

Mandibular avascular osteonecrosis caused by bisphosphonate – a case report and brief review

Osteonecrose avascular de mandíbula por uso de bisfosfonato – relato de caso e breve revisão

Abstract

Purpose: To present a case of total bilateral jaw necrosis in a patient with primary breast cancer and bone metastases treated with zoledronic acid and discuss the adverse effects of bisphosphonates and the best moment to perform dental procedures.

Case description: A female patient, 62 years old, with primary breast adenocarcinoma underwent chemotherapy and zoledronic acid because of bone metastases on the right hip. After 7 months, she was submitted to debridement of exposed bone on the anterior mandible, which resulted in skin fistulae and severe pain. Computerized tomography showed bone sequestration hypodensity at the right and left mandibular body and mentum with excessive uptake of the labeled drug as seen by bone scintigraphy. The patient received amoxicillin, gluconate and chlorhexidine mouthrinse and hydrogen peroxide; partial closure of skin fistulae was achieved. After 4 months, the patient returned with submandibular tissue necrosis, intra- and extra-orally exposed mandible with active discharge. After 5 days of palliative treatment, the patient died from sepsis.

Conclusion: Local infection/inflammation should be treated before the use of bisphosphonates, and topic and systemic pharmacologic treatment should be combined with a strict follow-up. For selected cases, the osteonecrosis treatment may include conservative debridement, pain control, topic and systemic antimicrobial control, and, in extremely severe cases, radical surgery.

Key words: osteonecrosis; bisphosphonates; zoledronic acid

Resumo

Objetivo: Apresentar um caso de necrose total de mandíbula, bilateral, em uma paciente com neoplasia primária de mama e metástases ósseas tratadas com ácido zoledrônico endovenoso, e discutir os efeitos adversos de bisfosfonatos e o momento adequado para realização de procedimentos odontológicos.

Descrição do caso: Paciente do sexo feminino, 62 anos, com adenocarcinoma de mama primário foi submetida a quimioterapia e uso de ácido zoledrônico devido a metástases ósseas no quadril direito. Após 7 meses, realizou-se debridamento de osso exposto na região anterior da mandíbula, resultando em fístulas e dor severa. Os exames de tomografia computadorizada e de cintilografia óssea revelaram hipodensidade do sequestro ósseo no corpo mandibular e no mento com presença excessiva da droga nestes sítios. Após antibioticoterapia e uso de enxagatatórios bucais houve fechamento parcial das fístulas. Após 4 meses, a paciente retornou com necrose submandibular e osso mandibular exposto intra e extraoralmente com drenagem. Após 5 dias de tratamento paliativo a paciente morreu de sepsis.

Conclusão: Focos de infecção e/ou processos inflamatórios locais devem ser tratados previamente ao uso de bisfosfonatos. Indica-se o tratamento farmacológico tópico e sistêmico, e a preservação do caso. Terapias para osteonecrose, em determinados casos, envolvem debridamento conservador, controle da dor, manejo antimicrobiano tópico e sistêmico e, em casos extremos, cirurgia radical.

Palavras-chave: Osteonecrose; bisfosfonato; ácido zoledrônico

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Introduction

The aim of this paper is to present the clinical case of a patient with primary breast cancer and bone metastases, who developed total bilateral jaw necrosis after treatment with EV zoledronic acid. Additional aims are the discussion of adverse effects, the best timing to perform dental procedures, and the management of osteonecrosis in patients using bisphosphonates.

The treatment with bisphosphonates has been clearly established for patients with bone malignancies (multiple myeloma, hipercalcemia secondary to neoplasm), bone metastases due to cancer (breast, prostate, lung and kidney) and to non-malignant diseases (osteoporosis, steroid-induced bone resorption and Paget's disease) (1,2). Approximately half of the patients with bone metastases from solid primary tumors show one or more skeletal events, such as pathologic fractures, spinal chord compression, radiotherapy or bone surgery, and hipercalcemia (3). Bone metastases are the most common cause of oncogenic pain (4). Treatments presently available for patients with bone metastases are radiotherapy, chemotherapy, hormonal therapy, surgery, EV bisphosphonates, and palliative care (3).

Bisphosphonates are synthetic chemical analogues to the natural pyrophosphate. They accumulate on bone formation sites turning them more resistant to dissolution by osteoclasts and modulating the transformation of osteoblasts into osteoclasts (5). They also promote osteoclast apoptosis (6) and have an anti-tumoral action reducing angiogenesis (2). Generally bisphosphonates are given orally including etidronate, sodium riserdonate, tiludronate, and alendronate. Bisphosphonates used to treat primary and secondary bone malignancies are more potent and are administered EV. Common commercial drugs in Brazil are the pamidronate disodium Aredia® – Novartis Biociências S.A, São Paulo, SP, Brazil) and the zoledronic acid (Zometa® – Novartis Biociências S.A, São Paulo, SP, Brazil).

The adverse effects of EV bisphosphonates include systemic inflammatory reactions (fever, myalgia, arthralgia, nausea,

vomiting and edema); ocular complications (conjunctivitis, uveitis, scleritis, episcleritis, eyelid edema and orbit or optic nerve inflammation); acute and chronic renal impairment, electrolyte changes (low serum levels of calcium, phosphorus magnesium, high serum levels of magnesium); mandible and maxilla necroses and other complications (7-11) (Table 1).

Table 1. Frequency of some adverse effects in patients with primary or secondary bone metastases after using zoledronic acid.

Adverse effect	Frequency	Reference
Fewer	55%	Kohno et al. (7)
Myalgia	25%	Saad et al. (8)
Pain	>50%	Migliorati et al. (9)
Eye complications	0.05%	Durnian et al. (10)
Renal impairment	9-10%	Rosen et al. (11)
Hypocalcaemia	39%	Kohno et al. (7)

Maxillary and mandible osteonecrosis due to bisphosphonates has been reported in the literature recently (Table 2). In the 19th century it was seen in phosphorus plant workers, but presently it has been described in patients using bisphosphonates (10,12). Previous dental treatments and asymptomatic chronic inflammation are important predisposing factors (13,14).

A systematic review of 386 cases (15) showed that osteonecrosis is more frequently found in the mandible (65%) than in the maxilla (26%), but it can affect both jaws (9%) simultaneously. Approximately one third of the cases are painless (16) and it is more often observed in women (3:2 ratio in the described cases). Multifocal or bilateral necrosis is more common in the maxilla (31%) than in the mandible (23%). In 60% it took place after tooth extractions or other alveolar surgery, but in 40% it occurred spontaneously. According to Ruggiero et al., 5 out of 63 patients developed pathologic fractures (14); from 211 patients treated with zoledronic acid, 10% had osteonecrosis (17).

Table 2. Case series of maxilla and mandible necroses associated with bisphosphonate use [adapted from Woo et al. (15)].

Study	N	Site (n)	Previous surgery n (%)	Use of zoledronic acid (n)
Ruggiero et al. (14)	63	Mandible (39) Maxilla (23) Both (1)	54 (86)	zoledronic acid (9) pamidronate disodium and zoledronic acid (13)
Marx et al. (16)	119	Mandible (81) Maxilla (33) Both (5)	55 (46)	zoledronic acid (48) pamidronate disodium and zoledronic acid (36)
Migliorati et al. (9)	18	Mandible (8) Maxilla (2) Both (1) Unknown (7)	6 (33)	zoledronic acid (8) disodium and zoledronic acid (6)
Pires et al. (20)	12	Mandible (8) Maxilla (3) Both (1)	8 (67)	zoledronic acid (3) pamidronate disodium and zoledronic acid (5)

Mandible-maxillary osteonecrosis prevention includes the elimination of any periodontal, periapical inflammation or infection, avoiding surgical treatments such as tooth extraction or periodontal treatment prior to the treatment with biphosphonates (10,13). The time interval should be at least 1 month (16). The use of mouthrinse based on 0.12% chlorhexidine gluconate aims at controlling periodontal pathogens. The use of tissue conditioners under total or partial muco-supported prosthesis is also indicated. Surgical procedures or implants should be avoided in patients using or planning to use biphosphonates. Careful oral assessment should be carried out before using this drug (10,16,18-19). In the treatment of patients with maxillomandibular osteonecrosis one should use large spectrum systemic and topic antibiotics, with or without surgery (16,18).

Case report

A female patient, 62 years old, with primary breast adenocarcinoma diagnosed on October 2003 started chemotherapy on November 2003. On July 2004, bone metastases on the right hip were diagnosed. She started using zoledronic acid (Zometa®) 4 mg in pump infusion for 15 min every 3 weeks for 12 months.

After 7 months using the drug, she noticed exposed bone in her mandible. She complained of mild pain, especially in the morning. She reported having been submitted to oral surgeries for debridement of exposed bone on the anterior mandible on March and July 2005. After the second surgery, she noticed bulging at the submentum and after some days she observed skin fistulae with reddish-whitish discharge.

Her oral maxillofacial assessment was performed on January 2006 due to moderate to severe pain, mainly in the morning. The clinical exam revealed four active skin fistulae at the submentonian and submandibular areas (Fig. 1) with pain at palpation. The oral cavity exam showed mandibular edentulism, bone exposure at the right and left alveolar ridge and mucosa with chronic inflammation (Fig. 2).

Computerized tomography showed bone sequestration hypodensity at the right and left mandibular body and at the mentum. On the left, it extended to the mandibular angle. No bone metastases were seen in these regions (Fig. 3). Bone scintigraphy showed excessive uptake of the labeled drug in the above-mentioned areas.

Amoxicillin, 500 mg every 8 h for 21 days was introduced. The patient also used gluconate and chlorhexidine mouthrinse at 0.12% (Periogard®, Colgate-Palmolive Indústria e Comércio Ltda., São Paulo, SP, Brazil) and hydrogen peroxide 10 volumes at 10%, 3 times a day, in continuous use. Partial closure of skin fistulae was achieved after this period, and the use of mouthrinse was continued.

After 4 months of follow-up with neither worsening nor improvement, the patient returned with submandibular tissue necrosis and intra- and extra-orally exposed mandible with active discharge. After 5 days of palliative treatment, the patient died from sepsis.



Fig. 1. Extra-oral exam revealed the presence of 4 active cutaneous fistulae at the sub-mentum and sub-mandible area.



Fig. 2. Inferior jaw edentulism and bone exposition at the right and left alveolar ridges. The bone is yellowish and irregular. The adjacent oral mucosa shows chronic inflammation.



Fig. 3. The CT shows hypodense areas at the right and left maxilla and mandible bodies, as well as at the mentum.

Discussion

The use of EV or oral bisphosphonates for the treatment of bone metastases (1,2) and the possible mechanisms of action by direct effect on the cells or indirect action on angiogenesis has been reviewed in the recent literature (2,5,6). It is estimated that the bone metastases rate in breast cancer ranges between 65 and 75%, and the use of zoledronic acid reduces complications due to bone metastases in 39% (7).

However, several cases of maxilla and mandible osteonecrosis were described in patients using more potent bisphosphonates (9,12). According to Durie et al. (17), the incidence of mandible or maxilla osteonecrosis in a study performed in USA was 6%. In patients with previous dental

treatment osteonecrosis increased to 80% (13,14). Therefore, any infection or inflammation should be treated before starting the use of bisphosphonates.

The treatment of osteonecrosis in the maxilla and mandible associated with the use of bisphosphonates still is controversial. Marx et al. (16) and Carter et al. (18) recommend that no surgery for total resection of the necrotic bone should be performed because this necrosis affects the whole bone and not only the exposed area to the oral cavity. Thus topic and systemic pharmacologic treatment and strict follow-up are indicated to control the condition and avoid further complications. Additional studies are needed to establish the best treatment of osteonecrosis to provide its remission and a better quality of life to the patient as well as controlling long-lasting chronic infections.

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