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Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus

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ABSTRACT

This work provides a systematic review of the literature from January 2003 to April 2014 pertaining to the incidence, pathophysiology, diagnosis, and treatment of osteonecrosis of the jaw (ONJ), and offers recommendations for its management based on multidisciplinary international consensus. ONJ is associated with oncology-dose parenteral antiresorptive therapy of bisphosphonates (BP) and denosumab (Dmab). The incidence of ONJ is greatest in the oncology patient population (1% to 15%), where high doses of these medications are used at frequent intervals. In the osteoporosis patient population, the incidence of ONJ is estimated at 0.001% to 0.01%, marginally higher than the incidence in the general population (<0.001%). New insights into the pathophysiology of ONJ include antiresorptive effects of BPs and Dmab, effects of BPs on gamma delta T-cells and on monocyte and macrophage function, as well as the role of local bacterial infection, inflammation, and necrosis. Advances in imaging include the use of cone beam computerized tomography assessing cortical and cancellous architecture with lower radiation exposure, magnetic resonance imaging, bone scanning, and positron emission tomography, although plain films often suffice. Other risk factors for ONJ include glucocorticoid use, maxillary or mandibular bone surgery, poor oral hygiene, chronic inflammation, diabetes mellitus, ill-fitting dentures, as well as other drugs, including antiangiogenic agents. Prevention strategies for ONJ include elimination or stabilization of oral disease prior to initiation of antiresorptive agents, as well as maintenance of good oral hygiene. In those patients at high risk for the development of ONJ, including cancer patients receiving high-dose BP or Dmab therapy, consideration should be given to withholding antiresorptive therapy following extensive oral surgery until the surgical site heals with mature mucosal coverage. Management of ONJ is based on the stage of the disease, size of the lesions, and the presence of contributing drug therapy and comorbidity. Conservative therapy includes topical antibiotic oral rinses and systemic antibiotic therapy. Localized surgical debridement is indicated in advanced nonresponsive disease and has been successful. Early data have suggested enhanced osseous wound healing with teriparatide in those without contraindications for its use. Experimental therapy includes bone marrow stem cell intralesional transplantation, low-level laser therapy, local platelet-derived growth factor application, hyperbaric oxygen, and tissue grafting. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: OSTEONECROSIS OF THE JAW; BISPHOSPHONATES; DENOSUMAB; IMAGING; RISK FACTORS; DIAGNOSIS; TREATMENT; MANAGEMENT

Introduction

This work provides a systematic review of the literature and international consensus on the classification, incidence, pathophysiology, diagnosis, and management of osteonecrosis of the jaw (ONJ) in both oncology and osteoporosis patient populations. Resulting recommendations for the diagnosis and management of ONJ are also presented. This review updates previous systematic reviews and consensus statements regarding the management of ONJ.[1,2]

Bisphosphonate (BP)-associated ONJ is defined by the American Society for Bone and Mineral Research (ASBMR) as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care

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provider, in a patient who was receiving or had been exposed to a BP and who has not received radiation therapy to the craniofacial region.[3] The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recently (2014) updated their definition of medication-related ONJ to (1) current or previous treatment with antiresorptive or antiangiogenic agents; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.[4]

The International Task Force on Osteonecrosis of the Jaw (hereafter, this Task Force or the Task Force) defines ONJ as: (1) exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider; (2) exposure to an antiresorptive agent; and (3) no history of radiation therapy to the craniofacial region. Early data suggest that antiangiogenic agents may contribute to the development of ONJ in the absence of concomitant BP therapy; the Task Force plans to address this in more detail in a subsequent document as more evidence emerges.

Oral ulceration with bone sequestration

The Task Force is also of the view that bone necrosis may occur in the absence of antiresorptive therapy, with attendant oral ulceration and bone sequestration (OUBS). However, such occurrences, typically associated with significant morbidity, are uncommon. OUBS was initially described as "lingual mandibular sequestration and ulceration" because of the predilection for involvement of the posterior lingual mandibular bone, but this terminology has been replaced by OUBS. The sequestrum can slough spontaneously, resulting in rapid resolution. However, in some cases, conservative surgical removal of the dead bone is indicated to permit efficient healing.[5–7] The incidence of OUBS in the general population is not well defined. It is possible that cases of OUBS may be captured in incidence data pertaining to drug-related ONJ. Currently, it is not known what proportion of the spontaneous sequestration cases persist beyond 8 weeks and there are no studies identifying the prevalence or incidence of OUBS. OUBS was not included in the main systematic review, which pertains to drug-related ONJ; however, this Task Force conducted a separate literature search on OUBS and, at the end of this document, has provided a summary of that search as well as current recommendations pertaining to diagnosis and management based on international consensus.

Methods

In January 2012, an International ONJ Task Force was formed with expertise from basic science and from multiple medical, dental, and surgical specialties. There was representation from 14 national and international societies addressing bone health (The sponsoring societies are the American Society of Bone and Mineral Research, American Association of Oral and Maxillofacial Surgeons, Canadian Association of Oral and Maxillofacial Surgeons, Canadian Academy of Oral and Maxillofacial Pathology and Oral Medicine, European Calcified Tissue Society, International Bone and Mineral Society, International Society of Clinical Densitometry, International Osteoporosis Foundation, International Association of Oral and Maxillofacial Surgeons, International Society of Oral Oncology, Japanese Society for Bone and Mineral Research, Osteoporosis Canada, Pan Arab Osteoporosis Society and The Endocrine Society). The Task Force formalized nine key questions to be addressed relevant to the diagnosis and management of ONJ in oncology and osteoporosis patient populations (Supporting Table S1). A systematic review of published literature was completed based on these key questions. A search strategy was developed by combining medical subject headings and/or text words from four categories: interventions (BPs and denosumab); population (oncology and osteoporosis); areas of interest for the review (classification, diagnosis, incidence, risk factors, treatment); and outcome (osteonecrosis of the jaw). All searches were limited to human studies published in the English language and excluded reviews, editorials, and letters. The electronic search was conducted in Medline (January 1, 2003 to April 10, 2014) and EMBASE (January 1, 2003 to April 10, 2014) using OVID (see Supporting Table S2 for search strategies). The results from both databases were combined and duplicates excluded. The Cochrane Database of systematic reviews was also searched for applicable references. A manual search of the bibliography of identified published articles was also performed. In order to obtain additional unpublished data, personal communication with relevant experts was conducted and pharmaceutical companies were invited to submit relevant information. A total of 46 records were included from manual searches and expert communication. The total number of references were reviewed was 933 and from these, 599 papers were reviewed in full (see Supporting Fig. S1 for articles reviewed and retained for each of the nine questions).

The published literature was critically appraised and graded based on quality of evidence (see Supporting Table S3 for Level of Evidence scales and Supporting Tables S4 and S5 for Evidence Grades, respectively). All assessments were made in duplicate with disagreements discussed between reviewers until consensus was achieved. If no consensus was possible, a third reviewer would have provided the final decision. However, adjudication by a third reviewer was not necessary in any instance.

The key questions and a summary of the current evidence were reviewed in detail by the ONJ Task Force at an in-person meeting in October 2012. The panel members were divided into subgroups, with each subgroup being responsible for responding to a specific question, each represented in a section of this systematic review. Each subgroup communicated electronically, and regularly scheduled conference calls were implemented in order to address points of controversy in order to arrive at consensus. The co-chairs reviewed the sections from each of the subgroups and completed the manuscript. The manuscript was circulated to the Task Force and was modified until consensus was achieved on each of the sections; there were a total of 21 circulations and manuscript revisions. A second in-person meeting occurred in October 2013, followed by teleconferences to ensure that all recommendations had consensus agreement. Consensus was not achieved regarding appropriate terminology for staging of ONJ because of limited available prospective data. After approval by each of the supporting societies, the manuscript was finalized. Funding and in-kind support for the ONJ Task Force has been received solely from the sponsoring societies; industry support was not requested nor received.

This guideline will be updated every 5 years or as required using the same criteria outlined above.

Results and Discussion

Supporting Table S6 provides the key recommendations with their supporting levels of evidence.

1. How is ONJ defined, and staged?

As noted in the Introduction, this Task Force defined ONJ as (1) exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider; (2) exposure to an antiresorptive agent; and (3) no history of radiation therapy to the craniofacial region.

The first report describing ONJ was published in 2003,[8] and the first peer-reviewed article describing ONJ was published by Ruggiero and colleagues[9] in 2004. In 2007, the definition of ONJ was formalized by AAOMS[10] and further clarified by the ASBMR[3] as "area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a BP and had not had radiation therapy to the craniofacial region."

Recently, ONJ has been identified in BP-naïve patients receiving denosumab (Dmab),[11–14] which necessitated accommodation of Dmab in the definition. Emerging data has also suggested an association between antiangiogenic agents and the development of ONJ and a subsequent paper is planned to address this as more data emerge.

Diagnosis

The differential diagnosis of ONJ includes other previously-defined clinical conditions such as alveolar osteitis, sinusitis, gingivitis/periodontitis, periapical pathosis, and some forms of cement-osseous dysplasia showing secondary sequestration. Bone inflammation and infection are usually present in patients with advanced ONJ, and appear to be secondary events.

In a Beagle model with increasing doses of BPs, regions of matrix necrosis increased in size and number with no evidence of infection or microbial colonization initially, but after time, exposed bone and surrounding soft tissue became secondarily infected resulting in a clinical picture similar to osteomyelitis.[15] However, the histologic analyses of these bone specimens rarely demonstrated the criteria required to establish a diagnosis of acute or chronic osteomyelitis (typical histologic findings include regions of nonviable bone with surrounding bacterial debris and inflammatory cell infiltration). Analyses of the physical properties of resected necrotic bone from ONJ patients have also failed to demonstrate any unique features that would serve as a reliable biomarker for ONJ.[16,17]

Patient history and clinical examination remain the most sensitive diagnostic tools for ONJ. A clinical finding of exposed bone in the oral cavity for 8 weeks or longer in the absence of response to appropriate therapy is the consistent diagnostic hallmark of ONJ.

Areas of exposed and necrotic bone may remain asymptomatic for prolonged periods of weeks, months, or even years.[17] These lesions most frequently become symptomatic with inflammation of surrounding tissues. Signs and symptoms may occur before the development of clinically detectable osteonecrosis and include pain, tooth mobility, mucosal swelling, erythema, ulceration, paresthesia, or even anesthesia of the associated branch of the trigeminal nerve.[18,19] Some patients may also present with symptoms of altered sensation in the affected area because the neurovascular bundle may become compressed from the surrounding inflammation.[20,21] These features may occur spontaneously or, more commonly following, dentoalveolar surgery. The vast majority of case series have described ONJ occurring at sites of prior oral surgery, particularly at extraction sites.[22–29] Exposed bone has also been reported as occurring spontaneously in the absence of prior trauma or in edentulous regions of the jaw or at sites of exostoses in oncology patients. Intraoral and extraoral fistulae may develop when necrotic mandible or maxilla becomes secondarily infected.[30] Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula may be the presenting feature in patients with maxillary bone involvement.[31]

Staging

Evidence identified for the staging of osteonecrosis of the jaw is reviewed in Supporting Table A1. Because there was so little evidence reviewed for the staging section, recommendations from this section should be considered consensus statements rather than evidence-based statements.

The clinical staging system currently being used was developed by Ruggiero and colleagues[32] and has been adopted by AAOMS.[10,33] This system is of value in identifying the stage characteristics of the condition and providing appropriate terminology for diagnosis and management (Supporting Table S7). Patients with Stage 1 disease have exposed bone and are asymptomatic with no evidence of significant adjacent or regional soft tissue inflammation or infection. Stage 2 disease is characterized by exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection. Stage 3 disease is characterized by exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection, in addition to a pathologic fracture, an extraoral fistula or oral-antral fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus.

Nonspecific oral signs or symptoms not explained by common periapical or periodontal disease in the absence of clinically exposed bone may develop in patients in the presence or absence of antiresorptive therapy. These symptoms include bone pain, fistula track formation, abscess formation, altered sensory function, or abnormal radiographic findings extending beyond the confines of the alveolar bone. The term "Stage 0" ONJ is used by AAOMS[2] to refer to any or all of these symptoms or signs in patients on antiresorptive therapy. Members of this Task Force, however, expressed concern that the use of such Stage 0 terminology may lead to overdiagnosis of ONJ because these same presenting symptoms may ultimately lead to an alternative diagnosis. A recent study by Schiodt and colleagues[34] concluded that the non-exposed variant of ONJ is the same disease as exposed ONJ and further recommended that the non-exposed disease could be classified as either Stage 1, 2, or 3, dependent on the underlying characteristics of the disease. The demographics of patients on antiresorptive medications overlap those of patients with chronic periodontal and periapical disease. Thus, many patients on antiresorptive

therapy will present to the dentist's office for common dental care. Overdiagnosing patients with ONJ could lead to detrimental effects in their skeletal health, especially if modification or discontinuation of the antiresorptive medication is entertained.

Odontalgia is caused by a number of conditions, necessitating careful exclusion. Radiographic findings of altered bone morphology, increased bone density, sequestration, or periosteal bone formation in a patient with odontalgia may be early radiographic features suggestive of a prodromal phase of ONJ and such patients require close follow-up and monitoring by the oral health care provider (see Supporting Table S8). It appears from the limited data available that up to 50% of such patients may progress to the development of clinical ONJ with bone exposure.[19] Several members of the Task Force felt that this condition could be referred to as "preclinical ONJ." However, because at least 50% of these lesions do not progress to overt ONJ, the Task Force felt unable to unanimously support the designation "preclinical ONJ" as appropriate for this particular clinical manifestation until further prospective data become available.

ONJ lesions occur more commonly in the mandible than the maxilla (65% mandible, 28.4% maxilla, 6.5% both mandible and maxilla, and 0.1% other locations; see Supporting Table A2) and are also more prevalent in areas with thin mucosa overlying bone prominences such as tori, exostoses, and the mylohyoid ridge.[9,32,35] The extent of lesions can vary and range from a nonhealing extraction site to exposure and necrosis of large sections of the mandible or maxilla.[18] The exposed bone is typically surrounded by inflamed erythematous soft tissue. Purulent discharge at the site of the exposed bone is evident in the presence of secondary infection.[36,37] Microbial cultures from areas of exposed bone usually isolate normal oral microbes.[38,39] However, in the presence of extensive soft tissue involvement, microbial cultures may identify coexisting oral pathogens and enable the selection of an appropriate antibiotic regimen. Interestingly, although ONJ is exclusive to the jaws by definition, it should be noted that osteonecrosis of the external auditory canal in patients on BP therapy has also been reported.[40–46]

2. How common is ONJ?

For the full review of evidence regarding the prevalence and incidence of ONJ in osteoporotic and oncology populations, please refer to Supporting Tables A3 and A4, respectively.

2a. Osteoporosis

There are very limited prospective cohort data evaluating the frequency of ONJ in the osteoporosis patient population, making it difficult to accurately evaluate its incidence. The published data evaluating the incidence of ONJ have largely been obtained from case-series, retrospective observational studies, or retrospective cohort studies, typically from pooled data from insurance or healthcare databases. Pooled data can be problematic in that search terms may not be specific to ONJ.

Prevalence

The prevalence of ONJ in patients prescribed oral BPs for the treatment of osteoporosis ranges from 0% to 0.04%, with the majority being below 0.001%.[47–57] The prevalence of ONJ in those prescribed high dose intravenous (i.v.) BPs is significantly higher than that seen with low dose i.v. or oral BPs, with prevalence rates of 0% to 0.348% and the majority being under 0.005%.[47,48,58–60] Felsenberg[61] noted a prevalence of ONJ in patients treated with BPs for osteoporosis of <1/100,000. Lo and colleagues[52] evaluated the Kaiser Permanente database and found the prevalence of ONJ in those receiving BPs for more than 2 years to range from 0.05% to 0.21% and appeared to be related to duration of exposure. In Canada, Khan and colleagues[62] completed a survey of oral surgeons in Ontario and found the prevalence of ONJ in those on BPs to be approximately 0.001%.

Barasch and colleagues[24] completed a case-control study and noted an association between oral BPs and ONJ with an odds ratio (OR) of 12.2 (95% confidence interval [CI], 4.3 to 35). This study, however, included patients with cancer on oncologic doses of BPs, which likely increased the incidence of ONJ. Vestergaard and colleagues[63] evaluated jaw-related events in BP users with nonusers in a historical cohort study and noted a hazard ratio (HR) of 3.15 (95% CI, 1.44 to 6.87) with alendronate use.

Incidence

The incidence of ONJ in patients prescribed oral BPs for the treatment of osteoporosis ranges from 1.04 to 69 per 100,000 patient-years.[62,64–66] The incidence of ONJ in patients prescribed i.v. BPs for the treatment of ONJ ranges from 0 to 90 per 100,000 patient-years.[58,59,65,67,68] Last, the incidence of ONJ in patients who are prescribed Dmab ranges from 0 to 30.2 per 100,000 patient-years.[69–72] In Australia, Mavrokokki and colleagues[54] conducted a national survey and found the incidence of ONJ in osteoporotic patients receiving BPs to be 0.01% to 0.04%. However, in Sweden, Ulmner and colleagues[66] surveyed oral surgery and dental clinics and estimated an incidence of 0.067%. Zavras and Zhu[73] evaluated medical claims in the United States and found no association between oral BP use and the risk of minor jaw surgery. However, in those receiving i.v. BPs there was a fourfold increased risk of minor jaw surgery, possibly reflecting an increased risk of ONJ. Similar findings were noted by Pazianas and colleagues.[74]

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial involving 7765 patients receiving either zoledronic acid 5 mg or placebo over 3 years, a single adjudicated case of ONJ was identified in each arm. Both patients had additional risk factors for ONJ (prednisone use in the patient receiving placebo and diabetes with dental abscess in the patient receiving zoledronic acid) and both resolved with antibiotics and debridement.[67] The data from four additional randomized controlled trials (RCTs) evaluating 5 mg zoledronic acid were combined with the data from the HORIZON Pivotal Fracture Trial and the overall incidence of ONJ was reviewed.[75] The additional trials included: the HORIZON Recurrent Fracture Trial with 2127 subjects after a recent low-trauma hip fracture followed for 1.9 years[58]; the Glucocorticoid-Induced Osteoporosis Trial involved 833 subjects and compared zoledronic acid 5 mg or risedronate 5 mg over 1 year[76]; the Male Osteoporosis Trial involved 302 subjects followed over 2 years receiving either zoledronic acid 5 mg annually or alendronate 70 mg orally weekly[77]; and the Prevention of Osteoporosis Trial evaluated 581 subjects over 2 years randomized to either zoledronic acid 5 mg annually versus placebo.[78] The combined adverse event database was searched for possible cases of ONJ using preferred Medical Dictionary for Regulatory Activities terms and no additional

cases of ONJ were identified in these four additional RCTs. In all, the incidence of adjudicated ONJ was <1 in 14,200 patient treatment years with zoledronic acid 5 mg.

In the completed Phase II and III clinical trials evaluating Dmab in the treatment of postmenopausal osteoporosis, no cases of ONJ were positively adjudicated in placebo-treated or Dmab-treated subjects after more than 16,000 patient-years of follow-up.[71,79–82]

In the extension of the Phase III clinical trial evaluating Dmab in postmenopausal women with osteoporosis (FREEDOM extension), eight cases of ONJ were identified.[69] Four cases developed in the long-term treatment group with patients receiving 5 to 6 years of Dmab. Two of the four patients continued on Dmab, while two discontinued drug therapy. All cases that developed ONJ healed following treatment. ONJ developed in two patients receiving Dmab in the crossover extension study at 1.5 years and 2 years of exposure; one patient continued on Dmab, while the other discontinued therapy with both healing thereafter. In the seventh year of the FREEDOM extension trial, one additional case of ONJ was observed in the long-term study and one in the crossover study. All cases healed with conservative therapy (normal soft tissue covering previously exposed bone). Three of these individuals stopped treatment, but one continued Dmab therapy without recurrence of ONJ.

From the currently available data, the incidence of ONJ in the osteoporosis patient population appears to be very low, ranging from 0.15% to less than 0.001% person-years of exposure and may be only slightly higher than the frequency observed in the general population. It will, however, be important to quantify this, identify those at a greater risk of ONJ, implement measures to further decrease the likelihood of ONJ developing in patients taking BP or Dmab therapy for osteoporosis.

2b. Oncology

In general, the oncology patient with bone metastases is exposed to more intensive osteoclast inhibition than those with osteoporosis and the incidence of ONJ is much higher. The majority of the cases of ONJ have occurred with the use of high-dose i.v. BPs in the oncology patient population.

Data evaluating the incidence of ONJ in those with cancer include limited prospective studies as well as retrospective studies and case-series.

Prevalence

The prevalence of ONJ in oncology patients treated with i.v. BPs ranges from 0% to 0.186%.[47,83–107]

Incidence

The incidence of ONJ in oncology patients treated with i.v. BPs ranges from 0 to 12,222 per 100,000 patient-years,[14,23,62,65,108–148] and the incidence of ONJ in oncology patients treated with Dmab ranges from 0 to 2,316 per 100,000 patient-years.[14,120,123,136,140–142,149]

The Phase III, randomized placebo-controlled studies comparing zoledronic acid 4 mg with Dmab 120 mg dosed monthly for the management of bone metastases have been pooled and analyzed for ONJ adverse events. In these studies, where counseling on oral health was provided, the incidence of ONJ was approximately 1% to 2%. In these pooled studies of Dmab, in comparison to BPs, a similar or slightly higher numerical incidence of ONJ was seen with Dmab, but was not statistically significant.[20] Additional details of this study are outlined below, and similar results have been noted in other studies.[14,26,28,120,123,139,149–153]

In patients with cancer, the incidence of ONJ appears to be related to dose and duration of BP or Dmab exposure.[50,105,106,125] There is considerable variability in the reported incidence and prevalence of ONJ occurrence in association with monthly administration of i.v. BPs.[26,28,29,65,83,85,99,103,105–107,109,113,119,122,125,132,139,150,154–161]

The incidence of ONJ in the oncology patient population may be affected by the type of malignancy being treated.[28,65,85,99,107,119,132,150,154–156,159,162] Confounding variables also include the use of other drugs that may also impact bone health, such as glucocorticoids, or antiangiogenic drugs, such as bevacizumab. Christodoulou and colleagues[113] retrospectively evaluated the incidence of ONJ among 116 patients receiving i.v. BPs. The prevalence of ONJ was 1.1% for those on i.v. BPs alone; however, this increased to a prevalence of 16% in those on BPs in addition to antiangiogenic agents (bevacizumab and sunitinib).

In a placebo-controlled trial in 1432 men with prostate cancer receiving androgen deprivation therapy (716 Dmab, 716 placebo), there were 33 cases of ONJ in the Dmab arm (cumulative incidence 5%), and none in the placebo arm.[149] This was a time-to-event (discovery of bone metastasis) study with some subjects followed up to 42 months.

The incidence of ONJ has been reviewed in an integrated analysis of three clinical trials comparing Dmab 120 mg monthly to zoledronic acid 4 mg monthly in the prevention of skeletal-related events (SREs): pathological fracture; radiation therapy to bone; surgery to bone; and spinal cord compression.[26] These trials were in patients with breast cancer, prostate cancer, multiple myeloma, or solid tumors with bone metastases. Dmab use was associated with significantly fewer SREs in the breast and prostate cancer trials. Overall, in 5723 patients studied over approximately 30 months, there were 89 ONJ cases: 52 in the Dmab arms (1.8%) versus 37 in the zoledronic acid–treated arm (1.3%). Although there were more ONJ cases in the Dmab-treated subjects, the difference was not statistically significant—the combined three trials had only sufficient power to detect a difference in relative risk of 76% between treatment arms.[152]

In a recent meta-analysis of seven randomized controlled trials, Dmab was associated with an overall 1.7% risk of ONJ and an increased risk of developing ONJ in comparison to a combination of BP-treatment or placebo-treatment groups. However, the increased risk of ONJ with BP therapy alone was not statistically significant. At this time there are not enough data to determine if there is a difference in the risk of ONJ with high-dose Dmab therapy versus high-dose intravenous BP therapy.[163] Cessation of Dmab therapy may be associated with more rapid rate of resolution of ONJ than occurs with BPs; however, this requires further prospective study.

3. Who develops ONJ? What are the risk factors and comorbidity?

For a complete listing of the evidence reviewed for this topic, please refer to Supporting Table A5. A summary table of risk factors can be found in Supporting Table S9.

Epidemiological data on the prevalence and incidence of ONJ are limited and, when available, typically not based on prospective studies or population-based surveys.

Significant risk factors for the development of ONJ in the oncology population, in declining order of importance, include: i.v. BPs (both dose of BP and duration of exposure impact ONJ risk)[24]; zoledronic acid[83,105,112,150,164]; pamidronate[150]; Dmab (from incidence and prevalence data); radiation therapy[24]; dental extraction[24,105,150,161,165]; chemotherapy[84]; periodontal disease[166]; oral BP use[24]; osteoporosis[105]; local suppuration[24]; glucocorticoid therapy[106]; diabetes[28]; denture use[150,165,167]; erythropoietin therapy[106]; tobacco use[28]; hyperthyroidism[28]; renal dialysis[106]; cyclophosphamide therapy[106]; etidronate[168]; and increasing age.[106,161]

Significant risk factors for the development of ONJ in the osteoporosis patient population, in declining order of importance, include: suppuration[24]; BP use[24]; dental extraction[24]; and anemia.[24]

Although Dmab was not identified as a risk factor in any of the searches, the data presented in the incidence and prevalence section would suggest that it is an additional risk factor, similar to BPs. It should be noted that both the BPs and Dmab are essentially included in the definition of drug-associated ONJ, so defining either as a risk factor for drug-related ONJ is methodologically perilous. However, it is clear that both of these drugs increase the incidence and prevalence of ONJ in both osteoporotic and oncology populations, as described in section 2 (How common is ONJ?), and are thus strongly implicated as being risk factors for ONJ.

4. Why does ONJ develop?

The pathophysiology of ONJ is not well understood. Until recently, most studies addressed the potential role of BPs, but the knowledge that Dmab therapy also increases the risk of ONJ[13,69] emphasizes the need to explore mechanisms common to both interventions. All of the evidence reviewed regarding the pathophysiology/etiology of ONJ is provided in Supporting Table A6. A summary of these data is provided in Supporting Table S10.

Infection

The sequence of events leading to the development of ONJ is unclear; in particular, it is unknown whether necrosis precedes or follows infection. Dental disease is a well-established risk factor for ONJ,[35] implicating infection and inflammation in the pathogenetic process. Aggregates of bacteria and polymorphonuclear leukocytes are commonly seen in ONJ tissue and the presence of bacterial microfilms has been described in close association with active osteoclastic resorption on the bone surface.[38,166] Bacteria are known to stimulate bone resorption[169,170]; hence, the microorganisms present may directly contribute to bone necrosis. In addition to preexisting dental trauma and disease, inhibitory effects of BPs on the proliferation and viability of oral keratinocytes[171–176] may further damage the integrity of the oral mucosa and increase the risk of infection. Activation by BPs of gamma delta T cells may stimulate the production of proinflammatory cytokines and later depletion of these T cells may impair the immune response to infection.[177–179]

Bone turnover

Suppression of bone turnover may also play a role in the development of ONJ.[180,181] The association of ONJ with potent antiresorptive drugs[62,69] and the increased risk with higher doses of BPs and Dmab would be consistent with this contention.[14,62,120] In Beagle dogs treated with high doses of BPs, areas of necrosis in the mandible sometimes develop, with nonviable osteocytes in the affected bone.[15] However, low bone turnover is not characteristically seen in affected tissue from ONJ patients[166]; furthermore, ONJ has not been reported in other conditions associated with low bone turnover.

Vascularity

BPs are known to have antiangiogenic properties[177–179] and it has been suggested that these may also contribute to the development of ONJ. ONJ has been described in several patients treated for cancer with antiangiogenic agents, in particular sunitinib[182] and bevacizumab,[157] although in these patients other risk factors were also present. Dmab is not known to have antiangiogenic effects, and normal vasculature has been reported in most histological studies of ONJ tissue.[166,183] Animal studies with BPs do not support any diminution of vascular volume with BP administration.[184]

Genetic predisposition

Not all patients with similar comorbidities and similar medical management develop ONJ; hence, pharmacogenomics may influence the risk of developing ONJ. It has been suggested that polymorphisms in the farnesyl pyrophosphate synthase[185] or cytochrome P450 CYP2C8 genes[186,187] might predispose some individuals to develop ONJ. Genomewide association case-control studies have been performed in oncology patients and this is an area undergoing further exploration.[188,189]

5. What is the role of imaging in diagnosis and management?

The evidence reviewed for the imaging of ONJ can be found in Supporting Table A7.

ONJ is a clinical diagnosis based on history and physical exam. Radiographic features of ONJ remain relatively nonspecific. Plain film radiography is usually unremarkable in the early stages of the disease because decalcification is limited.[190] The presence of localized or diffuse osteosclerosis or a thickening of the lamina dura on plain film imaging may predict future sites of exposed necrotic bone.[190] Poor ossification at a previous extraction site may also be an early radiographic feature of ONJ. Findings on computed tomography (CT) are nonspecific and may include areas of focal sclerosis, thickened lamina dura, early sequestrum formation, and reactive periosteal bone.[191–194] CT imaging is of value in delineating the extent of disease and is helpful in planning surgical intervention.[192,195] Features noted on bone scanning include increased tracer uptake at sites that subsequently develop necrosis.[196] The utility of nuclear bone scanning in patients at risk of ONJ requires further study.[196,197]

Imaging modalities used as adjunctive assessment in the evaluation of the ONJ patient may include plain radiographs, CT, magnetic resonance imaging (MRI), and functional imaging with bone scintigraphy and positron emission tomography (PET).

Each one of these approaches has advantages and limitations. Supporting Figs. S2 and S3 provide clinical and radiographic images of patients with Stage 1 and 2 ONJ, respectively. Plain radiographs are often sufficient to support the diagnosis of ONJ for reasons described below, thus precluding the need for additional, more costly imaging procedures. However, advanced imaging may become necessary if the diagnostic information obtained via plain films is incomplete.

Radiographs—intraoral and panoramic radiographs

Intraoral (periapical and bitewing) radiographs are easy to acquire, inexpensive, and deliver a low radiation dose. Images are of high resolution and are useful in assessing early features of ONJ, including thickening of the lamina dura, increased trabecular density of the alveolar bone, and widening of the periodontal ligament space.[198] In addition, they provide useful information regarding the presence of carious lesions, periodontal disease, or periapical disease, which are all important risk factors for ONJ.[199]

Panoramic radiographs are also of value and provide assessment of both arches, as well as adjacent anatomic structures including the maxillary sinus, nasal cavity, mental foramen, and mandibular canal. The typical radiographic findings of ONJ on intraoral and panoramic radiographs are increased trabecular density, incomplete healing of extraction sockets, sequestrum formation, thickening of the mandibular canal or sinus floor cortication, and periosteal bone formation.[30,192,195,200,201]

Intraoral and panoramic projections are useful screening tools for assessing the presence of dental disease and the severity and extent of osteonecrotic changes, as well as for follow-up of patients with ONJ. However, if the diagnostic information is ambiguous or more detailed investigation of the dental and osseous health is required, more advanced imaging is necessary as described in the following sections.

CT and cone beam CT

CT has clear advantages over 2D imaging in characterizing the features of ONJ. The cortical and trabecular architecture of the maxilla and mandible can be evaluated as well as the presence of periosteal bone reaction, presence of sequestrum, and integrity of adjacent vital structures, allowing for earlier detection of ONJ lesions.[193,200]

Common CT findings in ONJ patients include diffuse osteosclerosis, areas of osteolysis, cortical erosion, increased periosteal bone formation, and sequestration. Potential fistula track formation and incomplete extraction socket healing may be seen.[30,200–203] Typically, these radiographic changes extend beyond the clinically exposed bone areas. In early stages of ONJ, increased trabecular density may not be detected on panoramic radiographs but may be seen on CT.[204] CT radiographic findings may underestimate the extent of bony changes as assessed during surgery.[193] CT may demonstrate radiographic evidence of altered bone architecture at the symptomatic site and aid in disease diagnosis.[190,205] Radiographic features of osteosclerosis can be seen in the absence of clinically exposed bone,[38] and in individuals with symptoms of bone pain careful evaluation is advised because these radiographic features may be a reflection of an early prodromal phase of ONJ.

Cone beam CT (CBCT) offers similar advantages to CT in evaluating the osseous structures of the face, while delivering significantly less radiation. CBCT allows improved detection of periodontal and periapical disease in comparison to dental radiographs, particularly if a small field of view (FOV) is used.[206,207] There are no conclusive definitive studies regarding the use of CBCT use and the diagnosis of ONJ. Data are limited to preliminary investigations.

A major disadvantage of CBCT is the low contrast resolution and poor soft tissue detail. However, the ability of CBCT to image bony structures is similar to that of CT.[207] Because of the high-resolution volumetric imaging, CBCT shows improved diagnostic ability for periodontal and periapical disease in comparison to conventional radiographs.[206] CBCT imaging findings of the osteonecrotic areas are similar to those with CT, and include increased bone density, osteolysis, cortical erosions, sequestration, and periosteal bone reaction.[192,208,209]

MRI

MRI offers similar advantages to CT in evaluating the osseous ONJ changes, while it appears to be superior in assessing bone marrow change at the early stage of ONJ, as well as the soft tissue changes surrounding the osteonecrotic area.

One of the most consistent and earliest MRI findings is a decrease of bone marrow signal intensity on T1-weighted images that can be present prior to clinical features of ONJ.[193,197,201,210] T2-weighted and short T1 inversion recovery (STIR) sequences may show increased signal intensity because of high water content,[204] while irregular gadolinium enhancement of bone marrow and soft tissues around osteolytic areas is observed.[197,201,210] In advanced disease the bone marrow signal intensity on T2-weighted and STIR images can be variable: the exposed bone shows decreased signal intensity, and the unexposed diseased bone shows increased signal intensity.[201,211] Sequestra display a low-signal-intensity center with a high-signal-intensity rim on the T2-weighted image.[197,212] Soft tissue thickening and edema and lymph node enlargement can also be observed.[36,210] Similar to CT, MRI shows increased ability to detect osseous ONJ changes compared to panoramic radiographs; however, it may also fail to demonstrate the full extent of bony changes seen on surgical exploration.[193]

Nuclear imaging with scintigraphy and PET

Bone scintigraphy using Tc99m methylene diphosphonate (MDP) or hydroxymethylene diphosphonate (HDP) has a high sensitivity for detecting early disease. Bone scintigraphy shows increased radionuclide uptake with increased perfusion and increased blood pool. Single-photon emission CT (SPECT) and fusion SPECT/CT provide more precise localization of osteonecrotic areas with surrounding areas of increased radionuclide uptake.[191,213] In 67.5% of patients with ONJ, increased Tc99m-MDP or HDP was observed in areas that later developed clinical osteonecrosis; thus, bone scans may be useful in early identification of ONJ.[196,214] However, it is not uncommon for conditions other than ONJ to produce increased uptake in the jaw, including tumor or periodontal disease.[215,216]

PET alone or in combination with CT has also been used for the assessment of ONJ patients, using both F-18 fluoride (NaF) and F-18 fluorodeoxyglucose (FDG) tracers.[214,217,218] Interestingly, FDG-PET uptake appears to increase with ONJ severity, although a clear relationship has not been established, which is possibly due to the small number of patients in the study.[217]

In summary, imaging is of value in diagnosing ONJ. This is particularly the case in those individuals on antiresorptive therapy with ONJ-like symptoms, but without obvious bone exposure. Because periapical and periodontal disease is an important risk factor for ONJ, identifying early dental disease with imaging and proceeding with dental preventive measures may decrease the risk of ONJ and minimize the need for dental extractions.[118,219] In addition, imaging enables exclusion of other conditions that may contribute to necrosis, such as metastatic disease.[220,221] There are no pathognomonic features of ONJ on imaging that definitively differentiate ONJ from other conditions.[222] However, imaging can assist in identifying the extent of bone and soft tissue disease as well as providing information on dental, periodontal, and periapical health. A summary of imaging findings with ONJ is presented in Supporting Table S11.

Recommendations for imaging

A. Individuals on low-dose antiresorptive treatment without signs or symptoms of ONJ do not require any additional imaging over and above routine dental evaluation.[223–225]

B. Patients on high-dose antiresorptive treatment without ONJ are at significant risk of developing ONJ and early identification of dental disease is important.[118,219] Following a complete examination of the oral cavity, high-risk patients should ideally receive bitewing and periapical intraoral radiographs of all existing teeth as well as panoramic radiographs. When available, CBCT 3D imaging using high-resolution protocols could also be performed, given the superior ability of CBCT (compared to conventional radiographs) in diagnosing periapical and periodontal disease. Following a baseline evaluation of oral health, additional conventional and CBCT radiographs are performed only if necessary in the presence of oral complaints or signs or symptoms of ONJ.[226]

C. In patients in whom ONJ is a clinical consideration on low-dose or high-dose antiresorptive therapy presenting with oral symptoms, CBCT or CT imaging may aid in evaluating early changes in the cortical and trabecular architecture of the maxilla and mandible. Imaging also allows assessment of possible sequestrum or fistula track formation and evaluation of the status of any involved teeth. If both CBCT and CT are available, small-FOV, high-resolution CBCT is preferred because it delivers less radiation and provides similar diagnostic information as CT. CBCT may be performed in conjunction with bitewing, periapical, and panoramic radiographs. If clinically indicated, MRI may provide additional information of the presence and extent of osteonecrosis.

D. In patients with clinical ONJ under conservative management (Stage 1 and 2), the nature and extent of osseous changes around the area of clinical bone exposure can be evaluated with CT or small-FOV high-resolution CBCT imaging. Dental disease in all existing teeth should also be determined with bitewing, periapical, and panoramic radiographs.

E. In patients with clinical ONJ where surgical intervention is considered (Stage 2 and 3), CBCT or CT may be complemented with MRI, bone scan, or PET for a more thorough evaluation of involved bone and soft tissues.

6. Are biomarkers useful in identifying ONJ?

Please refer to Supporting Table A8 for a full description of all the papers reviewed in this section.

ONJ is a complication associated with the use of the antiresorptive therapies, either with BPs and/or Dmab. Marx and colleagues[227] suggested that quantification of bone resorption may be useful for prognosis. They reported data on 30 women treated with oral BPs for low bone density who had subsequently presented with ONJ. Seventeen of these women were still taking oral BP at the time of presentation, and had C-terminal telopeptide (CTX) values of 30 to 102 pg/mL (mean 73 pg/mL). After 6 months off BPs, CTX values were 162 to 343 pg/mL (mean 228 pg/mL), a mean rise of 26 pg/mL/month. ONJ healed in all patients over the following 18 months, and the authors concluded that this was causally associated with the higher bone turnover. Although this is possible, the hypothesis was not formally tested because none of the patients were assessed while continuing BP therapy. At presentation, there was no correlation between CTX and clinical severity in this cohort, nor in 60 other ONJ patients receiving i.v. BPs. They concluded that if CTX is >150 pg/mL in patients receiving oral BPs then invasive oral surgical procedures can be completed with minimal risk of osteonecrosis, although no data supporting this statement are presented (Marx criteria: CTX <100 pg/mL = high risk, 100 to 150 pg/mL = moderate risk, and >150 pg/mL = minimal risk).

Cross-sectional studies in patients with ONJ have evaluated the association between CTX levels and disease severity. Although Bagan and colleagues[228] found no relationship in 15 oncology patients, Kwon and colleagues[229] found that CTX levels were related ($r = 0.47$) to the number of the ONJ lesions and their stage in 18 patients receiving oral BP therapy, although CTX levels were not different from those in BP-treated osteoporosis patients without ONJ.[230]

The utility of CTX has been evaluated in its ability to predict outcomes in patients with ONJ. In each of these studies, many patients were "at risk" by the Marx criteria. Atalay and colleagues[231] found that CTX did not predict treatment prognosis in 20 cancer patients, despite a wide range of baseline CTX values. CTX levels in BP-treated subjects have been assessed as a predictor of ONJ risk after oral surgery. Kunchur and colleagues[232] measured CTX in 222 BP users undergoing extractions. Only one patient developed ONJ and had a moderate level of CTX (126 pg/mL). Lee and Suzuki[233] assessed CTX levels in 54 patients on oral BPs undergoing oral surgery and despite a very wide range of CTX values prior to surgery (39 to 330 pg/mL; mean of 161 pg/mL), no patient developed ONJ. Similarly, O'Connell and colleagues[234] measured CTX values in 23 patients on BPs, 21 with osteoporosis and two with cancer, prior to oral surgery (CTX range, 50 to 370 pg/mL; mean 180 pg/mL). After 5 months of observation, no patient had developed ONJ. In the HORIZON trial, one case of ONJ developed in 5903 patients given zoledronic acid, and a second case developed in the 5140 placebo-treated subjects.[75] In this trial, 43% of patients had serum CTX <100 ng/mL 6 months after zoledronic acid and would be considered at "high risk" by the Marx criteria, yet ONJ risk was no higher than in the placebo group. The very low incidence of ONJ in osteoporosis subjects indicates that even very large studies are underpowered to answer this question.

Few other biomarkers of bone turnover have been assessed with respect to ONJ management or to their utility in making decisions regarding the individual patient's risk for ONJ. One study found that neither N-terminal telopeptide (NTX) nor bone alkaline phosphatase was associated with the development of ONJ.[235] Lehrer and colleagues[236,237] performed two studies

with neither finding an association of ONJ with CTX, NTX, bone alkaline phosphatase, or osteocalcin.

Thus, although low CTX is a reflection of recent antiresorptive treatment, current data do not establish it as having a useful role in managing patients with or at risk of ONJ.

7. Can ONJ be prevented and what is the role of drug interruption?

Supporting Table A9 presents all the data with respect to prevention of ONJ.

Recommendations to reduce the risk of ONJ include completion of necessary oral surgery prior to initiation of antiresorptive therapy,[154,219,238,239] the use of antibiotics before and/or after the procedure,[22,25,239–242] antimicrobial mouth rinsing,[22,25,241] appropriate closure of the wound following tooth extraction,[240–242] and maintenance of good oral hygiene.[103,238,240,241,243,244]

The etiology of ONJ continues to be further investigated. Poor oral health, minor oral surgery, and use of potent antiresorptive agents appear to be associated with the condition. In an attempt to prevent ONJ, optimizing oral health prior to the initiation of BP and Dmab therapy is emphasized. Indeed, this simple intervention appears to be efficacious in reducing the risk of ONJ as noted by Ripamonti and colleagues[219] and Dimopoulos and colleagues,[118] and Montefusco and colleagues[239] retrospectively assessed the role of prophylactic antibiotics prior to dental procedures for the prevention of ONJ in a group of patients with multiple myeloma. Interestingly, of the 178 patients assessed, eight cases of ONJ developed, but all cases occurred in the group not provided with prophylactic antibiotics. It was concluded that a course of antibiotics prior to dental procedures may prevent the occurrence of subsequent ONJ.

Following the initial reports of ONJ in association with BP use in 2003, the vast majority of cases (>90%) have occurred in cancer patients receiving sixfold to 10-fold higher doses of BPs than those used to treat osteoporosis. Invasive oral surgery procedures have been identified as an important risk factor for ONJ. Therefore, it is recommended by the Task Force that patients who undergo invasive oral surgery have their antiresorptive therapy withheld following the procedure until soft tissue healing has occurred. However, it is acknowledged that there is little evidence to support this recommendation in terms of changing the outcome of the dental procedure because BPs remain in bone for many years. In patients taking lower-dose BPs for osteoporosis, the risk of ONJ is recognized to be extremely low (1 in 10,000 to 1 in 100,000 patients, compared with ~1% to 2% per year for cancer patients receiving higher doses of BPs). In 2011, the American Dental Association Guidelines recognized the lower risk in osteoporosis patients, and stated that discontinuation of oral BP was not necessary prior to dental procedures.[245]

In determining the best approach for each individual patient with respect to ongoing antiresorptive therapy it is necessary to stratify risk and weigh the risks of ONJ with the risk of fracture in osteoporosis patients and the risk of SREs in oncology patients. The ONJ risk will be impacted by comorbidity as well as the extent of the planned surgery.

Clinical judgment is always essential, and in patients who may require extensive invasive oral surgery, as well as those with multiple risk factors for ONJ (diabetes, periodontal disease, glucocorticoid treatment, immune deficiencies, smoking, etc.), it may be advisable to stop antiresorptive therapy if it is possible to do so without adverse consequences for bone health. In such circumstances the Task Force recommends stopping antiresorptive therapy.

For cancer patients requiring oncology doses of i.v. BPs or Dmab, a thorough dental examination with dental radiographs should be ideally completed prior to the initiation of oncology-dose antiresorptive therapy in order to identify dental disease before drug therapy is initiated. Any necessary invasive dental procedure including dental extractions or implants should ideally be completed prior to initiation of BP or Dmab therapy. Non-urgent procedures should be assessed for optimal timing because it may be appropriate to complete the non-urgent procedure prior to osteoclast inhibition, delay it until it is necessary, or perhaps plan for it during a drug holiday; however, there are no compelling data to guide these decisions.

Injudicious discontinuation of osteoporosis therapy can lead to increased risk of fractures, including hip and vertebral fractures. The decision to discontinue therapy with bone active agents must also consider the risk of fracture and implications for skeletal health.

In the presence of ONJ in a patient receiving BP or Dmab, it is recommended that oncology-dose antiresorptive drug therapy be withheld until soft tissue closure with well-epithelialized mucosa is achieved.

8. How should ONJ be managed?

A review of all the evidence for the treatment of ONJ is found in Supporting Table A10.

There are no universally accepted treatment protocols for ONJ. In the absence of a defined treatment algorithm for ONJ, there is a generally accepted approach of palliation of symptoms and controlling associated infection. Treatment strategies range from conservative nonsurgical therapy to early surgical intervention. The extent of surgery also varies and is dependent upon the stage of disease.

Treatment

Many variables may contribute to the treatment decision-making tree, including age, sex, disease status (osteoporosis, metastatic disease versus multiple myeloma, for example), ONJ stage and lesion size, medication exposure, and medical and pharmacological comorbidities. The specifics of how these factors influence the course of ONJ and its treatment response are largely unknown and, as such, clinical judgment should guide individual treatment approach.

Other important factors to consider in this group of patients are prognosis and life expectancy, quality of life, and an individual's ability to cope with their ONJ lesion(s). A similar-sized lesion may be asymptomatic in one patient, but pose considerable difficulties in another.

Conservative management

The majority of patients with ONJ have been managed conservatively. Conservative therapy includes maintaining optimal oral hygiene (diligent home self-care and regular professional dental care), elimination of active dental and periodontal disease, topical antibiotic mouth rinses, and systemic antibiotic therapy, as indicated. This is consistent with the previous recommendations of the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS), AAOMS, and

the American Dental Association,[1,2,33,245] and is supported by many practitioners.[132,246] Conservative therapy is the mainstay of care and although it may not necessarily lead to complete resolution of lesions, it may symptomatically provide long-term relief.[26,247] Among patients with breast cancer and multiple myeloma, Fortuna and colleagues[248] reported a more rapid response to conservative therapy in the breast cancer group compared to those with multiple myeloma.

Recent case reports of successful treatment of ONJ with teriparatide are encouraging[249,250] and this may become a conservative treatment choice for those with osteoporosis and without cancer or prior radiation therapy to bone. Because teriparatide has been reported to facilitate osseous wound healing in the oral cavity,[249] it may be a viable approach for patients on antiresorptive therapy for the treatment of osteoporosis. Considering the low risk of ONJ in patients with osteoporosis being treated with osteoporosis doses of antiresorptive agents and the absence of evidence that changing to teriparatide would alter the outcome of an invasive dental procedure in someone who does not have ONJ, it is not recommended at this time to switch to teriparatide in those at a low risk of ONJ or fracture. However, in an osteoporotic patient with established ONJ, treatment with teriparatide may be of value as observed in published case reports.[251–256]

The same approach should not be used in patients with cancer, a history of skeletal radiation, or with active bone metastases, because these patients are at risk for the development or advancement of bone malignancies and teriparatide should be avoided unless prospective studies demonstrate a favorable benefit-to-risk ratio for its use.

Other experimental treatment approaches found in the literature awaiting further substantiation include topically applied ozone,[257] bone marrow stem cell intralesional transplantation,[258] and addition of pentoxifylline and tocopherol to the standard antibiotic regimen.[259] The latter reportedly reduced both ONJ symptoms and the amount of exposed bone. One in vitro study suggested that geranylgeraniol might potentially prevent BP-induced predisposition to ONJ.[260] Favorable outcomes have been reported with low-level laser therapy, in conjunction with conservative and/or surgical debridement, but further confirmation is needed.[261,262]

Conservative therapy should be continued as long as there is not: (1) obvious progression of disease; (2) pain that is not being controlled by conservative means; or (3) a patient who has had antiresorptive therapy discontinued by their oncologist because of ONJ.

Surgical management

Early treatment recommendations for ONJ discouraged surgical intervention with conservative therapy continuing indefinitely or until there was progression of disease. However, there are now many reports demonstrating success with surgical management of these lesions. With surgery, a full-thickness mucoperiosteal flap should be elevated and extended to reveal the entire area of exposed bone and beyond to disease-free margins. Resection of the affected bone should be extended horizontally and inferiorly to reach healthy-appearing, bleeding bone. Sharp edges should be smoothed and primary soft tissue closure achieved in a tension-free fashion with sutures that resorb after 1 week.[263] Several authors have reported better outcomes with larger resections compared to limited debridement and/or conservative therapy.[264,265]

We propose that if surgery is indicated, resection with tension-free closure affords the most positive results.

Adjunctive treatments, in combination with surgery, have been also described in the literature. Vescovi and colleagues[262] achieved good results treating ONJ lesions with laser-assisted surgical debridement; in contrast, Atalay and colleagues[231] found no statistically significant benefit of this approach in comparison to conventional surgery. Martins and colleagues[266] conducted a preliminary retrospective survey of patients undergoing antibiotic therapy plus surgery followed by low-level laser therapy and platelet-rich plasma applied to the surgical wound, and observed improved healing.

Promising results have also been reported with surgical debridement in combination with platelet-derived growth factor (PDGF) applied to the site in Stage 2 ONJ cases.[242] Pautke and colleagues[267] reported that intraoperative fluorescence guidance was helpful in identifying surgical resection margins in Stage 2 ONJ cases. Hoefert and Eufinger[268] suggested that longer-term preoperative antibiotics (23 to 54 days) resulted in improved surgical outcomes versus short-term antibiotic therapy (1 to 8 days). Surgical success rates have been higher in patients with multiple myeloma or in those with osteoporosis receiving low-dose BP therapy in comparison to patients with solid tumors.[269]

Adjunctive therapy with hyperbaric oxygen (HBO) in combination with surgery has been investigated[270,271] with encouraging results. Further research is required with these innovative combination therapies prior to formalizing treatment recommendations.

In summary, in the absence of debilitating ONJ lesions, conservative therapy with optimal oral hygiene, topical antibiotic rinses, and systemic antibiotics are advised as needed for pain or infection.[238]

For nonresponsive ONJ lesions, surgery is an option and includes ostectomy of the affected area with resection margins that extend into adjacent normal-appearing bone. Soft tissue closure should be tension-free with no underlying sharp edges of bone that could lead to mucosal breakdown.

In the presence of a pathologic fracture or ONJ extending to the sinus or inferior border of the mandible, or if the ostectomy to healthy tissue leads to a discontinuity defect, consideration should be given to microvascular composite tissue grafting at the time of surgical resection in the mandible and the same or obturator construction for the maxilla.

At present, other adjunctive procedures as discussed in this section may be considered, but all require further research to define their value.

9. Research and future directions

It has been 10 years since the original case descriptions of ONJ were reported. The insights gained during this past decade into the pathophysiology of ONJ as well as mechanisms involved that could be targeted for therapeutic approaches have increased, but are not at a sufficient level to enable the development of optimal care strategies for our patients.[272] Over these 10 years, the paucity of scientifically sound information has often led to confusion among patients and healthcare providers. We need to do better and must rely on the scientific community, supported by governmental agencies, pharmaceutical companies, and foundations, to expand our knowledge and improve patient care.

The pathophysiology of ONJ needs to be more clearly delineated using well-characterized animal models that lend themselves to better understanding the human condition. Several ONJ animal models have been described in mice, rats, minipigs, and dogs treated with high doses of bisphosphonates.[15,273–289] Most of these models use tooth extraction,[275,280–286,288] while others stimulate experimental periodontal or periapical disease[273,274,279,287] to induce ONJ-like lesions. Recently, ONJ was described in mice treated with RANKL inhibitors without BPs, indicating the central role of osteoclast inhibition in ONJ pathogenesis.[289] These animal models capture several of the clinical, radiographic, and histologic features of ONJ. However, differences in bone composition, bone remodeling, and overall metabolism between animals and humans have been problematic. None have effectively captured the full picture of the human condition such that interventional approaches can be reliably tested.

ONJ appears to occur most commonly in those with metastatic bone disease receiving high doses of osteoclast inhibitors concurrently with anticancer therapy. In this patient population, the risk-benefit profile associated with the osteoclast inhibitors is unique from other indications for an antiresorptive therapy, in that their risk of skeletal complications of malignancy is estimated as one event occurring every 3 to 4 months in the absence of osteoclast inhibition.[290] These SREs may be catastrophic, for example spinal cord compression resulting in paralysis, or hypercalcemia of malignancy, which is often a life-threatening event. When administered at U.S. Food and Drug Administration (FDA)-recommended dosing, the use of potent osteoclast inhibitors reduces the risk of skeletal-related events by approximately 20% to 50%.[291] Hence, the oncology patient with metastatic bone disease, and their clinical care team, may view the risk of ONJ as the lesser of two evils. However, the risk of ONJ is much lwer than the risk of SRE for the vast majority of cancer patients.

As advances in osteoclast inhibition and anticancer therapies are made, it is critical that treatment regimens be assessed for both short-term and long-term adverse events, including ONJ. This is the case for both early-stage and late-stage cancers. In early-stage breast cancer, there are evolving data that the potent osteoclast inhibitors may have an anticancer effect in postmenopausal women. Therefore, it is possible that the BPs may be used in a larger patient population including those who may not have low bone mass. In one adjuvant zoledronic acid Phase III study, approximately 2% of the patients with breast cancer treated with zoledronic acid developed ONJ,[133] although other studies have reported a lower incidence.

Further research will provide effective strategies to prevent ONJ as well as define the risk of SRE and ONJ in individuals with metastatic bone disease. A greater understanding of these risks will enable clinicians to more effectively tailor drug therapy with respect to dose and frequency of administration of the osteoclast inhibitor in order to minimize both the risk of SRE and ONJ. The management of these individuals requires a multidisciplinary approach to develop evidence-based clinical practice algorithms. The panel will provide guidance through expert opinion and best evidence currently available for the oncology patient in a subsequent document.

Ongoing registries of ONJ include independent international studies and a study funded by Amgen. There is an ongoing biomarkers study as well as ongoing case-control ONJ studies and correlative investigations incorporated into BP and Dmab clinical trials. The results of these studies will add prospective epidemiologic information on risk factors associated with the development of ONJ. In addition, basic science studies of the mechanism of ONJ include investigation of the effect of antiresorptive therapy on wound healing, the oral mucosal barrier, and identification of biomarkers predictive of the development of ONJ.

There is considerable room for clinical, translational, and basic science research because the cellular mechanisms involved in oral wound healing and the influences of antiresorptive medications need to be clarified. Much of the hope for progress resides in the field of osteoimmunology. Although osteoclasts have been the focus of studies in the mineralized tissue field for decades, the dependence of oral wound healing on osteoclasts is understudied. The temporal nature of osteoclastic activity in oral wounding and the role of osteoclasts as phagocytic cells in the wound environment are of interest. For example, are the signaling molecules different in activated osteoclasts depending on the mineral surface they are associated with? Do osteoclasts associate differently with bacterial toxin-contaminated surfaces? What is the impact of antiresorptives in the inflammatory lesion? The role of osteocytes in osseous necrosis, remodeling, and antiresorptive drug actions requires further investigation. The impact of antiresorptive drugs on non-osteoclast bone marrow cells such as macrophages is ill-defined. Do BPs or anti-RANKL antibodies alter the profile of classical M1 macrophages, M2 alternatively activated macrophages, or pro-resolving macrophages?

There is a clear need for improved diagnostic and prognostic factors for ONJ. Improved prospective studies in patients at risk for ONJ could provide better insight into predictors of the condition as well as optimizing preventive approaches. What is the impact of inhibiting osteoclasts early during wound healing (eg, immediately postextraction) when osteoclasts are responsible for recontouring the wound margins versus later (eg, when the immature woven bone is remodeled to form mature lamellar bone)?

Finally, current therapeutic options are inadequate for the prevention and treatment of ONJ. It is challenging to do large clinical trials with the patient population currently presenting with ONJ. However, we do not yet have in-depth studies of the effects of any drugs used for the treatment of osteoporosis and cancer on osseous tissues in the oral cavity. Such studies are necessary to clarify potential issues specific to craniofacial bones. A detailed trajectory of healing postextraction in patients on antiresorptives relative to patients on anabolic agents or normal healthy controls has not been performed and would provide valuable new insights into skeletal site specificity and oral wound healing.

Oral Ulceration and Benign Sequestration

A literature search was conducted specifically pertaining to oral ulceration and benign sequestration (OUBS) on June 25, 2014 (http://www.ncbi.nlm.nih.gov/pubmed/?term=oral+ulceration+and+sequestration). The literature search yielded 11 total citations, three of which were not related and were discarded. The remaining eight papers were case reports or case series.[5,292–298] Two additional investigations were added through expert review.[6,7]

Diagnosis

This condition presents as a variably painful ulceration, usually involving the posterior lingual mandible at the level of the mylohyoid ridge.[5–7,292] There is a hard insensitive base formed by exposed non-vital bone. The ulcer can persist for periods that vary between a few days to several months. Occlusal radiographs show a localized radiopacity, representing the necrotic bone, superficial to the lingual cortical plate. Similar lesions can occur over oral exostoses. Histopathologic exam of the necrotic bone base shows irregular zones of resorption, microbial colonization, and often, adherent fragments of acutely inflamed granulation tissue. The condition occurs in the absence of predisposing systemic disease or antiresorptive therapy.

Pathophysiology

The pathogenesis is not well understood. However, ulceration, either traumatic or in the form of an aphthous ulcer, is thought to be the initial pathologic event.[5–7,292] Sequestration could occur following subsequent disruption of blood supply from the periosteal layer to the poorly vascularized superficial cortical bone and possible secondary infection. The devitalized and secondarily infected bone base then impedes resolution of the ulcer. The predilection of the condition for posterior lingual mandibular bone has resulted in suggestions that the anatomic site might be of etiologic importance. Of possible significance, many of these cases occur in patients who have lost posterior molars or have restorations, which do not recapitulate the normal lingual inclination of the molars. Thus, the protective lingual inclination of the molars over the mylohyoid ridge is lost and the nonkeratinized mucosal lining over the projecting mylohyoid ridge would not be shielded from chronic trauma during mastication. After the ulcer has formed, it would be further susceptible to secondary infection because it is located in a relatively stagnant oral region. The suggestion that an aphthous ulcer, rather than a traumatic ulcer, might be the primary lesion could result in the same sequence of pathologic events, and these are not mutually exclusionary suggestions.

Management

This is usually a self-limited condition that heals with conservative measures.[5–7,292] The necrotic bone may undergo spontaneous exfoliation. If the sequestrum is mobile, the process can be expedited with gentle manipulation of the sequestrum through the ulcer base. If the dead bone is adherent to the underlying cortex, surgical removal might be required. However, often a patient approach with supportive management involving antimicrobial rinses, such as chlorhexidine or tetracycline, will result in detachment of the sequestrum from underlying vital bone and eventually permit spontaneous exfoliation. Once the necrotic bone has been removed, efficient healing occurs.[299]

Future research directives

There is a need for further research on OUBS. Studies are required to evaluate the incidence and prevalence of this condition. The proportion of OUBS conditions that can result in significant morbidity in terms of size, duration, and pain should be assessed. Development of a staging system would be of value, particularly with respect to optimization of treatment strategies. The role of this condition as an initiating event for the significant drug-associated ONJs should be evaluated.

Disclosures

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