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Biophosphonate-Related Osteonecrosis of the Jaws

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In 2003 and 2004, the first reports of patients who developed necrosis of the jawbones while taking bisphosphonates appeared in the literature; most patients were on this drug for treatment of cancer and some for osteoporosis [1–3]. Since then, more than 500 cases have been identified and the number of these cases continues to grow. This article reviews the action of bisphosphonates, the condition called *bisphosphonate-associated osteonecrosis of the jaws*, strategies to minimize occurrence, and treatment of this condition.

Nomenclature

A universally accepted term for this new condition has not been established, which has caused some degree of confusion. This complication has been referred to in the literature as BRONJ (bisphosphonate-related osteonecrosis of the jaw), BRON (bisphosphonate-related osteonecrosis), BON (bisphosphonate osteonecrosis), BAONJ (bisphosphonate-associated osteonecrosis of the jaw), and simply ONJ (osteonecrosis of the jaw). Based on the clear association between bisphosphonate therapy and jaw necrosis that has been established in numerous retrospective studies, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has decided to

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adopt the term *BRONJ* for this entity [4], and this term will be used throughout this article.

Action of bisphosphonates

The actions and pharmacology of bisphosphonates have been well reviewed and only a summary is offered here [5–7]. Bisphosphonates are analogs of inorganic pyrophosphates. Pyrophosphates are well-known in dentistry, because they are a component of tartar-control toothpaste and inhibit calcium precipitation [8]. Unlike pyrophosphates, bisphosphonates contain a carbon rather than oxygen molecule. This P-C-P structure allows the molecule to bind to the hydroxyapatite crystals with high affinity, while the presence of nitrogen in one of the side chains confers markedly increased potency to the drug (Fig. 1). The early forms of bisphosphonate, such as etidronate and clodronate, do not contain nitrogen and therefore are less potent; they are available only in the oral preparation. The later forms of bisphosphonates contain nitrogen and some are available as intravenous preparations, making them much more bioavailable (Table 1). Pamidronate and alendronate contain nitrogen in an alkyl chain and are 10 to 100 times more potent than etidronate and clodronate. The most potent of the bisphosphonates (such as zoledronic acid and risedronate) contain nitrogen within a heterocyclic ring. The half-life of bisphosphonates is approximately 10 years, and therefore prolonged use of this drug causes substantial drug accumulation within the skeleton. The drug is tightly bound to the apatite crystals until it is released during osteoclastic-mediated bone resorption.

Antiresorptive activity

One of the most important and powerful effects of bisphosphonates is inhibition of osteoclastic activity, and herein lies one of its most important applications in clinical practice, both for managing osteoporosis and cancers in the skeletal system. When bone resorption occurs, bisphosphonates are released from the hydroxyapatite crystal and are taken up by osteoclasts. Metabolites of non-nitrogen containing bisphosphonates (such as etidronate and clodronate) are cytotoxic to the osteoclasts and lead to their death. Nitrogen-containing bisphosphonates, however, act by way of the mevalonate

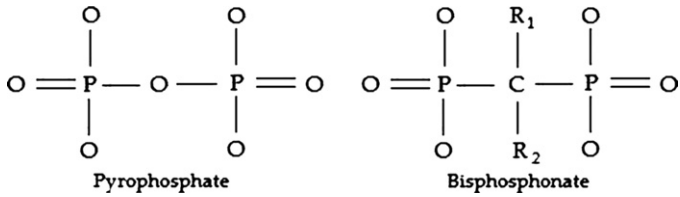

Fig. 1. Structure of pyrophosphate (*left*) and bisphosphonate (*right*). For bisphosphonates, R_1 acts as a "bone hook" for attachment of the molecule to bone, whereas R_2 determines potency.

Table 1
Bisphosphonate medications and their relative potency

Generic name	Brand name/delivery	Manufacturer	Indication	RP
Clodronate	Bonefos, PO	Hoffman/ LaRoche	Not available in the United States	50
Pamidronate	Aredia, IV	Novartis	Bone cancer	100
Alendronate sodium 1000	Fosamax, PO	Merck	Osteoporosis	500–1000
Risedronate	Actonel, PO	Proctor & Gamble	Osteoporosis	5000
Ibandronate	Boniva, PO/IV	Roche	Osteoporosis	5000–10,000
Zoledronic acid	Zometa, IV	Novartis	Bone cancer[a]	>10,000

Abbreviations: IV, intravenous; PO, per oral; RP, relative potency.

[a] Intravenous zoledronic acid also has been approved for the treatment of osteoporosis (4–5 mg dose, once per year).

pathway (for cholesterol synthesis), inhibiting protein prenylation, a process essential for normal functioning of vital intracellular proteins, ultimately leading to osteoclast apoptosis (programmed cell death) [7,9]. Bisphosphonates also inhibit differentiation of osteoclasts and stimulates osteoblasts to produce osteoclast-inhibiting factor [10]. Therefore, the net result is reduced numbers of osteoclasts and reduced bone resorption. Because bone resorption is coupled to osteoblastic bone formation for remodeling, bone turnover (ie, resorption and deposition) becomes severely suppressed. However, the bone continues to mineralize and could become brittle and less elastic. In one case report, bisphosphonate taken at high doses led to an osteopetrotic-like state [11].

Tumoricidal activity

Many studies have shown that nitrogen-containing bisphosphonates also reduce the activity of cancer cells and control metastases [9,10,12]. This process may be related to inhibition of protein prenylation leading to disruption of intracellular activity within the cancer cells [9]. However, the alteration of the microenvironment itself, caused by reduced bone resorption alone, could also account for control of metastases [13]. Bisphosphonates also reduce adhesion, invasion, and viability of cancer cells and may activate gamma delta T cells, which have tumoricidal activity [14].

Antiangiogenic activity

In vitro, zoledronic acid inhibits angiogenesis mediated through basic fibroblast growth factor and may induce apoptosis of endothelial cells [15]. Antiangiogenic activity may also occur through lowering circulating levels of vascular endothelial growth factor and platelet-derived growth factor, both of which are proangiogenic [16,17].

Clinical applications

Bisphosphonates are widely used in the management of four main conditions: osteoporosis, Paget's disease of bone, multiple myeloma, and cancers that have metastasized to the bones. This article focuses only on the oncologic aspects of bisphosphonate use.

Multiple myeloma is a malignancy of plasma cells that primarily affects the skeletal system. Patients develop multiple lytic bone lesions containing malignant plasma cells, and as a result may develop skeletal-related events (SRE), such as bone pain, fractures, necessity for surgery and radiation, and hypercalcemia. Patients also develop hypergammaglobulinemia from secretory activity of these cells, which can lead to renal failure. Clinical trials show that bisphosphonates significantly reduce these SREs, and pamidronate and zoledronic acid are widely used for treating multiple myeloma [18,19]. Other agents for treating this disease include thalidomide, glucocorticoids such as dexamethasone, and proteasome inhibitors such as bortezomib, usually in combination [20,21]. These agents also have antiangiogenic properties.

Similar SREs are noted in patients who have metastatic cancers (with metastatic breast and prostate cancers being the most common), and bisphosphonates also have been shown to significantly reduce SREs in these patients [22,23].

Early reports of bisphosphonate-associated osteonecrosis of the jaws

The earliest reports of bona fide cases of BRONJ occurred in 2003 [1–3], and have been followed by many more case reports and large case series [24–27]. All cases have occurred in the maxilla or mandible except for a single case that occurred after ear surgery [28].

Etiopathogenesis

The exact mechanism for the development of BRONJ is unclear. The current hypothesis focuses on severe suppression of bone turnover, coupled with the unique conditions affecting the jaws and not other bones. These conditions include the following: (1) the jaw bones are separated from the oral environment from a very thin mucosa (only several mm thick for the most part) and this barrier is readily breached even with simple physiologic activities such as mastication, (2) the oral cavity is filled with bacteria and the jaws are often involved in infection through either the periodontal ligament or the pulp, (3) dentoalveolar surgery is a common procedure (eg, extractions, periodontal surgeries, apicoectomies) in which bone is exposed to a bacteria-rich environment, and (4) the rate of turnover of the jawbones is higher than that for the long bones [29].

One possible mechanism of action is that after a sufficient concentration of bisphosphonates has accumulated, the jawbones become hypodynamic and turn over at a low rate. When infection or surgery requires increased

bone turnover for healing, this does not occur. How the bone actually becomes necrotic and exposed is unclear at this time. However, there is a condition that mimics BRONJ that occurs spontaneously, involves only a few millimeters of necrotic bone that heals without incident, and occurs in healthy adults. This benign sequestration of the lingual plate is a well-recognized phenomenon and its putative mechanism of action is trauma to the lingual periosteum, loss of vascular supply of bone supplied by that area of periosteum, death of bone with sequestration, and healing [30]. The lingual plate/mylohyoid area is also a common site for spontaneously occurring BRONJ.

Risk factors for bisphosphonate-associated osteonecrosis of the jaws

Not all patients who use bisphosphonates develop BRONJ. The factors that affect its development are:

1) The use of nitrogen-containing bisphosphonates, particularly zoledronic acid [31]. Zoledronic acid used alone produced 9.5-fold and 4.5-fold greater risk compared with pamidronate used alone or with zoledronic acid, respectively [32]. However, BRONJ has been seen in a patient who had myeloma who took only oral clodronate, a first-generation non–nitrogen-containing bisphosphonate [33].
2) The cumulative dose of bisphosphonates. This factor also indirectly relates to the patient's underlying condition, because patients who have cancer receive much higher doses of bisphosphonates than those who have osteoporosis. For example, a patient who has osteoporosis who requires intravenous bisphosphonate therapy receives 4 to 5 mg of zoledronic acid per year compared with a patient who has myeloma who receives 4 mg of zoledronic acid every 4 weeks. The median time of exposure to zoledronic acid with development of BRONJ ranged from 9 to 30 months and is significantly shorter compared with other bisphosphonate regimens [25,31,34,35]. However, the exposure can be as little as 3 months. The risk for developing BRONJ increases over time, with a cumulative hazard of 1% within the first year of treatment with zoledronic acid, and 15% at 4 years [31].
3) Dentoalveolar surgery. Approximately 60% of all cases are associated with either tooth extraction or other surgery (eg, periodontal and apical surgery and implant placement) [24,25,36]. However, tooth extractions are the most common inciting factor [26]. One study showed that the prevalence of BRONJ in patients who had cancer who did not undergo extractions was 1% compared with 7% to 9% in those who did [35]. BRONJ has been reported in patients after surgical endodontic procedures [37,38].
4) Trauma. Many cases occur on the lingual mandible (where the mucosa is especially fragile) and on tori [25].

Other factors that may contribute to the development of ONJ, but for which the evidence is less robust, include dental infections. By the time BRONJ develops, it is difficult to determine if the infection caused BRONJ or was merely a consequence of BRONJ.

Other factors, such as route of administration (intravenous preparations are more frequently associated with BRONJ) and age, are indirectly related to the factors noted earlier. For example, patients who have cancer affecting the skeleton (usually older patients) typically are exposed to the more potent bisphosphonates, such as zoledronic acid and pamidronate, both of which are only available as intravenous preparations, and are used more frequently.

Whether the antiangiogenic activity of bisphosphonates plays an important and direct role in BRONJ is unclear. Other comorbidities have not been entirely elucidated, but include concomitant use of antiangiogenic agents and vascular compromise. Thalidomide, which has antiangiogenic properties, has been shown to increase the risk 2.4-fold [32], although this has been disputed [26]. One study showed that patients who had BRONJ were more likely to have associated diabetes mellitus, although most patients already had diabetes when their cancer was diagnosed [39]. Another study showed that patients who developed BRONJ had hyperparathyroidism and mild hypocalcemia compared with controls [40].

Prevalence

The prevalence varies from 4% to 7% within any one center. Most of the studies were performed through retrospective chart reviews or telephone interviews [41,42].

Although most patients who developed BRONJ underwent dental extractions, the number of patients who had extractions or other dentoalveolar surgery and did not develop BRONJ is unclear.

Diagnosis and clinical presentation of bisphosphonate-associated osteonecrosis of the jaws

Standardization of diagnostic criteria for this new clinical entity is important to facilitate future clinical and epidemiologic research and help distinguish BRONJ from other intraoral osteonecrotic conditions exhibiting delayed healing. The AAOMS established a working definition for BRONJ that is fairly concise and specific [4]. Patients may be considered to have BRONJ if they have all of the following characteristics: (1) current or previous treatment with a bisphosphonate, (2) exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks, and (3) no history of radiation therapy to the jaws. Patients who are considered at risk according to the AAOMS criteria have no evidence of exposed or necrotic bone but have been exposed to either intravenous or oral nitrogen-containing bisphosphonates for long periods.

The American Society for Bone and Mineral Research (ASBMR) has also made recommendations for a provisional case definition for confirmed and suspected cases of bisphosphonate associated osteonecrosis [43]. A confirmed case is identical to the AAOMS definition for BRONJ. A suspected case fulfills all the criteria of a confirmed case, except that the necrotic bone has been present for less than 8 weeks. Suspected cases should be followed up to determine if they eventually meet the criteria of a confirmed case.

Diagnosis of BRONJ is primarily based on patient history and clinical examination. Patients present with exposed, necrotic bone varying in size from a few millimeters to several centimeters; only 60% of cases report pain, and some cases may remain asymptomatic for weeks, months, or years [3,24,25]. These lesions frequently become symptomatic when surrounding tissues become inflamed or an infection develops. Signs and symptoms that may occur before the development of clinically detectable BRONJ include pain, tooth mobility, mucosal swelling, erythema, ulceration, and the development of sinus tracts. These somewhat nonspecific signs and symptoms are similar to those of banal odontogenic infections. Some patients may also present with complaints of altered sensation or paresthesia in the affected area as the neurovascular bundle becomes affected by inflammation or infection around the necrotic bone. Chronic maxillary sinusitis secondary to BRONJ with or without an oral-antral fistula may be the presenting symptom in patients who have maxillary bone involvement [3].

Lesions have been observed more commonly in the mandible than the maxilla (2:1 ratio) [24], and more commonly in areas with thin mucosa overlying bony prominences, such as tori, bony exostoses, and the mylohyoid ridge [3,25]. Most cases occur at the site of prior dentoalveolar surgery (Fig. 2). However, exposed bone has also been reported in patients who have no history of trauma or in edentulous regions of the jaw (Fig. 3). The size of the affected area can be variable, and ranges from a nonhealing

Fig. 2. BRONJ after a tooth extraction.

Fig. 3. BRONJ in the mylohyoid area.

extraction site to exposure and necrosis of the entire jaw (Fig. 4). The area of exposed bone may be surrounded by inflamed erythematous soft tissue. When infected, purulent discharge may be seen at the site of the exposed bone and intra- and extraoral fistulae (Fig. 5). The AAOMS has proposed a clinical staging system based on the presence of symptoms and extent of disease (Table 2) [4,44].

Radiographic findings

Conventional radiographs will not show a change until the bone is demineralized 30% to 50%. Therefore, and also partly because of the two-dimensional nature of these films, panoramic and periapical radiographs may not show significant changes in the early stages of osteonecrosis.

Fig. 4. Extensive BRONJ seen in this surgical specimen of the mandible.

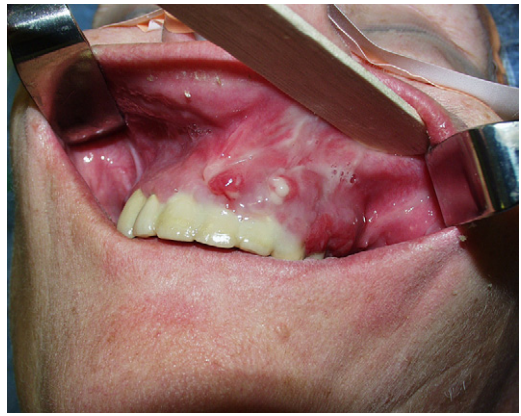

Fig. 5. BRONJ associated with sinus tract of anterior maxilla.

However, some studies suggest that early bone changes include diffuse osteosclerosis, thickening or loss of lamina dura, and widening of the periodontal ligament space (Fig. 6) [44]. Little or no ossification at a previous extraction site after the conventional 6 months of healing is also an important radiographic sign (Fig. 7). Early or late radiographic changes may

Table 2
Staging and management of bisphosphonate-associated osteonecrosis of the jaw

Stage	Clinical presentation	Management
At risk	No exposed bone	Patient education
1	Asymptomatic exposed bone with little soft tissue inflammation	Patient education; antibacterial rinses[a]; careful follow-up[b]
2	Exposed bone with pain, and usually with associated surrounding soft tissue inflammation or infection	Patient education; antibacterial rinses[a]; antibiotics[c]; superficial debridement of bone to dislodge loose fragments and smooth rough contours; careful follow-up[b]
3	Exposed bone with pain and usually with associated soft tissue inflammation or infection; may see osteolysis extending to the inferior border of mandible or pathologic fracture; may see extraoral fistula	Patient education; antibacterial rinses[a]; antibiotics[c]; palliative surgery; careful follow-up[b]

[a] Such as 0.12% chlorhexidine digluconate.

[b] Follow-ups for asymptomatic patients should occur every 2 to 3 months, and every 1 to 2 weeks until the acute symptoms have resolved for stage 2 and 3 disease.

[c] Commonly used antibiotics include penicillin, amoxicillin, cephalexin, clindamycin, metronidazole, or first-generation fluoroquinolones.

Fig. 6. Radiograph showing loss of lamina dura, widening of the periodontal ligament space, and marked osteosclerosis.

mimic classic periapical pathology, osteomyelitis, or, in cancer patients, raise the suspicion of primary (myeloma) or metastatic bone disease. If a strong clinical suspicion exists of metastatic disease within the jaw, and the diagnosis of this will alter clinical treatment decisions, a bone biopsy should be considered. Otherwise, bone biopsies in patients who have been exposed to intravenous bisphosphonate therapy should not be performed given the potential for creating a nonhealing bone wound.

When extensive bone involvement is present, regions of mottled bone or sequestra formation similar to that of diffuse osteomyelitis are noted. In more advanced stages of BRONJ, the osteolytic changes can extend to the inferior border of the mandible and may result in a pathologic fracture (Fig. 8).

CT scans can provide more accurate three-dimensional information about the extent of the necrosis and is often useful for planning surgical debridement procedures [45]. However, this modality has not proved helpful

Fig. 7. Panoramic radiograph showing persistence of extraction sockets in right and left mandible.

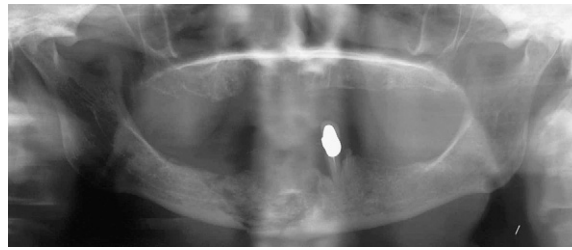

Fig. 8. Panoramic radiograph showing extensive involvement of the mandible with pathologic fracture of anterior portion.

for early identification of BRONJ in asymptomatic individuals. MRI can detect marrow edema, which may be an early sign of bone ischemia and necrosis, such as is seen in avascular necrosis of the hip secondary to long-term use of steroids. However, whether this modality is helpful for detecting early lesions of BRONJ is unclear, although established lesions are detectable as expected [45]. Technetium 99m sestamibi is not taken up in areas of BRONJ [18], although fluorodeoxyglucose–positron emission tomography (FDG-PET) integrated with CT may show focal uptake [46]. All imaging modalities have proved helpful in determining the extent of the existing necrotic process, especially in advanced lesions, but have not shown any efficacy in assessing patients at risk for BRONJ. New avenues of research include the use of dental cone tomography, which uses only approximately 10% of the radiation of routine CT scans [47,48].

Histopathology and microbiology

Microscopic examination of debrided specimens of exposed bone typically will show necrotic bone with associated bacterial debris and granulation tissue [26,49,50]. Microbial cultures from areas of exposed bone will usually isolate normal oral microbes and are therefore not always helpful [26]. However, when extensive soft tissue involvement is present, microbial culture data may help define comorbid oral infections and facilitate the selection of an appropriate antibiotic regimen.

The presence of actinomycetes in the culture and within biopsy specimens must be interpreted with caution. The presence of actinomycetes alone does not indicate a diagnosis of actinomycosis, because they are a common endogenous pathogen in dental plaque. The diagnosis of actinomycosis is made if actinomycotic organisms are present and associated with suppuration within the necrotic bone fragments, and actinomycetes was cultured from a sterile area within the bone and not from a swab of necrotic bone exposed to the oral cavity. The presence of pain, suppuration, and/or draining sinus tracts together with both diagnostic criteria also helps to confirm this diagnosis [51].

Differential diagnosis

Several other conditions may also lead to necrosis of the bone with sequestration. Odontogenic infections, left untreated, may result in osteomyelitis, although this does not usually present with clinical exposure of the dead bone.

Postradiation osteonecrosis of the jaws is in many ways similar to BRONJ and occurs after a patient has received high doses of radiation to the jawbones, usually for the treatment of primary head and neck malignancies. However, these conditions have a marked difference in presentation, in that more than 95% of osteoradionecrosis occurs in the mandible, because one of the primary mechanisms is reduced vascularity and sclerosis of vessels as a result of the high doses of radiation. The mandible has a limited blood supply compared with the maxilla (which is supplied by many collateral vessels) and is therefore more frequently involved [52].

Benign sequestration of the lingual plate differs from BRONJ in that the lesions are much smaller (usually several millimeters only), the patients are young to middle-aged adults who have not been exposed to bisphosphonates, the lesions last only a few days before the piece of bone is either spontaneously exfoliated or removed by a dental care provider, and no sequelae are present [30].

Necrotizing periodontitis is usually seen in patients who have suppressed immune systems, particularly those who have HIV infection or severe malnutrition [53,54]. It is caused by a polymicrobial infection of the periodontium that cannot be adequately contained by the patient's poor immune function, leading to destruction and exposure of bone. This condition may spread from the bone to involve the adjacent soft tissues, a condition known as *noma* or *necrotizing stomatitis*. It is endemic within African nations that have high rates of malnutrition. Herpes zoster infections of the maxilla and mandible have been reported to lead to necrosis of the soft tissues and underlying bone. The putative mechanism is one of vascular compromise [55,56].

Management

The goal of management for patients at risk for developing BRONJ or who have active disease is to preserve the quality of life through controlling pain, managing infection, and preventing the development of new areas of necrosis. The BRONJ treatment algorithms that have been published are either a consensus of expert opinions or based on case series data [4,25,44,57]. These management strategies have varied according to the risk for developing BRONJ or the stage of disease.

Prevention strategies (oral bisphosphonate therapy)

Low-dose oral bisphosphonate therapy is primarily used for patients who have osteoporosis, and is rarely used for treating myeloma or metastatic

carcinoma. The incidence of BRONJ in the osteoporosis population has been cited as 1 in 100,000 patient years [58], although a more recent study shows that it may be as high as 1 in 2260 to 8470 patients [35]. Patients who have myeloma are often treated with clodronate (an oral non–nitrogen-containing bisphosphonate) in European countries [59]; clodronate is not approved for human use in the United States but may be associated with a lower incidence of BRONJ.

The risk is associated with cumulative dose/number of years of use. Different periods deemed "safe", such as 3 or 5 years, are based on anecdotal data [4]. Patients should undergo routine dental care with regular radiographic examinations, be educated about the risk for developing BRONJ, and provide informed consent for surgical procedures.

Current evidence does not contraindicate the placement of dental implants. However, the studies are small and do not include the longer periods of bisphosphonate exposure [60].

Prevention strategies (intravenous bisphosphonate therapy)

For the most part, patients who have cancer undergoing bisphosphonate therapy should be managed with preventive measures. The main emphasis is to minimize the risk for occurrence of BRONJ, which translates into minimizing the need for dentoalveolar surgery. Therefore, optimizing dental health is the main objective in managing these patients. The best way to optimize dental health is to educate all patients about their risk for developing BRONJ and evaluate each patient fully for odontogenic infections using full mouth intraoral and panoramic radiographs. All carious teeth should be identified and restored. All nonvital teeth should be either endodontically treated or extracted, especially if they have not started bisphosphonate therapy. If periapical lesions are present and require apical surgery, this procedure should be weighed against an outright extraction. Discussion of the risks and benefits of all surgical procedures, including periodontal surgery, must be undertaken and this should be reflected on the consent form. Patients should be followed until all surgical sites are completely healed. Routine dental care, such as restorations and scaling, and prophylaxis should be performed regularly and patients should be encouraged to keep routine follow-up appointments and be educated on the importance of maintaining excellent oral hygiene.

Staging and management of bisphosphonate-associated osteonecrosis of the jaws

The clinical staging system was developed to more accurately categorize patients who have BRONJ, direct rational treatment guidelines, and collect data to assess the prognosis in patients who have used either intravenous or oral bisphosphonates (Table 2) [4,44]. Data are being collected on how different management strategies related to staging correlate with outcome;

that is, resolution of lesions, progression of lesions, or occurrence of new lesions.

Except for patients who have stage 3 disease who require surgical resections for palliation, surgical interventions may result in an increased area of exposed bone [3]. Patients and clinicians must realize that a cure may not always be possible. Nevertheless, some patients show complete resolution of BRONJ with conservative therapy [61].

Patients who have established BRONJ are likely at risk for developing it at another site, and therefore should be educated on the benefits of prophylactic dental care and avoid dentoalveolar surgery, if possible. However, extraction of nonvital or periodontally involved teeth embedded in necrotic bone may be necessary.

Although hyperbaric oxygen (HBO) therapy had not been found to be useful in earlier small case series, a more recent study found that HBO used in combination with surgery after 6 months of discontinuation of bisphosphonates led to complete resolution of BRONJ [27].

Resolution of BRONJ or clinical improvement after resection and topical application of autologous platelet-rich plasma [62,63], Nd:Yag laser biostimulation [64], or systemic administration of teriparatide, a form of synthetic parathormone [65], has been documented. Prospective randomized studies are required to accurately assess the efficacy of these treatments.

Should bisphosphonates be discontinued?

Bisphosphonates are very efficacious in controlling bone pain and reducing the incidence of SREs in patients who have myeloma and metastatic disease. Whether discontinuation of intravenous bisphosphonates offers any short-term benefit in the management of BRONJ is unclear. However, if systemic conditions permit, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk for new areas of BRONJ to develop, and reducing clinical symptoms [4].

The decision to discontinue bisphosphonate therapy should be made only by the treating oncologist in consultation with the treating dental specialist, because discontinuation puts the patient at risk for an SRE. The benefits of therapy must be carefully weighed against risks for fracture, cancer progression, and hypercalcemia. At some institutions, the recommendation is to use intravenous bisphosphonates in patients who have cancer for 2 years and to discontinue the drug if the patient is experiencing remission or a stable state, with the option to continue or restart therapy if disease worsens or symptoms progress [66,67].

Monitoring of patients

The more commonly used bone markers include bone specific alkaline phosphatase, *N*-telopeptide cross-linked, or *C*-telopeptide cross-linked (both markers of collagen breakdown or bone resorption). Others include

osteocalcin, pyridinoline and deoxypyridinoline. Many of these have been studied in clinical trials for osteoporosis [68].

Although no controlled studies have shown that these markers for bone turnover are useful for monitoring the progress of BRONJ, these are being used [69]. Alkaline phosphatase and *N*-telopeptide cross-linked levels are clearly high in patients who have bone metastases and myeloma, and higher levels clearly correlate with imminent risk for a SRE, cancer progression, or death [70]. Disease causes the levels of these markers to rise, and the use of bisphosphonates will cause these markers to fall. Studies are underway to monitor levels of other markers of bone metabolism, such as receptor activator for nuclear factor kappa B ligand (RANKL) and osteoprotegerin.

Summary

Bisphosphonates are very effective drugs for treating osteoporosis, Paget's disease of bone, and other metabolic bone diseases, multiple myeloma, and metastatic cancer to the bones. In placebo-controlled trials, the use of bisphosphonates significantly reduced SREs in patients who had cancer. Bisphosphonates also reduces vertebral and nonvertebral fractures in patients who have osteoporosis by 25% to 77% [71,72]. The development of BRONJ as an adverse reaction does not diminish its importance in health care.

Dental professionals should be aware of this condition and be sure to take a careful medication and health history for all patients. Patients taking a bisphosphonate should not be denied regular dental care, but should be educated about this condition and encouraged to maintain an excellent level of dental hygiene and care.

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