REVIEWS

Osteonecrosis of the jaw and bisphosphonates in cancer: a narrative review

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Abstract | Bisphosphonate-associated osteonecrosis (BON) is a complication that almost exclusively affects the jaw bones. The clinical presentation of BON often mimics that of other conditions, such as routine dental disease, osteoradionecrosis or avascular necrosis; therefore, diagnosis can be difficult. As this complication has only been recognized within the past 10 years, management strategies for patients with BON are poorly defined. Physicians must choose between continuing the bisphosphonate therapy (to reduce the risk of skeletal complications in patients with metastatic bone disease or osteoporosis) and discontinuing the drug (to possibly improve the odds for tissue healing). A conservative or aggressive management strategy must be chosen with limited evidence that the outcome of either strategy will be successful. BON is most prevalent in patients with cancer using intravenous nitrogen-containing bisphosphonates. The pathobiology of this complication is not fully understood and the diagnosis relies on the clinical manifestations of the condition. Future research should focus on the pathobiological mechanisms involved in the development of BON, which could help explain why this complication affects only a small number of those who use bisphosphonates, and also suggest strategies for prevention and management.

Introduction

Bisphosphonates have become the standard of care in the treatment of patients with osteoporosis[1,2] and in the prevention and treatment of skeletal complications in patients with cancer.[3–5] As with other drugs, bisphosphonates can cause adverse effects.[6–9] Both oral and intravenous administration of bisphosphonates have been associated with osteonecrosis of the jaw bones,[10] defined as the presence of exposed, necrotic bone in the oral cavity for >6 weeks in patients with no history of radiation therapy to the head and neck but with a history of bisphosphonate use (Figure 1).[11,12] This type of osteonecrosis is known by several different acronyms, but in this Review we will use bisphosphonate-associated osteonecrosis (BON). Early reports of BON came from the USA[13–16] but the number of cases reported worldwide continues to grow.[17–25] Cases are particularly prevalent in patients with multiple myeloma, breast, lung and prostate cancer,[13,15,16] who are being treated with intravenous bisphosphonates.

In 2006, a comprehensive narrative review addressed various issues related to BON.[26] Since then, a number of publications have been published in the dental and medical literature that address the possible pathobiological mechanisms, prevalence, diagnosis and management of BON. In this updated narrative Review, we examine current aspects of bisphosphonate therapy and provide a definition for BON that can be used in future studies. We describe the pathobiology, diagnosis, presentation, incidence and prevalence of BON, as well as highlighting risk factors and tumor types associated with this complication. The main focus of this Review will be on new treatment protocols for BON and their outcomes in patients with cancer whose treatment includes intravenous bisphosphonates, as this is the population most affected by BON. Patients with osteoporosis who receive bisphosphonate therapy are also at risk of BON; however, the prevalence and severity of BON in these patients is much less than in those with cancer. Nevertheless, most of the information presented in this Review can be applied to any patient receiving bisphosphonate therapy.

Bisphosphonates in cancer therapy

Over the past decade, several large, randomized clinical trials have demonstrated that treatment with bisphosphonates can reduce the incidence of skeletal complications and improve the quality of life of patients with metastatic bone disease or multiple myeloma.[27–32] These findings have resulted in the widespread use of monthly intravenous administration of a nitrogen-containing bisphosphonate for these patients. Within 2 years of diagnosis, if these drugs are not used, ~50–66% of these patients will experience a skeletal-related event (defined in some studies as a new pathological fracture, spinal cord compression, bone surgery, radiation therapy to bone, or hypercalcemia).[33] Two frequently used intravenous

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nitrogen-containing bisphosphonates are pamidronate and zoledronic acid. Pamidronate reduces the occurrence of skeletal-related events in patients with multiple myeloma or breast cancer with osteolytic bone disease.[27,28] Zoledronic acid has also proven efficacious, not only in these settings but also in patients with other solid tumors (such as lung and prostate cancer) that have metastasized to bone, regardless of whether the lesions are osteolytic, osteoblastic or mixed.[29–32] The trials that assessed the efficacy of pamidronate and zoledronic acid typically had a follow-up of ~2 years and the results confirmed that treatment with these bisphosphonates reduced the incidence of skeletal-related events in these patients. Guidelines have suggested that treatment with bisphosphonates should only be administered for >2 years in patients with active disease and that they should receive the drug every 3 months after the first 2 years of their treatment.[34] However, no clinical trials have been completed to assess these recommendations.

The results of a study published in 2010 suggest that in patients with multiple myeloma the occurrence of skeletal-related events is not only associated with decreased quality of life but also shortened survival.[35] In addition, study results that demonstrated the antitumor effects of bisphosphonates in the laboratory[36] are now supported by the results of several clinical trials.[37,38] Specifically, in a large trial, patients with multiple myeloma who had not previously been treated with either chemotherapy or bisphosphonates (all of whom started chemotherapy during the trial) were randomized to receive monthly zoledronic acid or daily administration of oral clodronate.[37] The patients randomized to receive zoledronic acid showed not only improved bone-related morbidity but also improved overall survival. In addition, results of a large, randomized trial show that in premenopausal women with localized breast cancer who are treated with hormonal manipulation and also received zoledronic acid every 6 months, disease progression is delayed overall at both osseous and nonosseous sites.[38] These studies suggest that this potent bisphosphonate, in addition to treating bone disorders, could prevent the development or worsening of cancer. Thus, these findings, along with the constantly improving survival of cancer patients, will probably lead to an increase both in the number of patients with cancer receiving these drugs and in the duration of their use.

As a result of the increased use of intravenously administered bisphosphonates, a rising incidence of several adverse effects, including BON, has been recognized. A report published in 2009 emphasized that good dental care is important to reduce the occurrence of this rare complication.[39] Although BON can result in clinically important problems for some patients, others only experience intermittent, minimal symptoms. Importantly, ongoing monthly intravenous bisphosphonate therapy results in an absolute reduction in skeletal-related events of ~15% per year compared to placebo treatment in patients with metastatic bone disease or multiple myeloma.[28] However, the randomized trials only lasted for ~2 years, and no data exist on the long-term efficacy and

Key points

- Higher levels of evidence than those currently available are needed to help establish the natural history, true prevalence, prevention and treatment strategies and prognosis for bisphosphonate-associated osteonecrosis (BON)
- Most studies of BON are case series, which are susceptible to bias as they lack a comparator group
- Prospective studies with well-documented follow-up of patients and participation of a dental expert seem to yield higher prevalence rates than other study designs, such as retrospective studies
- Diagnosis of BON requires exposed necrotic bone that does not respond to conventional therapy for osteonecrosis in a patient receiving bisphosphonates with no history of head and neck irradiation
- Patients with BON refractory to conservative local debridement and use of topical and systemic antibiotics might respond positively to more aggressive surgical flaps and bone resection
- The assessment of healing after patients have been treated for BON is not well defined; evidence of healing should comprise improvements in symptoms, mucosal healing and radiographic parameters

Figure 1 | An area of osteonecrosis of the torus palatino in a patient who was taking a bisphosphonate and with no history of radiation therapy to the head and neck. A yellowish piece of bone can be seen protruding from an area of mucosal breakdown. A sinus tract has formed in the midline of the bony growth (arrow).

safety of treatment with bisphosphonates. Several trials involving treatment with oral bisphosphonates show that discontinuation of these drugs after several years of continuous treatment is associated with a higher risk of bone loss and fracture than is observed among those who continue therapy with bisphosphonates.[40,41]

The rate of bone loss and the associated risk of fracture for patients with multiple myeloma who discontinue these drugs will probably be much higher than it is among postmenopausal women with osteoporosis. Findings reported in the past 2 years of the potentially clinically important benefits of zoledronic acid for both overall survival[37] and delay in progression of cancer[37,38] are an important consideration in deciding upon the duration of therapy and whether to discontinue bisphosphonate treatment in a patient with BON.

Clinical trials are ongoing to determine whether less-frequent (every 3 months) dosing is effective after initial once-monthly intravenous bisphosphonate therapy;

however, the results of these studies are not yet available.[42] Information is lacking on whether these modifications in dosing schedule following initial monthly therapy have any effect on the risk of BON. Research groups are evaluating the use of bone markers to determine the optimal dosing frequency for zoledronic acid in patients with cancer but these trials have not yet been completed. In the meantime, as zoledronic acid seems to have an additional effect on improving the outcome of patients with multiple myeloma or breast cancer, in terms of not only bone disease but also overall survival, we recommend continuation of bisphosphonate treatment on a once-monthly basis. In addition, no data suggest an ongoing benefit once these drugs are discontinued or that less-frequent dosing (less than once monthly) is effective in patients with metastatic bone disease. Ultimately, the clinician must weigh up the risks and benefits of long-term therapy and a reduced frequency of dosing with these drugs as further information emerges on these clinically important issues.

Diagnosis of BON
Clinical symptoms

Currently, a diagnosis of BON is made on the basis of the presence of clinical manifestations, as no diagnostic tests are available. BON is defined as the presence of necrotic bone for >6 weeks in an area of the oral cavity that is normally covered by mucosa, in a patient currently or previously exposed to a bisphosphonate and with no history of radiation therapy to the head and neck.[11,43,44] Patients with BON might not respond adequately to conventional therapy for osteonecrosis, such as local necrotic bone debridement, topical rinses and the use of systemic antibiotics. If an oral area of exposed bone in a patient who has been treated with bisphosphonates persists for 6–8 weeks either without specific treatment or despite local debridement with topical and systemic antibiotic therapy, the diagnosis of BON can be confirmed.

However, in some patients with BON the oral mucosa covering the area of diseased bone is not open; therefore, the necrotic bone cannot be clinically visualized. In such cases, the oral mucosa covering the involved area might be erythematous, swollen, painful and have a draining sinus tract, indicating the presence of infection.[45] These findings might predate the development of bone exposure at the site. Although this presentation is classified by the existing systems as stage 0, it is important to recognize that bone disease is already present but is not visible clinically, as it is covered by oral mucosa.[12] Exposed necrotic bone frequently develops after dental extractions, or might appear spontaneously and be asymptomatic (painless) or symptomatic (presence of pain). The necrotic bone has a grayish yellow, irregular surface and is asymptomatic to probing. Surrounding tissues might become inflamed, swollen and be painful when secondary infection is present. Depending on the extent of the infection and tissue involvement, paresthesia, lymphadenopathy, mobility of adjacent teeth, sinus tract formation and detachment of sequestered necrotic bone into the oral cavity might occur.

Imaging techniques

Several imaging techniques have been used to assess the extent of bone involvement in patients with BON.[46–49] Radiographic imaging techniques have been used to detect early bone changes and to assess the degree of bone involvement when clinical disease is not visible. Imaging findings can also help to guide therapeutic decisions and monitor progression of disease or response to therapy.[50,51] However, conventional radiography might under-represent the area of bone involvement because this technique lacks the sensitivity to detect the extent of bone necrosis. Conventional dental radiography can reveal osteosclerosis, osteolysis, mixed lesions with reactive periosteum, and pathologic fractures associated with BON.[52,53] Osteosclerosis of the lamina dura might be an early indication of metabolic bone changes and could be a precursor of BON; however, further investigation is required to establish this link.[54,55]

Bone scintigraphy and MRI might be able to detect early bone changes that predict the development of BON and could indicate the extent of disease.[47,48] In one of these studies (a retrospective chart review), 35 patients with metastatic cancers or multiple myeloma underwent ^{99}Tc methylene diphosphonate bone scintigraphy.[48] In all, 23 of these patients (66%) showed tracer uptake in areas that, according to the researchers, later developed BON. However, they did not provide any evidence that an oral examination conducted at the time of scintigraphy would have found clinical signs of BON.[48]

During surgery, imaging can also be used to assist surgeons in determining the extent of bone involvement and, therefore, how much bone needs to be removed. Cone beam CT and MRI evaluation can detect bone pathology more precisely than conventional panoramic radiographs.[56] However, the relevance of these techniques for early detection of preclinical BON and preoperative assessment of the extent of BON lesions is currently unknown.[56–58]

The diagnosis of BON, therefore, continues to be based on clinical signs and symptoms that persist for >6 weeks. Patients receiving bisphosphonate therapy, or those with past exposure to bisphosphonates, and with suspicious signs and symptoms in the oral cavity should be referred to a dental professional with experience in BON.

Prevalence of BON

Although several small studies[59–66] have attempted to determine the prevalence of BON, differences in study design, different inclusion and exclusion criteria and a lack of documented clinical data and follow-up of patients make it difficult to establish precise values for these parameters. A very important issue is that the diagnosis of BON is based on clinical manifestations often when symptoms are present, rather than epidemiologic assessment of potential risk groups with or without symptoms. Confirming a diagnosis of BON is difficult without well-documented clinical data (such as the presence of exposed necrotic bone in the oral cavity of a patient using a bisphosphonate, duration of exposure to the drug, and lack of response to conventional therapy

for osteonecrosis). Many studies of BON lack this critical information, as they are often based on retrospective chart reviews, do not include a complete oral evaluation of the participants by a dental professional with experience in the diagnosis of BON or do not include adequate follow-up of patients. In such studies, the true number of cases of BON cannot be ascertained owing to a range of flaws in their design (Box 1). For the purpose of this Review, therefore, prevalence is the proportion of people with BON among those who are treated with bisphosphonates at a given time and incidence is the risk of developing BON during a specific period of time.

Prevalence studies (published during 2005–2008) that used a variety of designs indicated an estimated BON prevalence of 3–18% among patients who are treated with an intravenous bisphosphonate.[59–67] The variation in prevalence values can be attributed to the type of tumor evaluated (such as multiple myeloma, breast or prostate cancer), the specific bisphosphonate used, dosage and duration of exposure to the drug. In a comprehensive narrative review published in 2006, the prevalence of BON in various geographic populations of patients with the same types of cancer was estimated to be between 6% and 10%.[26] Furthermore, 93% of all cases of BON reported to the FDA up to September 2008 involved the use of intravenous medication to prevent skeletal-related events.[68] The remaining 7% of cases were attributed to oral bisphosphonates used for the prevention of osteoporosis.[68]

Case series (published during 2008–2010) with prospective follow-up of patients that included the participation of dental professionals trained in the diagnosis of BON showed higher prevalence rates than earlier studies. Up to 18% of patients with prostate cancer and 5% of patients with breast cancer developed BON.[65,67] A large cohort of patients with cancer from Thessaloniki, Greece, included 1,621 patients treated with intravenous bisphosphonates during 2000–2008. In this study, the crude BON incidence rates were 8%, 3% and 5% in patients with multiple myeloma, breast cancer or prostate cancer, respectively.[69] However, two retrospective chart reviews of patients using intravenous bisphosphonates[70,71] and a survey of patients who were receiving oral bisphosphonates[72] found much lower overall incidence rates for these same three cancers of 5.0% (multiple myeloma),[70] 1.0% (breast cancer),[71] and 0.10% (prostate cancer).[72] This finding further emphasizes the fact that retrospective study designs and surveys might lack specific documentation to confirm or rule out a diagnosis of BON, which affects the determination of incidence and prevalence of this complication (Box 1). A systematic review published in 2010 clearly demonstrates that prospective studies and case series with complete documentation of cases and with the participation of dental experts usually yield a higher weighted prevalence of BON than do studies without these features.[73]

Pathobiology of BON

The pathobiology and natural history of BON are still under investigation, and the mechanisms that lead to its

Box 1 | Common design flaws in studies of BON

- Use of web-based surveys of patients' data that do not include comprehensive clinical information, which means that the diagnosis cannot be confirmed
- No information on the total number of patients with the same disease and treatment seen in the institution where the study was conducted (the denominator); therefore, true prevalence cannot be calculated
- No detailed clinical data collected by a dental professional with expertise in BON
- Inadequate follow-up of patients to document post-therapy mucosal and bone healing
- No information presented as to whether the patients with BON were all diagnosed in-house or whether some were referred to the institution by outside practitioners
- Reliance on prevalence data provided by manufacturers of bisphosphonates (which are based only on those cases reported to them by consumers or health-care professionals)
- Sample selection bias (patients who present to experienced providers or referred for tertiary care might represent particularly severe and symptomatic cases)

Abbreviation: BON, bisphosphonate-associated osteonecrosis.

development have not been completely elucidated.[74,75] Current evidence suggests that the inhibition of bone turnover caused by bisphosphonates might be central to the development of BON.[76] Additional mechanistic processes have been proposed to be involved in the pathogenesis of BON, but scientific evidence of their involvement is not yet fully characterized (Box 2).[77] The process of BON development might be initiated by microdamage and microcracks in the jaw bones that occur during daily activity (such as chewing or jaw trauma) that are not remodeled because bisphosphonates inhibit bone-resorption and remodeling by osteoclasts. The bone-forming activity of osteoblasts could potentially also be inhibited by these agents, albeit only indirectly.[78–80] This possible inhibitory and toxic effect of bisphosphonates on osteoblasts is still being investigated, but these effects could represent an additional compromise of the bone-remodeling system.[81] The inhibitory effects of bisphosphonates on bone turnover result in accumulation of newly formed bone that is deposited over old, damaged bone, which might lead to bone matrix necrosis.[76,82]

Changes at the level of the physiology of bone multicellular units and the possible multiple anti-angiogenic effects of bisphosphonates could result in decreased (or complete loss of) intraosseous vascularity.[75,83,84] The process of bone necrosis might still take place in a closed environment, even without exposure of bone to the external environment, although surgical dental procedures can act as a trigger of bone breakdown. In the past 2 years, inflammatory cells have been hypothesized to infiltrate damaged bone, which lowers the pH around the damaged area.[85,86] This acidic environment might facilitate breaking of the strong bonds between bisphosphonates and the bone matrix,[87] which

- High concentrations of free bisphosphonate are toxic to cells and tissues and might lead to mucosal ulceration, bone exposure and bacterial contamination with formation of a biofilm on the bone surface. The biofilm cannot be treated with systemic antibiotics because of a lack of vascularization in the necrotic bone
- Inflammation in and around bone microcracks promotes a reduced pH and promotes the release of bisphosphonates from the bone matrix, resulting in high local concentrations of the drug
- Suppression of bone turnover by bisphosphonates prevents remodeling of bone microcracks and microdamage, leading to persistent inflammation
- Possible anti-angiogenic effects of bisphosphonates include reduced mobilization of endothelial cells, which are also involved in bone remodeling
- Oral pain and discomfort might lead to tooth extraction, resulting in increased exposure of necrotic bone and perpetuation of the osteonecrosis process
- Altered T-cell-mediated immunity represented by an imbalance between adaptive regulatory T cells and inflammatory interleukin 17 producing T-helper cells could result in altered inflammatory response during bone healing

Abbreviation: BON, bisphosphonate-associated osteonecrosis.

results in the drug being released from the bone matrix. At this point, pain might occur in some patients, even in the absence of clinical bone exposure. Free bisphosphonate is toxic to the surrounding tissues and leads to cell death, tissue breakdown and exposure of bone to the oral cavity.[88] Bacteria from the oral environment can then gain access to affected bone and freely populate the area, resulting in the formation of a biofilm. In an area of necrotic bone, the biofilm cannot be reached by systemic antibiotics because of the lack of tissue vascularization, which leads to the consolidation of osteonecrosis and results in the perpetuation of the process.[77,89] Several reports indicate the presence of *Actinomyces* spp. in biopsy specimens from patients with BON; these micro-organisms probably represent secondary colonization. If future research shows that these micro-organisms participate in the pathogenesis of this complication, early identification and treatment of infections could lead to improved management of BON.[90]

The sequence of events described above occurs in a patient who has no oral disease at the time bisphosphonate therapy starts. In a patient with poor oral health (decayed and broken teeth, poor dentistry, periodontal disease), inflammation and infection are already active in the soft tissue and might extend into the jaw bones. Cancer, chemotherapy, comorbidities and use of other medications can contribute to the pathogenesis of BON. These factors can create a poor environment for tissue and wound healing, which can promote the development of osteonecrosis and lead to osteomyelitis.

Interesting experimental evidence obtained from a mouse model suggests that altered T-cell-mediated immunity (namely suppression of regulatory T cells and activation of proinflammatory T-helper cells that produce interleukin 17) might be involved in the pathogenesis of BON.[91] In this model, BON lesions are induced by treatment with zoledronic acid and dexamethasone. An infusion of mesenchymal stem cells prevents BON from developing and also reverses the disease process in these mice, leading to healing of the BON lesions.[91]

Risk factors for BON

Individuals with cancer that has metastasized to the bone who are using intravenous nitrogen-containing bisphosphonates are at the highest risk of developing BON. Among the intravenous nitrogen-containing bisphosphonates, zoledronic acid has a stronger association with the development of BON than pamidronate or ibandronate.[69] This finding suggests that the bisphosphonate used could affect the risk of BON. A systematic review published in 2010 reported that the overall prevalence of BON in patients who were treated with intravenous zoledronic acid was 8.6%, compared with 7.3% in patients who received intravenous pamidronate. In patients who used both of these intravenous medications, the overall prevalence of BON was 21%.[73] Patients with multiple myeloma, breast or prostate cancer have the highest incidence of BON.[92] Cumulative doses of bisphosphonates, poorly fitting dental appliances, dental extractions, and denture trauma are key risk factors in the development of BON. The Greek longitudinal cohort study identified dental extractions and poorly fitting dentures as risk factors for this complication.[69] The results of a study published in 2010 demonstrate that patients with multiple myeloma have the highest prevalence (and, therefore, risk) of BON.[73]

Other factors that could influence the development of BON, include chemotherapy, anti-angiogenic drugs (such as thalidomide), diabetes mellitus, smoking, genetic susceptibility and obesity.[93] However, the only common factor found in all cases of BON is previous or current exposure to a bisphosphonate—the critical risk factor. Some clinicians suggest that low serum levels of calcium and high serum levels of parathyroid hormone could contribute to BON development.[94] An animal model has demonstrated an increased prevalence of BON in rats with vitamin D deficiency.[95] However, this intriguing experimental finding has yet to be replicated in human studies.

Management of patients with BON
Presentation and staging
The clinical spectrum of BON can vary from a single small area of asymptomatic exposed necrotic bone that shows no signs of inflammation or infection to multiple extensive areas of exposed, necrotic, alveolar bone, purulent secretion, severe pain, skin fistulation and jaw bone fracture. In 2007 (with an update in 2009[12]), the American Association of Oral and Maxillofacial Surgeons proposed a staging system to guide clinicians who manage patients with BON in the decision-making process of how to treat these patients. Also in 2007, it was proposed that early stages of BON should be included in the staging system.[43] This issue was addressed in the only updated version of the staging system currently in use (Box 3).[12]

Treatment
Management of BON is difficult.[96–101] The limited case series that have assessed treatment approaches have resulted in uncertainty as to the most appropriate treatment regimen. The most aggressive and advanced cases

of BON are often referred to oral experts for management. However, mild cases or those that are identified early might often be treated by the medical oncologist. In such patients, BON might remain stable and never require aggressive management. In the authors' clinical experience, spontaneous healing of bone and mucosa can occur in some patients after the necrotic bone is sequestered.

Treatment of patients with BON is difficult because the condition has proven to be refractory to management with the protocols used for patients with other types of osteonecrosis that show local or regional involvement of bone (osteoradionecrosis and avascular necrosis). BON, in contrast to these types of osteonecrosis, is the result of a systemic effect that might involve only the alveolar bone in the head and neck area. Initial attempts to treat patients with BON were based on invasive surgery to remove the necrotic bone, in addition to treatment with antibiotics, periodic debridement, local antibacterial rinses and hyperbaric oxygen therapy.[52,102,103] However, BON did not respond to primary surgical management, which led experts to recommend conservative medical management.[96,104] These conservative protocols include therapy for active infections with both systemic and topical antibacterial agents, minor debridement to smooth sharp bone edges, and periodic follow-ups that are determined by the severity of each individual case.

To evaluate the current literature on the management of patients with BON and outcomes of therapy, we assessed 17 studies that described the medical or surgical treatment of patients with BON.[17,21,25,65,66,101,105–115] None of these articles represented a randomized, controlled trial. Most were case series of patients diagnosed as having BON, which hinders comparisons of the different treatment protocols used and limits interpretation of the study results. For these reasons, we used simple descriptive statistics rather than inferential statistics to analyze their findings.

A total of 682 patients with BON were included in these 17 studies: 258 men (39%) and 396 women (61%), plus 28 patients from one study that did not record the sex of participants. In total, 92 of these patients (14%) had osteoporosis and 588 (86%) had cancer. The remaining two patients had rheumatoid arthritis and Paget disease of bone, respectively. In studies that reported which jaw bone was affected by BON, the mandible was affected in 379 (66%) of the cases, the maxilla in 164 (28%) and 32 patients (6%) had BON of both jaw bones. An oral bisphosphonate was used to treat 95 (14%) patients and 587 (86%) received an intravenous infusion. These data confirm previous findings that BON is more common in women than in men, the mandible is more frequently affected than the maxilla, and that individuals with cancer treated with an intravenous infusion of a bisphosphonate are the group at the highest risk of BON.[11,13,15–25]

The outcomes associated with different management protocols, however, reveal that more invasive treatment strategies are being used in advanced cases (Table 1). In addition to the studies that evaluated medical approaches we, therefore, also evaluated studies of patients with BON being treated with surgical procedures, such as bone resection or flap surgery to enable primary closure

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Box 3 | Staging system for BON*

At risk category

No apparent necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates

Stage 0

No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms

Stage 1

Exposed and necrotic bone in asymptomatic patients without evidence of infection

Stage 2

Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone without purulent drainage

Stage 3

Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (such as inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture; extra-oral fistula; oral antral and/or oral nasal communication; or osteolysis extending to the inferior border of the mandible or the sinus floor

*Staging system proposed by the American Association of Oral and Maxillofacial Surgeons.[12] Abbreviation: BON, bisphosphonate-associated osteonecrosis.

Table 1 | Outcomes of BON treatment protocols

Treatment protocol	n	Healing (%)
Medical treatment	120	17.6
Surgical debridement	118	17.3
Surgical flap and/or resection	316	46.3
Type of healing reported		
Mucosal healing*	380	56.2
Bone healing‡	40	5.9

Data from 682 patients with bisphosphonate osteonecrosis.[17,21,25,65,66,101,105–115] *No indication of the treatment protocol used. ‡All patients were treated with surgical flap or resection, oral and topical antibiotics; bone healing confirmed by radiography. Abbreviations: BON, bisphosphonate-associated osteonecrosis; n, number of patients.

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of the surgical site.[109,113,115] In these protocols, systemic antibiotics were used in combination with surgery and oral antibacterial rinses complemented the local wound therapy. The data do not indicate whether staging of BON guided the treatment decision-making process. In some studies, all patients were treated with invasive surgery (flap and bone resection).[109,113,115] Although the patients in these studies were followed up for 2–4 years, only clinical healing of the surgical site was confirmed in most of the patients; complete bone healing after surgery was not confirmed. Confirmation of mucosal healing along with an assessment of bone integrity would be ideal and should be the aim of future studies.[110] However, bone might arguably never return to normal in a patient exposed to a bisphosphonate, and consequently freedom from symptoms and mucosal coverage should perhaps be the primary goal of

therapy. Patients treated for BON should also be followed up regularly to check for recurrence or new lesions.

Newer treatment protocols for patients with BON include administration of tetracycline before surgery and bone resection guided by illumination with a Wood lamp and cone beam CT. This strategy can detect vital bone, which incorporates the antibiotic and, therefore, fluoresces under ultraviolet light.[117] Er:YAG laser treatment is a possible new method for resecting necrotic bone, eliminating bacteria from the remaining bone and stimulating tissue healing.[118,119] However, randomized, controlled trials are needed to confirm the usefulness of this technique. Other researchers have proposed that BON lesions can be reduced in size and severity by switching from a nitrogen-containing bisphosphonate to a non-nitrogen-containing bisphosphonate (such as etidronate).[120] However, non-nitrogen-containing bisphosphonates have shown little clinical benefit in the treatment of patients with metastatic bone disease.[4]

Several studies address new techniques to treat patients with BON, such as discontinuation of bisphosphonate therapy before treatment. However, the evidence is insufficient at this point to conclude that discontinuing this therapy facilitated the resolution of BON. In summary, in spite of the lack of supporting scientific evidence, there are several proposed management protocols for patients with BON. The authors of these protocols suggest that treatment decisions should be guided by the severity and staging of BON. A conservative approach seems to be sufficient for most patients with BON, whereas more aggressive and invasive therapy should be reserved for nonresponsive patients with an advanced stage of BON.[121]

Conclusions

BON is a rare complication associated with bisphosphonate therapy that mostly affects individuals with cancer who are treated with intravenous medication. Focused research is needed to identify the pathobiological mechanisms underlying this condition, which seem to be multifactorial. Currently, the true prevalence of BON is unknown and will only be determined when data from either cross-sectional studies or robust longitudinal studies become available. The diagnosis of BON is primarily based on clinical manifestations and no well-established preventive and curative protocols exist. The large number of published case series should ensure that health-care professionals are aware of the existence of BON. Higher levels of evidence than those currently available are needed to identify the best management strategies. Cohort studies will be important in the determination of prognosis; randomized trials will be important in the determination of the best therapeutic interventions and to determine whether or not discontinuation of bisphosphonates after BON develops facilitates management of the lesion. The evidence that immunity mediated by T cells might be involved in the pathobiology of BON opens a new line of research that will aid understanding of the mechanisms involved in BON. Infusion of systemic mesenchymal stem cells can both prevent and cure BON in mice, which suggests that this type of therapy could be used in humans.

Review criteria

We searched MEDLINE and PubMed for articles published between January 2008 and April 2010 using the MeSH terms "bisphosphonate" and "osteonecrosis". Only articles published in the English language were considered. We selected articles for discussion that included information on definition, diagnosis, clinical signs and symptoms, radiological findings, prevalence and incidence, risk factors, associations with specific cancers, pathobiology and current treatment protocols. Some key papers published before 2008 were also included to ensure the accuracy of information.

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