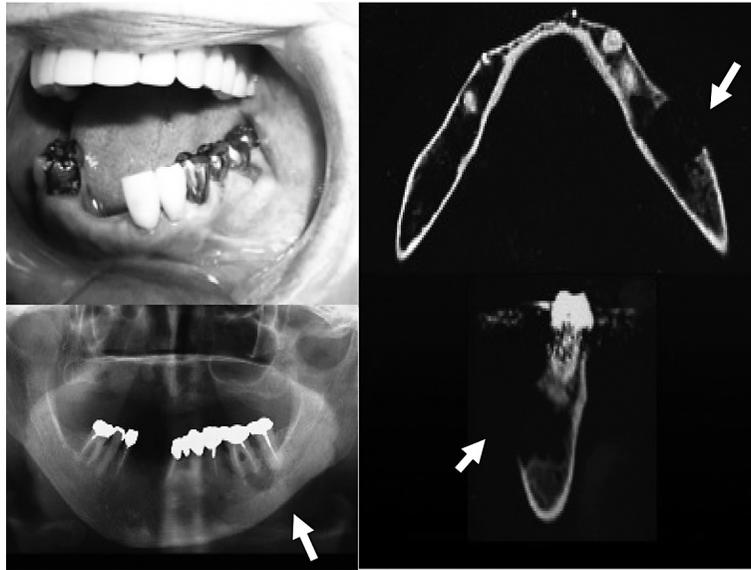


Fig. 1 Photograph, panoramic radiograph, and CT of case 1 at initial examination; 76-yr-old patient with BRONJ (stage 2).

0.7/100,000 patients-treatment years¹). Based on the occurrence of side effects and the results of a population-based study in Australia, the incidence of BRONJ was estimated to be 0.01–0.04% in patients treated with oral alendronate once per week, increasing to 0.09–0.34% after tooth extraction¹⁶). On the other hand, the incidence of parenteral BP-related BRONJ is 0.8–1.2% on average⁹), increasing up to 21% after BP administration for 3 years or more¹⁷). It is evident that the incidence of osteonecrosis of the jaw associated with parenteral BPs is higher than that with oral BPs. However, the situation has been complicated by the recent development of new parenteral BPs for osteoporosis patients. Furthermore, the exact incidence of BRONJ in Japan is unknown and remains to be investigated. In this study, 8 patients were treated with parenteral BP (zoledronate), and cases 6, 7 and 8 showed progression of BRONJ to a more serious stage than that observed in oral BP patients. Pharmacologically, BPs inhibit osteoclastic activity and reduce the progression of osteoporosis. It is well known that BPs remain bound to bone

hydroxyapatite for almost 10 years⁵). Therefore, the discontinuation of BP administration in dental treatment is a controversial issue. According to the above-cited position paper, conservative procedures are desirable, and unnecessary aggressive curettage is contraindicated. Administration of BP in patients with BRONJ is discontinued based on the following guidelines¹⁹.

1. Patients treated with parenteral BP for malignant bone diseases

Cancer patients and those at high risk for hypercalcemia, bone pain, or pathological fracture caused by a malignant tumor greatly benefit from treatment with a parenteral BP. Thus, discontinuation of parenteral BP is often difficult in these cancer patients, even when BRONJ occurs.

2. Patients treated with BP for osteoporosis

When BRONJ occurs in patients with osteoporosis, temporary discontinuation of BP or a switch from BP to other drugs should be considered if there is little risk for fracture. In fact, discontinuation of oral BP has been

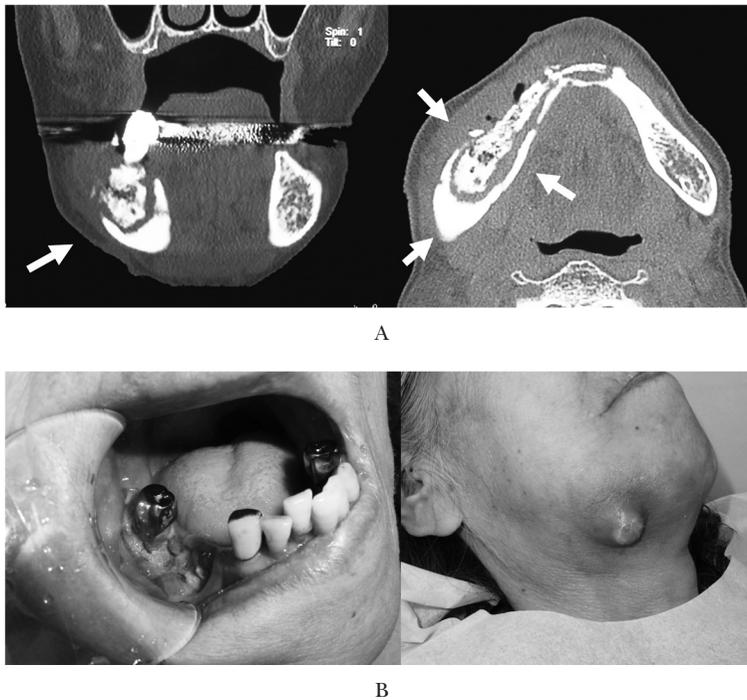


Fig. 2 A: Axial (left) and coronal (right) image of CT of case 5 at initial examination; 84-yr-old patient with BRONJ (stage 1).
 B: Photographs show intraoral (left) and extraoral fistula (right) with pus discharge after 8 months (stage 3).

shown to be effective for spontaneous separation and discharge of the sequestrum or improvement of symptoms after curettage.

In fact, it was possible to discontinue BP in 7 of the present 13 (53.8%) patients in collaboration with the prescribing physician. In particular, temporary discontinuation was possible in 3 of the cancer patients. However, this did not always result in a clinical improvement.

In case 1 (Tables 1, 2 and Fig. 1), diabetes mellitus and hypertension were observed in a patient who had received oral risedronate (weekly dose of 2.5 mg) for osteoporosis for more than 4 years. In 2006, she underwent removal of the mandibular torus close to the left side of the first molar. After that, she complained of swelling and soft tissue ulceration (stage 2). At first, she was treated with oral clarithromycin (daily dose of 400 mg). Sequestration was observed in this patient

at 14 months of follow-up. Treatment with BP had already been discontinued for over 3 months in this patient in collaboration with the prescribing physician. She subsequently underwent sequestrectomy with PCBM graft and tooth extraction. Sequestration and bacterial infection were observed in all the present cases. Eventually, healing of the mucosa and improved clinical symptoms were observed after surgery.

In case 5 (Tables 1, 2 and Fig. 2), diabetes mellitus was observed in a patient who had been treated with oral alendronate (weekly dose of 35 mg) for osteoporosis for more than 2 years. In 2012, she complained of swelling and an intraoral fistula (stage 1). At first, she was treated with intravenous ampicillin (daily dose of 2 g). Treatment with BP had already been discontinued in this patient for 8 months in collaboration with the prescribing physician. However, progression of BRONJ with

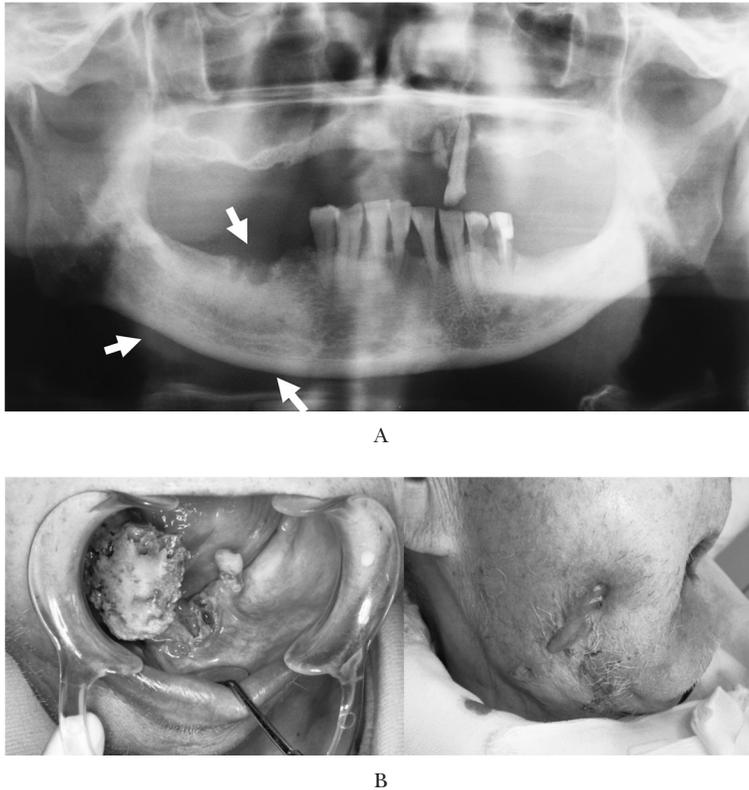


Fig. 3 A: Panoramic radiograph of case 8 at initial examination; 71-yr-old patient with BRONJ (stage 2).
 B: Photographs show pathological fracture (left) and extraoral fistula (right) with pus discharge after 3 months (stage 3).

an extraoral fistula were observed (stage 1→3). Currently she is being followed up and receiving a mouth wash with a benzethonium chloride rinse.

Case 8 (Tables 1, 2 and Fig. 3) was a patient who had been treated with intravenous zoledronate (monthly dose of 4 mg) for prostate cancer with bone metastasis for more than 3 years. In 2011, he underwent extraction of the right-side first molar. After that, he complained of pain, pus discharge and foul odor (stage 2). At first he was treated with oral clarithromycin (daily dose of 400 mg). A pathological fracture was then found during the subsequent 3-month follow-up (stage 3). It was not possible to discontinue BP treatment in this patient due to skeletal pain related to bone metastasis. He underwent

partial sequestrectomy during BP administration. Sequestration and bacterial infection were observed in all the present cases. Eventually, progression of BRONJ with an extraoral fistula was observed (stage 2→3). Currently, this patient is being followed up and receiving mouth wash with a benzethonium chloride rinse.

Thus, despite the publication of several sets of guidelines, the optimum treatment for BRONJ remains unclear. Basically, the principal goal in treating BRONJ is to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis. One recent study reported the involvement of oral bacteria in the development of BRONJ, which could explain why BRONJ develops only in the jaw-

bones¹²⁾. Sequestration and bacterial infection were observed in all the present cases.

Therefore, antibiotic treatment has an extreme therapeutic effect on BRONJ. We usually use oral clarithromycin (daily dose of 400 mg) or amoxicillin (daily dose of 750 mg). The Japanese position paper recommends non-surgical treatment strategies. However, recent studies have reported that positive surgical debridement might have been variably effective in eradicating necrotic bone as compared to conservative treatment^{7,10)}. Furthermore, one very recent study reported the usefulness of hyperbaric oxygen in the treatment of BRONJ⁶⁾. The efficacy of this approach is currently under investigation in randomized controlled trials. The efficacy of these treatment modalities is insufficiently understood as yet and needs to be established through additional research and controlled studies. Some papers reported that medications such as corticosteroids and other chemotherapeutic agents pose a high risk for BRONJ, and are categorized as a drug-related problem¹⁹⁾. Systemic factors such as diabetes mellitus have also variably been reported to increase risk for BRONJ¹¹⁾. In the present study, 2 of the patients were treated with corticosteroid for rheumatoid arthritis another 3 had diabetes mellitus. Some recent case reports noted that anti-RANKL (receptor activator of nuclear factor-kappa B ligand) antibody, denosumab, and the molecularly-targeted anticancer drug sunitinib caused osteonecrosis of the jaw with different mechanisms of action^{8,14)}. For this reason, recently this disease has been called “DIONJ; drug induced osteonecrosis of the jaw” instead of BRONJ. The position paper in Japan reported that preventative dental treatment decreased BRONJ risk and recommended that patients undergo dental evaluation and receive necessary treatment prior to initiating BP therapy¹⁹⁾. However, they emphasized that this recommendation was not evidence-based. Therefore, it is necessary to accumulate further clinical data in order to establish more effective treatment strategies for BRONJ.

Conflict of Interest

The authors declare no conflict of interest.

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