Send Orders for Reprints to reprints@benthamscience.ae

Current Medicinal Chemistry, **2017**, *24,* **1-9**

REVIEW ARTICLE

Osteonecrosis of the Jaw and Angiogenesis Inhibitors: A Revival of A Rare But Serous Side Effect

Lorenzo Antonuzzo[1*], Alice Lunghi[1], Paolo Petreni[1], Marco Brugia[1], Alice Laffi[1], Elisa Giommoni[1], Marinella Micol Mela[1], Francesca Mazzoni[1], Vanni Balestri[2] and Francesco Di Costanzo[1]

[1]*Azienda Ospedaliero-Universitaria Careggi, Medical Oncology Unit, Largo Brambilla 3, 50139 Firenze, Italy;* [2]*Azienda Ospedaliero-Universitaria Careggi, Unit of Special Care Dentistry, Largo Brambilla 3, 50139 Firenze, Italy*

Abstract: Osteonecrosis of the jaw (ONJ) is a rare treatment related side effect that was firstly described in 2002 through a case report in metastatic bone cancer patient treated with bisphosphonates (BPs) therapy. ONJ is defined as an eight weeks or longer clinical finding of exposed bone in the oral cavity without response to appropriate therapy. The diagnosis is mainly clinical but often requires a radiological confirmation with an orthopantomography. So it must be made by a dental specialist with sufficient experience on ONJ and requires a detailed anamnestic exploration of comorbidities and treatments history. In particular, ONJ affects a wide number of oncologic patients treated with BPs for bone metastatic cancers and, more recently, with anti-angiogenic drugs. The aim of this this paper is to describe diagnosis and classification of this rare but serious side effect and its pathophysiology. In particular, we provide a detailed description of clinical evidences upon the relationship between anti-angiogenic drugs and ONJ. Considering the evolving of cancer epidemiology with a greater number of cancer surviving patients, this side effect always deserves more attention. We conclude that ONJ must be always carefully investigated and prevented with a multidisciplinary approach involving oncologist, radiation oncologist and skilled dental practitioner when a cancer patient must begin a BP or an anti-angiogenic treatment.

ARTICLE HISTORY

Received: December 16, 2016
Revised: April 18, 2017
Accepted: May 05, 2017

DOI:
10.2174/0929867324666170511113811

Keywords: Osteonecrosis of the jaw, bisphosphonates, angiogenesis, anti-angiogenic drug, anti-VEGF, pathogenesis.

1. INTRODUCTION

Osteonecrosis of the jaw (ONJ) was initially described through case reporting in patients with metastatic bone cancer diseases treated with bisphosphonates (BPs) therapy. The incidence rates of intravenous BPs induced ONJ ranged from 0 % to 27.5%, with a mean incidence of 7% [1].

The first report describing ONJ ascribed to BPs was published in 2003 [2] and the first review about ONJ was published by Ruggiero in 2004 [3]. Since the identification of this problem, a clinical and radiological screening of the oral cavity, made by a dental practitioner, was identified to perform before the starting of BPs treatment. This procedure led to the reduction in incidence of ONJ appearance.

In 2007, the definition of BPs-associated ONJ (BRONJ) was formulated by the American Society for Bone and Mineral Research [4] and recently the special committee on medication-related ONJ of the American Association of Oral and Maxillofacial Surgeons AAOMS suggested changing the name from BRONJ, to medication-related ONJ (MRONJ) [5].

Various drug groups that promote the osteonecrosis of the jaw were identified and they include intravenous and oral BPs, Receptor Activator of Nuclear Factor κ B (RANK) ligand inhibitors (denosumab) and any angiogenesis inhibitors [5].

*Address correspondence to this author at the Medical Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50139 Firenze, Italy; Tel: + 39 055 7947908. Fax: +39 055 7948394. E-mail: lorenzo.antonuzzo@gmail.com

0929-8673/17 $58.00+.00

2. DIAGNOSIS

Patient history and clinical examination are requirement for ONJ diagnosis. An eight weeks or longer clinical finding of exposed bone in the oral cavity without response to appropriate therapy is the feature of ONJ. It can occur in both jaws, with a double incidence, on the mandible and in the jawbone [6].

Usually, the lesions are totally asymptomatic for a period that could last weeks or months, eventually years, and therefore become rarely symptomatic, frequently caused by inflammation of adjacent tissues. Once appeared, signs and symptoms include pain, tooth mobility, mucosal swelling, erythema, ulceration, paresthesia or anesthesia of the associated branch of the trigeminal nerve [7] that can be compressed from the surrounding inflammation [8,9]. These features may occur spontaneously or following dentoalveolar surgery; often ONJ occur at sites of prior oral surgery [10-15]. Bone inflammation and infection are usually present in patients with advanced ONJ, and appear to be secondary events. Intraoral and extra oral fistulae may develop when necrotic mandible or maxilla becomes infected. The ONJ differential diagnosis includes several clinical conditions such as alveolar osteitis, sinusitis, gingivitis/peri-odontitis and periapicalpathosis. The clinical and radiological diagnosis of ONJ early stages is often inconclusive. Typical radiographic findings of ONJ on orthopantomography are increased trabecular density, thickening of the mandibular canal or sinus floor cortication, sequestrum formation and periosteal bone formation. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) also can be used in order to allow a better diagnostic definition of ONJ. CT and cone beam CT allows improved detection of osseous ONJ changes (for example in ONJ, early stages increased trabecular density may not be observed on orthopantomography but it may be seen on CT scan) [16-20]. MRI results even more sensitive to orthopantomography and CT in assessing bone marrow changes at the early stage of ONJ and better shows the soft tissue changes surrounding the osteonecrotic area [21,22]. MRI and CT offer similar advantages and are helpful in planning surgery and treatment [21].

3. STAGING

Currently, four distinct clinical stages of MRONJ are described (Table **1**). When patients are treated with BPs or other anti-resorptive medications without any clinical or radiographic signs of ONJ, they are considered in an "at risk" category. Stage 0 category, added in the 2009 AAOMS guidelines, includes patients in BPs therapy with any clinical or radiographic evidence of necrotic bone but with non-specific symptoms or clinical and radiographic abnormalities findings [23, 24]. Four AAOMS clinical stages are described in Table **1**.

Table 1. MRONJ clinical stages.

AAOMS stages [5]	Definition
Stage 0	Patients with no clinical evidence of necrotic bone, but with non-specific symptoms or clinical and radiographic findings.
Stage 1	Patients with exposed bone who are asymptomatic without significant adjacent or regional soft tissue inflammation or infection.
Stage 2	Patients with exposure of necrotic bone with associated pain, adjacent or regional soft tissue inflammatory swelling or secondary infection.
Stage 3	Exposed necrotic bone with associated pain, adjacent or regional soft tissue inflammatory swelling or secondary infection, in addition to a pathologic fracture, an extraoral fistula or oral-antral fistula or radiographic evidence of osteolysis extending to the inferior border of the mandible or to maxillary sinus floor.

4. PATHOGENESYS AND RISK FACTORS

Many authors have tried to explain the etiology of ONJ but the exact pathophysiologic mechanism of the disease is not fully understood yet. Numerous hypotheses for explaining the development mechanism of ONJ are available in literature and include bone turnover suppression, bone infections, impaired vascularization, immune system malfunction and oral mucosal damages [14,25-30].

The exclusive location of the bone damage on jawbones, rather than the remnant skeleton, can be explained by data from studies conducted on animals that revealed a more evident bone remodeling and turnover in jaws when on BPs treatments [31]. Another hypothesis of the location onset is that jawbones are also frequently submitted to microtrauma, even caused by mastication [32].

Because ONJ was a lesion of the bone, all the drugs that interfere with bone homeostasis have been related to this disease, as BPs and denosumab.

BPs because of their chemical structure bind bone matrix with high affinity [33]. Moreover, the non-nitrogen BPs induce osteoclasts death directly [25], whereas the nitrogen-containing BPs inhibit mavelonate pathway by inhibition of farnesyl pyrophosphate synthetase, resulting into interruption of osteosclasts

differentiation and consequently into these cells apoptosis [26,27]. Finally, BPs activity leads to bone turnover suppression.

Another bone homeostasis pathway recently involved in ONJ occurrence is RANK and its ligand. Denosumab is a humanized monoclonal antibody directed against RANK ligand, which plays a critical role in regulating bone reabsorption. Given that denosumab plays a potent antiresorptive action on bone and ONJ is a result of a defective bone homeostasis, ONJ occurrence has been described with denosumab treatment [34,35].

Since ONJ is an avascular necrosis, there are incoming evidences in literature that angiogenesis is a relevant pathway in ONJ physiopathology. Osteogenesis and angiogenesis are closely related processes during bone remodeling and repair; it was demonstrated that during demineralized bone matrix induced osteogenesis, there is a rapid and intense angiogenetic load that is vital to the healing and bone induction ability [36]. Vascular endothelial growth factor (VEGF) is the essential mediator of angiogenesis and it is essential for osteogenic differentiation and bone formation; it has been hypothesized that bevacizumab, monoclonal antibody directed against circulating VEGF, could compromise micro vessel integrity in the jaw and lead to subclinical compromise of the bone, causing thereby a failure in repairing any eventual oral cavity microtrauma [37].

BPs also seem to have an anti-angiogenic effect [38,39]: Vincenzi *et al.* found decreased VEGF circulating levels after the administration of nitrogen-containing BPs [40]. Angiogenesis and ONJ have recently been linked by several reports about ONJ incidence in cancer patients treated with anti-angiogenic agents, as bevacizumab, sunitinib, aflibercept and regorafenib [41-44].

Another potential key point involved in ONJ development is the role of VEGF in maintaining immunologic host defense. VEGF receptors are expressed on macrophages surface and on monocytes, and their precursor is responsible for survival, differentiation and proliferation of these cells [45]. Blocking VEGF pathway, anti-angiogenic agents cause the reduction of macrophages' number and activities determining an increased risk for infections, followed by tissue necrosis [46]. Thus anti-angiogenic drugs, inhibiting VEGF pathway, may cause host defense impairment and increased necrosis risk.

Therefore, there is still much to understand on which role impaired vascularization plays in the development of ONJ. Below the description of anti-angiogenic drugs related with ONJ is presented in Table **3**.

Considering local risk factors, tooth extraction is the most accepted local risk factor for ONJ during BPs therapies, since it was often been performed in initial reports of ONJ development in literature [47]. Even teeth infections are involved in the development of osteonecrosis. Some studies demonstrated, in animals, that teeth inflammations or infections, with the concomitant use of anti-resorptive agents, are potential risk factors for ONJ [28,48,49]. BPs, inhibiting bone turnover, interfere with infected tissues clearance: therefore if necrotic and flogistic tissues are not removed, they should easily progress to chronic osteomyelitis [48]. Furthermore, there are reports of bacterial invasion by Actinomyces in bisphosphonates, sunitinib and bevacizumab related ONJ [37]. Since Actinomyces is a regular colonizer of the oral cavity, the Actinomyces-related infection in ONJ is probably an opportunistic infection [50]. Dental screening, made by a specialist with sufficient experience of ONJ, in association with accurate and continuous oral hygiene, is then recommended for patients before starting any anti-resorptive treatments.

Many authors believe that an immune system malfunction can promote the development of ONJ. The evidence of an ONJ higher risk with concomitant use of BPs and steroids or chemotherapy, which deface the immune system, sustains their opinion [14,29]. BPs plays their effect not only on bone cells but also on microenvironment's cells, such as endothelial cells, fibroblasts and keratinocytes [51]. The inhibition of these cells causes a mucosal damage in the oral cavity, thinning it, and consequently providing an access to the underlying bone, supporting bone infection and necrosis [52].

Known risk factors for developing ONJ, reported in Table **2**, appear to be BPs treatment, anti-RANKL antibody, cancer and its related therapies, in particular anti-angiogenic agents, invasive dental procedures and oral cavity diseases, lifestyle and old age [53,54]. In particular, BPs duration and intensity treatment influence ONJ risk. The risk is higher with parenteral than with oral BPs, especially for patients receiving monthly parenteral infusion [55,56]. Local risk factors, such as invasive dental procedures or concomitant oral cavity diseases increase risk for ONJ [12,57-59]. Dentoalveolar surgery, tooth extraction [12,60], implant placement and endodontic or periodontal procedures are known risk factors [5]. Other local risk factors are fractures,

pre-existing inflammatory dental diseases (*i.e.* periodontal disease or abscessed teeth) and dental carie [12,60,61]. Genetic factors also could play an important role in the development of MRONJ. Several reports described many single nucleotide polymorphisms (SNPs) that are associated to genes involved with bone turnover, collagen formation or metabolic bone diseases [62-64]. Prolonged steroids use [12] and mellitus diabetes [65] also seem to increase the incidence of ONJ but additional studies or reports are needed to better understand this complex illness.

Table 2. ONJ developing risk factors.

Drugs	Bisphosphonates [1,31,55,56] Anti-RANK ligand (denosumab) [34,35] Anti-angiogenic drugs (bevacizumab [37,66,67,70,71,81-85], sunitinib [42,86,87,73-77], aflibercept [43], regorafenib [44], sorafenib [77,79,80]) Steroids [12,29]
Local risk factors	Invasive dental procedures (tooth extraction, implant placement, etc) [5,11,12,60] Oral cavity disease (teeth or periodontal inflammations or infections) [60,61] Jawbones microtrauma [32]
Others	Age [12,29] Sex [54] Obesity [54] Lifestyle (alcohol, tobacco, etc) [14] Immune system malfunction [14] Comorbidity (mellitus diabetes, rheumatoid arthritis, osteomalacia, etc) [29,65] Genetic alterations (SNP on bone structural protein's gene) [62-64]

5. FOCUS ON ANTI-ANGIOGENIC DRUGS AND ONJ

5.1. Bevacizumab

Bevacizumab is a humanized recombinant monoclonal antibody that blocks circulating VEGF. Bevacizumab has been related with ONJ by several case reports about patients with bone metastatic breast and lung cancers. In 2008, two case reports described for the first time ONJ development in metastatic breast cancer patients treated with bevacizumab alone, without any history of BPs treatment [37,66]; subsequently, two other reports have been described [67,68]. Some studies evaluated ONJ occurrence risk in BPs/ bevacizumab combination treatments. A first study, carried out by Christodoulou, suggested an increased risk of ONJ [69] with the concomitant treatment. Otherwise, Guarneri *et al.* analyzed data from 3,560 patients treated with bevacizumab for locally recurrent or metastatic breast cancer deriving from three clinical trials, AVADO, RIBBON-1, and ATHENA. The ONJ overall incidence with bevacizumab was 0.3% in the blinded phase of the two randomized trials (AVADO and RIBBON-1) and 0.4% in the non-randomized safety study ATHENA. This described ONJ incidence is low and similar to that described in populations of patients with metastatic breast cancer receiving systemic antitumor therapies without bevacizumab. It was also noticed that in patients submitted to bevacizumab and BPs combination therapy, the incidence rate of ONJ occurrence rose from 0.9 to 2.4%. These results suggest that the addiction of bevacizumab could produce only a slight increase in ONJ incidence in comparison to BPs treatment alone [41]. Gaurnieri's data were in accordance with a retrospective analysis carried out at Memorial Sloan-Kettering Cancer Center by McArthur in 2008, who described, in a record of 8,681 patients treated with intravenous BPs and/or bevacizumab, a 2% incidence rate of ONJ in patients treated with bevacizumab and BPs whereas no cases of ONJ in patients receiving bevacizumab alone were described [70]. Another study, presented by Lescaille, evaluated the effect of bevacizumab on the severity of ONJ in a cohort of cancer patients treated with intravenous zoledronic acid. They reviewed 42 oncologic patients with ONJ between 2007 and 2010. This report showed that the combination of zoledronic acid and bevacizumab was associated with an increased risk of developing spontaneous ONJ; the number of ONJ lesions increased in the combination therapy group compared to the zoledronic acid alone group. These results suggested that combination between zoledronic acid and bevacizumab could predispose the development of ONJ [71]. Abovementioned studies suggest a correlation between anti-angiogenic agents, alone or in combination with BPs, and the development of ONJ, even if data are quite discordant. Additional information is therefore necessary to better understand the correlation between bevacizumab and ONJ.

5.2. Sunitinib

Sunitinib is an oral multi-targeted kinase inhibitor that inhibits VEGF receptors (VEGFR type 1 and 2), platelet-derived growth factor receptors (PDGFR-alpha and PDGFR-beta), stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 (FLT3), glial cell-line derived neurotrophic factor receptor (RET) and the receptor of macrophage-colony stimulating factor (CSF1R) [72]. Sunitinib and ONJ have been linked in a series of case reports of patients with bone metastatic renal cell carcinoma (RCC) treated with Sunitinib with or

Table 3. List of published papers on ONJ development during anti-angiogenic therapies in cancer patients.

Anti-angiogenic drug	Reference	Year of publication	Setting
Bevacizumab	Estilo *et al.* [37]	2008	Breast cancer
	Greuter *et al.* [66]	2008	Breast cancer
	McArthur *et al.* [70]	2008	Breast and lung cancer
	Serra *et al.* [81]	2009	Lung cancer
	Guarneri *et al.* [41]	2010	Breast cancer
	Katsenos *et al.* [82]	2012	Lung cancer
	Dişel *et al.* [67]	2012	Colon cancer
	Santos-Silva *et al.* [83]	2013	Renal cancer
	Sato *et al.* [84]	2013	Colon cancer
	Magremanne *et al.* [85]	2013	Glioblastoma multiforme
	Lescaille *et al.* [71]	2014	Bone metastases
Sunitinib	Brunello *et al.* [42]	2009	Renal cancer
	Hoefert *et al.* [86]	2010	Renal cancer
	Koch *et al.* [73]	2011	Renal cancer
	Agrillo *et al.* [87]	2012	Renal cancer
	Nicolatou-Galitis*et al.* [75]	2012	Renal cancer
	Fleissig *et al.* [74]	2012	Renal cancer
	Smidt-Hansen *et al.* [76]	2013	Renal cancer
	Fusco *et al.* [77]	2015	Renal cancer
Aflibercept	Ponzetti *et al.* [43]	2013	Colon cancer
Regorafenib	Antonuzzo *et al.* [44]	2016	Colon cancer
Sorafenib	Beuselink *et al.* [79]	2012	Renal cancer
	Fusco *et al.* [77]	2015	Renal cancer
	Garuti *et al.* [80]	2016	Hepatocellular cancer

without nitrogen-contain BPs [73-77]. A retrospective study of 44 RCC patients affected by exposed and non-exposed ONJ showed that in most cases, they were receiving, at the time of diagnosis, zoledronic acid in 93% of patients and anti-angiogenetic agents, mainly sunitinib in 80% [77]. This study, in comparison with other literature data, suggested a potential role of targeted agents in increasing risk of ONJ. The development of sunitinib-related ONJ could mainly be explained by VEGF signaling pathway interference [12].

5.3. Aflibercept

Aflibercept is a recombinant fusion protein, fused to the Fc portion of a human IgG1 immunoglobulin, which inhibits VEGF receptors 1 and 2 by binding their extracellular domain. It is used in association with fluorouracil and irinotecan (FOLFIRI schedule) in patients with progressive metastatic colorectal cancer after oxaliplatin-based first line. The first case of ONJ occurring was reported in 2013 in a patient treated with aflibercept plus FOLFIRI during the expanded-access program. This patient developed ONJ after having received eleven cycles (nearly six months) of chemotherapy with anti-angiogenetic agent; he was in risk for ONJ because of history of untreated periodontitis and episodic previous pyorrhea. He had no history of bone metastasis or anti-resorptive agent treatments [43].

5.4. Regorafenib

Regorafenib is a small-molecule multi-kinase inhibitor with an anti-angiogenic activity due to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition. In

2016, the first case of ONJ during Regorafenib treatment has been described in literature [44,78] by our group. It refers to a heavily pre-treated colorectal cancer patient, without any oral known risk factor or anti-resorptive treatment history, who developed lower jaw necrosis after twenty-two months of regorafenib treatment [44,78]. However, this case warrants further validation on the potential association between Regorafenib and the development of ONJ.

5.5. Sorafenib

Sorafenib is an oral multiple tyrosine kinase inhibitor that targets the VEGF receptor family (VEGFR-2 and VEGFR-3) and platelet-derived growth factor receptor family (PDGFR-beta and Kit), which play key roles in tumor progression and angiogenesis. It is used for advanced hepatocellular carcinoma (HCC) and for metastatic RCC. Several reports of ONJ occurrence during sorafenib therapy in RCC patients, with a median exposure to sorafenib treatment from 5 to 36 months, are listed in literature, always used in combination with BPs for bone metastasis control [77,79]. There is instead only one case of HCC patient (three months of sorafenib treatment only), without any history of BPs treatment but with a previous tooth extraction nearly ten months before [80].

DISCUSSION AND CONCLUSION

Osteonecrosis of the jaws (ONJ) is a rare but serious complication that emerged in cancer patients treated with BPs, denosumab and anti angiogenetic agents.

Although ONJ pathogenesis is not fully understood yet, it is evident that angiogenesis plays a relevant role in bone homeostasis and that anti-angiogenetic drugs could promote ONJ development.

In November 2010, the European Medicine Agency issued safety alert about ONJ risk during sunitinib or bevacizumab treatment [87]. Furthermore, the first case-report of ONJ in patients treated with aflibercept and in a patient under treatment with regorafenib or sorafenib is recently described in literature [43,44,80]. The number of case reports of anti-angiogenetic drugs-related ONJ seems to be growing; this would suggest that patients treated with anti-angiogenetic drugs may have an increased risk for the development of ONJ.

We hypothesized that duration of anti-angiogenic drugs exposure could be related to ONJ development risk, as described for BPs [59]; furthermore, we believe that the increasing life expectancy of cancer patients, as a result of the growing scientific knowledge and the increasing number of available drugs, is leading to the revival of serous side effect.

Therefore, medical oncologists should be aware of ONJ potential risk linked to new anti-angiogenic therapies and a preventive oral screening protocol should be identified to reduce the risk of ONJ development for patients subjected to prolonged treatments with these new anti-cancer drugs, alone or in combination with BPs. The screening protocol should be composed by a radiological and, subsequent, clinical evaluation made by a dental care specialist, with sufficient clinical experience of ONJ in order to identify and remove known risk factors before starting treatments. Moreover, more attention must be paid for initial and faded symptoms in patients submitted to BPs or anti-angiogenic prolonged therapies for early diagnosis and prompt treatment.

A right cooperation between medical oncologists, radiologists and dental care specialist is essential to minimize the burden of this potential serious side effect.

LIST OF ABBREVIATIONS

AAOMS	=	American Association of Oral and Maxillofacial Surgeons
BP	=	Bisphosphonate
BRONJ	=	Bisphosphonate-Related Osteonecrosis of the Jaw
CT	=	Computed Tomography
FLT3	=	FMS-like tyrosine kinase-3
HCC	=	Hepatocellular Carcinoma
MRI	=	Magnetic Resonance Imaging
MRONJ	=	Medication-Related Osteonecrosis of the Jaw
ONJ	=	Osteonecrosis of the Jaw
PDGFR	=	Platelet Derivate Growth Factor Receptor
RANK	=	Receptor Activator of Nuclear Factor κ B
RCC	=	Renal Cell Carcinoma
RET	=	REarranged during Transfection
SNP	=	Single Nucleotide Polymorphism
VEGF	=	Vascular Endothelial Growth Factor
VEGFR	=	Vascular Endothelial Growth Factor Receptor

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Kühl S, Walter C, Acham S, Pfeffer R, Lambrecht JT. Bisphosphonate-related osteonecrosis of the jaws-a review. Oral Oncol. 2012 Oct; 48(10): 938-47.

[2] Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003;61:1115–7.

[3] Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004;62:527–34.

[4] Khosla S, Burr D, Cauley J, *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;22:1479–91.

[5] Ruggiero SL, Dodson TB, Fantasia J, *et al.* American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw: 2014 update. J Oral Maxillofac Surg 2014;72:1938–1956.

[6] Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006 May 16;144(10):753-61. Review. Erratum in: Ann Intern Med. 2006 Aug 1;145(3):235.

[7] Sharma D, Ivanovski S, Slevin M, *et al.* Bisphosphonate-related osteonecrosis of jaw (BRONJ): diagnostic criteria and possible pathogenic mechanisms of an unexpected anti-angiogenic side effect. Vasc Cell. 2013;5:1–5.

[8] Zadik Y, Benoliel R, Fleissig Y, Casap N. Painful trigeminal neuropathy induced by oral bisphosphonate-related osteonecrosis of the jaw: a new etiology for the numb-chin syndrome. Quintessence Int. 2012;43:97–104.

[9] Otto S, Hafner S, Grotz KA. The role of inferior alveolar nerve involvement in bisphosphonate-related osteonecrosis of the jaw. J Oral Maxillofac Surg. 2009;67:589–92.

[10] Ferlito S, Puzzo S, Liardo C. Preventive protocol for tooth extractions in patients treated with zoledronate: a case series. J Oral Maxillofac Surg. 2011.

[11] Scoletta M, Arduino PG, Pol R, *et al.* Initial experience on the outcome of teeth extractions in intravenous bisphosphonatetreated patients: a cautionary report. J Oral Maxillofac Surg. 2011;69:456–62.

[12] Saad F, Brown JE, Van PC, *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;23:1341–7.

[13] Fitzpatrick SG, Stavropoulos MF, Bowers LM, *et al.* Bisphosphonate related osteonecrosis of jaws in 3 osteoporotic patients with history of oral bisphosphonate use treated with single yearly zoledronic acid infusion. J Oral Maxillofac Surg. 2012;70:325–30.

[14] Thumbigere-Math V, Tu L, Huckabay S, *et al.* A retrospective study evaluating frequency and risk factors of osteonecrosis of the jawin 576 cancer patients receiving intravenous bisphosphonates. Am J Clin Oncol. 2012;35:386–92.

[15] Yamazaki T, Yamori M, Ishizaki T, *et al.* Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. Int J Oral Maxillofac Surg. 2012;41:1397–403.

[16] Phal PM, Myall RW, Assael LA, Weissman JL. Imaging findings of bisphosphonate-associated osteonecrosis of the jaws. AJNR Am J Neuroradiol. 2007; 28:1139–45.

[17] Bianchi SD, Scoletta M, Cassione FB, Migliaretti G, Mozzati M. Computerized tomographic findings in bisphosphonate-associated osteonecrosis of the jaw in patients with cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007; 104:249–58.

[18] Bedogni A, Blandamura S, Lokmic Z, *et al.* Bisphosphonate-associated jawbone osteonecrosis: a correlation between imaging techniques and histopathology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008; 105:358–64.

[19] Elad S, Gomori MJ, Ben-Ami N, *et al.* Bisphosphonate-related osteonecrosis of the jaw: clinical correlations with computerized tomography presentation. Clin Oral Investig. 2010; 14:43–50.

[20] Shimizutani K. Recognition of bisphosphonate-related osteonecrosis of the jaw among oral and maxillofacial radiologists: results from a questionnaire-based survey in Japan. Oral Radiol. 2013; 29:98–10.

[21] Stockmann P, Hinkmann FM, Lell MM, *et al.* Panoramic radiograph, computed tomography or magnetic resonance imaging. Which imaging technique should be preferred in bisphosphonate-associated osteonecrosis of the jaw? A prospective clinical study. Clin Oral Investig 2010; 14:311–7.

[22] Krishnan A, Arslanoglu A, Yildirm N, Silbergleit R, Aygun N. Imaging findings of bisphosphonate-related osteonecrosis of the jaw with emphasis on early magnetic resonance imaging findings. J Comput Assist Tomogr. 2009; 33:298–304.

[23] Ruggiero SL, Dodson TB, Assael LA, *et al.* American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteo- necrosis of the jaws: 2009 update. J Oral Maxillofac Surg 2009;67.

[24] Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL. Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J. International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015 Jan;30(1):3-23.

[25] Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res. 2006 Oct 5;12(20 Pt 2):6222s-6230.

[26] Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int. 2008 Jun;19(6):733-59.

[27] Kumar V, Sinha RK. Bisphosphonate Related Osteonecrosis of the Jaw: An Update. J Maxillofac Oral Surg. 2014 Dec;13(4):386-93.

[28] Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, García-Hernández PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Fierlinger A, Lakshmanan MC. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized,. double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res. 2010 Feb;25(2):404-14.

[29] Jadu F, Lee L, Pharoah M, Reece D, Wang L. A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. Ann Oncol. 2007 Dec;18(12):2015-9.

[30] Lesclous P, Abi Najm S, Carrel JP, *et al.* Bisphosphonate-associated osteonecrosis of the jaw: a key role of inflammation? Bone 2009;45:843-52.

[31] Allen MR, Kubek DJ, Burr DB. Cancer treatment dosing regimens of zoledronic acid result in near-complete suppression of mandible intracortical bone remodeling in beagle dogs. J Bone Miner Res. 2010 Jan;25(1):98-105.

[32] Hoefert S, Schmitz I, Tannapfel A, Eufinger H. Importance of microcracks in etiology of bisphosphonate-related osteonecrosis of the jaw. a possible pathogenetic model of symptomatic and non-symptomatic osteonecrosis of the jaw based on scanning electron microscopy findings. Clin Oral Investig. 2010 Jun;14(3):271-84.

[33] Pazianas M. Osteonecrosis of the jaw and the role of macrophages. J Natl Cancer Inst. 2011 Feb 2;103(3):232-40.

[34] Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH et al, Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28:5132–5139.

[35] Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L *et al.* Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377:813–822.

[36] Rabie AB. Vascular endothelial growth pattern during demineralized bone matrix induced osteogenesis. Connect Tissue Res. 1997;36(4):337-45.

[37] Estilo CL, Fornier M, Farooki A, Carlson D, Bohle G 3rd, Huryn JM. Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol. 2008 Aug 20;26(24):4037-8.

[38] Wood J, Bonjean K, Ruetz S, Bellahcène A, Devy L, Foidart JM, Castronovo V, Green JR. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther. 2002 Sep;302(3):1055-61.

[39] Santini D, Vincenzi B, Dicuonzo G, Avvisati G, Massacesi C, Battistoni F, Gavasci M, Rocci L, Tirindelli MC, Altomare V, Tocchini M, Bonsignori M, Tonini G. Zoledronic acid induces significant and long-lasting modifications of circulating angiogenic factors in cancer patients. Clin Cancer Res. 2003 Aug 1;9(8):2893-7.

[40] Vincenzi B, Napolitano A, Zoccoli A, Iuliani M, Pantano F, Papapietro N, Denaro V, Santini D, Tonini G. Serum VEGF levels as predictive marker of bisphosphonate-related osteonecrosis of the jaw. J Hematol Oncol. 2012 Sep 17;5:56.

[41] Guarneri V, Miles D, Robert N, Diéras V, Glaspy J, Smith I, Thomssen C, Biganzoli L, Taran T, Conte P. Bevacizumab and osteonecrosis of the jaw. incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat. 2010 Jul;122(1):181-8.

[42] Brunello A, Saia G, Bedogni A, Scaglione D, Basso U. Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma. Bone. 2009 Jan;44(1):173-5.

[43] Ponzetti A, Pinta F, Spadi R, Mecca C, Fanchini L, Zanini M, Ciuffreda L, Racca P. Jaw osteonecrosis associated with aflibercept, irinotecan and fluorouracil: attention to oral district. Tumori. 2015 Sep 1:0.

[44] Antonuzzo L, Lunghi A, Giommoni E, Brugia M, Di Costanzo F. Regorafenib Also Can Cause Osteonecrosis of the Jaw. J Natl Cancer Inst. 2016 Feb 7;108(4).

[45] Sawano A, Iwai S, Sakurai Y, Ito M, Shitara K, Nakahata T, Shibuya M. Flt-1, vascular endothelial growth factor receptor 1, is a novel cell surface marker for the lineage of monocyte-macrophages in humans. Blood. 2001 Feb 1;97(3):785-91.

[46] Barleon B, Sozzani S, Zhou D, Weich HA, Mantovani A, Marmé D. Migration of human monocytes in response to vascular endothelial growth factor (VEGF) is mediated *via* the VEGF receptor flt-1. Blood. 1996 Apr 15;87(8):3336-43.

[47] Bagan JV, Murillo J, Jimenez Y, Poveda R, Milian MA, Sanchis JM, Silvestre FJ, Scully C. Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. J Oral Pathol Med. 2005 Feb;34(2):120-3. Review.

[48] Sedghizadeh PP, Kumar SK, Gorur A, Schaudinn C, Shuler CF, Costerton JW. Microbial biofilms in osteomyelitis of the jaw and osteonecrosis of the jaw secondary to bisphosphonate therapy. J Am Dent Assoc. 2009 Oct;140(10):1259-65.

[49] Wanger G, Gorby Y, El-Naggar MY, Yuzvinsky TD, Schaudinn C, Gorur A, Sedghizadeh PP. Electrically conductive bacterial nanowires in bisphosphonate-related osteonecrosis of the jaw biofilms. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Jan;115(1):71-8.

[50] Wong VK, Turmezei TD, Weston VC. Actinomycosis. BMJ. 2011 Oct 11;343:d6099.

[51] Walter C, Klein MO, Pabst A, *et al.* Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. Clin Oral Investig 2010;14:35-41.

[52] Scheper M, Chaisuparat R, Cullen K, Meiller T. A novel soft-tissue *in vitro* model for bisphosphonate-associated osteonecrosis. Fibrogenesis Tissue Repair 2010;1:3-6.

[53] Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone. 2011 Apr 1;48(4):677-92.

[54] Almazrooa SA, Woo SB. Bisphosphonate and nonbisphosphonate-associated osteonecrosis of the jaw: a review. J Am Dent Assoc 2009;140(7):864–867.

[55] Gliklich R, Wilson J. Epidemiology of bisphosphonate-related osteonecrosis of the jaws: the utility of a national registry. J Oral Maxillofac Surg 2009;67(5, Suppl):71–74.

[56] Palaska PK, Cartsos V, Zavras AI. Bisphosphonates and time to osteonecrosis development. Oncologist. 2009;14(11):1154.

[57] King AE, Umland EM. Pharmacotherapy. Osteonecrosis of the jaw in patients receiving intravenous or oral bisphosphonates. 2008 May;28(5):667-77.

[58] Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN. Frequency and risk factors associated with osteonecros is of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res. 2008 Jun;23(6):826-36.

[59] 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(34):8580.

[60] Filleul O,Crompot E,Saussez S. Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases. J Cancer Res Clin Oncol. 2010;136(8):111.

[61] 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 Nov;27(32):5356-62. Epub 2009 Oct 5.

[62] Nicoletti P, Cartsos VM, Palaska PK, Shen Y, Floratos A, Zavras AI. Genomewide pharmacogenetics of bisphosphonate-induced osteonecrosis of the jaw: the role of RBMS3. Oncologist. 2012;17(2):279-87.

[63] Katz J, Gong Y, Salmasinia D, Hou W, Burkley B, Ferreira P, Casanova O, Langaee TY, Moreb JS. Genetic polymorphisms and other risk factors associated with bisphosphonate induced osteonecrosis of the jaw. Int J Oral Maxillofac Surg. 2011 Jun;40(6):605-11.

[64] Marini F, Tonelli P, Cavalli L, Cavalli T, Masi L, Falchetti A, Brandi ML. Pharmacogenetics of bisphosphonate-associated osteonecrosis of the jaw. Front Biosci (Elite Ed). 2011 Jan 1;3:364-70.

[65] Peer A, Khamaisi M. Diabetes as a risk factor for medication-related osteonecrosis of the jaw. J Dent Res. 2015 Feb;94(2):252-60.

[66] Greuter S, Schmid F, Ruhstaller T, Thuerlimann B. Bevacizumab-associated osteonecrosis of the jaw. Ann Oncol. 2008 Dec;19(12):2091-2.

[67] Dişel U, Beşen AA, Özyılkan Ö, Er E, Canpolat T. A case report of bevacizumab-related osteonecrosis of the jaw: old problem, new culprit. Oral Oncol. 2012 Feb;48(2):e2-3.

[68] Pakosch D, Papadimas D, Munding J, Kawa D, Kriwalsky MS. Osteonecrosis of the mandible due to anti-angiogenic agent, bevacizumab. Oral Maxillofac Surg. 2013Dec;17(4):303-6.

[69] Christodoulou C, Pervena A, Klouvas G, Galani E, Falagas ME, Tsakalos G, Visvikis A, Nikolakopoulou A, Acholos V, Karapanagiotidis G, Batziou E, Skarlos DV. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology. 2009;76(3):209-11.

[70] McArthur HL, Estilo C, Huryn J, Williams T, Fornier M, Traina TA, Howard J, Hudis CA, Dickler MN. Osteonecrosis of the jaw (ONJ) among intravenous (IV) bisphosphonate- and/or bevacizumab-treated patients (pts) at Memorial Sloan-Kettering Cancer Center. (MSKCC) J Clin Oncol. 2008;26:9588.

[71] Lescaille G, Coudert AE, Baaroun V, Ostertag A, Charpentier E, Javelot MJ, Tolédo R, Goudot P, Azérad J, Berdal A, Spano JP, Ruhin B, Descroix V. Clinical study evaluating the effect of bevacizumab on the severity of zoledronic acid-related osteonecrosis of the jaw in cancer patients. Bone. 2014 Jan;58:103-7.

[72] Papaetis GS1, Syrigos KN. Sunitinib: a multitargeted receptor tyrosine kinase inhibitor in the era of molecular cancer therapies. BioDrugs. 2009;23(6):377-89.

[73] Koch FP, Walter C, Hansen T, Jäger E, Wagner W. Osteonecrosis of the jaw related to sunitinib. Oral Maxillofac Surg. 2011 Mar;15(1):63-6.

[74] Fleissig Y, Regev E, Lehman H. Sunitinib related osteonecrosis of jaw: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Mar;113(3):e1-3.

[75] Nicolatou-Galitis O, Migkou M, Psyrri A, Bamias A, Pectasides D, Economopoulos T, Raber-Durlacher JE, Dimitriadis G, Dimopoulos MA. . Gingival bleeding and jaw bone necrosis in patients with metastatic renal cell carcinoma receiving sunitinib: report of 2 cases with clinical implications. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Feb;113(2):234-8.

[76] Smidt-Hansen T1, Folkmar TB, Fode K, Agerbaek M, Donskov F. Combination of Zoledronic Acid and Targeted Therapy Is Active But May Induce Osteonecrosis of the Jaw in Patients With Metastatic Renal Cell Carcinoma. J Oral Maxillofac Surg. 2013 Sep;71(9):1532-40.

[77] Fusco V, Porta C, Saia G, Paglino C, Bettini G, Scoletta M, Bonacina R, Vescovi P, Merigo E, Lo Re G, Guglielmini P, Di Fede O, Campisi G, Bedogni A. Osteonecrosis of the Jaw in Patients With Metastatic Renal Cell Cancer Treated With Bisphosphonates and Targeted Agents: Results of an Italian Multicenter Study and Review of the Literature. Clin Genitourin Cancer. 2015 Aug;13(4):287-94.

[78] Lunghi A, Antonuzzo L, Laffi A, Giommoni E, Di Costanzo F. Response. J Natl Cancer Inst. 2016 Jul 7;108(9).

[79] Beuselinck B, Wolter P, Karadimou A, Elaidi R, Dumez H, Rogiers A, Van Cann T, Willems L, Body JJ, Berkers J, Van Poppel H, Lerut E, Debruyne P, Paridaens R, Schöffski P. Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases. Br J Cancer. 2012 Nov 6;107(10):1665-71.

[80] Garuti F, Camelli V, Spinardi L, Bucci L, Trevisani F. Osteonecrosis of the jaw during sorafenib therapy for hepatocellular carcinoma. Tumori, 2016 102(Suppl. 2). doi: 10.5301/tj.5000504.

[81] Serra E, Paolantonio M, Spoto G, Mastrangelo F, Tetè S, Dolci M.Bevacizumab-related osteneocrosis of the jaw. Int J Immunopathol Pharmacol. 2009 Oct-Dec;22(4):1121-3.

[82] Katsenos S, Christophylakis C, Psathakis K. Osteonecrosis of the jaw in a patient with advanced non-small-cell lung cancer receiving bevacizumab. Arch Bronconeumol 2012;48:218–9.

[83] Santos-Silva AR, Belizário Rosa GA, Castro Júnior Gd, Dias RB, Prado Ribeiro AC, Brandão TB. Osteonecrosis of the mandible associated with bevacizumab therapy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Jun;115(6):e32-6.

[84] Sato M, Ono F, Yamamura A. Onochi S [A case of osteonecrosis of the jaw during treatment by bevacizumab for sigmoid colon cancer]. Nihon Shokakibyo Gakkai Zasshi 2013;110:655–9.

[85] Magremanne M, Lahon M, De Ceulaer J, Reychler H. Unusual bevacizumab- related complication of an oral infection. J Oral Maxillofac Surg 2013;71:53–5.

[86] Hoefert S, Eufinger H. Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: presentation of three cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:463–9.

[87] 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;16:952–7.

[88] Giancola F, Campisi G, Russo LL, Muzio LL, Di Fede O. Osteonecrosis of the jaw related to everolimus and bisphosphonate: a unique case report? Ann Stomatol (Roma). 2013;4:20–21.

[89] Kim DW, Jung YS, Park HS, Jung HD. Osteonecrosis of the jaw related to everolimus: a case report. Br J Oral Maxillofac Surg. 2013;51:e302–e304.

[90] Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA *et al.* Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012;48:3082–3092.

[91] Khosla S, Burr D, Cauley J, *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;22:1479–91.

[92] Ruggiero SL, Dodson TB, Fantasia J, *et al.* American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw: 2014 update. J Oral Maxillofac Surg 2014;72:1938–1956.

PMID: 28494743