10.5005/jp-journals-10042-1060

REVIEW ARTICLE

Etiology and Treatment of Bisphosphonate-related Osteonecrosis of the Jaw

Antonio Crispino

ABSTRACT

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region of patients. Dental screening and adequate treatment are fundamental to reducing the risk of osteonecrosis in patients under antiresorptive or antiangiogenic therapy, or before initiating the administration. The treatment of BRONJ is generally difficult and the optimal therapy strategy is still to be established. This article elucidates the clinical indications and mechanism of action of bisphosphonates (BPs), reports some of the clinical diagnostic criteria for BRONJ, and describes the histopathological criteria for BRONJ diagnosis, the potential triggering pathways, and the available treatment strategies.

Keywords: Bisphosphonates, Jaw, Osteonecrosis.

How to cite this article: Crispino A. Etiology and Treatment of Bisphosphonate-related Osteonecrosis of the Jaw. J Health Sci Res 2018;9(1):11-14.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw has been defined as exposed jaw bone for longer than 8 weeks in a patient who has received current or previous treatment with a BP medication without evidence of local malignancy or prior radiotherapy to the site.[1] Bisphosphonates inhibit bone resorption by decreasing the action of osteoclasts, which are cells that break down bone. Also, BPs inhibit the increased osteoclastic activity and skeletal calcium release into the bloodstream induced by various stimulatory factors released by tumors.[2] It is expected that BPs will arrest bone loss and increase bone density, decreasing the risk of pathologic fracture resulting from progressive bone loss. Osteonecrosis is progressive and may lead to extensive areas of bony exposure and dehiscence.

Scientific Director

Magna Graecia Institute, Catanzaro, Italy

Corresponding Author: Antonio Crispino, Scientific Director Magna Graecia Institute, Catanzaro, Italy, Phone: +00390961759798 e-mail: crispino@ unicz.it

Clinical Aspects

The clinical features of BRONJ may vary according to the patient's clinical condition, their medical and dental background, and drug administration time and method, but it is usually characterized by an exposure of jaw bone surrounded by oral mucosa with inflammatory signs and pain symptoms.[3] The BRONJ incidence has been estimated to be 5:143,000 patients/year, who have undergone dental procedures, with an estimate of 0.8 to 12% in patients receiving intravenous administration for controlling malignant neoplasms and 0.00038 to 0.06% in patients treated with oral BP.[4] The BRONJ etiopathogenesis has been widely investigated and it is not yet fully defined. Currently, the interactions between bone metabolism, infection, local trauma, and theories of bone remodeling suppression, antigenic effect, and oral mucosa toxicity have been studied to elucidate its etiopathogenesis.[5]

Three stages of ONJ have been proposed and this classification is currently in use:

1. *Stage 5*: exposed bone with no infection and otherwise asymptomatic.
2. *Stage 2*: exposed bone with evidence of infection with or without purulent discharge.
3. *Stage 3*: exposed bone with infection and extension radiographically to the inferior border of the mandible or sinus floor in the maxilla or presence of an extraoral fistula or pathologic fracture.[6]

There are discussions whether to include a stage 0 category to represent cases with no bone exposure, but with nonspecific symptoms or radiographic findings not explained by an odontogenic cause in patients on antiresorptive medications.[7] The International Task Force did not recommend the use of stage 0 as it may potentially overdiagnose ONJ in a large number of individuals, who may never actually develop ONJ.[8,9]

Specific Laboratory Investigations

In addition to radiographic imaging, a complete blood count may help to assess the state of the patient in terms of possible infection. Cultures of the infected bone tend to yield normal oral flora; however, cultures of draining abscesses may be helpful in tailoring antibiotic treatment.[10]

Assays to monitor markers of bone turnover, such as serum or possibly urine N-telopeptide (NTx) and C-telopeptide (CTx) levels, may help in the future diagnosis of BRONJ. The NTx and CTx are fragments of collagen that are released during bone remodeling and turnover. The BPs reduce NTx and CTx levels. Monitoring of the risk of BRONJ development through the various phases of BP therapy may also be possible in the future using serum CTx levels, which are thought to be reliable indicators, although they are subject to some daily variations.[11,12]

According to recent literature, angiogenesis suppression may play an important role in development of BRONJ.[13]

Radiological Features

Radiographic findings of BRONJ are not specific and are found in other conditions like osteomyelitis, osteoradionecrosis, and metastatic bone lesions also. According to previous publications, the most commonly imagined finding in osteonecrosis of the jaws is osseous sclerosis. This can vary from subtle thickening of the lamina dura and alveolar crest to attenuated osteopetrosis like sclerosis. Other findings like osteolysis, soft tissue swelling, periosteal new bone formation, periapical lucencies, oroantral fistula, and sequesters are likely to correspond with the presence of infection. It is imagined that differential diagnosis includes chronic sclerosing osteomyelitis, osteoradionecrosis, bone metastasis, and Paget's disease.[14]

Risk Factors

A number of risk factors have been identified for ONJ[7]:

- Antiresorptive drug intake.
- Minor oral surgery (e.g., dental extractions, periodontal surgery)—it is still unknown how significant the risk is with minor oral surgery.

Other factors that may increase the risk of ONJ include:

- Concomitant use of steroids
- Antiangiogenic agent intake (used in various cancer therapies)
- Diabetes
- Smoking (perhaps)

While the American Association of Oral and Maxillofacial Surgeons group included antiangiogenics in their causative medication list, the evidence that this class of drugs alone increases the ONJ risk is based on case reports and requires substantiation.

Another most peculiar feature of BRONJ is the exclusive localization of osteonecrosis to the maxillary and mandibular bones. A few recent studies have reported that long-term BP therapy may induce osteonecrosis in bone of the hips as well as external ear canal that indicates possible systemic phenomenon of BP therapy. Mandibular and maxillary bones have two important components, such as alveolar bone and periodontium. These two structures of the jaw bone show particularly high bone turnover.[15,16]

TREATMENT

Dental Management

Aside from recognizing signs of the disease, it is important for dental patients at risk of developing ONJ to maintain meticulous oral hygiene and regular dental visits. In general, dental care should be optimized in individuals at risk for developing ONJ. It is important to maintain optimal dental health of both hard and soft tissues with regular professional maintenance and very good home care.[17]

Any surgical therapy should be minimized, especially if there is an alternative (endodontic treatment instead of extraction, for example). Any minor oral surgery—including extractions and periodontal surgery—should include antibiotic prophylaxis, both systemic and topical, careful surgical technique, minimizing sharp bony edges, and providing primary closure over bony wounds, wherever possible. There is no need for interruption of oral BP therapy, such as that taken for osteoporosis therapy, either before or after the minor surgical procedure.[18] For those on high-dose BP or denosumab intravenous (IV) therapy or with multiple risk factors for ONJ, it is recommended that the antiresorptive therapy be withheld following the oral surgery until the surgical site has healed with mature soft tissue closure over the wound. This typically requires 4 to 6 weeks. For individuals at a high risk of ONJ, it is critical to achieve primary closure and utilize perioperative antibiotics up to the week following and chlorhexidine mouth rinses immediately before and for the weeks following until soft tissue coverage has been achieved.

Other routine restorative, hygiene, orthodontic, and endodontic dentistry can be conducted as usual.[19]

Osteonecrosis of the Jaw Management

Most patients will not require surgical intervention. A patient failing conservative therapy or whose ONJ is progressing should be referred to and managed by an oral surgeon. As not all of them might be familiar with managing these patients, it is necessary to refer them to an experienced oral surgeon for appropriate care. This may require traveling to a larger urban center.[20] They may refer the patient back to their primary dental caregiver for ongoing care in the presence of persistent ONJ or in its absence following surgical treatment. There are, however, a small number of experienced hospital-based dentists,

who are able to evaluate and manage these patients nonsurgically in consultation with their medical oncologists. These clinicians are most familiar with this disease and may be the best to perform nonsurgical therapy and follow these patients conservatively.[21]

For stages 5 and 2, conservative therapy may be all that is required. Meticulous oral hygiene, preventive care, topical antibiotic rinses, such as chlorhexidine, and periodic systemic antibiotics should be used as needed. Patients require close follow-up with periodic radiographic assessment of their disease. While many patients are symptomatic from their ONJ lesions, a significant number are asymptomatic and require close monitoring while maintaining excellent oral hygiene and ensuring that the affected area is clean with monitoring for progression of disease.[22]

Spontaneous resolution of ONJ is possible. Early treatment recommendations discouraged surgical intervention, with conservative therapy continuing indefinitely or until there was progression of disease. Others have had reasonable success with surgical management. There is still no comfortable proven treatment algorithm for the various stages of the disease. The International Task Force believes that surgical intervention is required for stage-3 disease and stage-2 patients, who are showing progression or require continual antibiotic or narcotic analgesic therapy to control their symptoms.[23]

Common Initial Treatments

- Minor debridement, including minor sequestrectomy with elimination of sharp bone edges and sharp tooth surfaces, if these are symptomatic.
- Advise the patient to maintain local hygiene in areas of exposed bone (chlorhexidine gluconate 0.12%, 20 mL for 30 seconds three times daily).
- For bacteremia, prescribe systemic antibiotics to control bacterial infection. The recommended antibiotic is amoxicillin, 1,000 mg (5 tablets 3 times daily for 7 days) or clindamycin, 300 mg (5 capsules 4 times daily for 7 days). The prescriptions listed above represent a minimum dose. The addition of 250 mg of metronidazole 4 times daily may be indicated if anaerobic infection is suspected. In refractory patients or in severe cases, prescribe amoxicillin/clavulanate potassium (Augmentin®), 1,000 mg (5 tablets 2 times a day). It is important NOT to prescribe systemic antibiotic therapy if there is no infection (most commonly evidenced by pain) to prevent the development of resistant bacterial strains.[24]
- Conservative, noninvasive sequestrectomy performed periodically over the long term, with systemic antibiotics prescribed for flare-ups of infection and pain, may be the optimal therapy.
- For pain control, prescribe analgesics at the maximum cumulative dose.
- Mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Necrotic bone cannot be resorbed by the osteoclasts (BPs inhibit osteoclastic activity) and will inhibit healing, so it is important to remove it.
- The extraction of symptomatic teeth within exposed, necrotic bone also should be considered.[25]

CONCLUSION

Exact diagnostic criteria to distinguish BRONJ from other delayed healing conditions are not known as yet. According to the recent literature, patients may be considered to have BRONJ if all of the following four characteristics are present: current or previous treatment with BPs, exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks, no history of radiation therapy to the jaws, and no evidence of cancer at the site.[26]

The BRONJ is a multifactorial disease. It commonly develops in patients who receive either long-term nitrogen-containing IV BP therapy alone or associated with invasive dental procedure. Serum vascular endothelial growth factor levels and morning fasting CTx levels are useful assessment tools to predict risk and make appropriate lines of diagnosis and treatment. In cases of established disease, management strategies are mostly palliative and empirical.[27]

REFERENCES

1. Auluck A. How do I manage a patient with biphosphonate-related osteonecrosis of the jaw (BRONJ). J Can Dent Assoc 2016 May;82:g10.
2. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007 Oct;22(10):1479-1491.
3. Khan AA, Sándor GK, Dore E, Morrison AD, Alsahli M, Amin F, Peters E, Hanley DA, Chaudry SR, Dempster DW, et al. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol 2008 Jul;35(7):1391-1397.
4. Morrison A, Khan A, Tetradis S, Peters E. Osteonecrosis of the jaw: an update for dentists. J Can Dent Assoc 2015 Nov; 81:f19.
5. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero S, Taguchi A, Tetradis S, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015 Jan;30(1):3-23.
6. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related

osteonecrosis of the jaw—2009 update. J Oral Maxillofac Surg 2009 May;67(5 Suppl):2-12.
7. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003 Sep;61(9):1115-1117.
8. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004 May;62(5):527-534.
9. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on Denosumab. J Oral Maxillofac Surg 2010 May;68(5):959-963.
10. Peters E, Lovas GL, Wysocki GP. Lingual mandibular sequestration and ulceration. Oral Surg Oral Med Oral Pathol 1993 Jun;75(6):739-743.
11. Scully C. Oral ulceration: a new unusual complication. Br Dent J 2002 Feb;192(3):139-140.
12. Sonnier KE, Horning GM. Spontaneous bony exposure: a report of 4 cases of idiopathic exposure and sequestration of alveolar bone. J Periodontol 1997 Aug;68(8):758-762.
13. Kassolis JD, Scheper M, Jham, Reynolds MA. Histopathologic findings in bone from edentulous alveolar ridges: a role in osteonecrosis of the jaws? Bone 2010 Jul;47(1):127-130.
14. 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 Oct;102(4):433-441.
15. Khan AA, Rios LP, Sandor GK, Khan N, Peters E, Rahman MO, Clokie CM, Dore E, Dubois S. Bisphosphonate-associated osteonecrosis of the jaw in Ontario: a survey of oral and maxillofacial surgeons. J Rheumatol 2011 Jul;38(7):1396-1402.
16. Etminan M, Aminzadeh K, Matthew IR, Brophy JM. Use of oral bisphosphonates and the risk of aseptic osteonecrosis: a nested case-control study. J Rheumatol 2008 Apr;35(4):691-695.
17. Tennis P, Rothman KJ, Bohn RL, Tan H, Zavras A, Laskarides C, Calingaert B, Anthony MS. Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. Pharmacoepidemiol Drug Saf 2012 Aug;21(8):810-817.
18. Christodoulou C, Pervena A, Klouvas G, Galani E, Falagas ME, Tsakalos G, Visvikis A, Nikolakopoulou A, Acholos V, Karapanagiotidis G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology 2009 Feb;76(3):209-211.
19. Allen MR. Animal models of osteonecrosis of the jaw. J Musculoskelet Neuronal Interact 2007 Oct-Dec;7(4): 358-360.
20. Allen MR. Bisphosphonates and osteonecrosis of the jaw: moving from the bedside to the bench. Cells Tissues Organs 2009;189(1-4):289-294.
21. Saad F, Brown JE, Van PC, Ibrahim T, Stemmer SM, Stopeck AT, Diel IJ, Takahashi S, Shore N, Henry DH, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012 May;23(5):1341-1347.
22. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, Clezardin P. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002 Nov;62(22):6538-6544.
23. Santini D, Vincenzi B, Dicuonzo G, Avvisati G, Massacesi C, Battistoni F, Gavasci M, Rocci L, Tirindelli MC, Altomare V, et al. Zoledronic acid induces significant and long-lasting modifications of circulating angiogenic factors in cancer patients. Clin Cancer Res 2003 Aug;9(8):2893-2897.
24. Kumar V, Sinha RK. Bisphosphonate related osteonecrosis of the jaw: an update. Maxillofac Oral Surg 2014 Dec;13(4): 386-393.
25. Ficarra G, Beninati F. Bisphosphonates-related osteonecrosis of the jaws: an update on clinical, pathological and management aspects. Head Neck Pathol 2007 Dec;1(2):132-140.
26. Aas JA, Reime L, Pedersen K, Eribe ERK, Abesha-Belay E, Store G, Olsen I. Osteoradionecrosis contains a wide variety of cultivable and non-cultivable bacteria. J Oral Microbiol 2010 Jul;2:5072.
27. Stockmann P, Wehrhan F, Furlan SS, Stelzle F, Trabert S, Neukam FW, Nkenke E. Increased human defensine levels hint at an inflammatory etiology of Bisphosphonate-associated osteonecrosis of the jaws: an immunohistological study. J Transl Med 2011 Aug;9:135.