REVIEW ARTICLE

BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAWS

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Bisphosphonates are used widely for a variety of bone conditions, most notably intravenous bisphosphonate in the treatment of metastatic bone lesions and multiple myeloma and oral bisphosphonates for osteoporosis. Recently, a peculiar form of osteonecrosis limited to the jaws has been discovered especially with the use of intravenous bisphosphonates. We review briefly the mechanism of action of these drugs, the clinical features and staging of the disease, prevention strategies and management options.

Keyword: BRONJ, Multiple myeloma, Hyperbaric oxygen

Bisphosphonates

Bisphosphonates have a chemical resemblance with inorganic pyrophosphate, which inhibits bone resoption.[1,2] Their high affinity for hydroxyapatite directs them to areas of active bone turnover, where they tend to inhibit osteoclast-mediate bone resorption.[3] Once in an area of active bone turnover, they are internalised by osteoclasts and inhibit specific cell pathways, perform modulation of signals from osteoblasts to osteoclasts, causing osteoclast inactivation and leading metabolically active osteoclasts towards programmed cell death (apoptosis).[4]

The current indications for bisphosphonate administration include a variety of metabolic and oncologic bone diseases. Where oral bisphosphonates such as Etidronate, Alendronate and Risedronate are now routinely prescribed for patients with Paget's disease and postmenopausal osteoporosis[5], the more potent IV bisphosphonates such as Pamidronate and zoledronic acid are used to prevent severe bone pain, pathologic fractures, and hypercalcemia in metastatic cancers to bone and in treating bone resorption defects in multiple myeloma[6–8].

Bisphosphonates are generally well tolerated by patients. The adverse effects were known to be infrequent and consisted of high serum creatinine levels, transient low-grade pyrexia, fatigue, arthralgia, nausea, renal function impairment, hypocalcemia, and increased bone pain.[9] However, two pioneering reports by oral and maxillofacial surgeons led to the discovery of a disturbing sequel to bisphosphonate treatment, when Marx[10] in 2003 and

Ruggiero[11] in 2004 reported their respective series of patients on bisphosphonate therapy who had developed osteonecrosis limited to the jaws spontaneously or after dental or oral surgical procedure, with no seeming involvement of other skeletal bones.[11,12]

Bisphosphonate related osteonecrosis of the jaws (BRONJ)

The commonest term used to describe the avascular necrosis ensuing bisphosphonate treatment is BRONJ. Symptoms can include difficulties in eating and speaking, swelling, pain, bleeding, lower lip paresthesia, and loose and mobile teeth.[13] Though no consistent dental radiographic changes have been noted, there is a relatively strong association of BRONJ with a widened periodontal membrane space, particularly at the furcation of the molar teeth.[14] The radiographic findings are not specific, and when faced with such a lesion within the maxillofacial region, the dentist is faced with a dilemma because of the possibility of metastatic lesions in a patient on bisphosphonate therapy for bone cancer or MM; immediate biopsy should rule out any possible metastatic lesions. Frequent reports by surgeons all over the world led AAOMS to formulate a position paper on BRONJ, with suggestions for a working definition, clinical staging and treatment.[15] (Table-1) The criteria by which a diagnosis of BRONJ can be made include a history of current/previous treatment with a bisphosphonate; exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; with no history of radiation therapy to the jaws.

Table-1: Clinical staging of BRONJ [15]

Patients at risk	No apparent exposed/necrotic bone in patients who have been treated with either IV or oral bisphosphonates
Patients with BRONJ	
Stage 1	Exposed, necrotic bone that is *asymptomatic*
Stage 2	Exposed, necrotic bone associated with *pain and infection*
Stage 3	Exposed, necrotic bone in patients with pain, infection, and *pathologic fracture, extraoral fistula, or osteolysis* extending to the inferior border

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The BRONJ has been seen to have closer resemblance with osteopetrosis, which also has the endpoint of producing dead bone and therefore, should not be confused with other types of osteonecrosis occurring in the long bones. Clinicians are already well aware of the osteonecrosis occurring in the jaws in the form of ORN, which has again a distinctly different aetiology from BRONJ.[16,17] Probably the most plausible explanation given behind the aetiology of BRONJ relates to the bisphosphonates' strong affinity for active hydroxyapatite areas with inhibitive effects on osteoclasts. It is the greater blood supply and a faster bone turnover in the jaws (related to daily jaw function and bone remodelling around the periodontal ligament) that bisphosphonates tend to get highly concentrated in the jaws. Also the chronic invasive dental diseases and treatments and the thin mucosa over bone, the condition manifests exclusively in the jaws.[18] There is also experimental evidence that Pamidronate and Zoledronate inhibit capillary neoangiogenesis, which leads to development of BRONJ.

Intravenous bisphosphonate treatment with Zoledronate is seen to evoke BRONJ more quickly than Pamidronate.[14] Oral bisphosphonates tend to be less potent and therefore, restrict osteoclastic function less severely; with no significant prevalence of exposed bone unless much higher cumulative doses of these are given over longer durations.[14]

One of the commonest dental predisposing factors is the presence of periodontitis. Also important is the presence of mandibular tori especially in those cases that developed spontaneous bone exposure.[14] Mandible is seen to be almost twice more involved than maxilla.[15] Identification of risk factors and initiating events can help us to devise a strategy towards BRONJ prevention. Although a quarter of the cases are seen to be spontaneous, the rest are related to removal of a tooth, oral surgical procedure (periodontal or periapical surgery and dental implant placement) and around a quarter due to obvious existing periodontal disease.[14] Concomitant corticosteroid therapy, diabetes, alcohol consumption, smoking, poor oral hygiene and other chemotherapeutic agents are thought to be the risk factors behind the development of BRONJ.[15]

Prevention and treatment

It has been customary for maxillofacial oncologic surgeons and radiation therapists to refer patients for oral and dental evaluation before radiotherapy. It is also imperative that as soon as bisphosphonate therapy especially IV bisphosphonate is prescribed to a patient by the treating oncologist, the patient should be referred to an experienced dentist or oral and maxillofacial surgeon for an urgent examination. An attempt should be done to defer bisphosphonate therapy until oral and dental surgical treatments have been completed. The dental exam is done through clinical and imaging review; taking help from OPG and periapical views in area of concern. The dental treatment should aim at eliminating potential endodontic or periodontal foci of infections with the objective that any invasive dental or oral surgical procedure should be prevented in near and intermediate future. Pre-BRONJ therapy dental procedures can include extraction of unsalvageable teeth, dental restorations, endodontic and periodontal therapies, and well made dentures. Removable prosthesis is preferred over endosseous dental implants, as they can predispose to bone exposure. Deeply buried impacted teeth should be left undisturbed, but those with an oral communication are recommended to be removed and given a one month healing period. Likewise, tori that are of such size that causes thinning of the overlying mucosa should also be removed a month before start of BRONJ therapy; smaller tori can be left undisturbed. Invasive procedures including exodontia and oral surgical procedures should receive an antibiotic prophylaxis, for which penicillin remains the drug of choice. In case of penicillin allergy, erythromycin and metronidazole are considered good second line alternatives. Because of the frequent colonization of BRONJ foci with actinomyces and similar species against which Clindamycin has little value, Clindamycin use is not advocated in contrast to other instances of penicillin allergy. In case of invasive dental procedures being planned, it is ideal to defer bisphosphonate treatment for 1 month to allow sufficient time for bone remodelling. Once bisphosphonate treatment is started, the patient should be recalled every 4 months for monitoring of oral and dental health.[14]

While evaluating a patient who is receiving bisphosphonate therapy, the dental team should carefully evaluate the oral cavity for exposed bone in the areas which are most commonly affected, most notably the posterior lingual area of the mandible, and for radiographic disease signs such as osteolysis, osteosclerosis, widened periodontal spaces, and furcation involvement. Dental cleaning with topical fluoride treatment can be considered, and dental extractions be deferred if possible. However, if the tooth is unrestorable because of caries, root canal treatment and amputation of crown is a better option than extraction. Similarly, periodontally involved teeth demonstrating first or second degree mobility should be splinted rather than removed but a strong suspicion should be shown in cases of third degree of mobility which might indicate presence of osteonecrosis already. Elective oral surgical

procedures, such as removal of wisdom teeth or tori, periodontal surgery or dental implants, is strongly discouraged. Dentures should be checked for areas of sharp edges or friction, and can be relined with a soft liner.[14]

The management of established BRONJ cases poses a dilemma as these cases respond less predictably to the established surgical treatment algorithms for Osteomyelitis or osteoradionecrosis. Surgical debridement alone has not been uniformly effective in resolution of necrotic bone, and hyperbaric oxygen therapy has not proven to be effective either.[14,19]

The objectives of treatment in a case of established BRONJ are pain management, control of infection of hard and soft tissue, and minimizing the progression or occurrence of bone necrosis.

When an oral and maxillofacial surgeon comes across exposed bone in the jaws, the patient should be informed about the nature of the exposed bone and coordination of oncologist is sought. Generally, relatively aggressive treatments including debridements, coverage of exposed bone with flaps or bone contouring procedures prove to be counter productive, and have in many cases led to further exposed bone, worsening of symptoms and a greater risk for jaw fracture. Therefore, more conservative measures should be considered and only in cases of resistance to these measures, surgical treatment should be thought of. Because of an overall spread of the disease process, it is unlikely that viable, healthy bone can be obtained at the margins through aggressive surgical debridement as would be the procedure of choice in managing cases of jaw osteomyelitis. Once the bone turns non-vital, it does not remain painful anymore and remains sufficiently strong to support normal jaw function. However, with setting in of secondary infection, the condition has the potential to become painful and may have more serious sequelae such as cellulitis and fistula formation. The potential for a pathologic fracture occurs once debridement surgeries reduce the structural integrity of mandible due to repeated interventions. Also because of the fact that the pathophysiology of BRONJ is entirely different from that of osteoradionecrosis, hyperbaric oxygen treatment seems to have little or no value. Still, a few case reports have entailed use of HBO with success albeit with a bisphosphonate holiday.[20]

In those cases in which the necrotic areas are a constant source of soft tissue irritation, they should be removed or trimmed, with attempts to achieve some soft tissue coverage and minimization of exposure of additional bone. Healthy soft tissue coverage, however remains difficult to attain since epithelialisation is minimal. In those cases in which a pathologic fracture has occurred, segmental resection and immediate reconstruction with a reconstruction plate is required. Isolated case reports have also described success with autologous platelet-rich plasma in conjunction with bone resection.[21] But replacement with autogenous bone, be it vascularised free tissue transfer is not advocated. Successful reports of BRONJ treatment with vascularised reconstruction are scarce and too early to be labelled a success; these reconstructions have been done with the assumption that the osteonecrosis process was limited to a particular area of bone, which was removed and reconstructed with free fibular flap.[22] It is pertinent to mention that oncologist should be regularly consulted and informed about the course of the jaw disease. In cases of advanced BRONJ, the possibility of a drug holiday for 3–6 months should be thought of, as it may prove to aid in stabilizing the necrosis process.[13] Parathyroid hormone is also reported to have a role in resolution of mild cases of BRONJ.[23] However, it is also important to note that due to the long half-life of bisphosphonates, the clinical value of a drug holiday may be somewhat subdued and also the great difficulties in stabilizing the bone loss in cases of metastatic disease makes a drug holiday sometimes impossible.

Due to the frequent association of Actinomyces species with BRONJ, use of antibiotics in case of a surgical intervention is recommended along with 0.12% chlorhexidine and hydrogen peroxide mouthwashes. In more resistant cases, metronidazole can be added. The recommended treatment regimens are mentioned in Table-2.

Table-2: Treatment regimens for BRONJ[15]

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

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CONCLUSION

The danger of developing osteonecrosis of the jaws after bisphosphonate treatment especially intravenous preparations is real. Oncologists and dentists are required to be well conversant with the prevention and management of this condition. Prevention is clearly the best strategy as so far no treatment has been found to be consistently successful in dealing with this condition.

REFERENCES

1. Sato M, Grasser W, Endo N, Akins R, Simmons H, Thompson DD, *et al*. Bisphosphonates action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. J Clin Invest 1991;88:2095–105.
2. Russell RG, Bisaz S, Fleisch H, Currey HL, Rubinstein HM, Dietz AA, *et al*. Inorganic pyrophosphate in plasma, urine, and synovial fluid of patients with pyrophosphate arthropathy (chondrocalcinosis or pseudogut). Lancet 1970;2:899–902.
3. Rodan GA, Reszka AA. Bisphosphonate mechanism of action. Curr Mol Med 2002;2:571–7.
4. Rogers MJ, Gordon S, Benford HL, et al. Cellular and molecular mechanisms of action of bisphosphonates. Cancer 2000;88:2961–78.
5. American College of Obstetricians and Gynecologists, Women's Health Care Physicians. ACOG practice bulletin. Clinical management guidelines for obstetricians-gynecologists. Obstet Gynecol 2004;103:203–16.
6. Hortobagyi GN, Theriault RL, Porter I, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastasis. N Engl J Med 1996;335:1785–92.
7. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, *et al*. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996;334:448–93.
8. Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC, *et al*. American society of clinical oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol 2002;20:3719–36.
9. Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. Oncologist 2004;9:28–37.
10. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61:1115–7.
11. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff S. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62:527–34.
12. Robinson NA, Yeo JF. Bisphosphonates: a word of caution. Ann Acad Med Singapore 2004;33:48–9.
13. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonates-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. Cancer 2005;104:83–93.
14. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (Osteonecrosis/ osteopetrosis) of the jaws: Risk factors, recognition, prevention and treatment. J Oral Maxillofac Surg 2005;63:1567–75.
15. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007;65:369–76.
16. Marx RE. Osteoradionecrosis: A new concept of its pathophysiology. J Oral Maxillofac Surg 1983;41:351.
17. Marx RE, Johnson RP. Studies in the radiobiology of osteoradionecrosis and their clinical significance. Oral Surg Oral Med Oral Pathol 1987;64:379.
18. Marx RE, Cillo JE, Ulloa JJ. Oral Bisphosphonate-Induced Osteonecrosis: Risk Factors, Prediction of Risk Using Serum CTX Testing, Prevention, and Treatment. J Oral Maxillofac Surg 2007;65:2397–410.
19. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: Background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:433–41.
20. Freiberger JJ, Padilla-Burgos R, Chhoeu AH, Kraft KH, Boneta O, Moon RE, *et al*. Hyperbaric Oxygen Treatment and Bisphosphonate-Induced Osteonecrosis of the Jaw: A Case Series. J Oral Maxillofac Surg 2007;65:1321–7.
21. Curi MM, Cossolin GS, Koga DH, Araújo SR, Feher O, dos Santos MO, *et al*. Treatment of avascular osteonecrosis of the mandible in cancer patients with a history of bisphosphonate therapy by combining bone resection and autologous platelet-rich plasma: Report of 3 cases. J Oral Maxillofac Surg 2007;65:349–55.
22. Engroff SL, Kim DD. Treating bisphosphonate osteonecrosis of the jaws: Is there a role for resection and vascularized reconstruction? J Oral Maxillofac Surg 2007;65:2374–85.
23. Harper RP, Fung E. Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible application for intermittent low-dose parathyroid hormone [rhPTH(1-34)]. J Oral Maxillofac Surg 2007;65:573–80.

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