MAXILLA OSSEUS SEQUESTRE AND ORAL EXPOSURE
Effects of the Treatment of Multiple Myeloma with Bisphosphonates

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SUMMARY

Multiple myeloma, the second most common haematopoietic cancer, represents a collection of plasma-cell neoplasms that invariably become fatal when self-renewing myeloma cells begin unrestrained proliferation. The major clinical manifestation of multiple myeloma is related to loss of bone through osteolysis. The bone disease can lead to pathologic fractures, spinal cord compression, hypercalcemia, and pain. It is also a major cause of morbidity and mortality in these patients. These patients frequently require radiation therapy, surgery and analgesic medications. Bisphosphonates are specific inhibitors of osteoclastic activity, and are currently used to prevent bone complications and to treat malignant hypercalcemia in patients with multiple myeloma, or bone metastases from breast and prostate cancers. Recent published reports have documented a possible link between treatment with intravenous bisphosphonates and osteonecrosis of the jaw. Bisphosphonates have been demonstrated to alter the normal bone microenvironment and appear to have direct effects on tumours as well. These changes may contribute to the development of osteonecrosis of the jaw in these patients, particularly after tooth extractions or other invasive dental procedures. Osteonecrosis of the mandible has been reported in 3 patients from Centro Hospitalar de Vila Nova de Gaia (CHVNG) with multiple myeloma treated for over 18 to 48 months with intravenous bisphosphonate zoledronate. It has been postulated that bisphosphonates may cause oral avascular bone necrosis due to antiangiogenic effect leading to disruption of osteoclast-mediated bone resorption. Although this report serves to alert clinicians about the potential complication of bone necrosis in patients receiving bisphosphonates therapy, many questions remain concerning the underlying pathogenesis of this process. In these 3 described clinical cases, surgical debridment without flap elevation, intensive antibiotherapy and zolendronate treatment arrest made possible the partial recovery of the patients. We purpose this type of clinical approach in patients suffering from multiple myeloma and bone ostonecrosis induced by bisphosphonate treatment. Research to determine the mechanism of this dental phenomenon is needed to fully validate and substantiate the possible link between bisphosphonates treatment of multiple myeloma or other cancer diseases with avascular osteonecrosis of the jaws. Until then, clinicians involved in the care of patients at risk should consider this possible complication.

R E S U M O

EXPOSIÇÃO DE TECIDO ÓSSEO NA MAXILLA
Efeitos de Tratamento de Mieloma Múltiplo com Bifosfonatos

O mieloma múltiplo é o segundo tumor hematopiético mais comum e tem origem nas células da medula óssea produtoras de anticorpos (plasmócitos), no qual um clone de células plasmáticas anormais se multiplica, forma tumores na medula óssea e produz uma grande quantidade de anticorpos anormais que se acumulam no sangue ou na urina. Uma das manifestações clínicas do mieloma múltiplo está relacionada com a perda de tecido ósseo por osteólise. Desta forma, aumenta a predisposição para a ocorrência de fracturas, de compressão medular, acompanhando-se muito frequentemente este quadro clínico de hipercalcémia e de dor ao nível dos ossos. É igualmente a causa de morbilidade e de mortalidade destes pacientes. Normalmente, os doentes em que lhes foi diagnosticado mieloma múltiplo, requerem terapia com radiações, cirurgias e medicação analgésica forte. Os bifosfonatos são inibidores específicos da actividade dos osteoclastos, sendo frequentemente usados nos doentes com mieloma múltiplo, assim como aqueles com metástases ósseas de tumores sólidos com origem na mama ou na próstata, com a finalidade de controlar as complicações ósseas e para o tratamento da hipercalcémia maligna que se desencadeia. Publicações recentes têm vindo a estabelecer uma relação estreita entre a administração endovenosa de bifosfonatos e a osteonecrose dos ossos da mandíbula e da maxila. Demonstrou-se que os bifosfonatos alteram o micro-ambiente normal do tecido ósseo, tendo igualmente um efeito directo sobre as células neoplásicas. Estas alterações podem contribuir para o desenvolvimento de osteonecrose da maxila e/ou mandíbula nestes doentes, particularmente após extracções dentárias ou outros procedimentos invasivos do local. Osteonecrose da mandíbula foi descrita em três doentes do Centro Hospitalar de Vila Nova de Gaia (CHVNG) em que foi diagnosticado mieloma múltiplo e cujo tratamento incluía a administração endovenosa de zolendronato, por períodos relativamente longos, compreendidos entre os 18 e os 48 meses. Foi postulado que os bifosfonatos podem originar uma necrose avascular devido aos seus efeitos anti-angiogénicos, conduzindo a uma desregulação da actividade osteoclástica. Este trabalho tem por finalidade alertar os clínicos sobre esta potencial complicação de necrose óssea em pacientes a receber tratamento com bifosfonatos, no entanto, muitas questões se colocam no que diz respeito ao total conhecimento da patogénese deste processo. Propomos ainda uma abordagem terapêutica desta necrose avascular um pouco diferente daquela descrita em publicações científicas e médicas recentes. Consiste no debridamento sem levantamento de um retalho gengival, antibioterápia intensiva e suspensão da administração de bifosfonato. Este tratamento permitiu a recuperação parcial nestes três casos clínicos. Mais investigação é necessária para entender este mecanismo ao nível da mandíbula e / ou da maxila dos doentes, de modo a conseguir-se estabelecer um elo de ligação entre o tratamento do mieloma múltiplo (assim como de metástases ósseas de tumores sólidos) e a osteonecrose avascular.

INTRODUCTION

Multiple myeloma (MM) represents a collection of plasma-cell neoplasms sharing two prominent features: elevated production of monoclonal antibodies and bone destruction. So, the major clinical manifestation of MM is related to loss of bone through osteolysis[1]. Even patients responding to chemotherapy may have progression of skeletal disease[2,3], and recalcification of osteolytic lesions is rare. Bone loss either from direct tumoral involvement or from generalized osteoporosis can lead to pathologic fractures, spinal cord compression, hypercalcemia, and pain, and is a major cause of morbidity and mortality in these patients[4]. These patients frequently require radiation therapy, surgery, and use of analgesics. These complications result from asynchronous bone turnover wherein increased osteoclastic bone resorption is not accompanied by a comparable increase in bone formation. This increase in osteoclactic activity is mediated by the release of osteoclast-stimulating factors. These factors are produced locally in the bone-marrow microenvironment by cells of both tumour and non-tumour origin[5]. The enhanced bone loss results from the interplay between the osteoclasts, tumour cells and other non-malignant cells in the bone-marrow microenvironment[6]. The bisphosphonates are non-metabolized analogues of endogenous pyrophosphates (PP_i) that are capable of localizing to bone and inhibiting osteoclastic function. Bisphosphonates bind avidly to exposed bone mineral around reabsorbing osteoclasts, resulting in very high levels of bisphosphonates in the resorption lacunae. Because bisphosphonates are not metabolized, these high concentrations are maintained within bone for long periods of time. Bisphosphonates are then internalized by the osteoclast, causing disruption of osteoclast-mediated bone resorption[7,8]. Their potential for strong inhibition of osteoclastic bone resorption and their high affinity for hydroxyapatite crystals have progressively extended the field of their clinical indications[9-12]. Such compounds are able to chelate Ca^{2+} ions very effectively, and its high affinity for Ca^{2+} crystals, permits its binding to hydroxyapatite crystals in the mineralized bone matrix[13]. Although exact mechanism of this bisphosphonates-mediated osteoclast inhibition has not been completely elucidated, it has been established that these compounds affect bone turnover at various levels[7,8]. At the tissue level, bisphosphonates will inhibit bone resorption and decrease bone turnover as assessed by biochemical markers[7,8]. On a cellular level, the bisphosphonates are clearly targeting the osteoclasts and may inhibit their function in several ways: 1) inhibition of osteoclast recruitment[14]; 2) diminishing the osteoclast life span[15]; 3) inhibition of osteoclastic activity at the bone surface[16]. At a molecular level, it has been postulated that bisphosphonates modulate osteoclast function by interacting with a cell surface receptor or an intracellular enzyme[17]. Several structurally related bisphosphonates have been synthesized by changing the two lateral chains on the carbon or by sterifying the phosphate groups[18]. The resulting analogues vary extensively in their anti-resorptive potency, with analogues such as etidronate being the weakest, aledronate being stronger, and the new analogue, zoledronate, being the most potent[18,19]. Intravenous bisphosphonates are the current care standard for the treatment of hypercalcemia of malignancy (HCM) and for the prevention of skeletal complications associated with bone metastases[1,20,21]. Currently, zoledronic acid (2-[imidazol-1-yl]-1-hydroxyethylidene-1, 1-phosphonic acid, Zometa®, 4 mg via a 15-minute infusion) and pamidronate (Aredia®, 90 mg via a 2-hour infusion) are the only agents recommended by the American Society of Clinical Oncology (ASCO) for the treatment of bone lesions from breast cancer and multiple myeloma[22,23]. Furthermore, zoledronic acid is approved by both the U.S. Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for the prevention of skeletal complications in patients with multiple myeloma, bone metastases secondary to a variety of solid tumours, including breast, prostate and lung cancer and malignant hypercalcemia[24-27]. The intravenously administered bisphosphonates significantly reduced the development of skeletal complications and improved the survival of patients. Recent studies show the efficacy and increased convenience of the newer, more potent imidazole-containing bisphosphonate zoledronic acid in the management of the skeletal complications of myeloma[6,28]. If tolerated, it is not uncommon for these patients to be maintained on bisphosphonates therapy indefinitely[7]. The oral bisphosphonate preparations (alendronate, risedronate) are also potent osteoclast inhibitors, but they are not as efficacious in the treatment of malignant osteolytic disease and therefore are indicated only for the treatment of osteoporosis[7]. Bisphosphonates-associated osteonecrosis of the jaws (ONJ) is currently a very topical subject. This was initially thought to be an exceedingly rare condition. In a retrospective chart review of multiple myeloma and breast cancer patients who had received intravenous bisphosphonates at the Memorial Sloan-Kettering Cancer Center in 2003, ONJ was reported in 10.5%[29]. Osteonecrosis has not been seen at any other skeletal site in these patients. Bisphosphonates-

associated ONJ is characterized by dehiscence of the oral mucous membranes, with exposure of the underlying mandible or maxilla. The exposed bone is necrotic. More than 50% of the cases have been diagnosed following surgery, like extractions, implants and periodontal procedures. In some clinical cases, it does not respond to any form of treatment that has yet been attempted, like interruption of the chemotherapy and bisphosphonates administration. Hyperbaric oxygen reportedly has no effect[30]. Antibiotics cannot enter necrotic tissue, and so they are only used to manage cellulites in adjacent tissues. By default, conservative, symptomatic treatment is the current recommendation. Patients receiving bisphosphonates infusions are asked to avoid oral surgery[31,32]. The mechanism underlying the reaction is unknown, but it has been postulated that bisphosphonates inhibit new vessel formation. In many cases, dental extractions and other oral surgery have been identified as precipitants. Diagnosis of cancer, concomitant therapies (chemotherapy, radiotherapy and corticosteroids) and co-morbid conditions (anaemia, coagulopathies, infection, and pre-existing oral disease) are documented risks factors[33].

CASE REPORT

A first case reported in the CHVNG hospital is a 71-year-old man who was originally diagnosed IgA multiple myeloma in 2002 and the patient was simultaneously treated with chemotherapy (cyclophosphamide, 1 mg/day, and every month, by intravenous administration), eritropoetin (30000 U/day, every month, by subcutaneous administration), zoledronic acid (4 mg during 15 minutes per month, by intravenously administration), dexamethasone (40 mg, during 4 days, every month, *per os*) and thalidomide (100 mg/ day, *per os*) during 3 years. In July of 2003, it was performed a routine dental extraction of tooth 4.5 and a desvitalization of tooth 4.4. After tooth extraction, the patient still presented symptoms of mandible pain. These procedures did not resolve the patient clinical symptoms, which was followed by the routine dental extraction of tooth 4.4 in September of 2003. In April of 2004, the presenting symptoms were still mandible pain and already visible exposed bone at the site of the previous teeth extraction. In the orthopantomogram taken at that time, it was evident a circumscribed area of osseous necrosis of the right mandible. Figure 1 shows an orthopantomogram obtained in July of 2003, before extraction of tooth 4.5 and desvitalization of tooth 4.4. The patient was receiving the zoledronate infusion treatment. The orthopantomogram taken to the same patient mandible in April of 2004 is represented in figure 2. At this time, the dental extraction

of both teeth 4.4 and 4.5 from the right side was already performed and a slight bone necrosis with sequestered tissue could be already observed in the right mandible. At this point, the patient was receiving zoledronate by intravenously administration for a period of 2 years. Figure 3 is the orthopantomogram obtained in July of 2005, showing the presence of an extended zone of the bone necrosis exactly in the region of the extraction site after 3 years of zolendronate administration. Figure 4 is an image taken to the patient's right mandible in September of 2005 where it is clearly observed the exposed necrotic mandibular bone, correlative with the diagnosis of jaw avascular bone necrosis. The biopsy taken at that time consisted of removing from the dental extraction site a sample of the overlying tissue. On microscope examination, the specimen consisted of necrotic bone with associated bacterial debris and granulation tissue. Culture results revealed normal oral flora and a secondary bacteria infection with *Actinomycotic osteomyelitis*. This infection was treated with amoxicillin (500 mg, every 8 hours, during 4 months, *per os*) and the bisphosphonate administration was immediately interrupted. In November of 2005, a superficial osteotomy under local anaesthesia, of the necrotic bone was performed, but it was interrupeded by perfuse intra-osseous haemorrhagy. Figure 5 is the orthopantomogram obtained in November of 2005, taken immediately after the superficial osteotomy. The osteonecrosis area was partially removed.
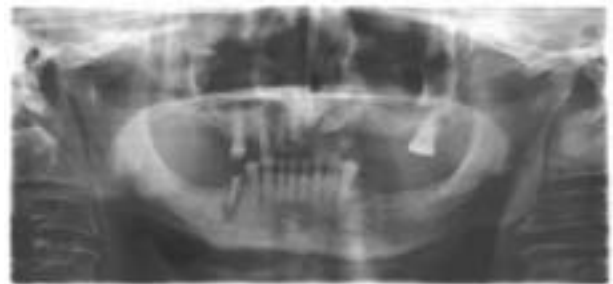

Fig. 1- Orthopantomogram obtained in July of 2003 before dental extraction of the teeth 4.4 and 4.5. The patient was receiving intravenous zoledronic acid treatment. The right mandible bone was apparently normal.
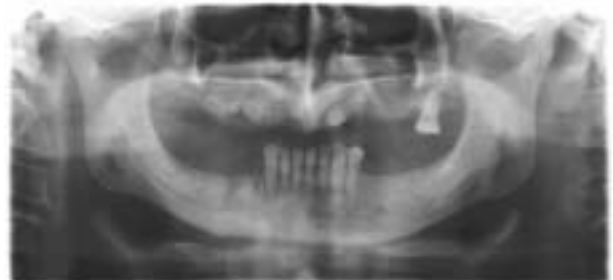

Fig 2 - Orthopantomogram control obtained from the patient mandible in April of 2004, 6 to 8 months after the teeth 4.5 and 4.4 extractions, respectively, from the right mandible.

Figure 3: Orthopantomogram obtained in June of 2005. An extended zone of the bone necrosis is present in the right mandible, probably associated to the zoledronic acid treatment (red circle).

Figure 4: Exposed necrotic mandible bone in a patient receiving intravenously zoledronic acid for 3 years and 5 months following a routine dental extraction of teeth 4.4 and 4.5 from the right mandible.

Figure 5: Orthopantomogram obtained in November of 2005 after the superficial osteotomy performance. Due to a perfuse intraosseus haemorrhage, the osteotomy was interrupted but the osteonecrosis area was partially removed (red circle).

The second clinical report refers a 66-year-old man who was diagnosed IgA multiple myeloma, in May of 2001. He received treatment during 3 years with intravenously zoledronic acid (4 mg during 15 minutes per moth) associated with chemotherapy (cyclophosphamide, 1 mg/day, and every month, by intravenous administration) and eritropoetin (30000 U/day, every month, subcutaneous administration). The patient was also being treated with dexamethasone (40 mg, during 4 days consecutively, every month, *per os*), filgastrin (30000000 U/day, every month, subcutaneous administration) and thalidomide (100 mg/day, *per os*). In March of 2004, it was performed a dental extraction of the tooth 4.6. The tooth 4.5 was extracted 6 months before. At that time the patient started to complain of jaw pain, difficulty in masticating and in brushing teeth. The clinical appearance simulated dental abscesses or osteomylitis. In July of 2005 biopsy of the involved area showed the presence of necrotic lacunae, bacterial debris, and granulation tissue with infiltration of lymphocytes and histiocytes. Culture results revealed a secondary infection with *Actinomycotic osteomyelitis*. The teeth extraction resulted in painful, nonhealing bone lesion in the mandible. Examination revealed an area of exposed, necrotic bone and the diagnosis was jaw avascular osteonecrosis. Figure 6 shows an orthopantomogram obtained in March of 2004, just before extraction of tooth

Figure 6: Orthopantomogram obtained in March of 2004, immediately before dental extraction of tooth 4.6 from the right mandible. The tooth 4.5 was extracted 6 months before. The patient received zoledronic acid intravenously for 3 years after the diagnosis of a IgA multiple myeloma. It was already present a local area of bone necrosis in the site of the first dental extraction (red circle)

4.6 from the right mandible. The tooth 4.5 was removed 6 months before. Figure 7 shows another panoramic radiography taken in June of 2005. In this X-Ray exam is visible a more extended area of bone destruction involving the right mandible in the region where it was performed 15

Figure 7: Orthopantomogram obtained in June of 2005, showing a more extended area of bone destruction (red circle) involving the right mandible due to bisphosphonates-associated osteonecrosis in the local where the dental extraction was performed.

months before the dental extraction. The secondary *Actinomycotic osteomyelitis* infection was treated with amoxicillin (500 mg, every 8 hours, during 3 months, *per os*) and the bisphosphonate treatment was immediately interrupted. Superficial debridement of the osseous necrosis area under local anaesthesia was attempted, without elevating a gingival flap.

The third case reported is a 40-year-old woman with a medical history of IgA multiple myeloma diagnosed in 2003. She was receiving chemotherapy (cyclophosphamide, 1 mg/day, and every month, by intravenous administration), zoledronic acid (4 mg infusion during 15 minutes per moth) and dexamethasone (40 mg, during 4 days, every month, *per os*) during 18 months. In November of 2004 it was performed a dental extraction of the mandible tooth 4.7. In August of 2005, a panoramic radiography revealed that there wasn't regeneration of the bone tissue and a process of osteonecrosis with reactive osteosclerosis was present. Examination revealed an area of exposed, necrotic bone, and the diagnosis was jaw avascular osteonecrosis. Figure 8 shows a panoramic radiograph obtained in November of 2004 of the mandible, immediately before the extraction

Figure 8: Orthopantomogram of the mandible before the dental extraction in a patient suffering from multiple myeloma that had previously received zoledronate for 18 months.

of tooth 4.7. Figure 9 shows the orthopantomogram taken in August of 2005, 9 months after the dental extraction. It reveals an exuberant osteonecrosis of the mandible in the region of the nonhealing extraction site. It was performed

Figure 9: Orthopantomogram of the mandible 9 months after the dental extraction of tooth 4.7. The mottled bone is observed in the region of the nonhealing extraction site, due to jaw bisphosphonates-induced osteonecrosis (red circle)

a biopsy of the involved area, that revealed the presence of necrotic lacunae, bacterial debris, granulation tissue with infiltration of lymphocytes and histiocytes. No evidence of metastatic bone disease was detected in any of the biopsied jaw lesions from the three previous case reports. Minor debridement procedures under local anaesthesia were also attempted, however it was required a major surgery to remove all of the involved bone. The patient is presently receiving treatment with cyclosporine (15 mg / kg / day, *per os*) in other to be performed a bone tissue autotransplantation.

DISCUSSION

The major clinical problems that arise in myeloma patients are related to the enhanced bone loss that commonly occurs in these patients. Even patients responding to chemotherapy may have progression of skeletal disease, and recalcification of osteolytic lesions is rare[2,3]. The treatment includes the administration of thalidomide, which is a radiosensitizing agent. Also it has been shown the benefit of adjunctive use of intravenously administered monthly bisphosphonates like the zoledronic acid or pramidronate, in addition to chemotherapy in safely reducing bone complications in myeloma patients. Bisphosphonates are effective inhibitors of bone resorption and reduce the risk of skeletal complications. Osteoclastic and osteocytes functions are part of the bone turnover cycle. This cycle is critical to maintain bone reserves and bone viability. If the osteoclastic function is severally impaired, the osteocytes are not replaced, and the capillary network in bone is lost, resulting in avascular bone necrosis[4]. The mechanism underlying the reaction is unknown, but it has been postulated that bisphosphonates inhibit new vessel formation, leading to avascular bone necrosis[34]. It is believed that bisphosphonates-related osteonecrosis results from altered bone homeostasis, to such extent that the bone's ability to heal after minor lesions is compromised. In certain conditions the bone may also become secondarily infected by *fungi* and bacteria. Osteonecrosis of the jaws may remain asymptomatic for many weeks or months and may only be recognized by the presence of exposed bone in the oral cavity. These lesions are most frequently symptomatic when sites become secondarily infected or there is trauma to the soft tissue via sharp edges of the exposed bone. Osteonecrosis may occur spontaneously or, more commonly, at the site of previous tooth extraction. Some patients may present with atypical complaints, such as *numbness*, the feeling of a *heavy jaw*, and various dysesthesias. The signs and symptoms that

may occur before the development of clinical osteonecrosis include a sudden change in the health of periodontal or mucosal tissue, failure of the oral mucosa to heal, undiagnosed oral pain, loose teeth, or soft-tissue infection. Studies involving larger patient numbers have shown that nearly 80% of cases were initiated by tooth removal[30]. It is not clear at the time of osteonecrosis appearance whether discontinuing bisphosphonates would significantly alter the risk or course of osteonecrosis of the jaw. Bisphosphonates aren't metabolised and have a strong affinity to bind to osteoclasts. They persist in bone tissue for months and sometimes years after discontinuing the drug. Withdrawal therapy does not seam to hasten recovery of the osteonecrosis[33]. In the 3 reported clinical cases, the treatment with zolendronate was suspended, which associated with surgical procedures and intensive antibiotherapy permitted the partial recovery of the patients. If osteonecrosis is suspected, panoramic and tomographic imaging may be performed to rule out other causes like alveolar dental cysts or impacted teeth. Smaller intraoral films can also be used to demonstrate subtle bone changes. Tissue biopsy should be performed only if metastatic disease is suspected, and microbial cultures (aerobic and anaerobic) may provide identification of pathogens causing secondary infections[33,34].

Potential risk factors for the development of osteonecrosis of the jaws may include: concomitant therapy with steroids, chemotherapy, and bisphosphonates therapy by intravenous administration, dental extraction, infectious disease, and/or trauma, head and neck radiotherapy, chemotherapy, immunotherapy, or other cancer treatment protocols, coagulophaties, periodontal disease, bone exostosis, previous invasive dental procedures, dental prostheses, vascular disorders, alcohol abuse and malnutrition [35,36].

A potential preventive measure prior to the initiation of intravenously bisphosphonates therapy will avoid any elective jaw procedure that requires bone heal. It is recommend a routine clinical dental exam that may include panoramic jaw radiography to detect potential dental and periodontal infections[31,37]. If bisphosphonates can be briefly delayed without the risk of a skeletal-related complication, teeth with a poor prognosis or in need of extraction should be extracted and other dental surgeries should be completed prior to the initiation of bisphosphonate therapy[31,37-39].

Bisphosphonate treatment must be performed together with oncologist and the oral maxillofacial surgeon or another dental specialist. Preventive dentistry procedures should be performed before the chemotherapy, immunotherapy, and/or bisphosphonate therapy (removing ab-scessed and nonrestorable teeth and involved periodontal tissues, functional rehabilitation of the teeth, oral self-care hygiene education)[39]. The efforts should focus on preventing the progression of lesions and limiting complications related to secondary infection. In established cases, the primary goals are palliative treatment and control of osteomyelitis. Oncologists should perform a brief visual inspection of the oral cavity at every follow-up visit. As a matter of fact, patients should be monitored every 3 moths or sooner (if symptoms continue or worsen), cessation or interruption of bisphosphonate therapy may be considered in severe cases, osteointegrated dental implants are contra-indicated and may result in further osteonecrosis. The objective of antibiotic therapy is to prevent secondary soft-tissue infection, pain and osteomyelitis.

CONCLUSION

Although the report of these 3 clinical cases serves to alert clinicians about the potential complication of bone necrosis in patients receiving bisphosphonate therapy, many questions remain, concerning the underlying pathogenesis of this process. Further research is needed to elucidate the precise relationship between bisphosphonates and jaw osteonecrosis. It can be hypothesized that a number of factors might intervene in raising the risk of this complication: (a) taxanes are increasingly used to treat patients affected by several types of tumours, including MM; (b) thalidomide, a drug with an antiangiogenic mechanism, is widely used to treat MM patients who are also receiving bisphosphonates; (c) due to the prolonged survival of cancer patients, they are to receive bisphosphonates for longer periods of time, without interruption; (d) a wider use of bisphosphonates specially the most powerful ones like zolendronic acid is being observed; (e) the availability of potent oral bisphosphonates, such as ibandronate, while rendering more convenient the administration of the drug, might make this pathology pass unnoticed or delay its diagnosis. It becomes important to adopt appropriate preventive dentistry with control of dental caries and periodontal disease. It seems prudent to make health care professionals and patients aware of the potential risk associated with the referred treatment. In the 3 described clinical cases, surgical debridment without flap elevation, intensive antibiotherapy and zolendronate treatment arrest made possible the partial recovery of the patients. We purpose this type of clinical approach in patients suffering from MM and jaw ostonecrosis induced by bisphosphonate treatment.

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