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Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management

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Bisphosphonates are a class of agents used to treat osteoporosis and malignant bone metastases. Despite these benefits, osteonecrosis of the jaws is a significant complication in a subset of patients receiving these drugs. Based on a growing number of case reports and institutional reviews, bisphosphonate therapy may cause exposed and necrotic bone that is isolated to the jaw. This complication usually presents after simple dentoalveolar surgery. The pathogenesis for this complication appears to be related to the profound inhibition of osteoclast function and bone remodeling. This report serves to alert dentists and dental specialists about the potential complication of maxillary and mandibular bone necrosis in patients receiving bisphosphonate therapy, and proposes a guideline for diagnosis, staging, and management.

Bisphosphonates are a new class of agents that have been increasingly recommended for use in patients with osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, osteolytic bone metastases, and osteolytic lesions of multiple myeloma. Despite the benefits related to use of these medications, osteonecrosis of the jaws is a significant complication in a subset of patients receiving these drugs. The phenomenon of bisphospho-

nate-related osteonecrosis (BRON) was recognized a few years after their approval for use. Reports first appeared in 2003, alerting the dental and medical communities of this complication.¹⁻⁴ There is an increasing number of BRON cases being diagnosed, and BRON is recognized as occurring in all countries where bisphosphonates are prescribed. Cases of BRON have been reported in scientific articles in refereed journals, abstract presentations at national scientific meetings, correspondence in the form of letters to the editor, authors replies, and editorials, and medical alerts and advisories to dentists and physicians.¹⁻²⁴ Some have questioned the association of bisphosphonates and osteonecrosis of the jaw, suggesting that a causal relationship has not been definitively proven.^{25,26} The similarity of BRON to cases of phosphorous necrosis of the jaw in workers exposed to white phosphorus (phossy jaw) during the late 19th and early 20th century has been reported by Hellstein et al.^{14,16} and Donaghue.²³ This historical fact lends support to the phenomenon of jaw osteonecrosis being linked directly to the bisphosphonate medications. Also of historical note is a 1995 case report by Starck and Epker²⁷ describing the failure of osseointegrated implants after bisphosphonate therapy for osteoporosis. However, that article does not describe osteonecrosis, and a direct cause and effect of bisphosphonate use and implant failure is difficult to establish based on the single case report. However, there is increasing concern that the oral bisphosphonates are implicated in osteonecrosis of the jaws, albeit less commonly than that observed with the more potent intravenously administered bisphosphonates. Based on the available data, and the authors' experiences, we review the background of this phenomenon and offer guidelines in the diagnosis and treatment of BRON and

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emphasize the important role of the general dentist and the dental specialist in the diagnosis and management of affected patients.

INDICATIONS FOR BIPHOSPHONATE USE

Cancer patients with metastatic or primary bone lesions often develop sequential skeletal complications. These complications may include pain, pathologic fracture, spinal cord compression, and hypercalcemia of malignancy.²⁸ Activation of osteoclasts, mediated by cytokines produced by tumor cells, leads to disruption of normal bone metabolism.²⁹ Patients with metabolic bone disease such as osteoporosis³⁰ and Paget's disease^{31,32} similarly have decreased bone strength and increased susceptibility to bone pain and fracture. Bisphosphonates are nonmetabolized analogs of pyrophosphate that localize to bone and prevent or ameliorate skeletal complications. The various bisphosphonates, approved for clinical use, differ based on structural alterations of the so-called R-2 side chain. These R-2 side chains determine the cellular effects and efficiencies as inhibitors of bone resorption. Once deposited on the surface of bone, bisphosphonates are internalized by osteoclasts, causing disruption of osteoclast-mediated bone resorption.²⁹ Bisphosphonates also have antiangiogenic properties, resulting in decreased circulating levels of vascular endothelial growth factor (VEGF).³³⁻³⁷ Antineoplastic effects of bisphosphonates also have been suggested.³⁸ The efficacy of these agents in reducing bone pain, skeletal complications, and hypercalcemia has been extensively documented in patients with metastatic breast cancer and multiple myeloma.³⁹⁻⁴¹ Efficacy of bisphosphonates in patients with progressive metastatic prostate carcinoma and other solid tumors has been reported, though not as extensively studied as with the aforementioned malignancies.^{42,43}

There are a variety of bisphosphonates that are approved for clinical use in the United States (Table I). The intravenous bisphosphonates are approved for patients with metastatic breast cancer, multiple myeloma, hypercalcemia of malignancy, and Paget's disease of bone and for treatment of documented bone metastases from any solid tumor. These intravenous bisphosphonates include pamidronate (Aredia), a second-generation bisphosphonate that is administered intravenously every 3 to 4 weeks at a typical dose of 90 mg, and zoledronic acid (Zometa), a third-generation bisphosphonate, administered intravenously every 3 to 4 weeks at a dose of 4 mg. In comparison with pamidronate, zoledronate is significantly more potent and more effective in controlling hypercalcemia of malignancy and reducing the overall number of skeletal complications.⁴¹ It is estimated that over 2.8 million cancer

Table I. Bisphosphonate medications approved for use in the United States

Generic Name	Brand name, delivery	Manufacturer	RP	FDA-a
Pamidronate	Aredia, IV	Novartis	100	1991
Tiludronate	Skelid, PO	Sanofi	10	1997
Alendronate	Fosamax, PO	Merck	1,000	1997
	sodium			
Etidronate	Didronel, PO	Proctor & Gamble	1	1997
Risedronate	Actonel, PO	Proctor & Gamble	5,000	1998
Zoledronic acid	Zometa, IV	Novartis	100,000	2001
Ibandronate	Boniva, PO	Roche	10,000	2005

Modified from Berenson et al.⁴¹ RP, relative potency; FDA-a, Food and Drug Administration approval; PO, oral; IV, intravenous.

patients worldwide have received intravenous bisphosphonate treatment since it was introduced.⁴⁴ A far greater number of patients are receiving oral bisphosphonates, such as alendronate (Fosamax) and risedronate (Actonel), for the treatment of postmenopausal osteoporosis and glucocorticoid induced osteoporosis. These medications are usually given once a week: alendronate 70 mg once weekly for the treatment of osteoporosis or less if it is being given for prevention of osteoporosis and risedronate 35 mg once weekly. Ibandronate (Boniva) is the most recent bisphosphonate to receive FDA approval (March 2005) for the treatment of osteoporosis and is dosed on a monthly regimen.

BIPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW

There are a growing number of cancer patients receiving intravenous bisphosphonate therapy who have developed exposed and necrotic bone of the mandible and maxilla. This complication has occurred either spontaneously or after simple dentoalveolar surgery. Similar troublesome clinical findings have been noted in some patients taking the less potent oral bisphosphonates for the treatment or prevention of osteoporosis.^{2,6,10,14,17,45} Novartis, the pharmaceutical company that manufactures pamidronate and zoledronate, received documentation of more than 600 cases of osteonecrosis of the jaw since they began tracking this complication.⁴⁴ This prompted the drug manufacturer to modify the U.S. package inserts for both Aredia and Zometa, listing osteonecrosis of the jaw as a potential complication. In addition, an expert panel was created to establish recommendations for the prevention, diagnosis, and treatment of osteonecrosis.⁴⁶ In September 2004, warning letters were issued to oncologists and oral and maxillofacial surgeons detailing these potential complications and alerting them of the potential for osteonecrosis. In May 2005, following a recommenda-



Fig. 1. Spontaneous bone exposure of the posterior mandible, lingual aspect.

tion from an Advisory Committee to the Food and Drug Administration, Novartis sent a similar alert to all dental health professionals, emphasizing potential oral complications.

Clinical features

Patients who present with BRON of the jaw are typically oncology patients with metastatic disease involving bone. Except for bisphosphonate treatment, the individual chemotherapeutic regimens for these patients vary in accordance with the tumor type. Osteonecrosis of the jaw may remain asymptomatic for weeks, months, or years and may result in pain or exposed maxillary or mandibular bone. These lesions are most frequently symptomatic when surrounding tissues become inflamed or there is clinical evidence of infection. Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. These may occur spontaneously (Fig. 1) or more commonly at the site of earlier dentoalveolar surgery (Fig. 2). Some patients may also present with complaints of altered sensation in the affected area. Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula can be the presenting symptom in patients with maxillary involvement. Similar clinical findings have been observed in some patients taking oral bisphosphonates for osteoporosis.

Radiographic changes are not evident until there is significant bone involvement. Therefore, panoramic and periapical radiographs may not reveal significant changes in the early stages of osteonecrosis. Early or late radiographic changes may mimic classic periapical



Fig. 2. Nonhealing extraction sites with exposed alveolar bone.

pathology or osteomyelitis or in cancer patients raise the suspicion of primary (myeloma) or metastatic bone disease. When there is extensive bone involvement, regions of mottled bone similar to that of diffuse osteomyelitis are noted. Widening of the periodontal ligament space may also be noted radiographically (Figs. 3 and 4). After prolonged exposure to the intravenous bisphosphonates, osteosclerosis of the bone may be noted radiographically, especially osteosclerotic lamina dura.

Potential risk factors

Recent retrospective clinical studies have identified several potential risk factors associated with the development of BRON.⁴⁷⁻⁵⁴ These include a history of dentoalveolar trauma, duration of bisphosphonate exposure, and the type of bisphosphonate. In the majority of BRON cases reported to date, recent dentoalveolar trauma was the most prevalent and consistent risk factor.^{45,54} This underscores the importance of maintaining good oral health and avoiding extractions in this population. The duration of bisphosphonate therapy also appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a greater risk of developing disease.¹⁹ In addition, the more potent intravenous bisphosphonates, such as pamidronate and especially zoledronate, appear to be significantly more problematic than the oral bisphosphonate medications.¹⁹

Staging

The extent of symptoms and clinical disease associated with BRON can vary despite similar disease processes, bisphosphonate dosage regimens, and treatment duration. Based on our observations and experience in diagnosis and management of 141 patients with this

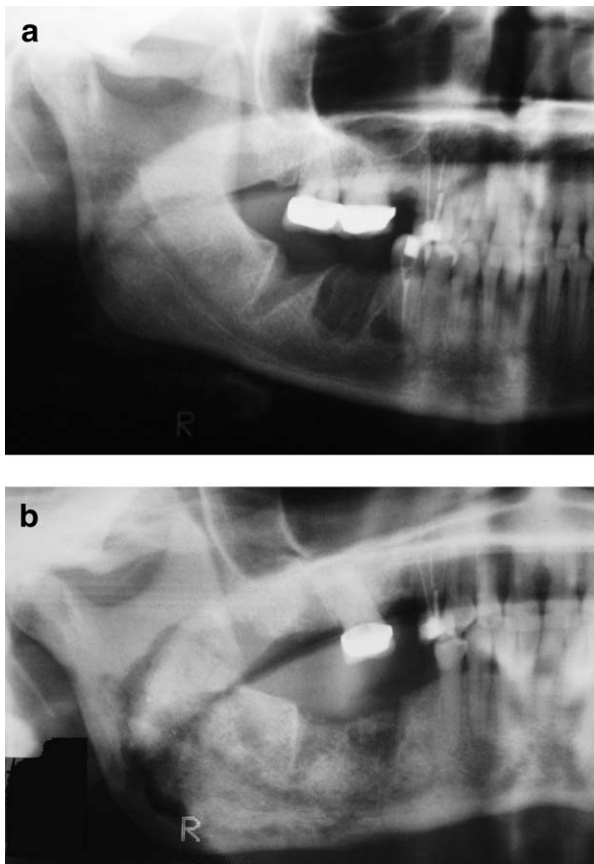


Fig. 3. A, Panoramic radiograph of nonhealing extraction sites in a breast cancer patient receiving bisphosphonate therapy. B, Panoramic radiograph of the same site 12 months later demonstrating a large area of bone sequestration and necrosis.

complication, we have implemented a staging system to stratify these patients (Table II).

Stage 1: disease characterized by exposed bone that is asymptomatic with no evidence of any significant adjacent or regional soft tissue inflammatory swelling or infection. It is recognized that patients may have symptoms of pain prior to the development of radiographic changes suspicious for osteonecrosis or clinical evidence of exposed bone.

Stage 2: disease characterized by exposed bone with associated pain, with adjacent or regional soft tissue inflammatory swelling or secondary infection.

Stage 3: Disease characterized by exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection that is difficult to manage with oral or intravenous antibiotic therapy. The presence of an extraoral cutaneous fistula secondary to jaw osteonecrosis or a pathologic fracture is common for patients at this stage. Often because of a greater volume of necrotic bone, these patients may



Fig. 4. Panoramic radiograph of a nonhealing extraction site and widening of the periodontal ligament space in a breast cancer patient receiving bisphosphonate treatment.

Table II. Clinical staging of BRON of the jaw

Stage 1	Exposed, necrotic bone that is asymptomatic
Stage 2	Exposed, necrotic bone associated with pain and infection
Stage 3	Exposed, necrotic bone in patients with pain, infection, and pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border

require surgical therapy to debride troublesome necrotic bone.

Pathogenesis

It appears that the pathogenesis of this process is most consistent with a defect in jawbone physiologic remodeling or wound healing.²⁹ Hypothetically, the mechanism by which bisphosphonates can have this effect centers on osteoclast inhibition and apoptosis. Impaired osteoclast function interferes with normal bone turnover and resorption. Bisphosphonates also have demonstrated effects unrelated to osteoclast inhibition. Pamidronate was reported to significantly depress bone blood flow in rats.^{35,36} The mechanism of this effect may be attributable to a complex interaction of pamidronate with growth hormone and insulin-like growth factor I, both of which are thought to play a role in the regulation of blood circulation in bones.^{35,36} Bisphosphonates inhibit endothelial cell function in vitro and in vivo.³⁷ Cells treated with bisphosphonates

demonstrate decreased proliferation, increased rate of apoptosis, and a decrease in capillary-tube formation.³⁷ Bisphosphonates also demonstrate antiangiogenic properties owing to their ability to significantly decrease circulating levels of the potent angiogenic factor VEGF, as demonstrated in breast cancer patients with bone metastases.^{33,34} These properties could also contribute to the apparent ischemic changes noted in the affected patients' jawbones.

Why are the jaws at increased risk?

Apparently, BRON exclusively affects the jaws. Most cases of BRON occur in patients who have undergone tooth extraction or some other form of surgical insult; however, a subset of edentulous and dentate patients have developed necrotic bone spontaneously (Fig. 1). The apparent selective involvement of the maxilla and mandible may be a reflection of the unique environment of the oral cavity. Typically, healing of an open bony wound (e.g., extraction socket) in the presence of normal oral microflora occurs quickly and without complication. However, when the healing potential or the vascular supply of the mandible or maxilla is compromised either by tumorcidal radiation doses or some other agent(s) or pathologic process, then minor injury or disease in these sites increases risk for osteonecrosis and possible secondary osteomyelitis. Also, bisphosphonates are preferentially deposited in bones with high turnover rates; because the maxilla and mandible are sites of significant remodeling, it is possible that the levels of bisphosphonate within the jaw are selectively elevated. However, we are not aware of studies demonstrating selective increase in bisphosphonate localization to certain bones such as the jaws.

Other medications in addition to bisphosphonates may also affect wound healing and also must be considered as possible cofactors. The similarity of BRON to a 19th century disease known as phossy jaw is striking and has been outlined by Hellstein et al.^{14,16} Phossy jaw represents osteonecrosis of the jawbones that developed in some employees working with white phosphorus in the munitions, fertilizer, and match-manufacturing industries. Affected individuals developed jaw necrosis, which clinically and histologically is similar to current cases of BRON.

Protocol and Treatment Recommendations

Patients who are about to start intravenous bisphosphonate therapy. The main (Table III) emphasis at this time should be to minimize the risk of occurrence of BRON. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following simple dentoalveo-

Table III. Treatment regimens

Stage 1	Daily oral antimicrobial rinses or irrigations (0.12% chlorhexidine) and regular clinical follow-up as disease activity dictates
Stage 2	Antimicrobial therapies based on culture and sensitivity data; analgesia and daily oral antimicrobial rinses or irrigations (0.12% chlorhexidine)
Stage 3	Surgical debridement of necrotic bone, antimicrobial therapy (oral or intravenous), and analgesia and daily oral antimicrobial rinses (0.12% chlorhexidine)

lar surgery (i.e., extraction, dental implant placement, or apical surgery). Therefore, measures optimizing dental health should be the main goal in patients who will receive bisphosphonate therapy. Initiation of bisphosphonate therapy should be delayed, if possible, until the dental health is optimized. This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient. Nonrestorable teeth and those with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery should also be completed at this time. It appears advisable that bisphosphonate therapy should be delayed at least 4-6 weeks to ensure adequate osseous healing. Dental prophylaxis, caries control, and conservative restorative dentistry are critical to maintaining functionally sound teeth. This level of care must be continued indefinitely. Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region. It is critical that patients are educated as to the importance of dental hygiene and regular dental evaluations and specifically instructed to report any pain, swelling, or exposed bone that would either predict or characterize BRON. It is important for us to inform the treating oncologists that these patient should be managed as if there were about to receive radiation therapy to the head and neck region. Osteoradionecrosis prevention protocols are guidelines that are familiar to most oncologists.

Patients receiving bisphosphonates with no evidence of osteonecrosis. The risk of developing osteonecrosis in asymptomatic patients who are receiving bisphosphonates (intravenous or oral) remains unknown. However, a recent web-based survey of 1,203 oncology patients (904 multiple myeloma and 229 breast cancer patients) reported that 6.9% of multiple myeloma patients and 4.3% of breast cancer patients had osteonecrosis of the jaw.¹⁹ Patients with "prior dental problems" were significantly more likely to develop these

complications. The data also suggested that those patients receiving zoledronate developed osteonecrosis more quickly (within 6 months of treatment) than those taking pamidronate.¹⁹ This likely reflects the increased potency of zoledronate compared with pamidronate. Patients receiving oral bisphosphonates were not included in the survey. Our experience indicates that patients with an established diagnosis of BRON are certainly at higher risk of developing osteonecrosis after any type of dentoalveolar surgery. Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery. If the tooth is considered nonrestorable the crown portion of the tooth can be removed and the endodontically treated roots left in place. Placement of dental implants should be avoided in the patient population exposed to the more potent intravenous bisphosphonate medications (zoledronic acid and pamidronate).

Patients who are receiving oral bisphosphonate therapy for the treatment of osteoporosis are also at risk for compromised jawbone healing but likely to a much lesser degree. Our data⁶ and those of others^{17,45} indicated that approximately 10% of BRON patients were receiving oral bisphosphonates. Thus BRON can manifest in this cohort of patients as jawbone osteonecrosis or osteonecrosis of tori either spontaneously or after minor trauma. Bisphosphonate-related osteonecrosis in this patient population may develop into a more significant problem than now realized, given the large number of patients taking oral bisphosphonates. In general, these patients seem to have less severe manifestations of necrosis and respond more readily to sequestrectomy or marginal resection. Although we do not consider oral bisphosphonate therapy an absolute contraindication in patients who require elective dentoalveolar surgery, we do suggest that patients be adequately informed of the potential risk of compromised bone healing and risk of BRON. The potential for complications in patients with a history of oral bisphosphonate use is probably related to the duration of exposure. The potential problems related to oral bisphosphonate clearly require further analysis and continued observation.

Patients with established BRON. Panoramic and tomographic imaging may be performed if osteonecrosis is suspected. Intraoral films can also be used to more accurately demonstrate subtle bone changes. However, a thorough history and intraoral clinical exam, coupled with radiographs, is the most effective way to establish the diagnosis. Microbial cultures may define comorbid oral infections and facilitate the selection of an appropriate antibiotic regimen. Tissue biopsy should be performed only if metastatic disease is strongly suspected or detection of such would alter clinical treatment de-

terminations. We have not identified evidence of metastatic disease or myeloma in the jawbone of those cancer patients biopsied for histopathologic diagnosis or debrided for clinical BRON. Although identification of these disease processes in the jawbones is certainly recognized, it has not been our experience to recognize neoplastic disease in the anatomic location of the necrosis. The microscopic examination of debrided or resected BRON specimens demonstrates necrotic bone with associated bacterial debris and granulation tissue. Notable is the absence of osteoclasts. We caution against the specific diagnosis of actinomycosis based purely on histologic grounds in the absence of microbial culture data.

The management of the symptomatic patient with BRON is difficult. These cases respond less predictably to the established surgical treatment algorithms for osteomyelitis or osteoradionecrosis. Surgical debridement has not been uniformly effective in eradicating the necrotic bone, and hyperbaric oxygen therapy has not been effective in limiting the progression of this process in the few patients who received it.^{6,45} It is difficult to obtain a surgical margin with viable bleeding bone, because the entire jawbone has been exposed to the pharmacologic influence of the bisphosphonate. Therefore, surgical treatment should be delayed if possible. Areas of necrotic bone that are a constant source of soft tissue irritation should be removed or trimmed, attempting to minimize exposure of additional bone. However, it is likely that the margin of the debridement will remain exposed and granulation tissue will surround the area of exposed bone. Epithelialization is an unlikely or transient phenomenon. Patients with established BRON should avoid elective dentoalveolar surgical procedures (i.e., extractions, dental implants, or apical surgery), because these surgical sites will likely result in additional areas of exposed necrotic bone. Symptomatic patients with pathologic mandibular fractures may require segmental resection and immediate reconstruction with a reconstruction plate. The potential for failure of the reconstruction plate because of the generalized effects of the bisphosphonate exposure needs to be recognized by the clinician and patient. Immediate reconstruction of these patients with nonvascularized or vascularized bone is not advocated, given the likelihood that necrotic bone may develop at the recipient site. It is important to realize that in this patient population the treatment objectives are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis.

Stage 1 disease may benefit from the use of oral antimicrobial rinses such as 0.12% chlorhexidine. In our experience, patients who present with stage 1 disease have done well with this type of conservative treatment. Stage 2 disease is more problematic. Use of oral antimicrobial

rinses and antibiotic therapy tailored to the culture and sensitivity results obtained from the necrotic bone and wound exudates may prove beneficial. It must be recognized that the pathogenesis of BRON is likely related to factors adversely influencing bone remodeling and not that of a primary infectious etiology. In our experience, most of the isolated microbes have been sensitive to the penicillin group of antibiotics. In some refractory cases, however, patients may require long-term antibiotic maintenance or a course of intravenous antibiotic therapy. Most of the BRON patients (67%) at our institution had stage 2 disease. In this group, 75% were stabilized with this treatment regimen.

Stage 3 disease represents the most challenging group of patients. A large burden of necrotic bone with secondary soft tissue swellings or cutaneous fistulae and secondary infection that is refractory to antibiotic therapy characterizes this stage. In addition, the pain that accompanies this necrotic bone impacts the quality of life. The surgeon is often compelled to offer resection of the maxilla or mandible in such cases. Our experience is that resection of the maxilla follows a more predictably successful course after surgery than marginal or segmental resections of the mandible. This notwithstanding, aggressive surgical management of stage 3 disease of the mandible is sometimes indicated and may offer long-term palliation with resolution of acute infection and pain. In our experience, 12 of 15 patients (85%) with stage 3 disease that were managed in this fashion are currently stable with resolution of the pain and infection. The patient and treating clinician's expectations must again recognize that BRON is quite different than osteoradionecrosis and bacterial-related osteomyelitis albeit similar clinically and radiographically.

Oncology patients benefit greatly from the therapeutic effects of bisphosphonates by controlling bone pain and incidence of pathologic fractures; thus, oncologists have been reluctant to stop bisphosphonate treatment. The cessation of intravenous bisphosphonate treatment in our experience has not had a major impact on the progression or treatment of this process. This is likely related to bisphosphonates avidly binding to bone and not being metabolized. Thus bisphosphonate levels remain high in bone for years. Therefore, discontinuation of intravenous bisphosphonate therapy is not likely to alter the clinical course of BRON and could result in a recurrence of bone pain and progression of metastases or lytic bone lesions. It is the responsibility of the oncologist, with input from the dental specialist or dentist, to determine if bisphosphonate therapy should continue.

CONCLUSION

Although the pathogenesis of BRON remains unclear, it appears that bisphosphonates are responsible for the emergence of this relatively new clinical entity. Because

pamidronate and zoledronic acid have become standard regimens for patients with breast cancer, multiple myeloma, and other selected malignancies, awareness of this complication and its clinical significance is critical. There is emerging evidence from clinical observations and early clinical trials suggesting that bisphosphonates may have antitumor activity, which in turn could broaden the indications for their use in the near future.³⁸ It is critical that the dentist be aware of this significant complication which can occur spontaneously or after any dentoalveolar procedure in the population at risk. Because review of the patient's medical history and the oral examination is currently the most effective and sensitive means of detecting BRON, dental professionals are in a unique position to identify and diagnose this disease process early in its course.

This report serves to alert dentists and dental specialists about the potential complication of bone necrosis in patients receiving bisphosphonate therapy and proposes a guideline for diagnosis, staging, and treatment. Further modifications of these guidelines will likely occur over time. Research is ongoing which will hopefully elucidate the pathogenesis as well as the precise relationship between bisphosphonates and osteonecrosis.

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