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Bisphosphonate-associated osteonecrosis of the jaw 2 years after teeth extractions: a case report solved with non-invasive treatment

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Abstract. – Bisphosphonates are a type of drugs known to inhibit bone resorption through complex interventions. Their primary mechanism of action is aimed at the cellular level, inhibiting osteoclast activity and, thus, bone resorption. Bisphosphonates are, therefore, very widely used, with many patients receiving continuous treatment for years. But it is well known that these drugs can produce osteonecrosis of the jaw and this is their principal risk. A 75-year-old woman received dental treatment before starting intravenous BP therapy for a breast cancer. She started intravenous bisphosphonate treatment with monthly protocol and after two years the patient presented a wound compatible with osteonecrosis of the jaw.

Key Words:
Bisphosphonates, Osteonecrosis of the jaw, Chlorhexidine.

Introduction

Bisphosphonates (BP) are a type of drugs known to inhibit bone resorption through complex mechanisms. Their primary action is aimed at the cellular level, inhibiting osteoclast activity and, thus, bone resorption, particularly when administered by intravenous infusion[1-3]. Bisphosphonates can be grouped into two basic categories: those containing nitrogen and those without. They vary in their antiresorptive potencies, approved clinical use, and method of administration. The newer generations of bisphosphonates contain the nitrogen moiety, creating drugs with much higher potencies. These drugs, namely zolendronate, pamidronate and alendronate, are also known to accumulate in bone. The nitrogen side chain prevents these drugs from being metabolized, allowing them to accumulate with ongoing effects[2,3]. Because some breast cancer treatments can cause bone loss (osteoporosis), many women being treated for breast cancer are also prescribed a BP. Some BPs, in addition to help to reduce bone loss, can also help treat breast cancer[4,5]. BPs are, therefore, very widely used, with many patients receiving continuous treatment for years. These drugs have proven benefit, not only in preventing bone loss but also in prevention of fragility fractures[6,7]. Increasing evidence is accumulating that bisphosphonates are able to directly affect tumoral cells, in addition to their direct effects upon osteoclasts. Bisphosphonates induce apoptosis of tumoral cells and inhibit tumoral cell growth. Moreover, there is increasing evidence that BP may also positively influence the osteoblast[8-11].

The potential anticancer activity of zoledronic acid (ZA) may be mediated through its effects on the bone marrow microenvironment. In addition, preclinical evidence suggests that ZA treatment also may interfere directly or indirectly with other processes in cancer progression and tumor growth[12]. BP in general and especially ZA are thought to promote apoptotic signals in both osteoclasts and keratinocytes that reduce and destruct the immune keratinocyte barrier of oral mucosa[13]. Osteonecrosis of the jaw (ONJ) is an oral complication of bisphosphonate medication[14]. By consensus, ONJ has been defined as the persistence of exposed bone in the oral cavity, despite an adequate treatment for 8 weeks, without local evidence of malignancy and no pri-

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or radiotherapy to the affected region[15]. Approximately 95% of ONJ patients suffer from cancer and receive bisphosphonates for the prevention or treatment of skeletal-related events[16-18]. To date, no risk factors have been statistically correlated to ONJ progression. History of tooth extraction and use of dentures have been suggested as risk factors[13]. Wilkinson et al[19] found not only a strong association between intravenous bisphosphonate therapy and jaw and facial bone disease but also a pattern in which risk estimates for this disease increased as the cumulative dose of intravenous bisphosphonate increased. This finding is consistent with the observation that bisphosphonates have a long half-life and remain in the bone for an extensive period of time. It has been speculated that over suppression of bone turnover may be related to the length and amount of exposure and the long half-life that characterize BP.

ONJ is more frequent in patients with intravenous administration of bisphosphonates[20,21]. Despite, many studies show that the benefits of bisphosphonate treatment in patients with malignant tumors are superior to the related risks, reason which has undoubtedly contributed to their widespread use[14,16,22]. Clinically, ONJ is characterized by the presence of ulcerated mucosa and exposed devitalized bone. Moreover, the surrounding soft tissues are often inflamed because of a secondary mucosal infection[1,9]. Pain, oral discomfort, purulent discharge, exudates and fistula are common[1,23,24]. Tooth extractions are often the predominating event preceding ONJ although other causes[25], such as periodontal disease, dental implant procedures, and non-fitting dentures, were also reported[4,5,9,25]. In oncology, the primary goal of BP therapy is to maintain or improve the quality of life of patients[9]. However, the occurrence of ONJ can lead to recurrent episodes of pain, swelling, and infection, reducing the quality of life, which the treatment with bisphosphonates was intended to safeguard[16]. Researchers believe that ONJ may develop because BPs stop the body from repairing microscopic damage to the jawbone. The risk of development of ONJ is dependent on cumulative dose and potency of the agent[26]. In consequence, patients with cancer are more likely than those with osteoporosis to develop ONJ because they receive more potent agents and more frequent dosing[27]. In the past few years, the occurrence of ONJ has been increasingly reported in patients undergoing treatment with BPs[9,23]. BPs reduce excessive bone turnover, resulting in preservation of structure and mineralization of the bone[5,13,28,29]. From the clinical point of view, bone necrosis of the jaws usually appears as an exposure of avascular bone[10]. Almasan et al[14] found a mandible/maxilla involvement ratio of 2/1, which it could attribute to the decreased vascularity of the mandible and to the existing local conditions. The exposed necrotic bone is infected and the area is usually painful; patients may complain of difficulty in eating and speaking, pain, bleeding and, when the necrosis is near to the mandibular branch of the trigeminal nerve, paresthesia. The main cause of bone necrosis is a defect in vascularization[30]. In the oral cavity, bone necrosis is probably related to the presence of poor oral health, which increases the risk of infection; in fact, bone necrosis is usually related to tooth extraction[9,10,14,19].

ZA is a bisphosphonate used in the treatment and prophylaxis of bone disease in patients with malignant tumors with bone implication. ZA is the most potent BP in clinical development[9]. Although the proper ZA treatment duration is yet to be established, currently available evidence suggests that bone morbidity is decreased for the period that the patient is receiving ZA treatment[13,29]. The duration of effect of a single dose of ZA found in the current study is unexpectedly long and a full biological explanation will require further studies. However, it is known that the duration of action of individual BPs varies according to their binding affinity to bone. This is extremely high for ZA compared with, for example, residronate[31]. Following the acute effects of a BP on local osteoclast function, the drug is presumably internalized by deposition of new bone but becomes biologically active again as this area undergoes subsequent remodeling months or years later. The high affinity of ZA for bone may result in the majority of this remobilized drug readhering to the bone surface and the consequent effects on bone cell function[6]. Based on the probable correlation between ONJ and BPs, before and during bisphosphonates therapy, a careful evaluation of the patients and a strict collaboration between dentists and oncologists is essential for the prevention of secondary effects[11]. The clinical decision to use a BP must, therefore, be made with clear risk/benefit assessment[6].

The aim of the present case is to illustrate the clinical manifestations of intravenous bisphosphonates therapy in areas were invasive dental treatment was carried out 2 years before and how was it solved with a treatment modality consisting of antibiotic therapy and clhorhexidine mouth rinses.

Case Report

A 75-year-old woman presented in Extremadura Health Service (Cáceres Health Center Area, Cáceres, Extremadura, Spain) in order to receive dental treatment before starting intravenous BP therapy for a breast cancer. No other systemic pathologies were present and the patient was not receiving any other pharmacological treatment. At this date, calculus removal was carried out and patient was instructed in adequate oral hygiene and mouth rinses of chlorhexidine 0.12% (Perio-Aid, Dentaid, Barcelona, Spain) were prescribed three times a day for a month. Clinical examination was carried out and anterior teeth, which correspond to teeth 1.1, 2.2, 3.1, 3.2 and 4.2, extracted because of their poor periodontal prognosis. Few months later she started intravenous treatment with ZA a monthly protocol of 4 mg of ZA intravenously. Next year she came periodically to revise her oral cavity, removement of dental plaque and reinforcing instructions of good oral hygiene. Neither teeth extractions nor invasive procedures were necessary during this period. Only conservational treatment consisting of dental filling was carried out, including antibiotic prescription (oral amoxicillin + clavulanate 875/125 mg, 1/8h/7d; GSK, Madrid, Spain) due to an abscess that was totally solved by an endodontic treatment).

Two years after treatment both lower canines and first left lower molar (teeth numbered 3.3, 3.6 and 4.3) needed to be extracted due to its mobility and the pain they were causing. In consequence, patient was derived to the specialist. The oncologist stopped the bisphosphonate treatment for one month; after this month, an antibiotic prophylaxis was given to the patient (2 g of oral amoxicillin, GSK, Madrid, Spain) 1 hour before the intervention) and each tooth was extracted atraumatically, leading 10 days between each tooth extraction. A month after teeth extractions, the patient came again to clinic because she had noticed an area of mucosal ulceration in the incisive area of the mandible. The patient presented a wound compatible with osteonecrosis in the anterior-inferior area, where teeth were extracted years before. Since then, the oncologist did not prescribe bisphosphonate treatment anymore. Upon examination, the patient presented an area of osteonecrosis of the anterior-inferior region with an area of ulcerated mucosa and exposed devitalized bone (Figure 1). Clinical examination revealed a rough, necrotic, yellow and brittle bone in this region. The surrounding soft tissue areas were inflamed due to secondary mucosal infection; however, she had no pain. The exposed bone had a yellow-white discoloration, probing of the bone was asymptomatic, and bleeding did not result. Histological analysis showed inflammatory infiltrate, acellular necrotic debris, thin-walled and dilated blood vessel, intensely basophilic bone spiculae with scalloped borders showing prominent bone resorption.

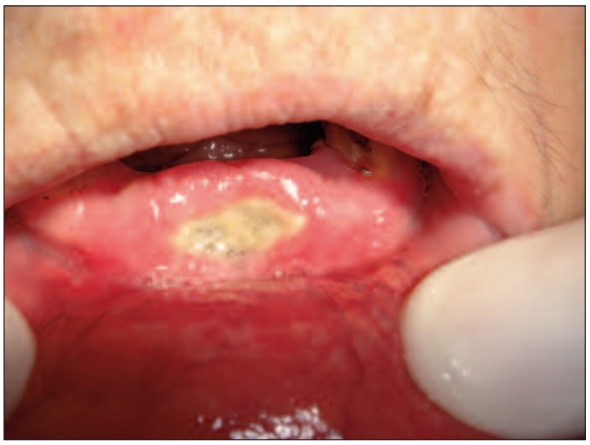

Figure 1. Initial necrotic area in mandible.

Bone edges were smoothed and the patient was treated with amoxicillin + clavulanate (500 mg orally three times per day for 10 days; GSK, Madrid, Spain) and chlorhexidine rinse 0.12% (Perio-Aid, Dentaid, Barcelona, Spain) three times daily for 30 seconds during one month. Upon this time, she had not received radiotherapy of the head or neck. Good oral hygiene habits were maintained by the patient, including diary use of chlorhexidine rinses. Moreover, she was given two antibiotic cycles: first, amoxicillin (GSK, Madrid, Spain) 500 mg orally 3 times a day for 10 days, and second clindamycin (GSK, Madrid, Spain) 300 mg orally, 3 times a day, 7 days, until

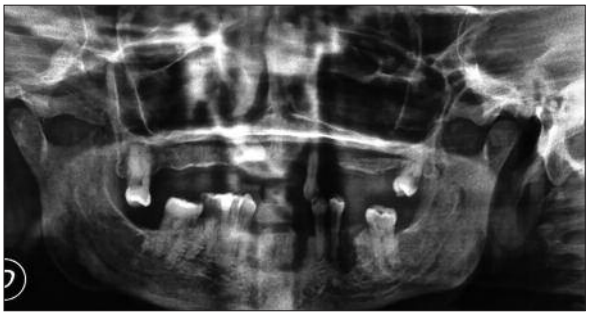

Figure 2. Radiographic aspect of the necrotic area before treatment.

marginal erythema disappeared. Successive oral cavity reviews were carried out periodically to the patient. Despite presenting no pain, the wound did not heal; it continued its progression as it was evident on the panoramic radiograph (Figure 2). In consequence, consultation with the patient's oncologist resulted in discontinuation of ZA treatment. The patient did not use any removable prostheses after teeth extractions.

Results

Two years after the appearance of the lesion, necrotic bone had completely come off. The patient brought the piece of bone wrapped up in a napkin (Figure 3). Under clinical examination it was observed a healthy-looking gum in the bottom of the hole led for the bone fragment (Figure 4). Patient did not refer any pain past or present. There was also radiographic evidence of bone healing. Three and six months postoperatively complete mucosal healing and lack of subjective complaints and objective signs of relapse were found. Progress at one year postoperatively was positive, radiographs revealing a slow but progressive healing of the right jaw bone area and the absence of any other areas of bone necrosis. ZA was initiated not initiated any more.

Discussion

BPs are an accepted standard of practice in the management of breast cancer. Although the association between ONJ and BPs had been called into question, the sheer number of cases reported since the widespread use of BPs began lends support to the view that there is probably a causal relationship[27]. Patients with breast cancer are often treated intravenously with ZA or other BPs to suppress osteoclast activity. As many studies have suggested, patients who receive intravenous BPs therapy along with additional chemotherapy and corticosteroids are at a high risk for ONJ[4,32]. Criteria for the point at which BPs should be started and stopped in the course of bone disease need to be determined[9]. Ruggiero et al[33] stated that "there is no evidence to suggest interrupting bisphosphonate therapy will prevent or lower the risk of ONJ". However, since the half-lives of various BPs have been reported to range from 147 hours (in plasma levels) to 10 years (in bone), it is possible that cessation may help in such cases[4,33,34]. Van den Wyngaert et al[16] conclude that the cessation of BP therapy does not imply necessarily a positive effect on the healing rate of ONJ lesions.

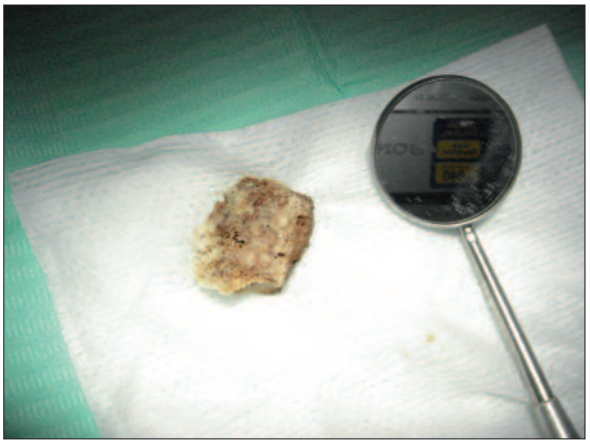

Figure 3. Bone fragment wrapped.

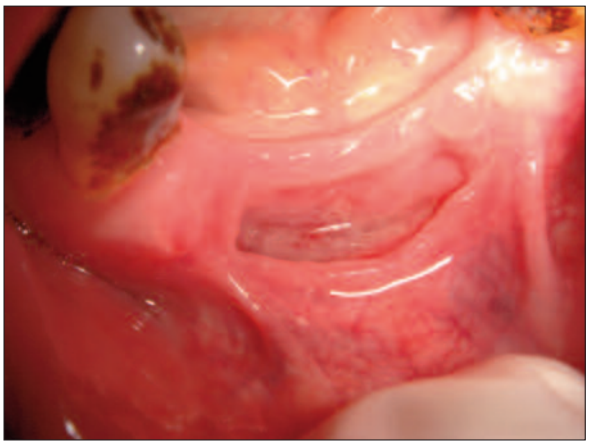

Figure 4. Healthy aspect of the gum after treatment.

For prevention of ONJ related to BPs, all patients who undergo this medication should undergo tooth removal of irrecoverable teeth 3-6 weeks before starting chemotherapy[14]. The importance of preventive measures has been suggested also by Bagán et al[35]. Cessation of BP therapy should be considered in minority of cases, basically if surgery is contemplated, because this may actually exacerbate the avascular process. The benefit of doing so has not yet been evaluated, so conservative therapy with antibiotics and mouth rinses with chlorhexidine is advocated[36]. In spite of the good results that generates, resection of ONJ is followed by a complicated postoperative course[16]. Moreover, zometa-related ONJ is less predictable from the stand-

point of proper healing than that associated with the oral BPs[37]. Fitzpatrick et al[38] presented three cases of BPs-associated ONJ treated exclusively with antibiotic therapy and daily chlorhexidine mouth rinses, showing improvement of the necrotic lesions. Results from the current literature suggest a link between ONJ and tooth extraction. In this sense, Barnias et al[20] found that, in 13 patients (from 17) dental extraction within the last year preceded the diagnosis of ONJ. These results are similar to those reported by other authors[3,4,13]. From the literature, we can assume that the continuous, potent decrease in bone turnover caused by ZA may lead to increased bone fragility in the long run and, in combination with other local factors that are present in the jaw, to the development of ONJ[20]. Therefore, all patients who are going to begin treatment with BPs should receive a dental examination and be informed about the potential adverse oral effects of these drugs. Patient management should be directed at reducing future needs of dentoalveolar surgery. Furthermore, prior to BP therapy, preventive treatment combined with suitable dental extractions, should be instituted to reduce the amount of dentoalveolar surgery, once BP treatment is initiated.

Finally, during BP therapy, customized oral home care, regular periodontal maintenance, and review of oral hygiene practices are important methods to reduce the necessity of invasive dental treatment and the possible appearance of OJN[3,13]. In this sense, root canal treatment is a safe procedure for patients under BP treatment. Smoking habit and periodontitis do not seem to contribute to the progress of ONJ in patients receiving BPs[39]. Woo and Solomon[27] found that treatment with intravenous BPs was associated with an increased risk of being diagnosed with an inflammatory condition or osteomyelitis of the jaw, compared with non-treatment group. The risk rose with increasing cumulative dose of the BP. ZA has been known to be the most potent BP, and previous authors reported that ZA was a stronger inducer of ONJ when compared with pamidronate[30,40-42]. The study of Vahtsevanos et al[39] clearly demonstrates that the longer ZA is administered, the higher the chances for developing this complication. Each dose of ZA administered doubles the likelihood of ONJ, and this effect is independent of the total doses administered to every patient. It is clear from the literature that drug induced ONJ is a recognized sequel of treatment with the new generation of BPs. Physicians need to be informed and educated about this new clinical entity, allowing for prophylactic care, early diagnosis, and prevention of potential devastating consequences[10]. Moreover, close coordination between the general practitioner who indicated the BP and the dentist is essential to reduce the risk of BP related ONJ in patients who are starting BP therapy[4,14,20].

The marked inhibition of bone remodeling that occurs with high doses of bisphosphonates predisposes patients to ONJ when there are additional demands on the bone that require remodeling or growth to maintain vitality. The oral cavity is never aseptic so the necrosis observed in these patients probably may also involve the effects of host bacterias, such as infection and pain. Bacterial products have been shown to increase bone resorption and to decrease bone formation. Moreover, the bone of the jaws is constantly undergoing impact loading, which may require a remodeling response[1]. The increasing number of bisphosphonates-related ONJ reported in the literature draws attention upon oral implications of this medication. Pain, discomfort, erythema and inflammation are common symptoms of patients with ONJ. However, in the case presented, the patient had no pain, probably due to the positive effect of clhorhexidine mouth rinses, which lead to maintain necrotic bone without infection, thus avoiding major complications. Currently, there is no effective therapy for BP-associated ONJ, so it remains important that cofactors continue to be investigated, given the many patients treated with BPs and the relatively few reported to have this condition so far. Further studies are needed to assess other potential risk factors and also to highlight the etiopathogenesis mechanism of ONJ. As in this case the oncologist indicated the moment of suppressing the BPs therapy in order to carry out the dental treatment, communication between professionals prescribing BPs and dental professionals may improve prevention and early detection of BPs-associated ONJ.

Conclusions

We showed the beneficial effect of antibiotic therapy and clhorhexidine mouth rinses in ONJ treatment. Tooth extraction is demonstrated to be predominant oral factor associated with the development of ONJ. This finding emphasizes the importance of assessing good oral health of patients and implementing preventive dentistry be-

fore initiating therapy. Currently, no evidence exists that discontinuing antiresorptive therapy improves the outcome of ONJ, so, once antiresorptive therapy has been initiated the aim should be avoidance of surgical procedures. Furthermore, if ONJ is developed, avoiding reinfection of the lesson is the main factor so it results interesting daily use of chlorhexidine mouth rinses in order to maintain aseptic the oral cavity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone. An emerging oral complication of supportive cancer therapy. Cancer 2005; 104: 83-93.
2) Agrillo A, Filiaci F, Ramieri V, Riccardi E, Quarato D, Rinna C, Gennaro P, Cascino F, Mitro V, Ungari C. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): 5 year experience in the treatment of 131 cases with ozone therapy. Eur Rev Med Pharmacol Sci 2012; 16: 1741-1747.
3) Mariotti A. Bisphosphonates and osteonecrosis of the jaws. J Dent Educ 2008; 72: 919-929.
4) Soolari N, Soolari A. Closure of an open wound associated with bisphosphonate-related osteonecrosis of the jaw in a breast cancer patient. Open Dent J 2011; 5: 163-167.
5) Van den Wyngaert T, Huizing MT, Fossion E, Vermorken JB. Bisphosphonates in oncology: rising stars of fallen heroes. Oncologist 2009; 14: 181-191.
6) Brown JE, Ellis SP, Lester JE, Gutcher S, Khanna T, Purohit OP, McCloskey E, Coleman RE. Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. Clin Cancer Res 2007; 13: 5406-5410.
7) Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA 1998; 280: 2077-2082.
8) Brown JE, Neville-Webbe H, Coleman RE. The role of bisphosphonates in breast and prostate cancer. Endocr Relat Cancer 2004; 11: 207-224.
9) Favia G, Piattelli A, Sportelli P, Capodiferro S, Iezzi G. Osteonecrosis of the posterior mandible after implant insertion: a clinical and histological case report. Clin Impl Dent and Relat Res 2011; 13: 58-63.
10) Merigo E, Manfredi M, Meleti M, Guidotti R, Ripasarti A, Zanzucchi E, D'Aleo P, Corradi D, Corcione L, Sesenna E, Ferrari S, Poli T, Bonaninil M, Vescovi P. Bone necrosis of the jaws associated with bisphosphonate treatment: a report of twenty-nine cases. Acta Biomed 2006; 77: 109-117.
11) Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Pugh J, Gaunt C, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R; AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 2011; 365: 1396-1405.
12) Gnant, M. Zoledronic acid in breast cancer: latest findings and interpretations. A review. Ther Adv Med Oncol 2011; 3: 293-301.
13) Kyrgidis A, Vahtsevanos K, Koloutsos G, Andreadis C, Boukovinas I, Teleioudis Z, Patrikidou A, Triaridis S. Bisphosponate-related osteonecrosis of the jaw: a case-control study of risk factors in breast cancer patients. J Clin Oncol 2008; 26: 4634-4638.
14) Almăsan HA, Băciut M, Rotaru H, Bran S, Almăsan OC, Băciut G. Osteonecrosis of the jaw associated with the use of bisphosponates. Discussion over 52 cases. Rom J Morphol Embriol 2011; 52: 1233-1241.
15) American Association of Oral and Maxillofacial Surgeons. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007; 65: 369-376.
16) Van den Wyngaert T, Claeys T, Huizing MT, Vermorken JB, Fossion E. Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome. Ann Oncol 2009; 20: 331-336.
17) Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy?. Ann Oncol 2006; 17: 1197-1204.
18) Palaska PK, Cartsos V, Zavras AI. Bisphosphonates and time to osteonecrosis development. Oncologist 2009; 14: 1154-1166.
19) Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst 2007; 99: 1016-1024.
20) Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, Koutsoukou V, Gika D, Anagnostopoulos A, Papadimitriou C, Terpos E, Dimopoulos MA. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005; 23: 8580-8587.
21) Agrillo A, Nastro Siniscalchi E, Facchini A, Filiaci F, Ungari C. Osteonecrosis of the jaws in patients assuming bisphosphonates and sunitinib: two case reports. Eur Rev Med Pharmacol Sci 2012; 16: 952-957.

22) Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. Oncologist 2004; 9: 28-37.

23) Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G. Bisphosphonate-induced osteonecrosis of the jaws: prospective study of 80 patients with multiple myeloma and other malignancies. Oral Oncol 2008; 44: 857-869.

24) Bedogni A, Blandamura S, Lokmic Z, Palumbo C, Ragazzo M, Ferrari F, Tregnaghi A, Pietrogrande F, Procopio O, Saia G, Ferretti M, Bedogni G, Chiarini L, Ferronato G, Ninfo V, Lo Russo L, Lo Muzio L, Nocini PF. Bisphosphonate-associated jawbone osteonecrosis: a correlation between imaging techniques and histopathology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 105: 358-364.

25) Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, Hutchinson M, Lathon PV, Sanchez G, Silver P, Chandra M, McCloskey CA, Staffa JA, Willy M, Selby JV, Go AS; Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) Investigators. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonates exposure. J Oral Maxillofac Implants 2010; 68: 243-253.

26) Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Moulopoulos LA, Bamia C, Terpos E, Tsionos K, Bamias A. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. Haematologica 2006; 91: 968-971.

27) Woo SB, Solomon DH. Bisphosphonate therapy for cancer and prevalence of inflammatory jaw conditions. J Natl Cancer Inst 2007; 99: 1016-1024.

28) Clemons MJ, Dranitsaris G, Ooi WS, Yogendran G, Sukovic T, Wong BY, Verma S, Pritchard KI, Trudeau M, Cole DE. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. J Clin Oncol 2006; 20: 4895-4900.

29) Body JJ. Breast cancer: bisphosphonate therapy for metastatic bone disease. Clin Cancer Res 2006; 12: 6258-6263.

30) Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32: 94-124.

31) Nancollas GH, Tang R, Phipps RJ, Henneman Z, Gulde S, Wu W, Mangood A, Russell RG, Ebetino FH. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone 2006; 38: 617-627.

32) Piesold JU, Al-Nawas B, Grötz KA. Osteonecrosis of the jaws by long term therapy with bisphosphonates. Mund Kiefer Gesichtschir 2006; 10: 287-300.

33) Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, Toth B, Damato K, Valero V. Practical guidelines for the prevention, diagnosis and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract 2006; 2: 7-14.

34) Chen T, Berenson J, Vescio R, Swift R, Gilchick A, Goodin S, LoRusso P, Ma P, Ravera C, Deckert F, Schran H, Seaman J, Skerjanec A. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. J Clin Pharmacol 2002; 42: 1228-1236.

35) Bagán J, Blade J, Cozar JM, Constela M, García Sanz R, Gómez Veiga F, Lahuerta JJ, Lluch A, Massuti B, Morote J, San Miguel JF, Solsona E. Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonate. Med Oral Patol Oral Cir Bucal 2007; 12: 336-340.

36) Hoefert S, Eufinger H. Relevance of a prolonged preoperative antibiotic regime in the treatment of bisphosphonate-related osteobnecrosis of the jaw. J Oral Maxillofac Implants 2011; 69: 362-380.

37) Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaw. J Oral Maxillofac Surg 2009; 67: 85-95.

38) Fitzpatrick SG, Stavropoulos MF, Bowers LM, Neuman AN, Hinkson DW, Green JG, Bhattacharyya I, Cohen DM. Bisphosphonates. Related osteonecrosis of the jaw in three osteoportic patients with history of oral bisphosphonate use treated with single yearly zoledronic acid infusion. J Oral Maxillofac Surg 2012; 70: 325-330.

39) Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, Boukovinas I, Koloutsos GE, Teleioudis Z, Kitikidou K, Paraskevopoulos P, Zervas K, Antoniades K. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 2009; 27: 5356-5362.

40) Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, Krikelis D, Terpos E. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006; 134: 620-623.

41) Badros A, Terpos E, Katodritou E, Goloubeva O, Kastritis E, Verrou E, Zervas K, Baer MR, Meiller T, Dimopoulos MA. Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 2008; 26: 5904-5909.

42) Estilo CL, Van Poznak CH, Williams T, Bohle GC, Lwin PT, Zhou Q, Riedel ER, Carlson DL, Schoder H, Farooki A, Fornier M, Halpern JL, Tunick SJ, Huryn JM. Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. Oncologist 2008; 13: 911-920.