

Clinical investigation of bisphosphonate-related osteonecrosis of the jaws in patients with malignant tumors

Sei-Kyoung Kim, Tae-Geon Kwon

Department of Oral and Maxillofacial Surgery, School of Dentistry, Kyungpook National University, Daegu, Korea

Abstract (J Korean Assoc Oral Maxillofac Surg 2012;38:152-9)

Objectives: This study evaluated bisphosphonate-related osteonecrosis of the jaws (BRONJ) in patients diagnosed with malignant bone tumors. Demographic findings, laboratory, and radiographic analyses were performed to characterize disease severity and progression.

Materials and Methods: Patients who had been diagnosed with BRONJ (2005-2010) at the authors' hospital according to the American Association of Oral and Maxillofacial Surgeons were investigated. Twenty-one patients (12 with multiple myelomas, 7 with breast cancer, and 2 with prostate cancer) who had been treated with bisphosphonates (BPs) for malignant bone tumors were included. Radiographic evaluations with a panorama, computed tomography, whole body bone scan, and laboratory findings were evaluated for erythrocyte sedimentation rate (ESR), c-reactive proteins (CRPs), and c-terminal cross-linked telopeptides (CTXs).

Results: The average age of the patients was 64.3 (range 51-80), and they were treated with BPs for an average of 35±19 months before BRONJ was diagnosed. Types of BPs were zoledronic acid (81%, intravenous [IV]), pamidronate (4.8%, IV), zoledronic acid+pamidronate (4.8%, IV), alendronate (4.8%, per os [PO]), and ibadronate (4.75%, PO). Extraction (67%) and persistent irritation of dentures (20%) were the most common triggering factors. BRONJ in the mandible was reported in 62% of the cases, in the maxilla 24%, and both 14%. BRONJ occurred more frequently in patients with multiple myelomas (n=12, 57.1%). Most of the patients revealed an advanced BRONJ stage; Stage I (n=2, 9%), Stage II (n=13, 62%), and Stage III (n=6, 29%).

Conclusion: The differences of the ESR, CRP, and CTX values between the BRONJ-recurring and non-recurring patients after the treatment were not evident. Later stage BRONJ patients showed lower CTX levels. A drug holiday after the diagnosis of BRONJ did not remarkably influence the surgical outcomes. However, the limited number of patients in the study should be considered.

Key words: Bisphosphonates, Jaw, Necrosis, Malignant tumors

[paper submitted 2012. 3. 29 / revised 2012. 5. 4 / accepted 2012. 5. 8]

I. Introduction

Bisphosphonates (BPs) has generally been used to increase bone density of patients with osteopenia such as osteoporosis and Paget's disease. It has been also used to relieve pain caused by bone metastasis for patients with malignant tumor including multiple myeloma, breast cancer, prostate cancer and lung cancer, and to prevent subsequent pathologic fracture^{1,2}.

BPs is divided into the 1st generation (alkyl or halide side group), the 2nd generation (amino-terminal group) and the 3rd generation (imidazol ring group). The 3rd generation BPs is 100,000 times more effective than the 1st generation and 100 times more effective than the 2nd generation. If a patient with malignant tumor has a focus of bone metastasis, generally the 2nd generation pamidronate or the 3rd generation zoledronate is injected intravenously^{3,4}.

BPs is deposited on the surface of bone where bone generation is processed actively to restrain growth of osteoclast and prevent its function. Also, it prevents adhesion of osteoclast into the place of bone resorption and decreases generation of cytokine that facilitates bone resorption⁵, prevents invasion of tumor cells into bone matrix, leads to tumor cell death⁵ and suppress growth factors that activates osteoblasts⁶.

Tae-Geon Kwon

Department of Oral and Maxillofacial Surgery, School of Dentistry, Kyungpook National University, 2175 Dalgubeol-daero, Jung-gu, Daegu 700-705, Korea
TEL: +82-53-600-7562 FAX: +82-53-426-5365
E-mail: kwondk@knu.ac.kr

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*This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF 2010-0011-445).

General side effects of BPs are fatigue during the early stage of administration, common cold-like symptoms, anemia, edema and nephrotoxicity⁷. But in 2003, bisphosphonate-related osteonecrosis of the jaw (BRONJ) was added as one side effect after Marx⁸ reported a case of BRONJ for the first time. So far, many cases of BRONJ have been reported worldwide. According to the diagnostic criteria of BRONJ announced by the American Association of Oral and Maxillofacial Surgery (AAOMS), BRONJ can be diagnosed when the patient has history of BPs administration, no history of radiation treatment, and shows bone exposure and osteonecrosis in jaw bone for more than 8 weeks⁹.

The mechanism of BRONJ generation has not yet been identified, but the most convincing hypothesis states that BPs limit osteoclast functions, which retard regeneration of jaw bone where bone is replaced faster than extremity bones by reducing bone turnover rate, and as a result, osteonecrosis occurs subsequent to trauma such as extraction or infection¹⁰.

After the report of Marx⁸, many research studies on BRONJ of malignant tumor patients were published internationally¹¹⁻¹⁶. However, analysis of BRONJ in malignant tumor patients in Korea had not been reported yet. This study analyzed the clinical aspects and laboratory findings of BRONJ in Korean malignant tumor patients, and evaluated their treatment progress and prognosis to establish adequate diagnostic and treatment assessment.

II. Materials and Methods

This study examined 21 BRONJ patients who had been diagnosed as BRONJ after receiving BPs for cancer treatment and treated from August 2005 to November 2010 at Oral

and Maxillofacial Surgery unit of Kyungpook National University Hospital. All patients met the criteria of BRONJ announced by AAOMS⁹.

For clinical diagnosis, panoramic radiography was taken during the initial medical examination, along with computed tomography (CT), bone scan and biopsy. For 12 patients, erythrocyte sedimentation rate (ESR) (TEST1 THL; SIRE Analytical systems, Udine, Italy), c-reactive protein (CRP) (Tina-quant; Roche Diagnostics, Indianapolis, IN, USA), c-terminal cross-link telopeptide (CTX) (Elecsys, beta-CrossLabs ECLIA; Roche Diagnostics, Basel, Switzerland) in serum were measured in the morning fasting status and compared with normal range of these tests.

The subjects were treated according to AAOMS guidelines⁹, patients were evaluated 1 week, 2 weeks, 4 weeks, 8 weeks and 6 months postoperatively. Treatment outcomes were divided according to the prognosis of the patients; complete response means the lesion was cured and bone exposure disappeared completely as in Fig. 1; partial response means bone exposure and pain were decreased; no response means that the cases with unsatisfying result, continuous pain and existing bone exposure that was not decreased. Each patient's prognosis was determined following more than 6 months of BRONJ treatment, and patients whose monitoring period was less than 6 months were excluded. This research was approved by Kyungpook National University Institutional Review Board (KNUH_IRB 10-1093).

III. Results

Average age of 21 cancer patients (5 males, 16 females) at the time of diagnosis with BRONJ was 64.3 years

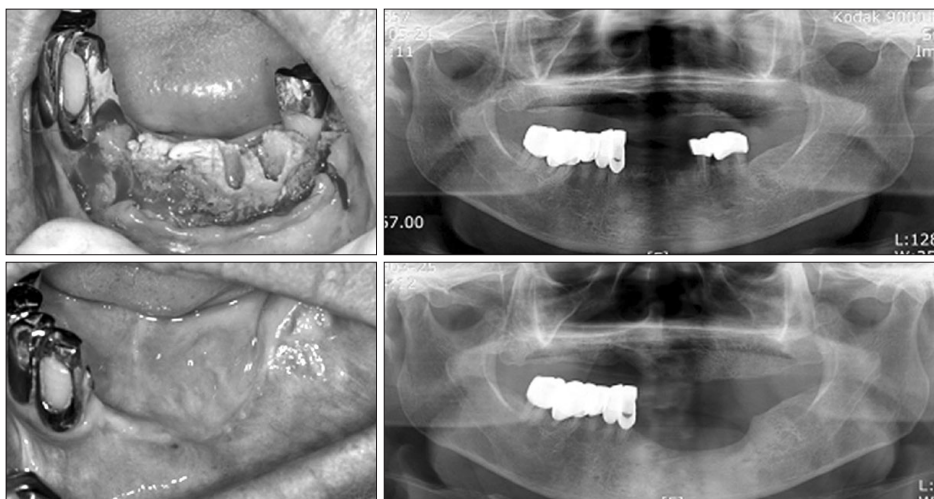


Fig. 1. One example of bisphosphonate-related osteonecrosis of the jaw related with Zometa injection for 12 months in patient with breast cancer (patient #14). The patient experienced a large area of exposure (upper panel) and had received surgical curettage and sequestrectomy. Six-month follow up after surgical treatment showed complete healing (lower panel).

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(ranged 51-80). The most common reason for BPs treatment was multiple myeloma (12 patients, 57.1%), followed by metastasis of breast cancer (7 patients) and prostate cancer (2 patients). Most patients received intravenous injections of zoledronate (17 patients, 81%), with the others received pamidronate (1 patient) and alternative injections of pamidronate and zoledronate (1 patient). Alendronate (1 patient) and ibandronate (1 patient) were administered orally. At the time of BRONJ diagnosis, the average period of intravenous BPs administration was 35.1 ± 20.0 months and oral BPs was 30.0 ± 9.0 months. Overall average period of BPs administration was 35.0 ± 19.0 months. Twelve patients (57.1%) had another disease with malignant tumor. The most frequently accompanying disease was high blood pressure (7 patients), and 3 patients had both high blood pressure and diabetes. Some patients had multiple diseases such as diabetes (5 patients), arthritis (4 patients), renal insufficiency, pneumonia, gastritis and gastric ulcer (1 patient). The most common triggering factor of BRONJ was extraction (14 patients, 67%), followed by persistent irritation of dentures (4 patients, 20%), implant and alveoloplasty (1 patient, 4.3%). In 1 patient, we could not find triggering factor. (Table 1)

All patients had bone exposure and pain. Fifteen patients

had purulent exudates in the infected area. BRONJ was located in the mandible (13 patients, 62%), maxilla (5 patients, 24%) and both (3 patients, 14%). Two patients (9%) had BRONJ in the anterior area only, 15 patients (72%) had it in the posterior area only, and 4 patients (19%) had it in both the anterior and posterior areas. Facial edema and fistulous opening were identified in 1 patient. According to the BRONJ staging defined by AAOMS, at the first medical examination 2 patients (9%) were in stage I, 13 patients (62%) were in stage II, and 6 patients (29%) were in stage III. (Table 2)

Average ESR was 42.3 ± 27.6 mm/h, higher than the normal range (0-20 mm/h, Kyungpook National University Hospital). Average CRP of 12 BRONJ patients were 2.1 ± 3.9 mg/d, higher than the normal value (0.5 mg/dL). Average osteocalcin (OCN) was 7.0 ± 4.7 ng/mL, which was within normal limits (4-12 ng/mL). Average alkaline phosphatase (ALP) of patients was 67.2 ± 18.9 u/L, which falls within the normal range (35-129 u/L). Average CTX of patients was 183 ± 124 pg/mL, significantly lower than the normal limits (400-500 pg/mL). These findings indicate that bone resorption was greatly reduced with BPs administration in current patients. Among 12 patients with CTX less than 150 pg/mL, none were in stage 0 or I; most were in stage II or III.

Table 1. Demographic data of the BRONJ patients related with malignant bone disease

Pt. No.	Age	Sex	Reason of BPs use	BPs	Route	Duration (months)	Co-morbid diseases	Related events
1	53	F	Multiple myeloma	Z	IV	44		
2	57	F	Multiple myeloma	Z	IV	21		Extraction
3	56	M	Multiple myeloma	Z	IV	60		Implant
4	68	F	Multiple myeloma	Z	IV	28	Degenerative arthritis	Alveoloplasty
5	60	F	Multiple myeloma	Z	IV	21		Extraction
6	51	F	Multiple myeloma	Z	IV	19		Extraction
7	64	F	Multiple myeloma	Z	IV	12	Diabetes	Extraction
8	66	F	Multiple myeloma	Z	IV	36		Extraction
9	70	F	Multiple myeloma	P	IV	84		Extraction
10	72	M	Multiple myeloma	Z	IV	12	Hypertension	Extraction
11	60	M	Multiple myeloma	Z	IV	48	Hypertension, renal failure	Extraction
12	76	F	Multiple myeloma	P+Z	IV	64	Pneumonia	Denture
13	58	F	Breast cancer	Z	IV	45		Extraction
14	55	F	Breast cancer	Z	IV	12		Extraction
15	74	F	Breast cancer	Z	IV	19	Hypertension, diabetes	Denture
16	51	F	Breast cancer	Z	IV	24	Hypertension, diabetes	Denture
17	65	F	Breast cancer	I	PO	24	Colitis, arthritis, hypertension	Extraction
18	64	F	Breast cancer	Z	IV	45		Extraction
19	62	F	Breast cancer	Z	IV	24	Diabetes	Extraction
20	75	M	Prostate cancer	A	PO	36	Hypertension, stomach ulcer, arthritis	Denture
21	80	M	Prostate cancer	Z	IV	48	Hypertension, arthritis, gastritis	Extraction

(BRONJ: bisphosphonate-related osteonecrosis of the jaw, Pt.: patient, BPs: bisphosphonate, F: female, M: male, Z: zoledronate, P: pamidronate, I: ibandronate, A: alendronate, IV: intravenous, PO: per os)

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Table 2. Clinical characteristics and outcomes of the treatments

Pt. No.	Clinical symptom	Site of lesions	Stage	Treatment	Recurrence	After final treatment
1	Bone exposure, pain	Mx. Post. area (#14, 15)	II	Sequestrectomy & curettage	Yes	F/U
2	Bone exposure, pain	Mn. Post. area	III	Sequestrectomy & curettage	Yes	Complete healing
3	Bone exposure, pain	Mn. Post. area (#36)	II	Sequestrectomy & curettage	No	Complete healing
4	Bone exposure, pain, pus discharge	Mx. Ant. area (#11-13), Mx. Post. area, Mn. Ant. area	II	Sequestrectomy & curettage	Yes	Complete healing
5	Bone exposure, pain, numbness	Mn. Post. area (#47)	II	F/U-Loss	No	
6	Bone exposure, pain, pus discharge	Mn. Post. area (#46)	II	Sequestrectomy & curettage	No	Complete healing
7	Bone exposure, pain, pus discharge	Mx. Post. area & Mn. Post. (#15, 17, 36)	II	Curettage	Yes	F/U
8	Bone exposure	Mn. Post. (#33-35)	I	Sequestrectomy & curettage	Yes	F/U
9	Bone exposure, pain, pus discharge	Mn. Post. (#37)	III	Sequestrectomy & curettage	No	Complete healing
10	Bone exposure	Mn. Ant. area (#33-43)	I	Sequestrectomy & curettage	Yes	F/U
11	Bone exposure, pain, pus discharge	Both Mn. Post. area (#34-37, 45, 46)	III	Excision	No	F/U
12	Bone exposure, pain, pus discharge, swelling	Mx. Ant. area & Post. area (#26, 27)	II	Debridment	No	F/U
13	Bone exposure, pain, pus discharge	Mx. Post. area (#15, 16)	III	Sequestrectomy & curettage	No	Complete healing
14	Bone exposure, pain, pus discharge	Mx. Post. area (#17), Mn. Ant. area	II	Sequestrectomy & curettage	No	Complete healing
15	Bone exposure, pain, pus discharge	Mn. Ant. area (#32)	II	Curettage	Yes	F/U
16	Bone exposure, pain, pus discharge	Mx. Post. area (#27)	II	Curettage	Yes	F/U
17	Bone exposure, pain, pus discharge, fistula	Mn. Post. area (#37, 38)	III	Sequestrectomy & curettage	No	Complete healing
18	Bone exposure, pain, pus discharge	Mx. Post. area (#26, 27) & Mn. Post. area (#44, 45)	II	Sequestrectomy & curettage	Yes	Complete healing
19	Bone exposure, pain, pus discharge	Mn. Post. area (#47)	II	Sequestrectomy & curettage	Yes	F/U
20	Bone exposure, pain, pus discharge	Mn. Post. area	III	Curettage	No	F/U-loss
21	Bone exposure, pain, pus discharge	Mn. Post. area	III	Sequestrectomy & curettage	No	Complete healing

(Pt.: patient, Mx.: maxilla, Mn.: mandibular, Post.: posterior, Ant.: anterior, F/U: follow up)

Sei-Kyoung Kim et al: Clinical investigation of bisphosphonate-related osteonecrosis of the jaws in patients with malignant tumors. *J Korean Assoc Oral Maxillofac Surg* 2012**Table 3.** BRONJ stage according to value of CTX

CTX (pg/mL)	Stage 0	Stage I	Stage II	Stage III
Less than 150	0	0	3	3
Over 150	0	1	4	1

(BRONJ: bisphosphonate-related osteonecrosis of the jaw, CTX: c-terminal cross-link telopeptide)

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Among patients where the results exceeded 150 pg/mL, 4 were in stage II and 1 was in stage III. (Table 3)

Two patients were cured by conservative treatment and medication while 19 patients underwent surgery. The surgery was conducted after 11±10 weeks (about 3 months) after initial diagnosis after the surgery. Sequestrectomy, curettage or block excision was conducted when sequestrum was identified clearly in CT images. Eight patients were referred to internal medicine when BRONJ occurred, and BPs was replaced with an alternative medication. Average drug holiday was 25±15 weeks (about 6 months). However,

compared with other patients who did not have drug holiday before the surgery, it did not remarkably influence the number the surgical treatment, outcomes after the first surgery, or the final treatment.

Among 19 patients who had been performed surgery, 1 died during treatment from metastatic cancer. BRONJ recurred at the same sites in 7 patients (37%) and at the different sites in 3 patients (16%). Among the 7 patients experiencing recurrence, 6 were female. The average age of all 7 patients was 63.6 years (53-72). Among 12 multiple myeloma patients, 5 (41.7%) were recurred BRONJ after the treatment. Among 7 breast cancer patients, 2 (28.6%) were BRONJ after the treatment. Most patients (n=6) failed to maintain proper dental hygiene. The differences of the ESR, CRP, and CTX values between the BRONJ-recurred and non-recurred patients after the treatment were not evident. (Table 4) For 3 patients who had BRONJ lesion in a different area, the reason of recurrence was additional extraction caused by improper dental care and denture irritation.

Table 4. Comparison of laboratory findings between patients experiencing recurrence after the initial treatment and those without recurrence

Pt. No.	ESR (mm/h)	CRP (mg/dL)	CTX (pg/mL)
Patients with recurrence after initial treatment			
3	16	12.15	170
9	46	0.3	81
11	44	3.94	188
12	86	3.28	99
14	89	1.2	458
18	25	0.2	59
Mean±SD	51±30	3.9±4.9	175±147
Patients without recurrence after initial treatment			
2	12	0.17	67
4	34	0.63	178
10	72	0.74	369
16	33	0.07	128
19	12	0.04	169
20	82	0.79	149
Mean±SD	40.4±29.8	0.4±0.35	176±102

(Pt.: patient, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, CTX: c-terminal cross-linked telopeptide, Mean±SD: mean±standard deviation)

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Among 19 patients (except 1 who died and 1 who did not participate in long-term examination), 10 patients showed complete response; and in 5 patients with bone exposure and pain, their conditions improved. Four patients are in long-term regular examination due to continuous bone exposure and pain.

IV. Discussion

BPs is used to prevent hypercalcemia in bone metastasis of patients with a malignant tumor including multiple myeloma, prostate cancer, breast cancer and lung cancer while reducing pain caused by bone metastasis^{2,17}. As the hypercalcemia is one of the general complications of cancer patients, which can cause nausea, convulsion, etc. with excessive dehydration, as well as pathologic fracture, control of hypercalcemia in metastatic tumor patients is one of the major concern.

BPs is an analogue of pyrophosphate. It has a relatively long half-life because of P-C-P structure and resistance against hydrolysis by enzymes, but is not absorbed readily in the gastrointestinal tract. As a result, it was developed as structural modification of pyrophosphate. BPs has chains of R1 and R2; R1 determines the binding capacity with bone matrix, and R2 determines pharmacological activity and potency. BPs is largely divided into non-nitrogen BPs

and nitrogen BPs based on the binding of R2 chain with nitrogen. Nitrogen BPs is more pharmacologically more effective. The 1st generation BPs has alkyl or halide side group without the nitrogen, such as etidronate, clodronate and tiludronate. The 2nd generation has amino-terminal group with 1 nitrogen, such as alendronate and pamidronate. The 3rd generation has an imidazole ring group and includes 2 nitrogen, such as risedronate, ibandronate and zoledronate³. The 2nd generation pamidronate and the 3rd generation zoledronate can be absorbed better than oral medications because these are intravenously administered and less than half of the drug (25-40%) is not metabolized and secreted as urine whereas all the rest of the drug remains in bone¹⁸. As a result, the 3rd generation BPs zoledronate is 100,000 times more effective than the 1st generation and 100 times more effective than the 2nd generation³. According to the guidelines from the American Society of Clinical Oncology, 90 mg of pamidronate should be injected intravenously for 2 hours on every 3-4 weeks, and 4 mg of zoledronic acid should be injected intravenously for 15 minutes on every 3-4 weeks¹⁷. Zoledronic acid is used for malignant tumor patients with bone metastasis because of the promising effect and convenience in administration. When using zoledronic acid for breast cancer or multiple myeloma patients for more than 25 months, the incidence of Skeletal-related events (such as hypercalcemia of malignancy, pathologic fractures) was reduced from 48-68%¹⁹ to 47%²⁰; for prostate cancer patients (treated for more than 24 months), it was reduced from 49% to 38%²¹, and in lung cancer patients (treated for more than 21 months), it was reduced from 46% to 39%²². And zoledronic acid lessens the invasion of cancer cells in vitro. Corey et al.²³ reported that infiltration of PC3 (prostate cancer cell) was greatly reduced in proportion to the dose of zoledronic acid. Also, Wood et al.²⁴ reported that in a mouse experiment, zoledronic acid blocked angiogenesis and prevented cancer cell growth. But in spite of such advantages, more than 90% of BRONJ patients are cancer patients who received BPs intravenously²⁵, and the incidence of BRONJ was reported as 0.8-18.6% in these patients⁹.

Even though mechanism of osteonecrosis of the jaw after BPs had not been clearly identified. Reduced osteoclast function and apoptosis of osteoclast after BPs are major drug effect but the one on the causative factors of BRONJ. Bone-bound nitrogen BPs does not hydrolyze after the osteoclastic bone resorption, which results in reduced osteoclast activity and subsequent cell death by inhibiting the mevalonate pathway²⁶. In other words, BPs suppress the function of

osteoclasts and resultant bone remodeling of jaw bone where bone is replaced faster than other extremity bones by reducing bone turnover rate. As a result, osteonecrosis occurs following trauma such as extraction or infection¹. The second hypothesis is soft tissue toxicity theory. BPs highly accumulated in the jaw bone and damages the oral epithelium, subsequently infects the jawbone and causes osteonecrosis²⁷. The third hypothesis involves the suppression of angiogenesis theory that states reduced blood supply to the jawbone causes osteonecrosis. But it lacks credibility because other anti-angiogenic agents do not readily cause BRONJ. In fact, the number of blood vessel in the jawbone of BRONJ patients is within normal range²⁷.

Eckert et al.²⁸ reported that among the 24 BRONJ patients, the average age of 22 cancer patients except 2 osteoporosis patients was 62.5 years (47-81), and Hoff et al.¹¹ showed 60.1 years (42-78), similar to this study (64.3 years). Other research of malignant tumor patients demonstrated a higher population of female than male patients^{11,28}, which is consistent with this study. Wang et al.¹⁴ reported that incidence of BRONJ in multiple myeloma patients was the highest (3.8%, n=11/292), compared with 2.9% for prostate cancer patients (n=2/69) and 2.5% for breast cancer patients (n=2/81). Also in this study, most BRONJ patients were multiple myeloma patients because of frequent used of zoledronic acid injected intravenously due to osteolysis of multiple myeloma that causes 100% bone metastasis¹⁷. The incidence of BRONJ was the highest when only zoledronic acid was injected, followed by when both zoledronic acid and pamidronate were used. When only pamidronate was injected intravenously, the lowest incidence of BRONJ was recorded¹¹. In this study, the average period of BPs administration when BRONJ occurred was 35.0 months, similar to the findings in research by Hoff et al.¹¹ (31.2 months). The most popular triggering factor of BRONJ was extraction (more than 60%). As shown in research by Bamias et al.¹³ (76.5%), Vahtsevanos et al.¹⁵ (57.5%) and Hoff et al.¹¹ (55.2%), extraction is an important factor of BRONJ. For the location of BRONJ, this study and the research of Eckert et al.²⁸ and Bamias et al.¹³ indicate that BRONJ generally occurred in the mandible. This study also proved that BRONJ occurred more frequently in the posterior area than the anterior area.

ESR is measured to diagnose and observe various diseases including infection, inflammatory, malignant and traumatic diseases. The average ESR was 42.3±27.6 mm/h, higher than the normal range (0-20 mm/h). CRP is measured for

infectious diseases or observe the progress because it shows nonspecific reaction to inflammation and damaged tissue. The average CRP of 12 malignant tumor patients with BRONJ was 2.1±3.9 mg/dL, higher than the normal value (0.5 mg/dL). These facts indicate that inflammatory reaction of BRONJ patients is high. OCN is a very special protein for bone. It is produced in osteoblasts and accumulated in the extracellular matrix of bone, with 30% of newly compounded OCN being emitted to blood. Therefore, OCN is used as an indicator of the level of osteogenesis²⁹. The average OCN of malignant tumor patients in this study was 7.0±4.7 ng/mL, within the normal range (4-12 ng/mL). ALP is another indicator of osteogenesis used widely for more than 50 years³⁰. Other potent indicator of osteoblast activity, ALP of patients in this study was 67.2±18.9 u/L, within the normal range (35-129 u/L). These indicate that the BPs use in cancer patients did not influence the osteoblastogenesis. CTX is a sensitive indicator of restrained bone resorption. When the CTX is measured, it more quickly reacts to BPs than other indicators of bone metabolism³¹. Normal value is 304±40 pg/mL for males in the 50-70 year-old range, and 394±46 pg/mL for males older than 70. For females, the normal range is 274-299 pg/mL pre-menopause and 452-556 pg/mL post-menopause. Average CTX of patients in this study was 183±124 pg/mL, significantly outside normal values, indicating that their bone resorption ability was greatly decreased. Such low CTX reflects the effect of BPs. To analyze the relationship between low CTX and the incidence of BRONJ, it is necessary to analyze a control group - no BRONJ with BPs. However, this study has fundamental limitation of lack of data of control group. Therefore, relationship between low CTX and the incidence of BRONJ should be studied further.

The influence of low CTX on the prognosis for BRONJ patients has not been clearly identified. Low CTX means bone resorption is reduced, and such suppression of bone metabolism may influence the prognosis. To examine further, this study analyzed the CTX of patients with or without recurrence of BRONJ lesion. However we could not find significant difference between the two groups. Although it is difficult to draw conclusive remarks due to limited number of patients, the current results showed no significant difference between the prognosis and CTX. It implies that it is difficult to consider CTX as a marker for predicting the prognosis. In this study, the higher the stage of BRONJ showed lower the value of CTX. However we could not show the cutoff value of CTX for treatment. Additional research based on more cases is required.

According to Eckert et al.²⁸, among 19 patients, 10 (52.6%) had a recurrence and suggested the reason of recurrence was insufficient surgical curettage of the lesion at the time of diagnosis. In our study, 7 of the 19 patients (37%) had recurrence. Although an accurate comparison is difficult because osteoporosis patients were included, according to the research of Mücke et al.³², an aggressive and extensive surgery decreased the recurrence rate by 28.7%. Also, Mücke et al.³² reported that bacterial infection around dead tissues and conservative non-surgical treatment increased the recurrence of BRONJ. AAOMS guidelines emphasize conservative treatment. However, our and those of others' result showed that the treatment strategy of the BRONJ need not to be remained in "conservative".

In this study, among 7 patients with BRONJ recurrence, 6 had improper oral hygiene. This implies that the recurrence can be occurred due to bacterial infection. According to the AAOMS guidelines, patients diagnosed with BRONJ should stop BPs administration for 6-12 months or use an alternative drug⁹. However, in this study, suspension of BPs administration did not change treatment outcomes or the recurrent rate. Hoff et al.¹¹ reported that for 3 multiple myeloma patients with BRONJ showed complete remission of BRONJ after stopping the zoledronic acid or using alternative medicine for 10 months. However, in 6 breast cancer patients with BRONJ who stopped administration of BPs or used an alternative drug BPs, BRONJ was not cured completely. Therefore, additional research is needed on the relation between suspension of BPs administration and treatment/recurrence of BRONJ.

BRONJ occurred more frequently in malignant tumor patients using BPs than osteoporosis patients. BRONJ in malignant tumor patients shows frequent recurrence ratio and difficult to have complete cure. Therefore, for malignant tumor patients, it is very important to prevent intra-oral risk factors before administration of BPs to prevent BRONJ. Dimopoulos et al.³³ prevented risk factors such as extraction and periodontal diseases in multiple myeloma patients and administered zoledronate after 6-8 weeks. As a result, the incidence of BRONJ decreased about 3 times. Ripamonti et al.³⁴ also removed risk factors from cancer patients in advance with an oral examination and administrated BPs. As a result, the incidence of BRONJ decreased by 70%. Therefore, as with patients receiving preventive dental treatment before radiation treatment or organ transplant, it is important to prevent intra-oral risk factors before administrating BPs for patients of malignant tumor or osteoporosis.

V. Conclusion

This study evaluated 21 patients with BRONJ who had been treated BPs for malignant bone tumor at Department of Oral and Maxillofacial Surgery, Kyungpook National University Dental Hospital, from August 2005 to November 2010. Based on the clinical features monitored in the progress of diagnosis and treatment, the following conclusions were obtained.

1. The highest incidence of BRONJ was found in multiple myeloma patients (12 patients, 57.1%). The period of BPs application was 35.0 ± 19.0 months. For triggering factors of BRONJ, 14 patients (67%) had BRONJ after extraction and 4 patients (20%) were related with persistent irritation from dentures.
2. BRONJ was located more in the maxilla than mandible, and more in the posterior area than anterior area. At the time of initial diagnosis, 2 patients (9%) were in stage I, 13 patients (62%) were in stage II and 6 patients (29%) were in stage III.
3. Though statistical verification is impossible due to the limited number of patients, there was no statistically significant difference between those suffering from recurrence and those remaining in remission in the values of ESR, CRP, and CTX. The higher the stage of BRONJ, the lower the value of CTX.
4. For malignant tumor patients, drug holiday after the diagnosis of BRONJ did not remarkably influence the surgical outcomes including treatment progress and frequency of recurrence.

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