BioMed Research International

# Adverse Reactions to Anticancer Drugs in the Oral Cavity

Lead Guest Editor: Olga Di Fede
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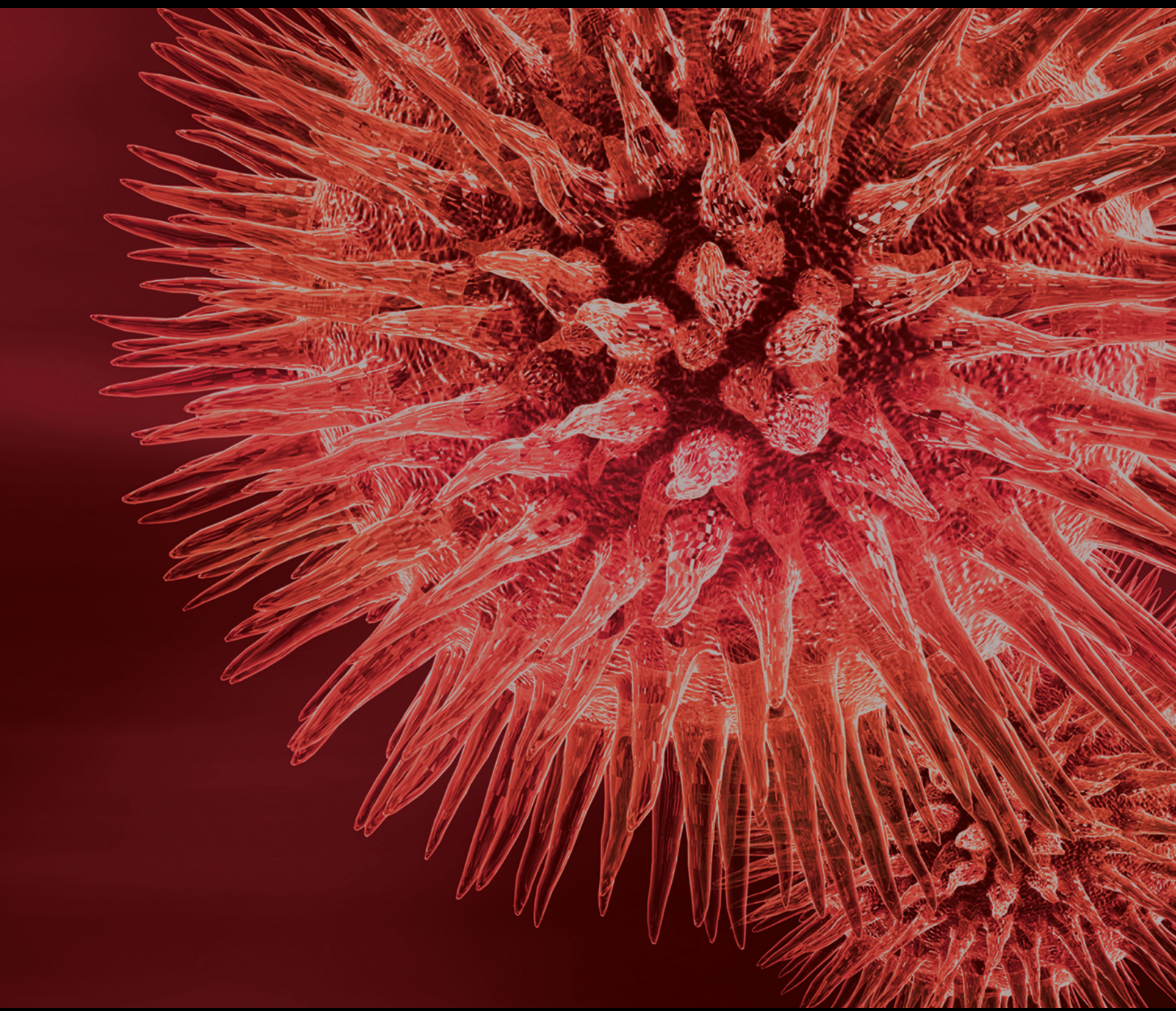

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# Contents

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*Editorial*

# Adverse Reactions to Anticancer Drugs in the Oral Cavity

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The development, testing, and adoption into clinical practice of anticancer medications have revolutionized cancer care over the past decades. A better understanding of the biology of cancer has translated into development of novel systemic agents, as well a more effective use of older chemotherapy agents. As a consequence, cancer mortality continues to decrease.

However, greater cure and disease control rates come at a price of an increased risk of adverse effects, which often affects the mouth and related structures including the oral mucosa, salivary glands, jawbones, and cranial nerves. Oral mucositis, hyposalivation, dysgeusia, and osteonecrosis of the jaw (ONJ) are some examples of the potential adverse effects of anticancer therapies to the oral cavity, which affect an increasing number of individuals living with cancer and cancer survivors and can lead to persistent discomfort, pain, dysfunction, and a notable reduction in the quality of life. Management of these oral adverse effects can be challenging, as it typically requires a multidisciplinary approach and a close collaboration between the cancer team and oral health care providers, both in primary care and in the specialist setting.

This special issue provides a useful update of some of the most significant adverse reactions to anticancer drugs in the oral cavity, with a view to inform clinical practice and inspire further research.

Multitargeted tyrosine kinase inhibitors including sunitinib, sorafenib, axitinib, and cabozantinib are increasingly used in the cancer setting, and C. Arena et al. provide in this special issue a useful systematic review on oral mucositis associated with these agents. Similarly, K. Pimolbutr et al. report on the development of ONJ associated with antiangiogenic agents in the subset of antiresorptive-naïve patients.

Prevention of toxicity is crucial in individuals due to commence and in those who have been using antiresorptive medications, and O. Di Fede et al. discuss the main strategies to reduce the risk ONJ in this patient population.

The surgical treatment of medication-related ONJ is a relatively new field of research, as this condition has been historically managed conservatively with a focus on pain management and resolution of infection. In this special issue, R. Mauceri et al. report on the use of Er,Cr:YSGG laser and platelet-rich plasma in the surgical treatment of ONJ, whereas R. Sacco et al. provide a systematic review of the efficacy of microsurgical reconstruction of the jaws using vascularized free flap in patients with medication-related ONJ.

We hope that the readers of BioMed Research International will find this special issue interesting and informative.

## Conflicts of Interest

Olga Di Fede, Noam Yarom, Jose Bagan, and Stefano Fedele declare that there are no conflicts of interest regarding the

publication. Sven Otto declares to receive honoraria for scientific lectures from AMGEN.

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*Noam Yarom*
*Jose Bagan*
*Sven Otto*
*Stefano Fedele*

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*Review Article*

# The Dental Management of Patients at Risk of Medication-Related Osteonecrosis of the Jaw: New Paradigm of Primary Prevention

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Medication-related osteonecrosis of the jaw (MRONJ) is a serious adverse reaction of antiresorptive and antiangiogenic agents; it is a potentially painful and debilitating condition that can considerably affect the quality of life of patients. Furthermore, even if its epidemiology and pathogenesis have still not been fully clarified, several risk factors related to MRONJ have been recognized in prevention protocols. Three main risk factors are as follows: (i) the type of ONJ-related medications: antiresorptive (e.g., Bisphosphonates, Denosumab) and antiangiogenic drugs (e.g., Bevacizumab, Sunitinib); (ii) the category of patient at MRONJ risk: cancer versus non-cancer patient; (iii) the typologies and timing of dental treatments (e.g., before, during, or after the drug administration). The aim of this paper is to describe the new paradigm by the Italian Society of Oral Pathology and Medicine (SIPMO) on preventive dental management in patients at risk of MRONJ, prior to and during/after the administration of the aforementioned ONJ-related drugs. In reducing the risk of MRONJ, dentists and oral hygienists are key figures in applying a correct protocol of primary prevention for pre-treatment and in-treatment patients. However, the necessity of a multidisciplinary standardized approach, with a sustained dialogue among specialists involved, should be always adopted in order to improve the efficacy of preventive strategies and to ameliorate the patient's quality of life.

## 1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a relatively rare but potentially serious and debilitating complication. It consists of progressive bone destruction in the maxillofacial area of patients exposed to the treatment with drugs associated with the risk of ONJ, in the absence of a previous radiation treatment [1–4]. The diagnosis of MRONJ is based on the patient's pathological and pharmacological history and on the clinical and radiological features of progressive bone destruction (both exposed and not exposed) [1, 5].

MRONJ epidemiology and pathogenesis are still unclear; however, in recent years, notable progress has been made regarding the prevention of MRONJ by studying local risk factors (e.g., presence of infective, dental-periodontal, and/or peri-implant disease) in patients at risk of MRONJ and by planning dental procedures [1, 5–9].

Primary prevention, whose main aim is the elimination of oral and dental risk factors, is targeted at restoring and/or maintaining good oral health and reducing the risk of an onset of pathological conditions or any other negative event. This approach has the greatest impact when aimed at protecting constantly the patient's oral health, which is at risk of MR ONJ by virtue of controlling local related risk factors [6, 9].

Subsequent to the initial reporting of MRONJ, fifteen years ago, attention has been focused on the association

between dental extraction and adverse event in patients who were already being treated with ONJ-related drugs [10–12]. More recently, the presence of infection at dental-periodontal and peri-implant locations has been underlined as being one of the main local risk factors of developing MRONJ, often being the main reason of surgical procedures of dental extraction or implant removal [1, 5, 13]. The link between periodontal disease and the development of MRONJ has been widely demonstrated, and the spreading of bacteria via the periodontal pockets is one of the main mechanisms for transmitting infection throughout the alveolar bone. Indeed, it is not only the presence of *Porphyromonas gingivalis* in the periodontal pockets but also IgG products which probably promote the development of MRONJ. The concurrent action of *P. gingivalis* and IgG products would appear to increase bone remodeling and contemporaneously produce pro-inflammatory effects, thereby reducing the healing process of periodontal tissue and encouraging the development of MRONJ. Therefore, a severe periodontitis will be determinant for a poor prognosis for the teeth, for whom the only resolution is extraction; the latter has already been discussed as a further trigger for the developing of MRONJ [1, 7, 8, 14–19].

Many studies have demonstrated how, prior to commencing treatment with ONJ-related drugs, dental screening and treatments of oral diseases can significantly reduce the occurrence of this adverse event [9, 20–22]. Already in 2009, Dimopoulos et al. underlined the importance of dental management in patients eligible for treatment with ONJ-related drugs; this primary preventive measure subsequently produced a reduction by one-third of the incidence of MRONJ in the enrolled patients [20]. Similar results have also been obtained from other research groups, which highlighted the crucial role played by the physician and the dentist in the primary prevention [9, 21–23]. It is the responsibility of the physician to provide all relevant information regarding the risk of developing MRONJ for patients who are about to commence treatment with antiresorptive (AR) and/or antiangiogenic (AA) drugs. Moreover, it is also the physicians' duty to advise the patients about the relevance of an examination by an oral health specialist with the aim of assessing the necessity for preventive dental management. This should be performed prior to commencing, during and also after the treatment with ONJ-related drugs, in order to eliminate any infective outbreaks of MRONJ [14, 24, 25]. It is the responsibility of the dentist to accurately assess risk factors leading to the development of MRONJ and suggest a strategy for removing these factors. The dentist must also stress the importance of maintaining effective dental hygiene, including regular check-ups, for the patient. Both are necessary for maintaining oral health, reducing the outbreak of MRONJ, and/or detecting possible signs of the early symptoms of this disease.

## 2. Variables of Patients at Risk of MRONJ

When planning primary prevention measures, every specialist assigned to the care and maintenance of oral health must bear in mind three variables related to the assessment of the risk of MRONJ.

*2.1. The Activity of ONJ-Related Drugs: Antiresorptive and Antiangiogenic Drugs.* Drugs involved in the etiopathogenesis of MRONJ belong basically to two main categories: those with a mainly antiresorptive property and those with mainly antiangiogenic property. The AR drugs includes the following:

(a) Bisphosphonates (BPs), synthetic analogues of pyrophosphates, which firmly bind to the hydroxyapatite and reduce bone metabolism/remodeling. They are long half-life medications, which constitute a determining variable for their residual power in a "non-active" form in bone tissue after treatment has been interrupted. Indeed, the half-life of BPs in circulation is quite short, ranging from 30 minutes to 2 hours; however, once they have been incorporated into bone tissue, they can persist more than 10 years, depending on the skeletal turnover time [25].

(b) Denosumab, a monoclonal human IgG2 antibody that highly binds the *receptor activator of nuclear factor-kB ligand* (RANK-L), blocks the osteoclast maturation, function, and survival. It has a half-life of 25–32 days [26, 27].

Of the drugs related to a risk of MRONJ with a main AA activity, the most common are Vascular Endothelial Growth Factor (VEGF) inhibitors (e.g., Bevacizumab), tyrosine-kinase inhibitors (TKIs) (e.g., Sunitinib), and the mammalian target of Rapamycin (mTOR) inhibitors (e.g., Everolimus) [3]. AA drugs are generally indicated only for the treatment of oncological pathologies, by inhibiting the various mechanisms involved in tumour neoangiogenesis. Moreover, as is the case with Denosumab, these drugs do not tend to accumulate in the bone, and they have a well-known half-life, which varies on the basis of the molecule (from 30 hours for Everolimus to 20 days for Bevacizumab) [3].

*2.2. The Categories of Patients at Risk: Cancer or Non-cancer.* On the basis of epidemiological data regarding the onset of MRONJ, the risk is greater for cancer patients, who are probably contemporaneously exposed to a high number of MRONJ risk factors [1, 5, 13]. Indeed, there is a frequency of adverse event between 0.2% and 6.7% in cancer patients exposed to ONJ-related drugs, while the risk of developing MRONJ in patients affected by osteometabolic diseases, such as osteoporosis, is very low, with a prevalence between 0% and 0.4% [5]. However, due to the huge number of patients in the world affected by osteometabolic diseases, in terms of frequency, approximately 40% of patients affected by MRONJ are non-cancer patients [28].

*2.3. Typologies and Timing of Dental Treatments .* The primary purpose of preventive dental approach is the detection and management of local risk factors related to MRONJ (Table 1). Due to the risk/benefit ratio of dental procedures and the risk of MRONJ, it is useful to distinguish three typologies of dental treatments: (i) *indicated*, which are necessary to prevent the risk of MRONJ; (ii) *possible*, which are considered irrelevant in regard to the risk of MRONJ; (iii)

*contraindicated*, which are associated with a recognized risk of MRONJ.

This distinction will be better detailed in the following paragraphs also with respect to patients' categories (cancer versus non-cancer patients) and to ONJ-related drugs exposure time. About the timing of dental procedures, patients can be divided into two categories:

If the patient has never taken ONJ-related drugs, also called in the pre-treatment phase, the patient's oral health must be precisely assessed by clinical and radiographic examinations (mandatory for cancer patients), in order to evaluate the patient's dental-periodontal status and to plane the adequate dental therapies compatible with systemic diseases and the oncologist/physician's opinion.

If the patient has already been exposed to ONJ-related drugs, hereafter defined as the in-treatment phase, this patient will be included in an assessment program of oral health, the aim of which is to obtain and maintain as low as possible the level of local risk factors for MRONJ.

It will be necessary to continually remind the patient of the necessity both of maintaining effective oral hygiene at home, via counselling strategies, and of monitoring early clinical signs or symptoms of MRONJ. Dental procedures for the patient (both cancer and non-cancer) in pre-treatment and in-treatment phases will now be discussed in order to enhance our understanding of this topic. Moreover, invasive and non-invasive dental procedures will be also differentiated on the basis of above mentioned distinction (*indicated, possible, contraindicated*) (see Tables 2 and 3). Of great assistance in this regard is the use of leaflets, such as those which can be downloaded from https://www.unipa.it/dipartimenti/di.chir.on.s./.content/documenti/ONJ-Leaflet-_SIPMO-by-Di-Fede-Campisi20-02-17.pdf. Additionally, the app DoctOral® provides an open-access consultation of guided paths and recommendations regarding the dental management of patients at risk of MRONJ; it is free available both for android (https://play.google.com/store/apps/details?id=com.olgadifede.olgapp&hl=it) and iOS system (https://itunes.apple.com/us/app/doctoral/id1071070334?l=it&ls=1&mt=8) [29].

Table 1: Oral risk factors of MRONJ [1].

| |
|---|
| *Oral risk factors* |
| (i) Dental/periodontal infection |
| (ii) Peri-implantitis |
| (iii) Unfitting removable denture |
| *Oral surgeries* |
| (i) Dental extraction |
| (ii) Dental implant surgery |
| (iii) Endodontic surgery |
| (iv) Periodontal surgery |
| (v) Regenerative bone procedures |
| *Anatomical conditions* |
| (i) Torus and exostosis |
| (ii) Pronounced mylohyoid ridge |

## 3. Cancer Patients in the Pre-treatment Phase

In the pre-treatment phase, cancer patients with good oral health must be informed and made aware of the risks inherent of MRONJ and the necessity of being enrolled onto a program with a 4-month follow-up, in order to monitor the status of the hard and soft tissues. Moreover, the patient should be encouraged to follow specific measures regarding secondary prevention (early recognition of the disease) and be informed about oral hygiene at home via counselling.

In cancer patients with tooth with poor or hopeless prognosis or other dental-periodontal infection, it would be desirable to defer the commencing of ONJ-related drugs after the tissue involved in any invasive dental treatment has healed. This includes at least the healing period of the soft tissue, which is usually approximately 45–60 days, prior to commencing AR/AA cancer treatment. For all other non-invasive dental procedures whose outcome is reliable, it is not necessary to defer cancer treatment. If cancer treatment cannot be delayed and invasive dental procedures are needed, it will be necessary to consider the patient as already being in treatment phase. Thereafter, the protocols of medical and surgical prophylaxis must be applied (see Section 5) [14, 25].

In greater detail, dentoalveolar surgeries are considered to be *indicated* invasive dental procedures; it would be convenient to reduce to a minimum any bone manipulation and encourage primary intention healing.

Other invasive procedures (e.g., implant surgery, pre-implant bone surgery, and mucogingival surgery) are *contraindicated*, since these are not aimed at the elimination of infection and they have often a rehabilitation/aesthetic aim; moreover, anyway these procedures will have an undefined long-term risk of developing MRONJ after the administration of ONJ-related drugs [14, 25, 26]. Dental treatments in cancer patients in the pre-treatment phase are described in Table 2.

## 4. Non-cancer Patients in the Pre-treatment Phase

Similarly, in this group of patients the primary objective is to maintain and/or reestablish as soon as possible an acceptable level of oral health, possibly before the administration of AR drugs or within its first six months [14]. If the patient presents with good oral health, it is beneficial to plan a six-month follow-up examination in order to maintain the primary prevention program.

In general, in a given non-cancer patient in the pre-treatment phase, surgical and non-surgical dental procedures are classified as *indicated* if regarding the treatment of infective conditions (e.g., dental-alveolar surgery, surgical and non-surgical endodontics, and surgical and non-surgical periodontics). All elective procedures (e.g., prosthetic rehabilitation with/without dental implant, or orthodontic treatment) are classified as *possible* with unknown or indefinable low risk of MRONJ. Dental treatments in non-cancer patients in the pre-treatment phase are described in Table 2.

Table 2: Main dental treatments with respect to patients' categories in the pre-treatment phase with drugs related to ONJ.

| Dental procedures on patients in the pre-treatment phase | Cancer patients | Non-cancer patients |
|---|---|---|
| Non-Surgical Procedures | | |
| Restorative dentistry | Indicated | Indicated |
| Endodontic treatment | Indicated | Indicated |
| Orthodontic treatment | Possible | Possible |
| Periodontal treatments: oral hygiene and non-surgical treatments | Indicated | Indicated |
| Prosthesis | Possible | Possible |
| Surgical Procedures | | |
| Dentoalveolar surgery | Indicated* | Indicated |
| Preimplant bone surgery | Contraindicated | Possible★ |
| Dental implant surgery | Contraindicated | Possible★ |
| Periodontal/endodontic surgery | Indicated§ | Indicated§ |

*Advisable to wait for wound healing (4–6 weeks) before initiating antiresorptive or antiangiogenic treatment for cancer therapy. When treatment with ONJ-related drugs cannot be deferred, dentoalveolar surgery is indicated; in this case, the surgical protocol and medical treatment of oncological patients already in-treatment with MRONJ-related drugs will also be performed. §To Perform only if any infective processes cannot be treated via periodontal/endodontic, non-invasive treatment. ★Advise the patient that the risk of MRONJ is indefinable in the long term.

Table 3: Main dental treatments in patients in-treatment phase with drugs related to ONJ.

| Dental procedures on patients in-treatment phase | Cancer patients | Non-cancer patients | |
|---|---|---|---|
| | | Category A | Category B |
| Non-Surgical Procedures | | | |
| Restorative dentistry | Indicated | Indicated | Indicated |
| Endodontic treatment | Indicated | Indicated | Indicated |
| Orthodontic treatment | Possible | Possible | Possible |
| Periodontal treatments: oral hygiene and non-surgical treatments | Indicated (every 4 months) | Indicated | Indicated |
| Prosthesis | Possible | Possible | Possible |
| Surgical Procedures | | | |
| Dentoalveolar surgery | Indicated | Indicated | Indicated |
| Preimplant bone surgery | Contraindicated | Possible☆ | Possible*☆★ |
| Dental implant surgery | Contraindicated | Possible☆ | Possible*☆★ |
| Periodontal/endodontic surgery | Indicated§ | Indicated | Indicated§ |

°Follow the surgical protocol + adapt the flaps, avoid of tension and suture in order to prioritize healing of the wound. §Perform only if any infective processes cannot be treated with non-invasive periodontal/endodontic procedures. ☆Advise the patient of an indefinable risk of MRONJ in the long term. ★Advise the patient of an indefinable risk of MRONJ in the short term.

## 5. Cancer Patients in Treatment Phase

From the first assumption of ONJ-related drugs for treating cancer, the patient is considered to be at a high risk of developing MRONJ [1, 5, 13, 14, 25, 27]. This is due to the contemporaneous presence of known, multiple risk factors.

Surgical procedures which are necessary for eliminating infective outbreaks of MRONJ are defined as *indicated* for cancer patients in-treatment in presence of dental diseases which cannot otherwise be resolved [1, 14].

The protocol regarding the dental extractions in cancer patients at risk of MRONJ promoted by the Italian Society of Oral and Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO) combines a medical prophylaxis with strictly surgical procedures. An example of a standardized protocol for dental extractions expects a medical prophylaxis that includes a 0.12% chlorhexidine (CHX) antiseptic mouthwash to be used at home 3 times a day, starting from 7 days prior to the planned dental procedure, associated with an antibiotic therapy (e.g., Ampicillin/Sulbactam im and Metronidazole per os) that must be administered from the day before the intervention and for at least 6 days following intervention. During the surgical procedures, it is advisable to use local anesthesia without adrenaline, to perform a full thickness flap, to gently remove the tooth, to do the alveoloplasty of the postextraction site (if necessary), and to apply a tension-free soft tissue closure, to promote the healing by first intention[26]. Moreover,

the use of ultrasound surgical equipment is preferable for bone manipulation, even if, currently, conventional dental instruments do not seem to increase the risk of MRONJ, notwithstanding their more invasive nature [14, 30, 31].

The post-operative medical therapy will be accompanied by a topical one, CHX mouthwash (3 times a day for 15 days), and growth-promoting treatment, as gel containing hyaluronic acid (three times per day for 15 days) [14, 26]. Sutures can be removed between the seventh and tenth day after intervention. Thereafter, periodic clinical check-up should continue with an accurate time schedule (at 3, 6, and 12 months) during the first year of follow-up.

When several dental extractions are necessary, it would be desirable to proceed one tooth at a time, particularly when ONJ-related drugs have not been suspended. Recently, surgical proposals have been considered, which also deploy a low-level, Nd:YAG laser and/or autologous platelet concentrates (APCs) [32, 33]. The application of APCs [34] with enhanced stability (e.g., plasma rich in growth factor (PRGF) and leucocyte-platelet-rich fibrin (L-PRF)) is yielding promising results in reducing the incidence of MRONJ following a dental extraction, thereby reducing the operating time and the extent of necessary surgery mucocele [34, 35].

When inflammatory-infective processes may be treated with periodontal and/or endodontic surgical procedures, the clinician should apply the same recommendations regarding dental extractions, and this also concerns medical prophylaxis and minimum bone manipulation [14].

The risk of developing MRONJ in in-treatment cancer patient undergoing dental implants is not only in the long term but it particularly increases in the short term. Therefore, dental implants are *contraindicated*, given the high degree of bone manipulation which is necessary for positioning the implant fixtures. Moreover, it can be added that the systemic health condition of a cancer patient could facilitate the rapid onset of a peri-implantitis, an additional great risk factor of MRONJ. Up to date, there are no published studies regarding the execution of pre-implant surgical treatment (e.g., guided bone regeneration) on in-treatment cancer patients. Notwithstanding a note of caution, it is the opinion of the authors that procedures relating to pre-implant treatment should be avoided in these patients, as well as the dental implant placement [1, 5, 14, 36].

All non-invasive dental treatments (e.g., restorative ) are not only considered as *indicated* but also of the utmost importance in reducing the spreading of infective processes [14, 37]. Notwithstanding this, some simple precautions prior to and during the dental examination should be taken: provide an antiseptic mouthwash to reduce the bacterial load in the oral cavity; do not use vasoconstricting anaesthetic; always work in isolation using a rubber dam, paying attention to the correct position of the clamps of the dam to avoid trauma to the oral mucosa. Moreover, during endodontic treatments, it is essential to avoid exceeding the limits of the root canal with endodontic instruments and root canal filling material [37].

As a non-invasive dental treatment, orthodontics is classified as an elective treatment and it is thus considered a *possible*, in absence of MRONJ cases published related to it. However, it has been suggested that orthodontic movements, which cause an increase in alveolar bone remodeling, in the cancer patients in-treatment may encourage the accumulation of drugs in the jawbone [38–40]. However, it must be underlined that cancer patient being treated with ONJ-related drugs will rarely request orthodontic treatment [14, 16, 39, 40].

Non-surgical periodontal therapy is strongly *indicated* and it should be carefully planned in order to remove regularly plaque and calculus and also periodically revise the oral health status of patient in-treatments [14–19, 25–27, 30–52]. Thus, it is essential to programme a four-month follow-up period for cancer patients in-treatment, without underestimating the contribution of the patient to the maintaining of effective oral hygiene at home and the self-screening of MRONJ[1, 4, 6, 14].

Dental prostheses in cancer patients in-treatment are *possible;* notwithstanding that nowadays there are few recommendations relating to this matter. Regarding the removable dentures, it is fundamental to reduce the pressure of the prosthesis on the oral mucosa and to maximize the stability, in order to avoid possible chronical trauma of oral mucosa [25, 53–56]. A four-month check-up period is desirable in cancer patients with removable dental prostheses, the aim of which is to constantly assess the fitting of the dentures and the absence of any area of compression and/or pressure ulcer, performing possible relining in soft resin, if needed [53–56]. Moreover, it is advisable that patients should not wear their dentures for approximately 8–12 hours per day (at least during the night).

Regarding the fixed prosthesis, it is important to pay particular attention to the biological width, avoiding the invasion of the junctional epithelium. Compatibly with the aesthetic needs of the patient, it would be ideal to provide a supragingival prosthetic margin, in order to facilitate check-ups and oral hygiene at home [57]. Dental treatments in cancer patients in the treatment phase are described in Table 3.

## 6. Non-cancer Patients in Treatment Phase

The dental management of a non-cancer patient already exposed to ONJ-related drugs is rather complex since it correlates with assessing risk according to variable gradients. These range from an undefined risk of MRONJ to a high risk of developing MRONJ. Indeed, the specific risk of MRONJ in the non-cancer patient varies according to the risk factors present; coexistence of more drug-related, systemic, and/or local risk factors is linked to various risk levels of MRONJ [14, 58].

Non-cancer patients are supposed to be divided into two categories regarding their risk to develop MRONJ; thereafter, from 6 months to within 3 years from the commencing of treatment, the patient who does not report other risk factors (systemic and/or local) will be classified in Category A and considered as a pre-treatment non-cancer patient at low risk of MRONJ.

Different in nature and variable is the assessment performed if the non-cancer patient has been in treatment for a period of time greater than 3 years or shorter than 3

years and simultaneously affected by systemic or local risk factors (Category B) (see Table 5); this patient will bear an incremental and indefinable risk of developing MRONJ, which is linked to one or more additional, reported systemic or local risk factors (see Table 6) [14, 17].

Surgical treatments (e.g., dental extractions, periodontal or endodontic surgery) aimed at removing infective outbreaks and the recovery of good oral health for Categories A and B are *indicated* procedures [14]. These procedures can be performed for non-cancer patients in-treatment in Category A, without applying specific medical and surgical protocols [59]. However, it will be necessary to use precautions with non-cancer patients in-treatment with Category B; these are similar to those described for the cancer patient in-treatment. For this reason, in patients in Category B, it is desirable to perform invasive treatments in combination with a prophylactic antibiotic therapy and to proceed tooth by tooth, particularly when the ONJ-related drug has not been suspended. Moreover, if available, it seems effective in applying low-level laser therapy (e.g., laser Nd:YAG) and APCs at the extraction site [32, 33]. After removing the sutures, it is of the utmost importance to perform periodic clinical-radiographic check-up (after 1, 3, 6, and 12 months) [25].

Elective invasive dental procedures, such as implantology and pre-implant bone surgery, in non-cancer patients in-treatment are not considered explicitly *contraindicated* but *possible* procedures, both for Categories A and B [60, 61]. Indeed, the risk/benefit ratio must be conscientiously assessed with the patient, who will be informed of the not definable risk of MRONJ: in the long term (e.g., risk of peri-implantitis) for Category A patients and in the long and short term (e.g., MRONJ related to the surgical procedures) for Category B. However, alternative treatment would be advised for patients included in Category B.

Promising results regarding the use of APCs during a surgical implant procedure have recently been reported for preventing MRONJ in non-cancer osteometabolic patients in-treatment by Mozzati et al., who have reported the absence of the development of MRONJ in a retrospective study one year after placing 1,267 implant placements on 235 patients, combined with the use of APCs [62].

As for cancer patients in-treatment, invasive and non-invasive dental treatments needed for the treatment of the prevention or the removal of inflammatory or infective lesions are mandatory in non-cancer patients in-treatments; in addition, prosthetic rehabilitation should contemplate the same recommendations [14, 25, 53–57].

Dental treatments of non-cancer patients in the in-treatment phase are described in Table 3.

## 7. Drug Suspension/Holiday

Regarding the latter, there has been much discussion in the literature about the validity of a temporary suspension of ONJ-related drugs; the aim of this biological window is to reduce the risk of an adverse event prior to surgical dental procedure. The temporary suspension of the ONJ-related drugs, the so-called drug holiday, must be compatible with basic pathologies and authorized by the prescriber. Such a suspension, when permitted, would be terminated preferably once the soft tissue had healed. Up to date, there is no scientific evidence which confirms the validity of the drug holiday, whether the drug/s are administered intravenously or orally, prior to the dental-alveolar surgery [1, 2, 5, 6, 14]. Specifically, the effects of BPs on the bone can be much prolonged over time, even after a single administration. The half-life of BPs is rather long, and they function by inhibiting osteoclast function for an unknown period of time. It can be hypothesized that suspending treatment could be associated with a reduction in the antiangiogenic effect of BPs on the periosteum and soft tissue [17, 63, 64]. This could contribute to vascularization improvement and encourage more rapid healing after surgery. Moreover, it could be useful in reducing the concentration of intravenous BPs at the extraction site in cancer patients, where their accumulation would increase tropism where there is extensive bone remodeling. Furthermore, about cancer patients in-treatment, any drug holiday should be considered to be a risky practice due to the possible progression of the oncological pathology and the absence of checking for bone-related events. In cancer patients in-treatment with different drugs by BP, suspending those is a desirable event. This will probably start from 7 days prior to any planned intervention (except for the Bevacizumab that should be suspended 6-7 weeks before), at least until the mucosal healing of the post-extraction site (see Table 4).The differing time periods are due to the fact that the well-known half-life of various MRONJ-related drugs is different. It is the experience of the authors that for the non-cancer patient included in category B, a drug holiday can already be considered useful one week before invasive dental procedures. However, this suspension is possible in cases where significant bone disequilibrium has not resulted, as assessed by the physician. BPs administration can resume 30–45 days after suspension, when the mucosa at the surgical site has healed (see Table 6). An interruption in BPs administration even months prior to surgery is suggested, where the systemic conditions of the patient permit this, and treatment is to be resumed after the total closing of any surgical wound. This approach, however, is based purely on expert opinion and it has not been yet validated in the literature. Since the beneficial effects of BPs in controlling basic diseases and related complications are well-known and while doubt remains regarding a BPs suspension, the patient must always be informed about the low predictability of such a suspension effect and the possible risks connected to the exacerbation of metabolic bone compensation. No drug suspension is necessary for the non-cancer osteometabolic patient in-treatment with Denosumab, given the latency period between subsequent Denosumab administrations, namely, every 6 months. It is appropriate to perform invasive procedures after 4 weeks from the last Denosumab administration and no later than the 6 weeks before the next administration, so as to ensure an adequate healing period. Should it be necessary to perform invasive procedures in a different time frame, it is advisable that these are planned within and not more than 45 days from subsequent administrations of Denosumab [6, 14, 52].

Table 4: Drug suspension for cancer patients; it must be agreed upon with the oncologist and performed according to the table.

| Drug holiday in cancer patients | | |
|---|---|---|
| Active pharmaceutical ingredient | Last administration | Resume treatment |
| Bisphosphonate (AR) | At least 1 week before | 4–6 weeks after |
| Denosumab (AR) | At least 1 week before | 4–6 weeks after |
| Bevacizumab (AA) | At least 6-7 weeks before | 4–6 weeks after |
| Sunitinib (AA) | At least 1 week before | 4–6 weeks after |
| Everolimus (AA) | At least 1 week before | 4–6 weeks after |

Table 5: A classification of non-cancer patients already in treatment with MRONJ-related drugs.

| Risk assessment of MRONJ in non-cancer patients | |
|---|---|
| Category A | Category B |
| (i) Patients eligible and not yet treated with ONJ-related medication<br>(ii) Patients exposed to ONJ-related medication for less than 3 years, in absence of other systemic risk factors | (i) Patients exposed to ONJ-related medication for more than 3 years<br>(ii) Patients exposed to ONJ-related medication for less than 3 years and in presence of other systemic risk factors<br>(iii) Patients assuming BPs by IM* |

*To date, there exists no data to distinguish groups of patients in treatment with zoledronate intravenous (annual medication intake) at greater or lesser risk of developing MRONJ.

Table 6: Drug suspension for non-cancer patients; it must be agreed upon with the prescriber and performed according to the table.

| Drug holiday in non-cancer patients | | |
|---|---|---|
| Active pharmaceutical ingredient | Last administration | Therapy resumption |
| Bisphosphonate* (AR) | 1 week before | 4–6 weeks after |
| Denosumab (AR) | No suspension** | |

*Administered by more than three years or for less than three years and in the presence of other systemic risk factors; **suspension is not needed thanks to the latency between drug administrations. It is useful to perform invasive procedures between the first and the third month from the last administration, so as to ensure an adequate period for healing before the next dose.

## 8. Conclusion

MRONJ is a rare but serious and highly debilitating disease since it can significantly compromise the patient's quality of life and reduce the compliance of the patients to AR/AA treatments. The number of cancer and non-cancer patients being treated with ONJ-related drugs and, therefore, the number of potentially adverse events seem constantly on the increase, also on the light of new drug related to ONJ. A multidisciplinary standardized approach with a sustained dialogue among clinicians involved in the treatment of patients at risk of MRONJ should be adopted in order to improve the efficacy of therapeutic strategies and to increase the patient's quality of life. The important role of the dentist in preventing the MRONJ, checking the local risk factors of MRONJ in pretreatment and in-treatment patients, is evident.

Moreover, it is necessary to intervene in possible early signs of MRONJ for the secondary prevention. The application of such protocols of primary and secondary prevention, together with the dentists actions, the clinicians' sinergy, and the adequate awareness of the patient, is the key to implementing policies aimed at a common goal, that is, the reduction in outbreaks of MRONJ.

## Disclosure

Authors ODF, VP, RM, VF, AB, LLM, and GC are members of SIPMO ONJ Board.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Olga Di Fede and Vera Panzarella contributed equally to this work.

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## References


[1] G. Campisi, S. Fedele, V. Fusco, G. Pizzo, O. Di Fede, and A. Bedogni, "Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents," *Future Oncology*, vol. 10, no. 2, pp. 257–275, 2014.

[2] A. Bedogni, V. Fusco, A. Agrillo, and G. Campisi, "Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ)," *Oral Diseases*, vol. 18, no. 6, pp. 621–623, 2012.

[3] V. Fusco, D. Santini, G. Armento, G. Tonini, and G. Campisi, "Osteonecrosis of jaw beyond antiresorptive (bone-targeted) agents: new horizons in oncology," *Expert Opinion on Drug Safety*, vol. 15, no. 7, pp. 925–935, 2016.

[4] V. Fusco, A. Bedogni, A. Addeo, and G. Campisi, "Definition and estimation of osteonecrosis of jaw (ONJ), and optimal duration of antiresorptive treatment in bone metastatic cancer patients: supplementary data from the denosumab extension study?" *Supportive Care in Cancer*, vol. 25, no. 2, pp. 345–349, 2017.

[5] S. L. Ruggiero, T. B. Dodson, and J. Fantasia, "American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update," *Journal of Oral and Maxillofacial Surgery*, vol. 72, no. 10, pp. 1938–1956, 2014.

[6] R. H. Goodday, "Preventive Strategies for Patients at Risk of Medication-related Osteonecrosis of the Jaw," *Oral and Maxillofacial Surgery Clinics of North America*, vol. 27, no. 4, pp. 527–536, 2015.

[7] K. Mcgowan, T. Mcgowan, and S. Ivanovski, "Risk factors for medication-related osteonecrosis of the jaws: A systematic review," *Oral Diseases*, 2017.

[8] A. Muthukrishnan, S. Al-Ismail, G. Bertelli, and P. Browne, "MRONJ risk reduction pathway - 360 degree survey," *British Dental Journal*, vol. 222, no. 5, pp. 386–390, 2017.

[9] A. M. Vandone, M. Donadio, M. Mozzati et al., "Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience," *Annals of Oncology*, vol. 23, no. 1, pp. 193–200, 2011.

[10] R. E. Marx, "Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic," *Journal of Oral and Maxillofacial Surgery*, vol. 61, no. 9, pp. 1115–1117, 2003.

[11] A. N. Chaudhry and S. L. Ruggiero, "Osteonecrosis and Bisphosphonates in Oral and Maxillofacial Surgery," *Oral and Maxillofacial Surgery Clinics of North America*, vol. 19, no. 2, pp. 199–206, 2007.

[12] S. L. Ruggiero and B. Mehrotra, "Bisphosphonate-related osteonecrosis of the jaw: diagnosis, prevention, and management," *Annual Review of Medicine*, vol. 60, pp. 85–96, 2009.

[13] A. Khan, A. Morrison, S. Ruggiero et al., "Response to Comments on "Diagnosis and Management of Osteoporosis of the Jaw: A Systematic Review and International Consensus"," *Journal of Bone and Mineral Research*, vol. 30, no. 6, pp. 1116-1117, 2015.

[14] A. Bedogni, G. Campisi, V. Fusco, and A. Agrillo, "Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione," *SICMF - SIPMO*, 2013, http://www.sipmo.it/wp-content/uploads/2014/07/RaccomandazioniPrevenzCuraOsteonecrosiMascellari.pdf.

[15] C. Tsao, I. Darby, and PR. Ebeling, "Oral health risk factors for bisphosphonate-related jaw osteonecrosis," *Journal of Oral and Maxillofacial Surgery*, vol. 71, no. 8, pp. 1360–1366, 2013.

[16] J. W. Hellstein, R. A. Adler, B. Edwards et al., "Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs," *The Journal of the American Dental Association*, vol. 142, no. 11, pp. 1243–1251, 2011.

[17] G. L. Borromeo, C. E. Tsao, I. B. Darby, and P. R. Ebeling, "A review of the clinical implications of bisphosphonates in dentistry," *Australian Dental Journal*, vol. 56, no. 1, pp. 2–9, 2011.

[18] M. N. Pemberton, "Osteonecrosis of the jaw. Note on dental procedures.," *BMJ (Clinical research ed.)*, vol. 340, p. c1317, 2010.

[19] D. Rosella, P. Papi, R. Giardino, E. Cicalini, L. Piccoli, and G. Pompa, "Medication-related osteonecrosis of the jaw: Clinical and practical guidelines," *Journal of International Society of Preventive and Community Dentistry*, vol. 6, no. 2, p. 97, 2016.

[20] M. A. Dimopoulos, E. Kastritis, C. Bamia et al., "Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid," *Annals of Oncology*, vol. 20, no. 1, pp. 117–120, 2009.

[21] R. Bonacina, U. Mariani, F. Villa, and A. Villa, "Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: a review of 282 patients.," *Journal of the Canadian Dental Association*, vol. 77, p. b147, 2011.

[22] F. Saad, J. E. Brown, C. Van Poznak 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," *Annals of Oncology*, vol. 23, no. 5, pp. 1341–1347, 2012.

[23] A. Bramati, S. Girelli, G. Farina et al., "Prospective, mono-institutional study of the impact of a systematic prevention program on incidence and outcome of osteonecrosis of the jaw in patients treated with bisphosphonates for bone metastases," *Journal of Bone and Mineral Metabolism*, vol. 33, no. 1, pp. 119–124, 2015.

[24] L. L. Russo, D. Ciavarella, C. Buccelli et al., "Legal liability in bisphosphonate-related osteonecrosis of the jaw," *British Dental Journal*, vol. 217, no. 6, pp. 273–278, 2014.

[25] Ministero della Salute, "Dipartimento della sanità pubblica e dell'innovazione. Raccomandazioni per la promozione della salute orale, la prevenzione delle patologie orali e la terapia odontostomatologica nei pazienti adulti con malattia neoplastica," http://www.salute.gov.it/imgs/C_17_pubblicazioni_2139_allegato.pdf.

[26] PROMaF protocol: Prevention and research on Medication-related Osteonecrosis of the Jaws", 2014, http://www.policlinico.pa.it/portal/pdf/news/2014/PROMaF/PROMaFxOperatoriSanitari-dic2014.pdf.

[27] P. Fung, G. Bedogni, A. Bedogni et al., "Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study," *Oral Diseases*, 2016.

[28] X. Zhang, I. S. Hamadeh, S. Song et al., "Osteonecrosis of the Jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS)," *Journal of Bone and Mineral Research*, vol. 31, no. 2, pp. 336–340, 2016.

[29] Campisi. Giuseppina, *Global Change and the Dentistry. A Whish from Italy and, DoctOral , App for the [DoctOral, thesis]*, 2017.

[30] E. Gaudin, L. Seidel, M. Bacevic, E. Rompen, and F. Lambert, "Occurrence and risk indicators of medication-related

osteonecrosis of the jaw after dental extraction: A systematic review and meta-analysis," *Journal of Clinical Periodontology*, vol. 42, no. 10, pp. 922–932, 2015.

[31] M. J. Heufelder, J. Hendricks, T. Remmerbach, B. Frerich, A. Hemprich, and F. Wilde, "Principles of oral surgery for prevention of bisphosphonate-related osteonecrosis of the jaw," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 117, no. 6, pp. e429–e435, 2014.

[32] P. Vescovi, I. Giovannacci, E. Merigo et al., "Tooth extractions in high-risk patients under bisphosphonate therapy and previously affected with osteonecrosis of the jaws: surgical protocol supported by low-level laser therapy," *The Journal of Craniofacial Surgery*, vol. 26, no. 3, pp. 696–699, 2015.

[33] M. Del Fabbro, G. Gallesio, and M. Mozzati, "Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature," *European Journal of Cancer*, vol. 51, no. 1, pp. 62–74, 2015.

[34] M. Scoletta, V. Arata, P. G. Arduino et al., "Tooth extractions in intravenous bisphosphonate-treated patients: A refined protocol," *Journal of Oral and Maxillofacial Surgery*, vol. 71, no. 6, pp. 994–999, 2013.

[35] R. Mauceri, F. Giancola, and V. Panzarella, "L-PRF application in extraction sockets of bisphosphonate-treated patients: preliminary results. 13th Biennial Congress of the European Association of Oral Medicine, 15-17 September 2016, Torino, Italy," *Oral Diseases*, supplement 5, pp. 5–51, 2016.

[36] I. Giovannacci, M. Meleti, M. Manfredi et al., "Medication-related osteonecrosis of the jaw around dental implants: Implant surgery-triggered or implant presence-triggered osteonecrosis?" *The Journal of Craniofacial Surgery*, vol. 27, no. 3, pp. 697–701, 2016.

[37] A. Moinzadeh, H. Shemesh, N. A. Neirynck, C. Aubert, and P. R. Wesselink, "Bisphosphonates and their clinical implications in endodontic therapy," *International Endodontic Journal*, vol. 46, no. 5, pp. 391–398, 2013.

[38] J. J. Zahrowski, "Bisphosphonate treatment: An orthodontic concern calling for a proactive approach," *American Journal of Orthodontics and Dentofacial Orthopedics*, vol. 131, no. 3, pp. 311–320, 2007.

[39] J. J. Zahrowski, "Optimizing orthodontic treatment in patients taking bisphosphonates for osteoporosis," *American Journal of Orthodontics and Dentofacial Orthopedics*, vol. 135, no. 3, pp. 361–374, 2009.

[40] S. Abela, M. Chotai, and D. Bister, "What you need to know about bisphosphonates: An overview and general recommendations for orthodontic treatment," *Journal of Orthodontics*, vol. 39, no. 3, pp. 186–192, 2012.

[41] G. Saia, S. Blandamura, G. Bettini et al., "Occurrence of Bisphosphonate-Related Osteonecrosis of the Jaw After Surgical Tooth Extraction," *Journal of Oral and Maxillofacial Surgery*, vol. 68, no. 4, pp. 797–804, 2010.

[42] S. Khosla, D. Burr, J. Cauley et al., "Bisphosphonate-associated osteonecrosis of the jaw: Report of a Task Force of the American Society for Bone and Mineral Research," *Journal of Bone and Mineral Research*, vol. 22, no. 10, pp. 1479–1491, 2007.

[43] S. L. Ruggiero, T. B. Dodson, L. A. Assael, R. Landesberg, R. E. Marx, and B. Mehrotra, "American association of oral and maxillofacial surgeons postion paper on bisphosphonate-related osteonecrosis of the jaws," *Journal of Oral and Maxillofacial Surgery*, vol. 67, no. 5, supplement 1, pp. 2–12, 2009.

[44] M. Dickinson, H. M. Prince, S. Kirsa et al., "Osteonecrosis of the jaw complicating bisphosphonate treatment for bone disease in multiple myeloma: An overview with recommendations for prevention and treatment," *Internal Medicine Journal*, vol. 39, no. 5, pp. 304–316, 2009.

[45] G. Lodi, A. Sardella, A. Salis, F. Demarosi, M. Tarozzi, and A. Carrassi, "Tooth Extraction in Patients Taking Intravenous Bisphosphonates: A Preventive Protocol and Case Series," *Journal of Oral and Maxillofacial Surgery*, vol. 68, no. 1, pp. 107–110, 2010.

[46] S. Ferlito, C. Liardo, and S. Puzzo, "Dental extractions in patient treated with intravenous bisphosphonates and risk of osteonecrosis of jaws: presentation of a preventive protocol and case series.," *Minerva stomatologica*, vol. 59, no. 11-12, pp. 593–601, 2010.

[47] M. Quirynen, W. Teughels, and D. Van Steenberghe, "Impact of antiseptics on one-stage, full-mouth disinfection," *Journal of Clinical Periodontology*, vol. 33, no. 1, pp. 49–52, 2006.

[48] M. Scoletta, P. G. Arduino, R. Pol et al., "Initial experience on the outcome of teeth extractions in intravenous bisphosphonate-treated patients: A cautionary report," *Journal of Oral and Maxillofacial Surgery*, vol. 69, no. 2, pp. 456–462, 2011.

[49] M. Mozzati, V. Arata, and G. Gallesio, "Tooth extraction in patients on zoledronic acid therapy," *Oral Oncology*, vol. 48, no. 9, pp. 817–821, 2012.

[50] A. Kyrgidis, A. Arora, and K. Antoniades, "Rubber dam clamp trauma, root canal therapy, and osteonecrosis of the jaw," *Journal of Oral and Maxillofacial Surgery*, vol. 69, no. 7, pp. 1854-1855, 2011.

[51] A. Kyrgidis, A. Arora, K. Lyroudia, and K. Antoniades, "Root canal therapy for the prevention of osteonecrosis of the jaws: An evidence-based clinical update," *Australian Endodontic Journal*, vol. 36, no. 3, pp. 130–133, 2010.

[52] T. Yoneda, H. Hagino, T. Sugimoto et al., "Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw," *Journal of Bone and Mineral Metabolism*, vol. 35, no. 1, pp. 6–19, 2017.

[53] A. Kyrgidis and K. Vahtsevanos, "Increased Risk for Bisphosphonate-Related Osteonecrosis of the Jaws in Patients Wearing Dentures Could be Attributable to Impaired Mucosal Cell Wound Healing," *Journal of Oral and Maxillofacial Surgery*, vol. 67, no. 6, pp. 1355-1356, 2009.

[54] L. Levin, A. Laviv, and D. Schwartz-Arad, "Denture-related osteonecrosis of the maxilla associated with oral bisphosphonate treatment," *The Journal of the American Dental Association*, vol. 138, no. 9, pp. 1218–1220, 2007.

[55] K. Niibe, T. Ouchi, R. Iwasaki, T. Nakagawa, and N. Horie, "Osteonecrosis of the jaw in patients with dental prostheses being treated with bisphosphonates or denosumab," *Journal of Prosthodontic Research*, vol. 59, no. 1, pp. 3–5, 2015.

[56] M. Göllner, S. Holst, M. Fenner, and J. Schmitt, "Prosthodontic treatment of a patient with bisphosphonate-induced osteonecrosis of the jaw using a removable dental prosthesis with a heat-polymerized resilient liner: A clinical report," *Journal of Prosthetic Dentistry*, vol. 103, no. 4, pp. 196–201, 2010.

[57] D. L. Stewart, "Prosthodontic treatment of a patient taking nitrogen-containing bisphosphonates to preserve the integrity of the epithelial attachment: A clinical report," *Journal of Prosthetic Dentistry*, vol. 106, no. 6, pp. 350–354, 2011.

[58] O. Di Fede, A. Bedogni, F. Giancola et al., "BRONJ in patients with rheumatoid arthritis: a multicenter case series," *Oral Diseases*, vol. 22, no. 6, pp. 543–548, 2016.

[59] M. Mozzati, V. Arata, and G. Gallesio, "Tooth extraction in osteoporotic patients taking oral bisphosphonates," *Osteoporosis International*, vol. 24, no. 5, pp. 1707–1712, 2013.

[60] A. Fernández Ayora, F. Herion, E. Rompen, J. Y. Reginster, M. Magremanne, and F. Lambert, "Dramatic osteonecrosis of the jaw associated with oral bisphosphonates, periodontitis, and dental implant removal," *Journal of Clinical Periodontology*, vol. 42, no. 2, pp. 190–195, 2015.

[61] T. Kwon, C. Lee, J. Park, S. Choi, G. Rijal, and H. Shin, "Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment," *Clinical Oral Implants Research*, vol. 25, no. 5, pp. 632–640, 2014.

[62] M. Mozzati, V. Arata, M. Giacomello et al., "Failure Risk Estimates After Dental Implants Placement Associated With Plasma Rich in Growth Factor-Endoret in Osteoporotic Women Under Bisphosphonate Therapy," *The Journal of Craniofacial Surgery*, vol. 26, no. 3, pp. 749–755, 2015.

[63] Y. Kobayashi, T. Hiraga, A. Ueda et al., "Zoledronic acid delays wound healing of the tooth extraction socket, inhibits oral epithelial cell migration, and promotes proliferation and adhesion to hydroxyapatite of oral bacteria, without causing osteonecrosis of the jaw, in mice," *Journal of Bone and Mineral Metabolism*, vol. 28, no. 2, pp. 165–175, 2010.

[64] D. M. J. Milstein, J. A. H. Lindeboom, and C. Ince, "The influence of zoledronic acid and cyclophosphamide on microcirculation regeneration in healing oral mucosal flaps," *Archives of Oral Biolog*, vol. 56, no. 6, pp. 599–606, 2011.

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*Clinical Study*

# Conservative Surgical Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw with Er,Cr:YSGG Laser and Platelet-Rich Plasma: A Longitudinal Study

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*Introduction*. The management of bisphosphonate-related osteonecrosis of the jaw (BRONJ), with no evidence-based guidelines, remains controversial. We aimed to evaluate the efficiency of a conservative surgical treatment combining Er,Cr:YSGG laser and platelet-rich plasma (PRP) for the treatment of BRONJ in cancer patients. *Methods*. We performed a longitudinal cohort study. Inclusion criteria were (1) age ≥ 18 years; (2) cancer diagnosis; (3) treatment with NBP because of the underlying cancer. *Results*. We consecutively recruited ten patients diagnosed with BRONJ in stage I or II. These patients underwent a surgical laser-assisted therapy together with autologous PRP. At the latest follow-up at 12 months, clinical improvement was observed in eight patients. Registration Number is IRCT20180329039159N1. *Conclusion*. We could successfully manage the BRONJ utilizing this combined protocol to heal the 30% of surgically treated sites and to improve the 50% of patients' lesions clinically. Our findings suggest that a surgical approach combined with Er,Cr:YSGG laser and PRP benefit cancer patients with general health issues.

## 1. Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a severe adverse reaction of bisphosphonates (BPs) treatment; it is a relative rare but potentially serious, painful, and debilitating complication that can significantly affect the quality of life of cancer patients [1, 2].

The optimal treatment of BRONJ remains controversial; but the main objectives in the treatment are to control infection, to slow the disease's progression, and to promote tissue healing [1–4].

The BRONJ treatments are classified into surgical and non-surgical options. The non-surgical treatments include the use of systemic antibiotic therapy and oral antiseptic rinses, variably combined with hyperbaric oxygen therapy, low-level laser therapy, and medical ozone applications [5–9]. The surgical treatments proposed in the literature are divided into conservative approaches such as bone debridement, sequestrectomy, or more aggressive therapies such as resections of affected bone and jawbone reconstruction, if indicated [4, 10–12].

In the past, the surgical treatments were reserved only for advanced stages of BRONJ; the Italian Society of Oral and Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO) in 2012 recommended conservative surgery in lesions belonging to stages I and II,

as defined by both societies, that can provide resolution of acute infection and offers long-term of well-being for patients [10, 11, 13–17].

A few clinical studies utilizing Er,Cr:YSGG laser-assisted conservative surgery have showed promising results in BRONJ treatment [6, 10, 15, 18].

Utilizing the Er,Cr:YSGG laser, during the necrotic tissue removal, eliminates thermal effect in cutting areas and surrounding tissues and provides antibacterial and biostimulative effects to reduce post-operative pain and promotes the tissue healing. The laser acts through a cutting effect in a "contact free" way and avoids any friction, which normally delays the healing's process and causes the thermal and mechanical trauma. It applies microfractures and microexplosions to remove the mineralized tissue and vaporize water to allow the rapid removal of the tissue layers that saves bone surface from any contaminations. The Er,Cr:YSGG laser, in particular, owns all these features, allowing a complete healing for both soft and hard tissues [19–23].

Autologous platelet concentrates, such as platelet-rich plasma (PRP), are increasingly applied as a new approach to regenerate tissues in oral surgery as they release high quantities of growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factors (VEGF), and transforming growth factor-b (TGF-b) [24–27]. PDGF plays a role in healing hard and soft tissues by stimulating mitogenesis, chemotaxis, and producing fibronectin. High VEGF in wound sockets improves the formation of bone matrix and stimulates the neoangiogenesis. TGF-b stimulates the fibroblast chemotaxis and produces fibronectin and collagen to repair connective tissues and regenerate bones [28–30]. Indeed, PRP accelerates epithelial wound healing, decreases tissue inflammation, improves the regeneration of bone and soft tissues, and promotes tissue vascularization. Considering these benefits, PRP would be effective in BRONJ patients in the way that releases growth factors and stimulates the bone healing and neoangiogenesis, which is usually suppressed by BPs [26, 31–37]. Moreover, PRP as an autologous product possesses biocompatibility and safety.

This study aimed to evaluate the effect on clinical healing of a combined treatment consisting of laser-assisted surgery and PRP in cancer patients affected by BRONJ.

## 2. Patients and Methods

*2.1. Study Design.* We performed a prospective cohort study on consecutive cancer patients followed at the Unit of Oral Medicine of the University Hospital "P. Giaccone" of Palermo. The Institutional Local Ethics Committee of the University Hospital "P. Giaccone" of Palermo approved the study in 2015.

Technical and surgical procedures were done in accordance with the Declaration of Helsinki revised in 2000. (Table 1). All participants signed the informed consent.

*2.2. Entry and Exclusion Criteria.* BRONJ was defined as exposed or non-exposed osteonecrosis of the mandible or maxilla [2]. Patients were eligible for the study if they had (1) age ≥ 18 years; (2) cancer; (3) treatment with BPs because of the underlying cancer. Patients were excluded from the study if they had (1): previous history of irradiation to the maxillofacial area; (2) neoplastic involvement of the jaws; (3) previous surgical treatment to the jaws; (4) poor general conditions.

Table 1: Technical procedures.

| Step | Procedure |
|---|---|
| **1** | Clinical Evaluation |
| **2** | Computer Tomography (CT) evaluation<br>Lesions' classification following SIPMO-SICMF staging system Scaling (when required) and oral hygiene instructions<br>Pre-operatory medical therapy prescription (Table 2)<br>Platelet rich-plasma (PRP) preparation |
| **3** | Surgical procedure (Figure 1)<br>Er,Cr:YSGG Laser surgery<br>PRP application<br>Flap suture |
| **4** | Suture removal and clinical control |
| **5** | Follow-up visits at 15 days, one month, three, six, twelve months |

We diagnosed BRONJ in all cases through a clinical-radiological approach combining clinical examination and Computed Tomography (CT) of the affected jaws. A radiologist with experience and a special interest in head and neck imaging assessed and reported CT scan, while the local clinical team was in charge of the final diagnosis.

*2.3. Clinical Examination.* At first visit, we collected the clinical, drug, and dental history of patients, which consisted of the following: (1) age; (2) sex; (3) reason for BPs usage; (4) BPs type; (5) duration of BPs treatment; (6) cumulative dose of BPs; (7) concurrent use of steroids; (8) history of chemotherapy; (9) concurrent use of antiangiogenics; (10) concomitant diseases; (11) risk factors for BRONJ (e.g. history of diabetes); (12) clinical features of BRONJ; and (13) patients' habits (e.g. smoking and oral hygiene). We classified lesions following SICMF-SIPMO clinical and radiological staging system of BRONJ [2, 5].

*2.4. Surgical Treatment.* All patients underwent perioperative pharmacological treatment based on the administration of ampicillin and sulbactam (pre-operative regimens: 1g i.m. 2xdaily starting 1 day pre-operatively; post-operative regimens: 1g i.m. 2xdaily for 7 days) and metronidazole (pre-operative regimens: 500 mg per os 3xdaily starting 1 day pre-operatively; post-operative regimens: 500 mg per os 3xdaily for 7 days). The use of antiseptic (chlorhexidine 0,2% mouthwashes 30 ml swished up to 60 seconds, 3x daily 7 days pre-operatively and 15 days post-operatively) and sodium-hyaluronate (local application 3x daily 10 days post-operatively) was also prescribed (Table 2); autologous PRP (Plateltex ACT System, Biomed, Modena, IT) and surgical therapy were then prepared. To prepare the PRP and to induce its gelation, the materials provided by the manufacturer were used and the provided instructions followed [38].

Table 2: Prescribed medical therapy to enrolled patients.

| | Operatory medical therapy |
|---|---|
| **Pre-** | Ampicillin and sulbactam: 1g i.m. 2xdaily starting 1 day before. Metronidazole: 500 mg per os 3x daily starting 1 day before.<br>Chlorexidine 0,2% mouthwashes 30 ml swished up to 60 seconds, 3x daily 7 days before. |
| **Post-** | Ampicillin and sulbactam: 1g i.m. 2xdaily for 7 days. Metronidazole: 500 mg per os 3x daily for 7 days.<br>Chlorhexidine 0,2% mouthwashes 30 ml swished up to 60 seconds, 3x daily 15 days post-operatively.<br>Local application of Sodium-hyaluronate 3xdaily 10 days post-operatively. |

All surgical procedures were performed under local anesthesia using 3% mepivacaine hydrochloride without adrenaline.

The surgical protocol consisted of elevation of a full-thickness mucoperiosteal flap to expose the surgical area; bony curettage (debridement) and sequestrectomy of the necrotic bone, whether required, using a Er,Cr:YSGG laser (Waterlase MD, Biolase Technology, San Clemente, CA, USA); application of autologous PRP; tension-free soft tissue closure (Figure 1).

The Er,Cr:YSGG laser permits photons with wavelength of 2.78 $\mu$m and a pulsed duration of 140-200 microseconds with a repetition rate of 20 Hz. The laser device uses a pulsed energy source; a sapphire MS75 tip (Biolase, Inc.) with a length of 6 mm and diameter of 750 $\mu$m was used with an 80% water and 40% air spray during irradiation. The sapphire tip was positioned 1 to 2 mm from the target tissue and was kept perpendicular to the irradiated bone surface. The power output of the laser can be varied from 0 to 6 W, while the beam spot size at the tip was 1.26·10 3 $mm^2$.

*2.5. Follow-Up.* We scheduled follow-up visits to remove the suture seven days after surgery and visited patients on the fifteenth day, and the visits were continued on months one, three, six, and twelve (Figures 2-3).

We performed Computer Tomography (CT) scans for all patients preoperatively and at the 12-month follow-up ($T_1$) to restage the disease.

*2.6. Main Outcome.* We defined successful treatment as the absence of clinical and radiological signs of BRONJ relapse (healing) or, in turn, the transition from a higher stage to a lower one (improvement).

*2.7. Statistical Analysis.* Statistical units are the patients who satisfy the inclusion criteria of the study. Descriptive statistic was carried out. We summarized continuous variables with means and standard deviations and computed categorical variables frequencies distributions. We analyzed qualitative variables, staging and bone status, and compared them at baseline (T0) and after the treatment (T1). We applied the Wilcoxon signed-rank test with continuity correction for BRONJ staging. We analyzed all data using R software version 3.3.2. A p-value less than 0.05 was considered statistically significant.

## 3. Results

*3.1. Patients' Features.* During the study period, ten cancer patients completed the protocol and were available for the analysis. They were mostly females (70%), with a mean age 75,2 ± 5,94 years. Multiple myeloma was the most common diagnosis (40%), followed by breast (30%) and prostate cancer (30%).

All patients but one had been on monthly infusions of zoledronic acid (mean duration: 31,8 ± 25,76 months); this latter was shifted from zoledronic acid to ibandronic acid during treatment. Two patients (20%) were on systemic corticosteroid therapy and five had been exposed to chemotherapy; only one patient received both steroids and chemotherapy (Table 3).

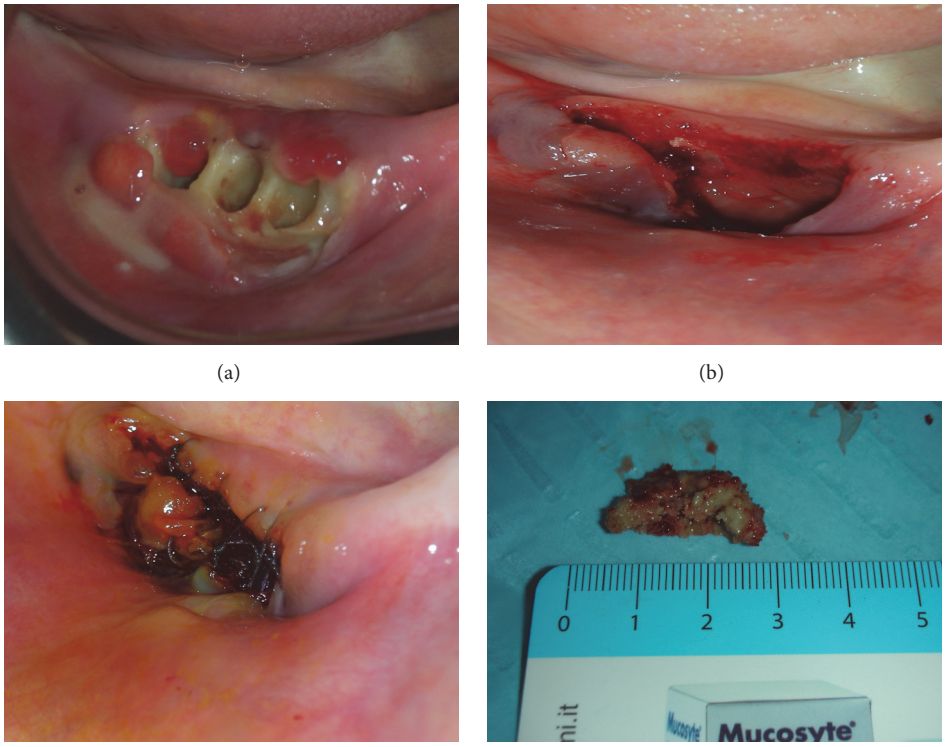
Mandible was the most frequent site of BRONJ (90%). Eight patients showed frank bone exposure at the first visit (80%), while 20% did not and were classified as non-exposed BRONJ cases, based on the presence of oral pain and radiological signs of bone necrosis.

At baseline ($T_0$), six patients were classified in stage IB (60%), two in stage IIA (20%), and the remaining two in stage IIB (20%) (Table 3), according to the SICMF-SIPMO clinical and radiological staging system of BRONJ [2].

*3.2. Main Outcome.* The wound healing was completed at the time of suture removal in 30% of patients. At the latest follow-up period ($T_1$), we observed a clinical improvement in 80% of patients after surgical therapy that was confirmed by Wilcoxon test (p-value = 0.01187). In particular, six patients showed non-exposed bone (60%). Among them, three (30%) had no clinical and radiological signs of BRONJ (complete healing). Five patients showed a clinical improvement of symptoms (50%), while 2 did not show clinical improvement (20%). These latter had been preoperatively classified in stage IIA. Overall, at $T_1$ four patients were in stage IA (40%) and three patients in IIA (30%). Results are shown in Table 4.

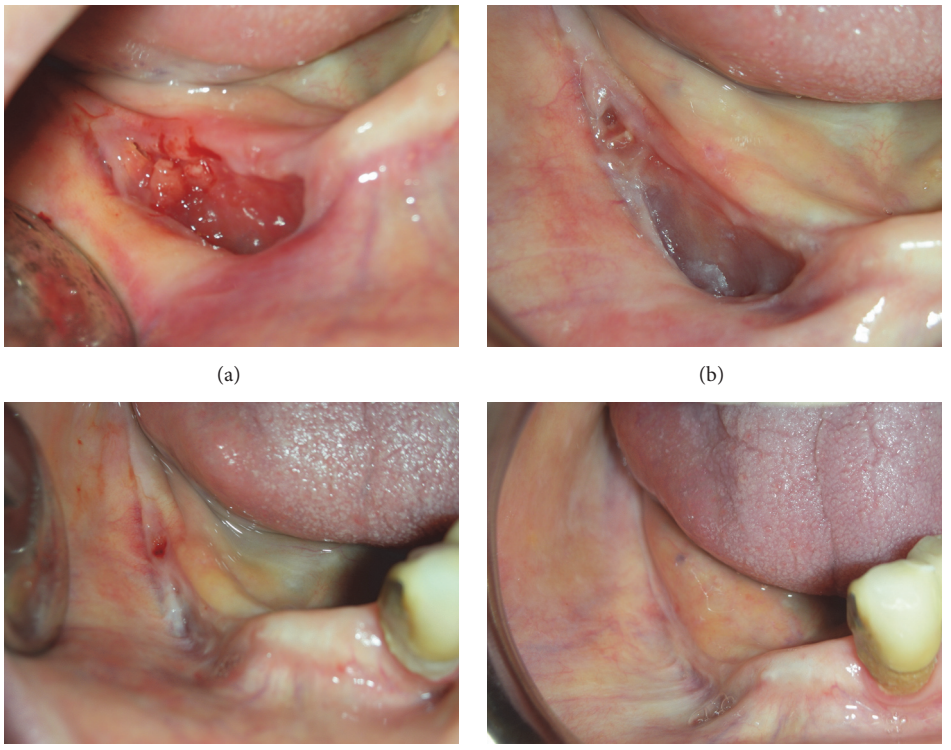
## 4. Discussion

We succeeded to manage BRONJ patients performing the conservative surgery treatment through Er,Cr:YSGG laser combined PRP, both able to enhance the bone and mucosal healing, with a successful outcome of 80% (30% patients with




(a) (b) (c) (d)

Figure 1: (a) Preoperative clinical view; (b) sutures; (c) postoperative view after sequestrectomy procedures; (d) bone fragment.



(a) (b) (c) (d)

Figure 2: (a) Clinical view after 7 days; (b) after 1 month; (c) after 6 months; (d) after 12 months.

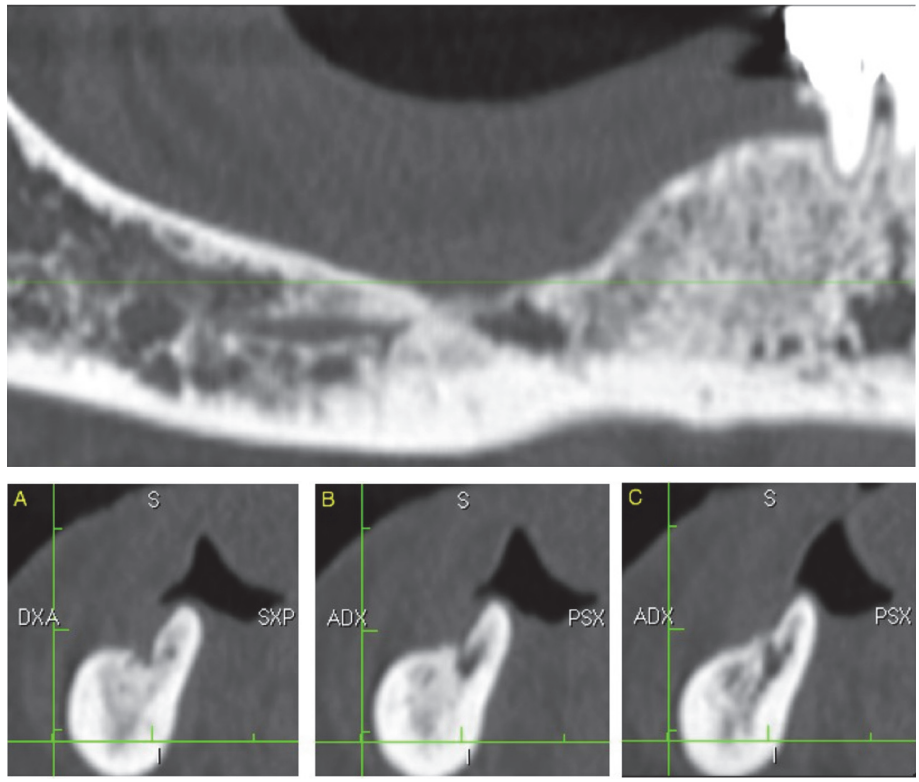



Figure 3: Radiologic outcome at 12 months' follow-up, CT scan slices.

no clinical and radiological signs of BRONJ relapse and 50% with clinical improvement).

The use of laser technology for BRONJ treatment and its beneficial effects on tissue healing has been widely investigated in the last years. Many authors suggested the combination of low-level laser therapy (LLLT) with traditional surgical approach, to biostimulate the tissues healing [6, 39–41].

The use of Er,Cr:YSGG laser has a great potential in the hard tissues surgery; indeed Er,Cr:YSGG laser enables efficient resection of the maxilla without using conventional rotary instruments, as the laser produces a clear and precise cut with minimal injury to contiguous hard and soft tissues [6, 20, 23, 42, 43].

This device showed good results in conservative surgery approach of BRONJ treatment in different stages. Vescovi et al. reported several studies regarding the use of Er:YAG laser to treat BRONJ lesions, showing that Er:YAG seems to represent a high percentage of success, with significantly better results compared with the traditional surgical approaches [15, 39, 44, 45].

Many authors suggested the application of PRP to improve postsurgical wound healing. PRP gel stimulates the release of growth factors and promotes angiogenesis and bone and mucosal healing. In addition, PRP is autologous, biocompatible, and safe product [24–27, 29].

The properties of autologous platelet concentrates appear particularly useful in BRONJ surgical therapy, as the lack of vascularization represents one of the major factors on pathogenesis of BRONJ.

Coviello et al. reported a case series with seven patients taking BPs and affected by BRONJ referable to tooth extraction. They treated four of BRONJ patients by standard surgical debridement and sequestrectomy, while applying supplementary autologous PRP in the three. The authors observed wound healing's improvement and bone exposure reduction in the PRP group [46].

Martins et al. also studied the association of laser phototherapy (LPT) and PRP on healing outcome of BRONJ in cancer patients. These authors retrospectively compared the effects on wound healing of this protocol with a nonsurgical (pharmacological therapy) and a surgical (pharmacological plus surgical therapy) one. They obtained higher rates of success, in terms of mucosal wound healing, in patients surgically treated with the LPT plus PRP protocol [47].

Longo et al. also achieved good results by studying the therapeutic effects in surgery therapy associated with PRP to promote BRONJ wounds healing [48]; performing a comparison with a surgical approach without PRP. They present higher success rate among patients treated with PRP (PRP group 93% of complete response versus control group 53% of complete response).

Lately, Kim et al. reported the application of leucocyte-rich and platelet-rich fibrin (L-PRF) in the treatment of BRONJ, with a complete resolution in 77% of cases treated

Table 3: Descriptive statistics of the 10 enrolled patients.

| | |
|---|---|
| Age (years) | 75,2±5,94 |
| Sex | |
| Male | 3 (30%) |
| Female | 7 (70%) |
| Smokers | 2 (20%) |
| Cancer | |
| Multiple Myeloma | 4 (40%) |
| Breast cancer | 3 (30%) |
| Prostate cancer | 3 (30%) |
| Comorbidities | |
| Diabetes | 2 (20%) |
| Hypertensions | 6 (60%) |
| Corticosteroids | 2 (20%) |
| Osteoporosis | 5 (50%) |
| Chemotherapy | 5 (50%) |
| Rheumatoid arthritis | 1 (10%) |
| Involved bone | |
| Maxilla | 1 (10%) |
| Mandible | 9 (90%) |
| BRONJ stage∗ | |
| I A | 0 |
| I B | 6 (60%) |
| II A | 2 (20%) |
| II B | 2 (20%) |
| Bone exposure | |
| Yes | 8 (80%) |
| No | 2 (20%) |
| Intravenous Bisphosphonates treatment time (mo) | 31,8±25,76 |

∗ BRONJ stage according to SICMF-SIPMO clinical and radiological staging system.

and a delayed resolution in 18% of cases [49]. Comparing these results with ours, the success percentages are almost similar.

Notably, Mozzati et al. described the treatment of 32 BRONJ cases all belonging to stage IIB with the application of plasma rich in growth factors (PRGF) and reported a success rate of 100% with only temporary postoperative complications[24]. In 2017, also Maluf et al. reported two cases of medication related ONJ (classifiable as stage II) completely healed after a surgical treatment combined with the application of L-PRF[50].

Del Fabbro et al., in their systematic review, illustrated the data about fourteen studies published between 2007 and 2014; the BRONJ surgical treatment with an adjunct autologous platelet concentrates showed a satisfactory healing in 91,6% of the cases [36]. All these data are in agreement with our results in the treatment of BRONJ stage IIB.

Our study's limitations include the limited sample size and the presence of confounding factors, such as applied comedications (e.g. corticosteroids and/or different chemotherapy) in some patients. Indeed, these drugs could inhibit cell proliferation and with an antiangiogenic action could suppress vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [51–53].

## 5. Conclusion

Despite progress in the prevention of BRONJ, a specific treatment protocol to manage BRONJ is still missing.

Surgical removal of the necrotic bone should be performed with the Er,Cr:YSGG laser, that possesses remarkable properties with antibacterial and biostimulative effects, reduce postoperative pain and promote the tissue healing. Additionaly, PRP is an autologous product, biocompatible, easy to handle, and rich in growth factors and ameliorates the tissues healing in residual postsurgical wounds.

More prospective studies are needed to confirm this statement with a larger patients' sample. Considering the limitation of the present study, we could show that conservative surgical approach with Er,Cr:YSGG laser combined PRP benefits the management of early stages' BRONJ in cancer patients.

Table 4: Data of patients (Pt) at baseline ($T_0$) and after the treatment ($T_1$): multiple myeloma (MM); chemotherapy (CT), corticosteroids use (CST), and BRONJ stage according to SICMF-SIPMO staging system and presence of bone status (H= healed; R= reduction; NR= no reduction; E= exposed bone; NE= nonexposed bone).

| Pt | Sex | Age | Cancer | Bps | Bps duration (mo) | CT | CST | Affected Jaw | Stage $T_0$ | Stage $T_1$ | Bone Status $T_0$ | Bone Status $T_1$ | Output |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 72 | Prostate | Zoledronate | 24 | No | No | Upper | I B | I A | E | E | R |
| 2 | F | 72 | MM | Zoledronate | 12 | Yes | No | Lower | I B | I A | E | E | R |
| 3 | F | 89 | MM | Zoledronate | 18 | Yes | Yes | Lower | II B | H | E | NE | H |
| 4 | F | 69 | Breast | Zoledronate | 36 | Yes | No | Lower | I B | H | E | NE | H |
| 5 | F | 80 | MM | Zoledronate | 60 | Yes | No | Lower | I B | I A | NE | NE | R |
| 6 | F | 74 | Breast | Zoledronate | 24 | No | No | Lower | II B | II A | NE | NE | R |
| 7 | F | 77 | Breast | Zometa + Ibandronate | 96 | No | No | Lower | I B | H | E | NE | H |
| 8 | M | 77 | Prostate | Zoledronate | 26 | Yes | No | Lower | II A | II A | E | E | NR |
| 9 | F | 70 | MM | Zoledronate | 18 | No | No | Lower | I B | I A | E | NE | R |
| 10 | M | 72 | Prostate | Zoledronate | 4 | No | Yes | Lower | II A | II A | E | E | NR |

## Ethical Approval

All procedures performed in this study that involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Consent

All participants included in this study signed the informed consent.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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## References

[1] S. L. Ruggiero, T. B. Dodson, and J. Fantasia, "American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update," *Journal of Oral and Maxillofacial Surgery*, vol. 72, no. 10, pp. 1938–1956, 2014.

[2] G. Campisi, S. Fedele, V. Fusco, G. Pizzo, O. Di Fede, and A. Bedogni, "Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents," *Future Oncology*, vol. 10, no. 2, pp. 257–275, 2014.

[3] V. Rollason, A. Laverrière, L. C. I. Macdonald, T. Walsh, M. R. Tramèr, and N. B. Vogt-Ferrier, "Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ)," *Cochrane Database of Systematic Reviews*, vol. 2016, no. 2, Article ID CD008455, pp. 1–35, 2016.

[4] N. H. Beth-Tasdogan, B. Mayer, H. Hussein, and O. Zolk, "Interventions for managing medication- related osteonecrosis of the jaw," *The Cochrane Database of Systematic Reviews*, Article ID D012432, 2017.

[5] L. Ramaglia, A. Guida, V. Iorio-Siciliano, A. Cuozzo, A. Blasi, and A. Sculean, "Stage-specific therapeutic strategies of medication-related osteonecrosis of the jaws: a systematic review and meta-analysis of the drug suspension protocol," *Clinical Oral Investigations*, vol. 22, no. 2, pp. 597–615, 2018.

[6] J. B. B. Weber, R. S. Camilotti, and M. E. Ponte, "Efficacy of laser therapy in the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ): a systematic review," *Lasers in Medical Science*, vol. 31, no. 6, pp. 1261–1272, 2016.

[7] C. I. Ripamonti, E. Cislaghi, L. Mariani, and M. Maniezzo, "Efficacy and safety of medical ozone ($O_3$) delivered in oil suspension applications for the treatment of osteonecrosis of the jaw in patients with bone metastases treated with bisphosphonates: preliminary results of a phase I-II study," *Oral Oncology*, vol. 47, no. 3, pp. 185–190, 2011.

[8] M. Zandi, A. Dehghan, A. Mohammadi-Mofrad, P. Amini, and F. Vahdatinia, "Short-term perioperative teriparatide therapy for the prevention of medication-related osteonecrosis of the jaw: A randomized, controlled preclinical study in rats," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 45, no. 2, pp. 275–280, 2017.

[9] G. A. C. Momesso, F. R. de Souza Batista, C. A. de Sousa et al., "Successful use of lower-level laser therapy in the treatment of medication-related osteonecrosis of the jaw," *Journal of Lasers in Medical Sciences*, vol. 8, no. 4, pp. 201–203, 2017.

[10] P. Vescovi, E. Merigo, M. Meleti, and etal., "Conservative surgical management of stage i bisphosphonate-related osteonecrosis of the jaw," *International Journal of Dentistry*, vol. 2014, 2014.

[11] M. Nisi, F. La Ferla, D. Karapetsa et al., "Conservative surgical management of patients with bisphosphonate-related osteonecrosis of the jaws: a series of 120 patients," *British Journal of Oral and Maxillofacial Surgery*, vol. 54, no. 8, pp. 930–935, 2016.

[12] A. Bedogni, G. Saia, G. Bettini et al., "Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis," *Oral Oncology*, vol. 47, no. 5, pp. 420–424, 2011.

[13] A. Bedogni, G. Campisi, V. Fusco, and A. Agrillo, "Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione," *SICMF-SIPMO*, 2013.

[14] F. Graziani, P. Vescovi, G. Campisi et al., "Resective surgical approach shows a high performance in the management of advanced cases of bisphosphonate-related osteonecrosis of the jaws: A retrospective survey of 347 cases," *Journal of Oral and Maxillofacial Surgery*, vol. 70, no. 11, pp. 2501–2507, 2012.

[15] P. Vescovi, M. Manfredi, E. Merigo et al., "Surgical approach with Er:YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT)," *Lasers in Medical Science*, vol. 25, no. 1, pp. 101–113, 2010.

[16] H. Y. Kim, S.-J. Lee, S. M. Kim et al., "Extensive Surgical Procedures Result in Better Treatment Outcomes for Bisphosphonate-Related Osteonecrosis of the Jaw in Patients With Osteoporosis," *Journal of Oral and Maxillofacial Surgery*, vol. 75, no. 7, pp. 1404–1413, 2017.

[17] T. Eguchi, I. Kanai, A. Basugi, Y. Miyata, M. Inoue, and Y. Hamada, "The assessment of surgical and non-surgical treatment of stage II medication-related osteonecrosis of the jaw," *Medicina Oral Patología Oral y Cirugia Bucal*, vol. 22, no. 6, pp. e788–e795, 2017.

[18] B. Atalay, S. Yalcin, Y. Emes et al., "Bisphosphonate-related osteonecrosis: Laser-assisted surgical treatment or conventional surgery?" *Lasers in Medical Science*, vol. 26, no. 6, pp. 815–823, 2011.

[19] S. Hafner, M. Ehrenfeld, E. Storz, and A. Wieser, "Photodynamic Inactivation of Actinomyces naeslundii in Comparison with Chlorhexidine and Polyhexanide - A New Approach for Antiseptic Treatment of Medication-Related Osteonecrosis of the Jaw?" *Journal of Oral and Maxillofacial Surgery*, vol. 74, no. 3, pp. 516–522, 2016.

[20] C. Noba, A. C. Mello-Moura, T. Gimenez, T. K. Tedesco, and C. Moura-Netto, "Laser for bone healing after oral surgery: systematic review," *Lasers in Medical Science*, vol. 33, no. 3, pp. 667–674, 2018.

[21] K. Rupel, G. Ottaviani, M. Gobbo et al., "A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ)," *Oral Oncology*, vol. 50, no. 11, pp. 1049–1057, 2014.

[22] J. Zeitouni, B. Clough, S. Zeitouni, M. Saleem, K. Al Aisami, and C. Gregory, "The effects of the Er:YAG laser on trabecular bone micro-architecture: Comparison with conventional dental

drilling by micro-computed tomographic and histological techniques," *F1000Research*, vol. 6, p. 1133, 2017.

[23] K. Baek, W. Deibel, D. Marinov et al., "A comparative investigation of bone surface after cutting with mechanical tools and Er:YAG laser," *Lasers in Surgery and Medicine*, vol. 47, no. 5, pp. 426–432, 2015.

[24] M. Del Fabbro, C. Bucchi, A. Lolato, S. Corbella, T. Testori, and S. Taschieri, "Healing of Postextraction Sockets Preserved With Autologous Platelet Concentrates. A Systematic Review and Meta-Analysis," *Journal of Oral and Maxillofacial Surgery*, vol. 75, no. 8, pp. 1601–1615, 2017.

[25] S. Marcazzan, S. Taschieri, R. L. Weinstein, and M. Del Fabbro, "Efficacy of platelet concentrates in bone healing: A systematic review on animal studies – Part B: Large-size animal models," *Platelets*, vol. 29, no. 4, pp. 338–346, 2018.

[26] J. Etulain, "Platelets in wound healing and regenerative medicine," *Platelets*, pp. 1–13, 2018.

[27] A. Albanese, M. E. Licata, B. Polizzi, and G. Campisi, "Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration," *Immunity & Ageing*, vol. 10, no. 1, article 23, 2013.

[28] D. M. Dohan Ehrenfest, T. Bielecki, R. Jimbo et al., "Do the fibrin architecture and leukocyte content influence the growth factor release of platelet concentrates? An evidence-based answer comparing a pure Platelet-Rich Plasma (P-PRP) gel and a leukocyte- and Platelet-Rich Fibrin (L-PRF)," *Current Pharmaceutical Biotechnology*, vol. 13, no. 7, pp. 1145–1152, 2012.

[29] X. L. Griffin, D. Wallace, N. Parsons, and M. L. Costa, "Platelet rich therapies for long bone healing in adults," *Cochrane Database of Systematic Reviews*, vol. 7, Article ID CD009496, 2012.

[30] D. M. Dohan Ehrenfest, L. Rasmusson, and T. Albrektsson, "Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF)," *Trends in Biotechnology*, vol. 27, no. 3, pp. 158–167, 2009.

[31] F. Passaretti, M. Tia, V. D'esposito et al., "Growth-promoting action and growth factor release by different platelet derivatives," *Platelets*, vol. 25, no. 4, pp. 252–256, 2014.

[32] S. Tong, J. Yin, and J. Liu, "Platelet-rich plasma has beneficial effects in mice with osteonecrosis of the femoral head by promoting angiogenesis," *Experimental and Therapeutic Medicine*, vol. 15, no. 2, pp. 1781–1788, 2017.

[33] N. Prataap, P. Sunil, C. Sudeep, V. Ninan, A. Tom, and M. Arjun, "Platelet-rich plasma and incidence of alveolar osteitis in high-risk patients undergoing extractions of mandibular molars: A case–control study," *Journal of Pharmacy and Bioallied Sciences*, vol. 9, no. 5, p. 173, 2017.

[34] M. Mozzati, G. Gallesio, V. Arata, R. Pol, and M. Scoletta, "Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: A report of 32 cases," *Oral Oncology*, vol. 48, no. 5, pp. 469–474, 2012.

[35] M. Scoletta, V. Arata, P. G. Arduino et al., "Tooth extractions in intravenous bisphosphonate-treated patients: A refined protocol," *Journal of Oral and Maxillofacial Surgery*, vol. 71, no. 6, pp. 994–999, 2013.

[36] M. Del Fabbro, G. Gallesio, and M. Mozzati, "Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature," *European Journal of Cancer*, vol. 51, no. 1, pp. 62–74, 2015.

[37] C. Fornaini, L. Cella, A. Oppici et al., "Laser and Platelet-Rich Plasma to treat Medication-Related Osteonecrosis of the Jaws (MRONJ): a case report," *Laser Therapy*, vol. 26, no. 3, pp. 223–227, 2017.

[38] L. Mazzucco, V. Balbo, E. Cattana, and P. Borzini, "Platelet-rich plasma and platelet gel preparation using Plateltex®," *Vox Sanguinis*, vol. 94, no. 3, pp. 202–208, 2008.

[39] G. Ghidini, M. Manfredi, I. Giovannacci, and etal., "Medication-related osteonecrosis of the jaw: risk factors in patients under biphosphonate versus patients under antiresorptive-antiangiogenic drugs," *Minerva Stomatol*, vol. 66, no. 4, pp. 135–140, 2017.

[40] G. A. Momesso, F. R. de Souza Batista, C. A. de Sousa et al., "Successful Use of Lower-Level Laser Therapy in the Treatment of Medication-Related Osteonecrosis of the Jaw," *Journal of Lasers in Medical Sciences*, vol. 8, no. 4, pp. 201–203, 2017.

[41] S. Latifyan, M. T. Genot, and J. Klastersky, "Bisphosphonate-related osteonecrosis of the jaw: a review of the potential efficacy of low-level laser therapy," *Supportive Care in Cancer*, vol. 24, no. 9, pp. 3687–3693, 2016.

[42] D. G. Panduric, I. B. Juric, S. Music, K. Molčanov, M. Sušic, and I. Anic, "Morphological and ultrastructural comparative analysis of bone tissue after Er:YAG laser and surgical drill osteotomy," *Photomedicine and Laser Surgery*, vol. 32, no. 7, pp. 401–408, 2014.

[43] J. C. Esteves, A. P. De Souza Faloni, P. D. Macedo et al., "Effects on bone repair of osteotomy with drills or with erbium, chromium: Yttrium-scandium-gallium-garnet laser: Histomorphometric and immunohistochemical study," *Journal of Periodontology*, vol. 87, no. 4, pp. 452–460, 2016.

[44] P. Vescovi, I. Giovannacci, S. Otto et al., "Medication-related osteonecrosis of the jaw: an autofluorescence-guided surgical approach performed with Er:YAG laser," *Photomedicine and Laser Surgery*, vol. 33, no. 8, pp. 437–442, 2015.

[45] I. Giovannacci, M. Meleti, D. Corradi, and P. Vescovi, "Clinical Differences in Autofluorescence Between Viable and Nonvital Bone: A Case Report With Histopathologic Evaluation Performed on Medication-Related Osteonecrosis of the Jaws," *Journal of Oral and Maxillofacial Surgery*, vol. 75, no. 6, pp. 1216–1222, 2017.

[46] V. Coviello, F. Peluso, S. Z. Dehkhargani, and etal., "Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients," *Journal of BIOLOGICAL REGULATORS & Homeostatic Agents*, vol. 26, no. 1, pp. 151–155, 2018, http://www.ncbi.nlm.nih.gov/pubmed/22475108.

[47] M. A. T. Martins, M. D. Martins, C. A. Lascala et al., "Association of laser phototherapy with PRP improves healing of bisphosphonate-related osteonecrosis of the jaws in cancer patients: A preliminary study," *Oral Oncology*, vol. 48, no. 1, pp. 79–84, 2012.

[48] F. Longo, A. Guida, C. Aversa et al., "Platelet Rich Plasma in the Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw: Personal Experience and Review of the Literature," *International Journal of Dentistry*, vol. 2014, Article ID 298945, 7 pages, 2014.

[49] J.-W. Kim, S.-J. Kim, and M.-R. Kim, "Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: A Prospective Feasibility Study," *British Journal of Oral and Maxillofacial Surgery*, vol. 52, no. 9, pp. 854–859, 2014.

[50] G. Maluf, R. J. Caldas, and P. S. Silva Santos, "Use of Leukocyte- and Platelet-Rich Fibrin in the Treatment of Medication-Related Osteonecrosis of the Jaws," *Journal of Oral and Maxillofacial Surgery*, vol. 76, no. 1, pp. 88–96, 2017.

[51] A. Soundia, D. Hadaya, N. Esfandi et al., "Zoledronate Impairs Socket Healing after Extraction of Teeth with Experimental Periodontitis," *Journal of Dental Research*, vol. 97, no. 3, pp. 312–320, 2017.

[52] Z. Jabbour, M. El-Hakim, J. E. Henderson, and R. F. De Albuquerque Jr., "Bisphosphonates inhibit bone remodeling in the jaw bones of rats and delay healing following tooth extractions," *Oral Oncology*, vol. 50, no. 5, pp. 485–490, 2014.

[53] N. Hagelauer, A. M. Pabst, T. Ziebart, H. Ulbrich, and C. Walter, "In vitro effects of bisphosphonates on chemotaxis, phagocytosis, and oxidative burst of neutrophil granulocytes," *Clinical Oral Investigations*, vol. 19, no. 1, pp. 139–148, 2015.

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*Review Article*

# Microsurgical Reconstruction of the Jaws Using Vascularised Free Flap Technique in Patients with Medication-Related Osteonecrosis: A Systematic Review

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*Background*. Osteonecrosis of the jaw (ONJ) has been reported to be associated with patients receiving primarily bisphosphonate (BP) therapies. However, lately it has been documented that other medications, such as RANK ligand inhibitor (denosumab) and antiangiogenic drug, can cause ONJ. Micro-osseous-vascular reconstruction of the jaws in patients affected by medication-related osteonecrosis of the jaw represents a viable option of treatment for patients affected by stage III of the disease. However, there are still considerable doubts about the success of this procedure in the short, medium, and long term. *Material and Methods*. A multidatabase (PubMed/MEDLINE, EMBASE, and CENTRAL) systematic search was performed. Any type of studies considering human patients treated with antiresorptive and antiangiogenic drugs was considered. The aim of the research is to primarily understand the success rate of micro-osseous-vascular reconstruction in the short, medium, and long period of time. This review has also the goal of better understanding any perioperative and postoperative complications resulting from the use of the reconstruction techniques. *Results*. Eighteen studies resulted eligible for the study. Fibula free flap is the most commonly utilised vascularised free flap reconstruction technique (80.76%). Ten out of eighteen studies reported no complications. Recurrence of osteonecrosis was registered in five cases (6.41%) after free flap reconstruction. The overall free flap success rate was 96.16%. *Conclusions*. Based on the limited data available in literature (Level 4 of the Oxford Evidence-based medicine scale), micro-osseous-vascular reconstruction of the jaws represents a valid treatment in patients with bisphosphonate-related osteonecrosis at stage III of the disease. However, additional data based on a larger cohort of patients are necessary to justify this type of intervention in patient affected by MRONJ.

## 1. Introduction

Bisphosphonates (BP) are antiresorptive drugs used in the management of conditions as diverse as osteoporosis and metastatic bone diseases. These drugs are widely administered and generally well tolerated by patients. In 2003, Marx et al. [1] first reported a nonhealing necrosis of the maxillofacial region in some patients taking BPs.

In the last decade researchers have discovered that BPs not exclusively cause osteonecrosis of jaws, as other drugs, such as antiresorptive (bone-targeted) agents like denosumab, but also were found to cause it. In addition, monoclonal antibodies able to bind and selectively inhibit VEGF-A, specifically mTOR inhibitors, can also cause osteonecrosis of the jaw [2–6].

For this reason, in 2014 the bisphosphonate-related osteonecrosis of the jaw (BRONJ) nomenclature was changed by the position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) special committee on Medication-Related Osteonecrosis of the Jaws (MRONJ) [7].

The term "medication-related osteonecrosis of the jaws" (MRONJ) refers to a complication associated with groups of medications, such as antiangiogenic or antiresorptive drugs [8]. These medications can have different indications depending on their mode of administration (Tables 1 and 2) [9, 10].

According to AAOMS, MRONJ is defined as an exposition of necrotic bone in the oral cavity lasting more than 8 weeks, in patients who took antiresorptive or antiangiogenic drugs; these patients have not been exposed to head and neck radiotherapy, nor show signs of bone metastases in the maxillofacial region [7].

A number of systemic risk factors have been associated with increased likelihood of MRONJ; they are summarised in Table 3 [11, 12].

Dental extraction or other surgical procedures such as apicectomies or cystectomies have been found in between 52% and 80% of MRONJ patients' medical history [13–15].

During the last decade AAOMS has revised and proposed a clinical staging classification system of the disease in an attempt to guide clinicians and surgeons to an appropriate therapeutic approach (Table 4).

The management of MRONJ is reported to be very challenging and with no current "gold standard". Published studies have reported a number of approaches to treatment, with widely varying success rates, ranging from no or limited to radical surgery. The ideal outcome is total eradication of MRONJ along with an improvement of patients' quality of life through pain release and infection management [16].

Conservative treatment was considered to be partially successful, with resolution reported in only 50% of cases; particular concerns have been reported on MRONJ at clinical stages II and III [17–19]. In case conservative treatments fail, surgical approaches like local debridement, osteoplasty, and segmental osteotomy are normally performed [20, 21].

However, patients that show evidence of MRONJ stage III with severe pain, infection, pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border of the mandible require an invasive type of surgery which might result in a disabling outcome [7, 16, 22].

The absence of a well-established surgical treatment protocol in scientific literature makes it difficult to conduct therapy in advanced cases of the disease.

Up to date, there is no standard treatment for MRONJ associated with antiresorptive and antiangiogenic therapies. Several treatment options have been described since MRONJ was first reported. Although the initial stages of MRONJ seem to respond quite well to conservative treatments or limited bone debridement if conservative treatment fails, the treatment for stage III lesions remains still controversial [23, 24].

The objective of this review is to evaluate the outcome of free vascularised osseous tissue transfer and/or osteofasciocutaneous free flap as treatment for patients affected by MRONJ stage III. Systematic reviews have been already published. However, these reviews were not performed in a standardised manner or did not follow strict criteria. Moreover the previous reviews did not consider antiangiogenic drugs in the search criteria. This has resulted in lack of quality assurance, summarised in Table 5 [25–27]. This review aims to improve the quality of previous research and expand on the current data available.

## 2. Materials and Methods

This systematic review was performed according to PRISMA guidelines [44].

The following the databases were used for the review: PubMed/MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). A three-stage screening approach was used to ensure precision and the quality of the search. The screening of titles and abstracts was carried out independently by three authors (AH, UH, and RS) to eliminate any irrelevant materials (i.e., reviews, animal studies, nonclinical studies, and studies that did not report on patients undergoing to free tissue graft). Disagreements were resolved by discussion.

A data screening and abstraction form was used to

(1) verify the study eligibility derived from the above inclusion/exclusion criteria,

(2) carry out the methodological quality assessment,

(3) extract data on study characteristics and outcomes for the included studies.

The authors of any studies eligible for inclusion in the review, yet without sufficient information, were contacted directly (Figure 1).

### 2.1. Criteria for Inclusion in This Review

*2.1.1. Types of Studies.* The types of studies included in the research strategy were published or unpublished randomised control trials, case-controlled trials, case series, retrospective studies, and case reports. Papers were obtained from January 2003 to June 2017. Animal studies and those including patients with previous history of radiation therapy to the head and neck regions were excluded. No language restrictions were imposed to the search.

*2.1.2. Types of Participants.* The review considered studies involving patients who developed MRONJ and subsequently underwent free vascularised osseous tissue transfer and/or osteofasciocutaneous free flap reconstruction. No restriction of age, gender, or ethnic origin was applied. There was no restriction on the minimum number of patients included in the studies.

*2.1.3. Types of Interventions.* Only free vascularised osseous tissue transfer and/or osteofasciocutaneous free flap reconstruction were considered.

*2.1.4. Types of Outcome Measures*

*Primary Outcomes*. Primary outcome measures of the review included the success rate of free flap without any restrictions in follow-up. The other considered measures were the

Table 1: Antiresorptive drugs used in oncologic and nononcologic patients. Btl: bottle; IM: intramuscular; IV: intravenous; MM: multiple myeloma; PO: orally; SC: subcutaneous; SRE: skeletal-related event; Tab: tablet.

| Pharmacologic active ingredient | Formulation | Route of administration | Indication and frequency |
|---|---|---|---|
| Alendronic acid (sodium salt) | Tab 70 mg<br>Tab 10 mg | PO | Treatment of postmenopausal osteoporosis (70 mg/week)<br>Treatment of osteoporosis in men (70 mg/week)<br>Treatment and prevention of osteoporosis induced by glucocorticoids (70 mg/week) |
| Alendronic acid + cholecalciferol | Tab 70 mg/5600 UI | PO | Treatment of postmenopausal osteoporosis in patients with unsupplemented vitamin D deficit (70 mg/week) |
| Ibandronic acid (monosodium salt monohydrate) | Tab 50 mg<br>Btl 6 mg/6 ml<br>Tab 150 mg<br>Btl 3 mg/3 ml | PO<br>IV<br>PO<br>IV | Prevention of SREs in breast cancer patients with bone metastases (50 mg/day p.o. or 6 mg every 3–4 weeks iv.)<br>Treatment of hypercalcemia of malignancy<br>Treatment of postmenopausal osteoporosis in patients at high risk of fracture (150 mg/4 weeks p.o. or 3 mg every 3 months iv.) |
| Neridronate acid (sodium salt) | Btl 25 mg/2 ml<br>Btl 100 mg/8 ml | IV/IM.<br>IV | Osteogenesis imperfecta (2 mg/kg/3 months)<br>Paget's bone disease (different schedules) |
| Pamidronic acid (disodium salt) | Btl 15 mg/5 ml<br>Btl 30 mg/10 ml<br>Btl 60 mg/10 ml<br>Btl 90 mg/10 ml | IV | Prevention of SREs in breast cancer patients with bone metastases or MM with bone lesions (60–90 mg every 3–4 weeks)<br>Treatment of hypercalcemia of malignancy |
| Zoledronic acid (monohydrate) | Btl 4 mg/5 ml<br>Btl 5 mg/100 ml | IV<br>IV | Prevention of SREs in cancer patients with bone metastases or MM (4 mg every 3–4 weeks).<br>Treatment of hypercalcemia of malignancy<br>Treatment of osteoporosis in postmenopausal women, in men at increased risk of fracture, including those with a recent hip fracture from minor trauma (5 mg once per year)<br>Treatment of bone Paget's disease |
| Denosumab | Btl 120 mg<br>Btl 60 mg | SC<br>SC | Prevention of SREs in cancer patients with bone metastases (120 mg every 4 weeks)<br>Treatment of hypercalcemia of malignancy.<br>Osteoporosis (60 mg sc. every 6 months) |

Table 2: Main antiangiogenic drugs used (IV: intravenous; MM: multiple myeloma; PO: orally; SC: subcutaneous; Btl: bottle; Tab: tablet).

| Pharmacologic active ingredient | Formulation | Route of administration | Indication and frequency |
|---|---|---|---|
| Bevacizumab | Btl 400 mg<br>Btl 100 mg | IV | Metastatic breast cancer (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks); colorectal cancer (5 mg/kg or 10 mg/kg every 2 weeks); lung/ovarian cancer (7.5 mg/kg or 15 mg/kg every 3 weeks); renal cell cancer (10 mg/kg every 2 weeks); glioblastoma (10 mg/kg every 2 weeks) |
| Sunitinib | Tab 12.5 mg | PO | Renal cell cancer, GISTs and neuroendocrine tumors (50 mg/day for 4 weeks) |
| Sorafenib | Tab 200 mg | PO | Renal cell cancer (800 mg/day) |
| Pazopanib | Tab 200 mg<br>Tab 400 mg | PO | Renal cell cancer (200–800 mg/day) |
| Thalidomide | Tab 50 mg | PO | Myeloma (400 mg/day for 6 weeks) |
| Lenalidomide | Tab 5, 10, 15 and 25 mg | PO | Myeloma (tailored doses) |
| Everolimus | Tab 5 and 10 mg | PO | Renal cell cancer, breast cancer (10 mg every day) |
| Temsirolimus | Btl 30 mg | IV | Renal cell cancer (25 mg every week) |

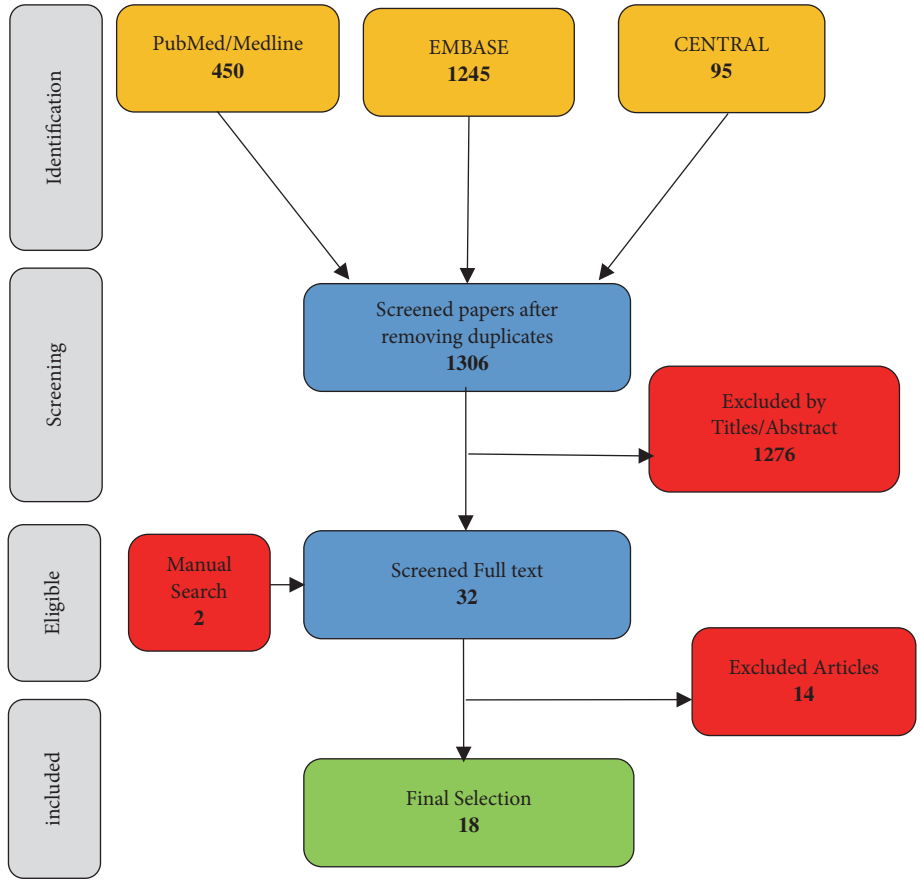


Figure 1: Review process for the titles, abstracts, and full-text reading of the selected references.

Table 3: Drug-related risk factor of osteonecrosis of the jaw in the cancer population according to Campisi et al. 2011 [11].

| Risk Factor | Strenght |
|---|---|
| Zoledronate vs Other Bisphosphonate | +++ |
| Intravenouse vs Oral Bisphosponate | ++ |
| Bisphosphonate cumulative dose | +++ |
| Bisphosphonate duration of treatment | +++ |
| Anti-angiogenic drugs | ++ |
| Denosumab | ++ |
| Chemotherapy | -/+ |
| Thalilomide | +/- |

frequency of MRONJ recurrence in the free flap or in the surgical residual jaw bone.

*Secondary Outcomes*. The secondary measures of the review entailed perioperative complications and those at follow-up, including the most common cause of the MRONJ and the time during which the patient was treated with the antiresorptive or antiangiogenic drugs prior ONJ.

*2.2. Data Extracted.* Data extracted from the eighteen studies included number of patients, patient sex, and age, predisposing factors for, and localisation of, MRONJ, type of antiangiogenic or antiresorptive drugs and their cumulative dose, clinical indications for the drug or combined therapy, extent of the surgical excision, type of free vascularised tissue reconstruction, free flap failure, immediate complications, follow-up time, and MRONJ recurrence.

All selected papers were carefully read to identify author(s), year of publication, study design, population and treatment characteristics, and number of patients with recurrent MRONJ.

In case of missing information, we contacted the authors and gave them 6 weeks to reply. If the information was still missing we then indicated the missing data as "Not Reported (NR)" in the text and in the tables.

## 3. Results

Results were expressed in descriptive statistics. No randomised controlled clinical trials or case-controlled studies comparing free flap reconstruction after resection in MRONJ patients were found. A total number of 18 articles we included in the study. All the published dates were described in case report (no. 6) and case series (no. 12) from 2008 to 2017 (Table 6). A total of 83 patients, 47 females (56.62%), 19 males (22.89%), and missing information for 20.49% (NR) of the

Table 4: MRONJ staging according the AAOMS [7].

| Stage | MRONJ clinical findings |
|---|---|
| At risk category | No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates |
| Stage 0 | No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms |
| Stage I | Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection |
| Stage II | Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage |
| Stage III | Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor |

Table 5: Systematic review currently published and their limitations.

| Systematic Review | Limitation |
|---|---|
| Sacco et al. (2011) [27] | English literature limited search; Single Electronic database search. |
| Vercruysse et al. (2014) [25] | Search Limited to BRONJ and or bisphosphonate related necrosis; No mentioning to language limitation; Review based on a single reviewer selection of articles |
| Neto et al. (2016) [26] | Single Electronic database search; Search Limited to BRONJ and or bisphosphonate related necrosis; No mentioning to language limitation; No mentioning reviewer involved in the search strategy. |

Table 6: Study selected with total number of patient treated.

| Study | Type of study | Patients number |
|---|---|---|
| Engroff and Kim (2007) [28] | Case series | 2 |
| Ferrari et al. (2008) [29] | Case Report | 1 |
| Mücke et al. (2009) [30] | Case series | 2 |
| Nocini et al. (2009) [31] | Case series | 7 |
| Seth et al. (2010) [32] | Case series | 11 |
| Bedogni et al. (2011) [33] | Case series | 3 |
| Pautke et al. (2011) [34] | Case report | 1 |
| Bittner et al. (2012) [35] | Case report | 1 |
| Ghazali et al. (2013) [36] | Case report | 1 |
| Hanasono et al. (2013) [37] | Case series | 11 |
| Horta et al. (2014) [38] | Case series | 1 |
| Spinelli et al. (2014) [39] | Case series | 8 |
| Vercruysse et al. (2014) [25] | Case series | 3 |
| Kim et al. (2015) [40] | Case series | 4 |
| Mücke et al. (2016) [41] | Case series | 14 |
| Neto et al. (2016) [26] | Case report | 1 |
| Sotsuka et al. (2016) [42] | Case report | 1 |
| Caldroney et al. (2017) [43] | Case Series | 11 |

cases, were treated using vascularised osseous tissue transfer and/or osteofasciocutaneous free flap reconstruction.

The most common indications for antiresorptive or antiangiogenic treatment were breast cancer (28.91%), multiple myeloma (22.89%), osteoporosis (14.45%), prostate cancer (9.63%), lung cancer (2.40%), myeloid-leukemia and osteoporosis (1.20%), pain syndrome (1.20%), and NR in the 19.32% of the cases (Table 7). The most common site for MRONJ was the mandible 97.59% and 2.41% in the maxilla (Table 8).

Zoledronate was responsible for the majority of the MRONJ with 42.16 %, then pamidronate 7.22%, alendronate 8.43%, ibandronate 2.40%, and etidronate 1.20%. A combination of the following drugs and the relative incidence percentage were also found responsible:

zoledronate and pamidronate (13.25%);
zoledronate and clodronate (1.20%);
zoledronate and denosumab (1.20%);
pamidronate and denosumab (1.20%);
alendronate, risedronate, and pamidronate (1.20%).

A total of 20.54% patients presented missing information with regard to the type of drug used.

69.90% of the cases missed information on the causes of the MRONJ.

The most commonly utilised vascularised free flap reconstruction was fibula free flap (81.92%), followed by iliac crest (12.04%) and scapula (6.02%).

The most frequent type of resection was subtotal (32.53%), followed by segmental (26.50%) and partial (2.40%). However a large percentage of missing data was found regarding the type of resection (NR 38.57%) (Table 9).

The patients were followed for a period of time ranging from 2 weeks up to 99 months.

Radiographic imaging with CT, cone-beam, and/or orthopantomogram was obtained during follow-up in 95% of the cases.

At follow-up and after free flap reconstruction, recurrence of MRONJ (6.02%) was observed in 5 patients: two of the patients (2.40%) on the contralateral unresected part

Table 7: Preoperative pharmacological analysis: type of drugs, indication for drug therapy, and time of drug exposure. ZOL: zoledronate; ALD: alendronate; PMT: pamidronate; COL: clodronate; DZM: denosumab; IBA: ibandronate; ETI: etidronate; mth: months; RSD: risedronate; NR: not reported.

| Study | Type of drug | Indication for drug therapy | time of drug exposure |
|---|---|---|---|
| Engroff and Kim (2007) [28] | PMT (x 1 case)<br>ZOL (x 1 case) | Brest Cancer (x 2 cases) | NR |
| Ferrari et al. (2008) [29] | PMT + ZOL | Multiple Myeloma | 21 mth (PMT)<br>3 mth (ZOL) discontinue therapy |
| Mücke et al. (2009) [30] | ZOL (x 2 cases) | Brest cancer (x 1 case);<br>Multiple Myeloma (x 1 case) | 50mth (ZOL)<br>36 mth (ZOL) |
| Nocini et al. (2009) [31] | PMT and ZOL (x 5 cases)<br>ZOL (x 2 cases) | Brest Cancer (x 5 cases);<br>Prostate Cancer (x 1 case);<br>Myeloid leukaemia and<br>Osteoporosis (x 1 case) | NR |
| Seth et al. (2010) [32] | ZOL (x 6 cases)<br>ALD (x 2 cases)<br>IBA (x 2 cases)<br>ETI (x 1 case) | Brest Cancer (x 5 cases);<br>Prostate Cancer (x 2 cases);<br>Multiple Myeloma (x 2 cases);<br>Osteoporosis (x 2 cases) | NR |
| Bedogni et al. (2011) [33] | NR | NR | NR |
| Pautke et al. (2011) [34] | ZOL | Prostate Cancer | 40 mth |
| Bittner et al. (2012) [35] | ZOL and PMT | Pain syndrome | 12 mth (ZOL)<br>3 mth (PMT) |
| Ghazali et al. (2013) [36] | ALD | Osteoporosis | 84 mth (ALD) |
| Hanasono et al. (2013) [37] | ZOL (x 9 cases)<br>PMT (x 2 cases) | Multiple Myeloma (x 5 cases);<br>Breast Cancer (x 2 cases);<br>Prostate Cancer (x 2 cases);<br>Osteoporosis (x 2 cases) | NR |
| Horta et al. (2014) [38] | ZOL | Lung Cancer | 36 mth (ZOL) |
| Spinelli et al. (2014) [39] | ZOL (x 3 cases)<br>PMT (x 3 cases)<br>ZOL and PMT (x 2 cases) | Multiple Myeloma (x 4 cases);<br>Brest Cancer (x 3 cases);<br>Prostate Cancer (x 1 case) | 1 x 27 mth (ZOL)<br>1 x 21 mth (ZOL)<br>1 x 35 mth (ZOL<br>1 x 22 mth (PMT)<br>1 x 30 mth (PMT)<br>1 x 19 mth (PMT<br>1 x 25 mth (ZOL and PMT)<br>1 x 17 mth (ZOL and PMT) |
| Vercruysse et al. (2014) [25] | 1 x ZOL<br>1 x ZOL + PMT<br>1 x ZOL + CLO | Multiple Myeloma (x 2 case);<br>Brest Cancer (x 1 case) | 1 x 22mth (ZOL)<br>1x 12 mth (PMT) + 26 mth (ZOL)<br>1x 96 mth (CLO) + 29mth (ZOL) |
| Kim et al. (2015) [40] | ALD (x 2)<br>ALD + RSD + PMT (x 1)<br>ZOL + PMT (x 1) | Osteoporosis (x 3)<br>Multiple Myeloma (x 1) | 1 x 48 mth (ALD)<br>1 x 120 mth (ALD<br>1 x 24 mth (ALD + RSD +PMT)<br>1 x 30mth (ZOL +PMT) |
| Mücke et al. (2016) [41] | NR | NR | NR |
| Neto et al. (2016) [26] | ZOL | Lung Cancer | 36 mth (ZOL) |
| Sotsuka et al (2016) [42] | ZOL | Brest Cancer | 59 mth (ZOL) |
| Caldroney et al. (2017) [43] | 7 x ZOL<br>2 x ALD<br>1 x ZOL + DZM<br>1 x PMT + DZM | Brest Cancer (x 4 cases)<br>Osteoporosi (x 3 cases)<br>Multiple Myeloma (x 3 cases)<br>Prostate Cancer (x 1 case) | NR |

of the jaw, other two patients (2.40%) on the margin of the resection, and one patient (1.20%) on the grafted flap. The overall free flap failure rate registered was 3.61% (Table 10).

*3.1. Review Quality Assessment Data.* All the studies and data extraction included in the systematic review were qualitative and the risk of bias assessed independently by the authors. The authors used the CARE Checklist for case report and the Modified Delphi Checklist for the case series studies.

In the six case report studies, we identified lack of clarity in many of the thirteen domains, with missing information. We found that the lack of clarity was predominantly on

Table 8: Preoperative epidemiologic analysis (age, sex, predisposing factors, and site of the necrosis involved). M: male; F: female; NR: not reported.

| Study | Type of study | Patients number | Age/Sex | Trigging cause | Site of the necrosis involved |
|---|---|---|---|---|---|
| Engroff and Kim (2007) [28] | Case series | 2 | 64 (F); 49 (F) | Dental extraction (x 2 cases) | Mandible (x 2 cases) |
| Ferrari et al. (2008) [29] | Case report | 1 | 66 (M) | NR | Mandible |
| Mücke et al. (2009) [30] | Case series | 2 | 48 (F); 60 (F) | Dental Extraction (x 1 case); Spontaneous (x 1 case) | Mandible (x 2 cases) |
| Nocini et al. (2009) [31] | Case series | 7 | NR (six F); (one M) | Oral surgery (x 5 cases); Infection (x 2 cases) | Mandible (x 7 cases) |
| Seth et al. (2010) [32] | Case series | 11 | 68 (M); 56 (F); 50 (F); 72 (F); 48 (F); 71 (F); 67 (F); 60 (F); 51 (F); 72 (M); 60 (F) | NR | Mandible (x 11 cases) |
| Bedogni et al. (2011) [33] | Case series | 3 | NR | NR | Mandible (x 2 cases); Maxilla (x 1 case) |
| Pautke et al. (2011) [34] | Case report | 1 | 76 (M) | Dental extraction | Mandible |
| Bittner et al. (2012) [35] | Case report | 1 | 41 (F) | Dental extraction | Mandible |
| Ghazali et al. (2013) [36] | Case report | 1 | 82 (F) | Dental extraction | Mandible |
| Hanasono et al. (2013) [37] | Case series | 11 | 63 (F); 57 (M); 65 (M); 75 (F); 72 (M); 68 (M); 60 (F); 64 (F); 70 (F); 75 (F); 67 (F) | NR | Mandible (x 11 cases) |
| Horta et al. (2014) [38] | Case series | 1 | 54 M | Spontaneous | Mandible |
| Spinelli et al. (2014) [39] | Case series | 8 | 73 (M); 77 (F); 64 (F); 53 (F); 62 (M); 68 (F); 57 (M); 64 (F) | Dental extraction (x 3 cases); Spontaneous x 5 | Mandible (x 8 cases) |
| Vercruysse et al. (2014) [25] | Case series | 3 | 54 (F); 70 (F); 64 (F) | Dental extraction (x 1 case); Spontaneous (x 2 cases) | Mandible (x 3 cases) |
| Kim et al. (2015) [40] | Case series | 4 | 69 (F), 68 (F), 62 (F), 70 (M) | NR | Mandible (x 4) |
| Mücke et al. (2016) [41] | Case series | 14 | NR | NR | Mandible (x 14 cases) |
| Neto et al. (2016) [26] | Case report | 1 | 58 (M) | Spontaneous | Mandible |
| Sotsuka et al. (2016) [42] | Case report | 1 | 50 (F) | NR | Maxilla |
| Caldroney et al. (2017) [43] | Case series | 11 | 56 (F); 65 (F); 60 (F); 61 (F); 65 (F); 64 (F); 68 (M); 67 (M); 73 (M); 72 (F); 73 (M). | NR | Mandible (x 11 cases) |

follow-up and diagnostic procedure at the time of follow-up. Hence we concluded the level of bias to be high for all the included case report studies.

In the twelve case series studies, we reported a consistent lack of clarity in some of the seven domains, predominantly regarding the outcome measurement methods. Moreover, we identified some missing information in few other domains; hence we considered the level of bias to be high for all studies

We contacted the authors of these clinical cases to clarify this bias; however we were unable to recover the missing information.

## 4. Discussion

Some antiresorptive drugs such as BP or denosumab have demonstrated to improve the quality of life in patients affected by bone metastasis, osteoporosis, osteopenia, and Paget disease. Additionally, a new antiangiogenic therapy has been successfully used for specific cancer treatments. However, this has remarkably increased the risk of developing MRONJ. This risk is greater in patients who require a higher administration dosage and an intake period greater than 2 years [14, 45, 46].

Table 9: Operative analysis: type of surgery, type of free flap, flap failure, immediate postoperative complications (FFF: fibula Free flap; ICFF: iliac crest free flap; SFF: scapula free flap).

| Study | Type of surgery | Type of free flap | Flap failure | Immediate post-operative complications |
|---|---|---|---|---|
| Engroff and Kim (2007) [28] | 2 x Segmental | 2 x FFF | 0 | Small Neck hematoma in one patient |
| Ferrari et al. (2008) [29] | Sub-total | 1x FFF | 0 | 0 |
| Mücke et al. (2009) [30] | 2 x Segmental | 1 x FFF; 1x ICFF | 0 | 0 |
| Nocini et al. (2009) [31] | 7 x Subtotal | 7 x FFF | 0 | Rupture of mini-plate in one patient |
| Seth et al. (2010) [32] | NR | 11 x FFF | 0 | Prolonged infection in one patient; Fistula and infection in three patients. |
| Bedogni et al. (2011) [33] | NR | 3 x FFF | 1 (a year later) | 0 |
| Pautke et al. (2011) [34] | Segmental | 1 x ICFF | 0 | Fistula resolved with removal of plate |
| Bittner et al. (2012) [35] | Segmental | 1 x SFF | 0 | 0 |
| Ghazali et al. (2013) [36] | Segmental | 1 x FFF | 0 | Sinus bradycardia |
| Hanasono et al. (2013) [37] | 6 x subtotal<br>5 x segmental | 11 x FFF | 1 | Hematoma in one patient; Pneumonia in one patient; Deep vein thrombosis in one patient; Small bowel obstruction in one patient. All complications occurred in FFF |
| Horta et al. (2014) [38] | 1 x segmental | 1 x FFF | 0 | 0 |
| Spinelli et al. (2014) [39] | 8 x subtotal | 8 x FFF | 0 | 0 |
| Vercruysse et al. (2014) [25] | 2 x Partial; 1 x Segmental | 3 x ICFF | 1 (segmental- 16 days later) | 1 (failure) |
| Kim et al. (2015) [40] | NR | 4 x FFF | 0 | 0 |
| Mücke et al. (2016) [41] | NR | 9 x FFF<br>5 x ICFF | NR | NR |
| Neto et al. (2016) [26] | 1 x segmental | 1 x FFF | 0 | 0 |
| Sotsuka et al. (2016) [42] | NR | 1 x FFF | 0 | 0 |
| Caldroney et al. (2017) [43] | 6 x segmental<br>5 x sub total | 4 x SFF<br>7 x FFF | 0 | Two cases with wound infection and dehiscence and one case the plate was removed. (3 different patients). One FFF and two SFF |

Moreover, literature has reported that demography, corticosteroid therapy, systemic factors, and genetic factors have been associated with MRONJ. A recent review report showed a wide-ranging MRONJ incidence from 0 to 27.5% in individuals exposed to intravenous BPs, with a mean incidence of 7%, whereas it ranges from 0.1% to 0.06% in oral administrations [47–49].

Etiopathogenesis of MRONJ is not yet fully understood.

Although no gold standard is currently available for the treatment of jaw osteonecrosis, a number of studies debate which MRONJ stage benefits the most from surgical therapy [24, 50]. In general, for early stages of the disease (MRONJ 0 and I) conservative treatments might be sufficient; surgical treatment should be restricted to advanced stages (MRONJ II and III) or after failure of conservative treatments [7, 50].

The majority of researches as well as AAOMS consider conservative treatments as the treatment of choice of MRONJ.

However, there is not a robust evidence from clinical trials as treatment recommendations mostly come from expert opinions and are, therefore, characterised by a low level of evidence [24, 47].

The authors of the 2009 AAOMS position statement recommend reserving resection and immediate reconstruction to patients with stage III of the disease; however, positive outcomes have been noted in patients with stages II and III. Having said that no recommendations were given on which type of reconstruction was to be considered the most predictable [47]. The benefits of surgical management of MRONJ have been extensively debated in literature and radical surgery seems to offer more predictable and curative

Table 10: Complications during follow-up time.

| Study | Follow-up time | Complications during follow-up (included plate removal) | MRONJ recurrence | Site of recurrence |
|---|---|---|---|---|
| Engroff and Kim (2007) [28] | 2x12 months | 0 | Recurrence in one patient | Contralateral |
| Ferrari et al. (2008) [29] | 1 x 12 months | Plate removal | 0 | 0 |
| Mücke et al. (2009) [30] | 2x 12 months | 0 | 0 | 0 |
| Nocini et al. (2009) [31] | 1x 6 months<br>1 x 16 months<br>1 x 23 months<br>1 x 24 months<br>1 x 19 months<br>1 x 33 months<br>1 x 34 months | 0 | Recurrence in one patient | Margin of the resection |
| Seth et al. (2010) [32] | 1 x 10.0 months<br>1x 0.5 months<br>1x 30.8 months<br>1x 21.4 months<br>1x 17.8 months<br>1x 23.7 months<br>1x 10.6 months<br>1 x 14.2 months<br>1x 13.9 months<br>1x 12.2 months<br>1x 6.1 months | 0 | 0 | 0 |
| Bedogni et al. (2011) [33] | NR | failure of the FFF 1 year later | 0 | 0 |
| Pautke et al. (2011) [34] | NR | plate removal | Recurrence in one patient | On the free flap |
| Bittner et al. (2012) [35] | NR | 0 | 0 | 0 |
| Ghazali et al. (2013) [36] | 24 months | 0 | 0 | 0 |
| Hanasono et al. (2013) [37] | 1 x 13.3 months<br>1x 20.1 months<br>1x 77.0 months<br>1x 23.8 months<br>1x 11.4 months<br>1 x 9.1 months<br>1x 9.1 months<br>1x 9.1 months<br>1x 8.1 months<br>2 x 3.0 months | 0 | 0 | 0 |
| Horta et al. (2014) [38] | 1 x 12 months | 0 | 0 | 0 |
| Spinelli et al. (2014) [39] | 1x 21.7 months<br>1x 25.1 months<br>1x 28.4 months<br>1x 32.2 months<br>1x 37 months<br>1x 28.4 months<br>1x 25.1 months<br>1x 32.9 months | 0 | 0 | 0 |
| Vercruysse et al. (2014) [25] | 1x 36 months<br>1x 65 months<br>1x 76 months | Plate removal in one patient | Recurrence in one patient | Contralateral |
| Kim et al. (2015) [40] | 1 x 99 months<br>1 x 18 months<br>1 x 12 months<br>1 x 7 months | Fracture of plate in one patient | 0 | 0 |
| Mücke et al. (2016) [41] | 34.25 ± 33.3 months | - | Recurrence in one of the patient | Margin of the flap |

Table 10: Continued.

| Study | Follow-up time | Complications during follow-up (included plate removal) | MRONJ recurrence | Site of recurrence |
|---|---|---|---|---|
| Neto et al. (2016) [26] | 1 x 48 months | 0 | 0 | 0 |
| Sotsuka et al. (2016) [42] | NR | 0 | 0 | 0 |
| Caldroney et al. (2017) [43] | 3 x 6 months<br>2 x 44 months<br>1 x 69 months<br>1 x 36 months<br>1 x 28 months<br>1 x 10 months<br>1 x 17 months<br>1 x 11 months | Plate removal in one patient | 0 | 0 |

results. However, surgical treatment of early stages of MRONJ remains controversial [47, 50–52].

Aggressive radical surgery is offered only to symptomatic patients with extensive osteonecrosis, including those who have previously failed conservative treatments [41].

This review has indicated that surgical therapy may represent a treatment option for patients affected by MRONJ stage III resulting in high success rates. Mucke et al. and Caldroney et al. have documented excellent outcomes in treating patient affected by MRONJ stage III in large cohort studies [30, 43]. Since 2008 microvascular reconstruction of the jaw has been documented as a viable option for MRONJ. This systematic review confirmed that microsurgical reconstruction therapy represents a feasible alternative in case of treatment escalation.

Even though the majority of papers included in this study were case reports and small case studies, the outcome of free flap treatment has been promising with a significant low recurrence of MRONJ and minimal surgical complications [25, 26, 28–43].

The MRONJ recurrence rate found by this systematic review was 6.02% (5 patients). The predominant recurrence sites were the contralateral unresected part of the jaw (2 cases) and the margin of the resection (2 cases), both bearing an overall recurrence rate of 2.40%. Just one case of recurrence was found on the vascular reconstruction.

Infection was the most frequent complication found with 6.02% incidence. The overall free flap success rate was 96.39%. Three free flaps failed during a follow-up period ranging from 2 weeks up to 99 months.

Amongst all the types of reconstruction, free flap fibula was the most chosen, followed by iliac crest and scapula with success rates, respectively, of 97.60%, 98.80%, and 100%.

Antiresorptive drugs were explicitly discontinued in only three studies out of the eighteen, while no mention was reported in the remaining studies [31, 33, 41]. It is unclear if the discontinuation strategy leads to a better surgical outcome due to the long skeletal life of some antiresorptive drugs.

In line with the growing body of literature, our findings confirm positive results in treating patients with MRONJ using free flaps microvascular reconstruction. In order to obtain a possible resolution of MRONJ, patients with reasonable life expectancy should be considered for microvascular flap reconstruction after aggressive resection of the diseased bone.

## 5. Conclusion

MRONJ is a significant adverse effect amongst patients under antiresorptive agents. Although MRONJ pathogenesis remains unclear, significant progress has been made with respect to the diagnosis and staging of the disease, as well as with risk-reduction strategies and treatments. This systematic review based on multiple-reviewer quality assessment criteria was only able to select articles that meet Level 4 of the Oxford Evidence-based medicine scale. Due to the nature of the MRONJ incidence and the critical condition of the patients affected by the primary disease, it is difficult to improve the quality of evidence unless a common effort is applied. Therefore, the authors believe that additional quality studies, such as control multicentre studies or case-controlled studies, are necessary to support the hypothesis of this study.

## Conflicts of Interest

This study was not supported by any company and all the authors have not conflicts of interest.

## Authors' Contributions

All the authors of this manuscript have substantial contributions to the conception or design of the work; to the acquisition, analysis, or interpretation of data for the work; to draft of the paper and revising it critically and finally approved the version to be published.

## References

[1] R. E. Marx, "Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic," *Journal of Oral and Maxillofacial Surgery*, vol. 61, no. 9, pp. 1115–1117, 2003.

[2] S. L. Ruggiero, B. Mehrotra, T. J. Rosenberg, and S. L. Engroff, "Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases," *Journal of Oral and Maxillofacial Surgery*, vol. 62, no. 5, pp. 527–534, 2004.

[3] S. Sivolella, F. Lumachi, E. Stellini, and L. Favero, "Denosumab and anti-angiogenetic drug-related osteonecrosis of the jaw: An uncommon but potentially severe disease," *Anticancer Reseach*, vol. 33, no. 5, pp. 1793–1798, 2013.

[4] A. R. Santos-Silva, G. A. Belizário Rosa, G. D. Castro Júnior, R. B. Dias, A. C. Prado Ribeiro, and T. B. Brandão, "Osteonecrosis of the mandible associated with bevacizumab therapy," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 115, no. 6, pp. e32–e36, 2013.

[5] L. Ramirez, R. M. Lopez, and E. Casanas, "New non-bisphosphonate drugs that produce osteonecrosis of the jaws," *Oral Health and Preventive Dentistry*, vol. 13, pp. 385–393, 2015.

[6] A. Brunello, G. Saia, A. Bedogni, D. Scaglione, and U. Basso, "Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma," *Bone*, vol. 44, no. 1, pp. 173–175, 2009.

[7] S. L. Ruggiero, T. B. Dodson, and J. Fantasia, "American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update," *Journal of Oral and Maxillofacial Surgery*, vol. 72, no. 10, pp. 1938–1956, 2014.

[8] D. Rosella, P. Papi, R. Giardino, E. Cicalini, L. Piccoli, and G. Pompa, "Medication-related osteonecrosis of the jaw: Clinical and practical guidelines," *Journal of International Society of Preventive and Community Dentistry*, vol. 6, no. 2, pp. 97–104, 2016.

[9] S. R. Nussbaum, J. Younger, C. J. Vandepol et al., "Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: Comparison of 30-, 60-, and 90-mg dosages," *American Journal of Medicine*, vol. 95, no. 3, pp. 297–304, 1993.

[10] J. R. Berenson, B. E. Hillner, R. A. Kyle et al., "American society of clinical oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma," *Journal of Clinical Oncology*, vol. 20, no. 17, pp. 3719–3736, 2002.

[11] G. Campisi, S. Fedele, V. Fusco, G. Pizzo, O. Di Fede, and A. Bedogni, "Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents," *Future Oncology*, vol. 10, no. 2, pp. 257–275, 2014.

[12] A. Khan, A. Morrison, S. Ruggiero et al., "Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus," *Journal of Bone and Mineral Research*, vol. 30, no. 1, pp. 3–23, 2015.

[13] K. Vahtsevanos, A. Kyrgidis, E. Verrou et al., "Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw," *Journal of Clinical Oncology*, vol. 27, no. 32, pp. 5356–5362, 2009.

[14] F. Saad, J. E. Brown, C. Van Poznak 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," *Annals of Oncology*, vol. 23, no. 5, pp. 1341–1347, 2012.

[15] M. J. Heufelder, J. Hendricks, T. Remmerbach, B. Frerich, A. Hemprich, and F. Wilde, "Principles of oral surgery for prevention of bisphosphonate-related osteonecrosis of the jaw," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 117, no. 6, pp. e429–e435, 2014.

[16] J. B. B. Weber, R. S. Camilotti, and M. E. Ponte, "Efficacy of laser therapy in the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ): a systematic review," *Lasers in Medical Science*, vol. 31, no. 6, pp. 1261–1272, 2016.

[17] C. Pautke, F. Bauer, S. Otto et al., "Fluorescence-guided bone resection in bisphosphonate-related osteonecrosis of the jaws: First clinical results of a prospective pilot study," *Journal of Oral and Maxillofacial Surgery*, vol. 69, no. 1, pp. 84–91, 2011.

[18] L. Montebugnoli, L. Felicetti, D. B. Gissi, A. Pizzigallo, G. A. Pelliccioni, and C. Marchetti, "Biphosphonate-associated osteonecrosis can be controlled by nonsurgical management," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 104, no. 4, pp. 473–477, 2007.

[19] T. van den Wyngaert, T. Claeys, M. T. Huizing, J. B. Vermorken, and E. Fossion, "Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome," *Annals of Oncology*, vol. 20, no. 2, pp. 331–336, 2009.

[20] C. Klingelhöffer, F. Zeman, J. Meier, T. E. Reichert, and T. Ettl, "Evaluation of surgical outcome and influencing risk factors in patients with medication-related osteonecrosis of the jaws," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 44, no. 10, pp. 1694–1699, 2016.

[21] B. Atalay, S. Yalcin, Y. Emes et al., "Bisphosphonate-related osteonecrosis: Laser-assisted surgical treatment or conventional surgery?" *Lasers in Medical Science*, vol. 26, no. 6, pp. 815–823, 2011.

[22] S. Otto, C. Schreyer, S. Hafner et al., "Bisphosphonate-related osteonecrosis of the jaws - Characteristics, risk factors, clinical features, localization and impact on oncological treatment," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 40, no. 4, pp. 303–309, 2012.

[23] P. J. Voss, J. Joshi Oshero, A. Kovalova-Müller et al., "Surgical treatment of bisphosphonate-associated osteonecrosis of the jaw: Technical report and follow up of 21 patients," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 40, no. 8, pp. 719–725, 2012.

[24] R. E. Marx, Y. Sawatari, M. Fortin, and V. Broumand, "Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment," *Journal of Oral and Maxillofacial Surgery*, vol. 63, no. 11, pp. 1567–1575, 2005.

[25] H. Vercruysse, T. D. Backer, and M. Y. Mommaerts, "Outcomes of osseous free flap reconstruction in stage III bisphosphonate-related osteonecrosis of the jaw: Systematic review and a new case series," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 42, no. 5, pp. 377–386, 2014.

[26] T. Neto, R. Horta, R. Balhau et al., "Resection and microvascular reconstruction of bisphosphonate-related osteonecrosis of the jaw: The role of microvascular reconstruction," *Head & Neck*, vol. 38, no. 8, pp. 1278–1285, 2016.

[27] R. Sacco, G. Sacco, A. Acocella, S. Sale, N. Sacco, and E. Baldoni, "A systematic review of microsurgical reconstruction of the jaws using vascularized fibula flap technique in patients with bisphosphonate-related osteonecrosis," *Journal of Applied Oral Science*, vol. 19, no. 4, pp. 293–300, 2011.

[28] S. L. Engroff and D. Coletti, "Bisphosphonate related osteonecrosis of the palate: report of a case managed with free tissue transfer," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 105, no. 5, pp. 580–582, 2008.

[29] S. Ferrari, B. Bianchi, A. Savi et al., "Fibula Free Flap With Endosseous Implants for Reconstructing a Resected Mandible

in Bisphosphonate Osteonecrosis," *Journal of Oral and Maxillofacial Surgery*, vol. 66, no. 5, pp. 999–1003, 2008.

[30] T. Mücke, S. Haarmann, K.-D. Wolff, and F. Hölzle, "Bisphosphonate related osteonecrosis of the jaws treated by surgical resection and immediate osseous microvascular reconstruction," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 37, no. 5, pp. 291–297, 2009.

[31] P. F. Nocini, G. Saia, G. Bettini et al., "Vascularized fibula flap reconstruction of the mandible in bisphosphonate-related osteonecrosis," *European Journal of Surgical Oncology*, vol. 35, no. 4, pp. 373–379, 2009.

[32] R. Seth, N. D. Futran, D. S. Alam, and P. D. Knott, "Outcomes of vascularized bone graft reconstruction of the mandible in bisphosphonate-related osteonecrosis of the jaws," *The Laryngoscope*, vol. 120, no. 11, pp. 2165–2171, 2010.

[33] A. Bedogni, G. Saia, G. Bettini et al., "Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis," *Oral Oncology*, vol. 47, no. 5, pp. 420–424, 2011.

[34] C. Pautke, S. Otto, S. Reu et al., "Bisphosphonate related osteonecrosis of the jaw - Manifestation in a microvascular iliac bone flap," *Oral Oncology*, vol. 47, no. 5, pp. 425–429, 2011.

[35] T. Bittner, N. Lorbeer, T. Reuther, H. Böhm, A. C. Kübler, and U. D. A. Müller-Richter, "Hemimandibulectomy after bisphosphonate treatment for complex regional pain syndrome: A case report and review on the prevention and treatment of bisphosphonate-related osteonecrosis of the jaw," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 113, no. 1, pp. 41–47, 2012.

[36] N. Ghazali, J. C. Collyer, and J. V. Tighe, "Hemimandibulectomy and vascularized fibula flap in bisphosphonate-induced mandibular osteonecrosis with polycythaemia rubra vera," *International Journal of Oral and Maxillofacial Surgery*, vol. 42, no. 1, pp. 120–123, 2013.

[37] M. M. Hanasono, O. N. Militsakh, J. D. Richmon, E. L. Rosenthal, and M. K. Wax, "Mandibulectomy and free flap reconstruction for bisphosphonate-related osteonecrosis of the jaws," *JAMA Otolaryngology - Head and Neck Surgery*, vol. 139, no. 11, pp. 1135–1142, 2013.

[38] R. Horta, D. Monteiro, T. Neto et al., "Microsurgical reconstruction for radiation- and bisphosphonate-induced mandible osteonecrosis based on patient-specific physiopathologic mechanisms," *The Journal of Craniofacial Surgery*, vol. 25, no. 5, pp. 1793–1796, 2014.

[39] G. Spinelli, M. Torresetti, D. Lazzeri et al., "Microsurgical reconstruction after bisphosphonate-related osteonecrosis of the jaw: Our experience with fibula free flap," *The Journal of Craniofacial Surgery*, vol. 25, no. 3, pp. 788–792, 2014.

[40] H. Kim, J. Hwang, and K. Ahn, "Fibula Free Flap for Mandibular Reconstruction using Simulation Surgery in Bisphosphonate related Osteonecrosis of the Jaw," *Journal of International Society for Simulation Surgery*, vol. 2, no. 1, pp. 1–6, 2015.

[41] T. Mücke, M. Jung, S. Koerdt, D. A. Mitchell, D. Loeffelbein, and M. R. Kesting, "Free flap reconstruction for patients with bisphosphonate related osteonecrosis of the jaws after mandibulectomy," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 44, no. 2, pp. 142–147, 2016.

[42] Y. Sotsuka, T. Fujiwara, K. Kawai, S. Nishimoto, and M. Kakibuchi, "Bilateral Maxillary Reconstruction Using Fibular Flap in Bisphosphonate-related Osteonecrosis," *Plastic and Reconstructive Surgery - Global Open*, vol. 4, no. 9, p. e1045, 2016.

[43] S. Caldroney, N. Ghazali, D. Dyalram, and J. E. Lubek, "Surgical resection and vascularized bone reconstruction in advanced stage medication-related osteonecrosis of the jaw," *International Journal of Oral and Maxillofacial Surgery*, vol. 46, no. 7, pp. 871–876, 2017.

[44] A. Liberati, D. G. Altman, J. Tetzlaff et al., "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration," *British Medical Journal*, vol. 339, Article ID b2700, 2009.

[45] D. H. Henry, L. Costa, F. Goldwasser et al., "Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma," *Journal of Clinical Oncology*, vol. 29, no. 9, pp. 1125–1132, 2011.

[46] P. P. L. Fung, G. Bedogni, A. Bedogni et al., "Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study," *Oral Diseases*, vol. 23, no. 4, pp. 477–483, 2017.

[47] S. L. Ruggiero, T. B. Dodson, L. A. Assael, R. Landesberg, R. E. Marx, and B. Mehrotra, "American association of oral and maxillofacial surgeons postion paper on bisphosphonate-related osteonecrosis of the jaws," *Journal of Oral and Maxillofacial Surgery*, vol. 67, no. 5, supplement 1, pp. 2–12, 2009.

[48] S. Kühl, C. Walter, S. Acham, R. Pfeffer, and J. T. Lambrecht, "Bisphosphonate-related osteonecrosis of the jaws—a review," *Oral Oncology*, vol. 48, no. 10, pp. 938–947, 2012.

[49] I. C. Benlidayi and R. Guzel, "Oral bisphosphonate related osteonecrosis of the jaw: a challenging adverse effect," *ISRN Rheumatology*, vol. 2013, Article ID 215034, 6 pages, 2013.

[50] P. Stockmann, E. Vairaktaris, F. Wehrhan et al., "Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: A prospective clinical study with 12 months follow-up," *Supportive Care in Cancer*, vol. 18, no. 4, pp. 449–460, 2010.

[51] S. L. Ruggiero, "Emerging Concepts in the Management and Treatment of Osteonecrosis of the Jaw," *Oral and Maxillofacial Surgery Clinics of North America*, vol. 25, no. 1, pp. 11–20, 2013.

[52] Z. Jabbour, M. El-Hakim, P. Mesbah-Ardakani, J. E. Henderson, and R. Albuquerque Jr., "The outcomes of conservative and surgical treatment of stage 2 bisphosphonate-related osteonecrosis of the jaws: A case series," *International Journal of Oral and Maxillofacial Surgery*, vol. 41, no. 11, pp. 1404–1409, 2012.

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*Review Article*

# Stomatitis and VEGFR-Tyrosine Kinase Inhibitors (VR-TKIs): A Review of Current Literature in 4369 Patients

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*Background*. Multitargeted tyrosine kinase inhibitors (TKIs) represent a new class of target-specific antineoplastic agents. These agents show some specific adverse events such as fatigue/asthenia, anorexia/loss of appetite, dysgeusia, diarrhea/abdominal pain, hypothyroidism, hypertension, myelosuppression, and stomatitis. *Materials and Methods*. A systematic search was performed on PubMed online database using a combination of MESH terms and free text words, "sunitinib" OR "sorafenib" OR "axitinib" OR "cabozantinib" OR "pazopanib" OR "regorafenib" OR "nintedanib" OR "vatalanib" combined through the use of Boolean operator AND with the key words "stomatitis" OR "mucositis," (i) on human subjects, (ii) written in the English language, and (iii) reporting about the incidence of stomatitis or oral mucositis. *Results*. The incidence of stomatitis of any grade was 35.2% for sunitinib, 20.52% for sorafenib, 20.63% for axitinib, and 34.21% for cabozantinib. All the agents showed high rates of low-grade stomatitis (G1-G2), while the onset of severe stomatitis (G3-G4) was very low. *Conclusions*. Analysis of the reports with patients treated with sunitinib, sorafenib, axitinib, and cabozantinib showed a clear prevalence of stomatitis grade 1 or grade 2. These data differ from those of patients treated with conventional chemotherapy in which mucositis is predominantly of grade 3 or grade 4.

## 1. Introduction

Traditional treatment of malignancies with chemotherapeutic agents often causes the damage of normal healthy cells [1]. Toxicities of the oral cavity, such as mucositis and stomatitis, are some of the most significant and unavoidable side effects associated with cancer treatment [2]. Oral toxicities have a huge impact on the patient with cancer and are a common cause of dose delays and interruptions of cancer therapy [3]. The terms "oral mucositis" and "stomatitis" are often used interchangeably to indicate oral complications of anticancer therapy, but they do not refer to the same process (Parkhill, 2013). Oral mucositis is a Medical Subject Headings term that describes inflammation of oral mucosa due to chemotherapeutic agents or ionizing radiation. Stomatitis is a less specific term used to describe any inflammatory condition of oral tissue. For such reason in the last decades, newer targeted agents have been developed, aiming to decrease the rates of side effects on healthy cells.

Multitargeted tyrosine kinase inhibitors (TKIs) represent a novel class of target-specific antineoplastic agents. The mechanism of action of this class of drugs is based on the block of several key tyrosine kinase pathways in human cancers, including the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and platelet-derived growth factor receptor (PDGFR) [4–6]. Molecules that inhibit VEGFR-Tyrosine Kinase Inhibitors (VR-TKIs) are an emerging class of highly effective targeted therapies due to their demonstrated efficacy in a variety of malignancies [5, 7–12]. FDA-approved VR-TKIs include sorafenib (renal cell carcinoma [RCC], hepatocellular carcinoma [HCC], and thyroid cancer), sunitinib (RCC, HCC, and gastrointestinal stromal tumor [GIST]), pazopanib (RCC and soft tissue sarcomas), cabozantinib (metastatic medullary thyroid cancer), and regorafenib (GIST and colorectal carcinoma [CRC]) [9, 10, 13–17].

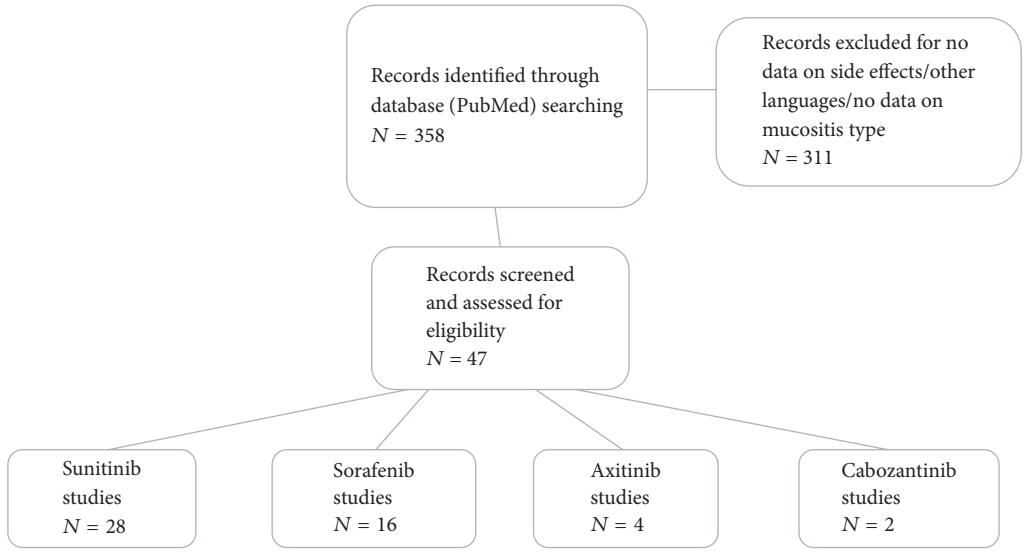


Figure 1: Flow chart showing the process of papers selection used in this review.

Even this kind of targeted therapy based on VR-TKIs showed some class-specific adverse events that include fatigue/asthenia, anorexia/loss of appetite, hand-foot skin reaction, stomatitis, dysgeusia, diarrhea/abdominal pain, hypothyroidism, hypertension, and myelosuppression [63–66]. Literature reported that 25% of patients treated with multitargeted angiogenesis kinase inhibitors develop an oral adverse event within 2 months of therapy [67].

## 2. Materials and Methods

The following review was performed to answer to the following question: "which is the rate of incidence of oral stomatitis in patients treated with VEGF TKIs?"

A systematic search was performed on the PubMed online database using a combination of MESH terms and free text words, "sunitinib" (free text) OR "sorafenib" (free text) OR "axitinib" (free text) OR "cabozantinib" (free text) OR "pazopanib" (free text) OR "regorafenib" (free text) OR "nintedanib" (free text) OR "vatalanib" (free text) combined through the use of Boolean operator AND with the key words "stomatitis" (MESH) OR "mucositis" (MESH), (i) performed on human subjects, (ii) reporting about the use of an mTOR inhibitor, (iii) written in the English language, and (iv) reporting about the incidence of stomatitis or oral mucositis.

Case reports and studies on animal model were excluded from this study. No restrictions were applied to the year of publication.

For each study, the following records were extracted: name of the first author, year of publication, number of patients enrolled, type of disease treated, number of events recorded, and grade of the events reported. To simplify the process of data extraction, an ad hoc extraction sheet was used. In addition, data were independently extracted by two authors (Lorenzo Lo Muzio and Claudia Arena) and checked in a joint session.

## 3. Results

*3.1. Bibliographic Research.* Titles and abstract of 358 potentially relevant studies were screened; of these, 311 studies were excluded because they did not meet the inclusion criteria (Figure 1). The full texts of 47 studies were read. Of the included studies, 28 referred to sunitinib use, 16 to sorafenib, 4 to axitinib, and 2 to cabozantinib. Of these, 5 referred to both sunitinib and sorafenib and 2 referred to both axitinib and sorafenib.

*3.2. Analysis of Data.* For sunitinib, 28 studies were analyzed (Table 1). A total of 2.596 patients were treated with sunitinib. The overall incidence of stomatitis of any grade with treatment was 35.2% (914 patients). Studies reported data about grade of stomatitis for 2068 patients and 739 cases were grade 1/2 (35.73%) and 90 were grade 3/4 (5.35%).

For sorafenib, 16 studies were analyzed (Table 2). A total of 1218 patients were treated with sorafenib. The overall incidence of stomatitis of any grade with treatment was 20.52% (250 patients). Studies reported data about grade of stomatitis for 830 patients and 174 cases were grade 1/2 (20.96%) and 19 were grade 3/4 (2.28%).

For axitinib, 4 studies were analyzed (Table 3). A total of 441 patients were treated with axitinib. The overall incidence of stomatitis of any grade with axitinib treatment was 20.63% (91 patients) and 79 cases were grade 1/2 (17.91%) and 12 were grade 3/4 (2.72%).

For cabozantinib, 2 studies were analyzed (Table 4). A total of 114 patients were treated with cabozantinib. The overall incidence of stomatitis of any grade with cabozantinib treatment was 34.21% (39 patients) and 34 cases were grade 1/2 (29.82%) and 5 were grade 3/4 (4.38%).

## 4. Discussion

Targeted therapy is a kind of chemotherapy that inhibits a molecular target which is abnormally expressed in malignancy.

Table 1: Report on all papers about sunitinib and stomatitis.

| | Authors | Year | Neoplasia | Number of cases | Stomatitis number | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| (1) | Arakawa-Todo et al. [18] | 2013 | Metastatic renal cell carcinoma<br>A: sunitinib 50 mg once daily was given in repeated 6-week cycles of 4 weeks followed by 2 weeks off | A: 15 | TOT: 9 (60%) | A: 9 (60%) | | A: 0 | |
| (2) | Armstrong et al. [19] | 2016 | Metastatic nonclear renal cell carcinoma<br>A: sunitinib 50 mg/day; 6-week cycles of 4 weeks with treatment followed by 2 weeks without treatment | A: 51 | A: 14 (27.45%) | A: 14 (27%) | | A: 0 | |
| (3) | Bang et al. [20] | 2011 | Advanced gastric cancer<br>A: sunitinib 50 mg/day for 4 weeks on treatment and 2 weeks off | A: 78 | A: 28 (35.9%) | A: 27 (34.6%) | | A: 1 (1.3%) | |
| (4) | Cardoso et al. [21] | 2012 | HER2-positive metastatic breast cancer<br>A: sunitinib 37.5 mg (starting dose across sunitinib combination studies) once daily by oral capsule on schedule 2/1 | A: 25 | A: 12 (48%) | A: 9 (36%) | | A: 3 (12%) | |
| (5) | Carrato et al. [22] | 2013 | Metastatic colorectal cancer randomized phase III trial<br>A: sunitinib plus FOLFIRI (fluorouracil, leucovorin, and irinotecan) | A: 386 | A: 35 (9%) | Not reported | | A: 35 (9%) | |
| (6) | Dirican et al. [23] | 2013 | Metastatic renal cell carcinoma<br>A: sunitinib: 50 mg per day was administered in repeated 6-week cycles of daily therapy for 4 weeks, followed by 2 weeks off | A: 23 | A: 6 (26.1%) | A: 4 (17.4%) | | A: 2 (8.7%) | |

Table 1: Continued.

| | Authors | Year | Neoplasia | Number of cases | Stomatitis number | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| (7) | Domagala-Haduch et al. [24] | 2016 | Advanced renal cell carcinoma<br>A: sunitinib: 50 mg/day for 4 weeks, and then it is stopped for 2 weeks | A: 39 | A: 13 (33.3%) | A: 11 (28.2%) | | A: 2 (5.1%) | |
| (8) | Goodman et al. [25] | 2007 | Refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma<br>A: sunitinib: 50 mg given daily for 4 weeks followed by a 2-week rest period (schedule 4/2) | A: 202 | A: 58 (29%) | A: 56 (27.7%) | | A: 2 (1%) | |
| (9) | Grünwald et al. [26] | 2011 | Metastatic renal cell carcinoma (RCC)<br>IL-21 administered subcutaneously (s.c.) in combination with sunitinib 50 mg once daily (OD) orally at the 4 weeks on/2 weeks off<br>A: rIL-21 3 $\mu$g/kg<br>B: rIL-21 10 $\mu$g/kg | A: 5<br>B: 4 | TOT: 4 (80%)<br>TOT: 1 (25%) | A: 4 (80%)<br>B: 1 (25%) | | A: 0<br>B: 0 | |
| (10) | Hong et al. [27] | 2009 | Advanced renal cell carcinoma patients<br>A: sunitinib (50 mg for 4 weeks on/2 weeks off schedule)<br>B: sunitinib 37.5 mg daily continuous dosing | A: 62<br>B: 14 | TOT: 48 (63.2%) | TOT: 40 (64.5%) | | TOT: 8 (10.5%) | |
| (11) | O'Donnell [28] | 2011 | Advanced renal cell carcinoma (RCC)<br>A: sunitinib<br>Seven patients started at a dose of 50 mg daily and nine patients started at a dose of 37.5 mg daily. The remaining three patients started at 25 mg daily | TOT: 19 | A: 8 (42.1%) | A: 7 (36.9%) | | A: 1 (5.26%) | |

Table 1: Continued.

| | Authors | Year | Neoplasia | Number of cases | Stomatitis number | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| (12) | Kim et al. [29] | 2014 | The starting sunitinib dose was 37.5 and 50 mg for 12 and 22 patients, respectively. A 4 weeks on/2 weeks off regimen was followed for 31 patients; a 2 weeks on/2 weeks off regimen for one patient; and a daily regimen for two patients | A: 34 | A: 13 (39%) | A: 10 (30%) | | A: 3 (9%) | |
| (13) | Lee et al. [30] | 2010 | Metastatic renal cell carcinoma<br>A: 6-week cycles of sunitinib treatment (50 mg once daily for 4 weeks on and 2 weeks off schedule) | A: 21 | A: 9 (42.8%) | A: 5 (23.8%) | | A: 4 (19%) | |
| (14) | Lee et al. [31] | 2015 | treatment-naïve patients with clear cell type metastatic renal cell carcinoma (mRCC)<br>A: sunitinib 50 mg, "2 weeks on, 1 week off"<br>B: sunitinib 50 mg, 4 weeks on, 2 weeks off | A: 38<br>B: 36 | A: 27 (71%)<br>B: 31 (86%) | A: 26 (68.4%)<br>B: 27 (75%) | | A: 1 (3%)<br>B: 4 (11%) | |
| (15) | Lee et al. [32] | 2013 | A: SU: 37.5 mg/die + oral capecitabine 800 mg/m$^2$ + cisplatin 60 mg/m$^2$<br>B: SU: 37.5 mg/die + oral capecitabine 1,000 mg/m$^2$ + cisplatin 60 mg/m$^2$<br>C: SU: 25 mg/die + oral capecitabine 1,000 mg/m$^2$ + cisplatin 80 mg/m$^2$<br>D: SU: 37.5 mg/die + oral capecitabine 800 mg/m$^2$ + oxaliplatin 110 mg/m$^2$<br>E: SU: 37.5 mg/die + oral capecitabine 1,000 mg/m$^2$ + oxaliplatin 110 mg/m$^2$<br>F: SU: 25 mg/die + oral capecitabine 1,000 mg/m$^2$ + oxaliplatin 110 mg/m$^2$ | A: 6<br>B: 7<br>C: 15<br>D: 23<br>E: 3<br>F: 22 | A: 5 (83.3%)<br>B: 3 (42.9%)<br>C: 8 (53.3%)<br>D: 10 (43.5%)<br>E: 1 (33.3%)<br>F: 7 (31.8%) | A: 5 (83.3%)<br>B: 3 (42.9%)<br>C: 6 (40%)<br>D: 10 (43.5%)<br>E: 1 (33.3%)<br>F: 7 (31.8%) | | A: 0<br>B: 0<br>C: 2 (13.3%)<br>D: 0<br>E: 0<br>F: 0 | |
| (16) | Lee et al. [6] | 2009 | Retrospective study<br>A: sorafenib 400 mg twice daily for RCC and HCC<br>B: sunitinib 50 mg daily, consisting of 4 weeks of treatment followed by a 2-week rest period in cycles of 6 weeks for RCC and GIST | A: 109<br>B: 119 | A: 28 (26%)<br>B: 43 (36%) | Not reported | | Not reported | |
| (17) | Marschner et al. [33] | 2017 | mRCC<br>A: sorafenib<br>B: sunitinib | A: 25<br>B: 152 | A: 3 (12.0%)<br>B: 29 (23.2%) | A: 2 (8%)<br>B: 27 (17.7%) | | A: 1 (4.0%)<br>B: 2 (1.6%) | |
| (18) | Mir et al. [34] | 2016 | mRCC<br>A: sunitinib 50 mg once daily for 4 weeks | A: 50 | A: 24 (12%) | A: 20 (40%) | | A: 4 (2%) | |

Table 1: Continued.

| | Authors | Year | Neoplasia | Number of cases | Stomatitis number | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| (19) | Patel et al. [35] | 2009 | Advanced renal cell carcinoma<br>A: temsirolimus 15 mg was administered by intravenous (I.V.) infusion once weekly, and sunitinib 25 mg was administered orally once daily for 4 weeks, followed by a 2-week rest period. | A: 3 | A: 1 | A: 1 (33.3%) | | A: 0 | |
| (20) | Porta et al. [36] | 2011 | mRCC<br>A: sunitinib<br>B: sorafenib | A: 85<br>B: 60 | A: 50 (58.8%)<br>B: 16 (26.7%) | A: 48 (56.4%)<br>B: 16 (26.7%) | | A: 2 (2.4%)<br>B: 0 | |
| (21) | Rock et al. [37] | 2007 | GIST<br>A: sunitinib 50 mg | A: 202 | A: 58 (29%) | A: 56 (27.7%) | | A: 2 (1%) | |
| (22) | Socinski et al. [38] | 2008 | Advanced non-small cell lung cancer<br>A: sunitinib 50 mg/d for 4 weeks followed by 2 weeks of no treatment in a 6-week cycle | A: 63 | A: 27 (43%) | A: 27 (43%) | | A: 0 | |
| (23) | Sonpavde et al. [39] | 2010 | Metastatic castration-resistant prostate cancer<br>A: sunitinib 50 mg/day: 4 weeks on followed by 2 weeks off | A: 36 | A: 2 (5.7%) | A: 1 | | A: 1 | |
| (24) | Sternberg et al. [40] | 2015 | Metastatic renal cell carcinoma (mRCC)<br>A: oral sunitinib 50 mg/day on a 4 weeks on/2 weeks off schedule | A: 521 | A: 192 (37%) | A: 159 (31%) | | A: 33 (6%) | |
| (25) | Van Der Veldt et al. [41] | 2008 | Advanced RCC<br>A: sunitinib 50 mg daily for 4-week treatment followed by 2-week rest period in a cycle of 6 weeks | A: 82 | A: 58 (70.73%) | A: 51 (62%) | | A: 7 (9%) | |
| (26) | Yildiz et al. [42] | 2011 | Advanced renal cell carcinoma<br>A: sunitinib 37.5 mg daily<br>B: sunitinib 25 mg | A: 67 | A: 36 (51%) | A: 36 (51%) | | A: 0 | |
| (27) | Yoo et al. [43] | 2010 | Renal cell carcinoma<br>A: sunitinib 50 and 37.5 mg daily | A: 65 | A: 37 (57%) | A: 31 (50%) | | A: 6 (10%) | |

Table 1: Continued.

| | Authors | Year | Neoplasia | Number of cases | Stomatitis number | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| (28) | Zhao et al. [44] | 2013 | Locally advanced clear cell renal carcinoma<br>A: sorafenib 400 mg orally twice daily for a 4-week cycle<br>B: sunitinib 50 mg orally daily for a 6-week cycle | A: 20<br>B: 23 | A: 8 (40%)<br>B: 7 (30%) | Not reported | | Not reported | |
| Total | | | | 2.596 | 914 (35.2%) | | | | |
| Total with grade | | | | 2.068 | 829 (40.08%) | 739 (35.73%) | | 90 (5.35%) | |
| Total not reporting grade* | | | | 142 | 50 (3.52%) | Not reported | | Not reported | |
| Total reporting only grade >2** | | | | 386 | 35 (0.06%) | Not reported | | 35 (0.06%) | |

*Note*. *Carrato et al. (2013) [22] did not report the grade of stomatitis; **Lee et al. (2009) [6] and Zhao et al. (2013) [44] reported the incidence rates limited to grade 3 and grade 4 treatment-related toxicities; for this reason, data about cases of stomatitis and stomatitis grades 1 and 2 are lower than real.

Table 2: Report on all papers about sorafenib and stomatitis.

| | Authors | Year | Neoplasia | Cases number | Stomatitis (%) | Stomatitis grade 1% | Stomatitis grade 2% | Stomatitis grade 3% | Stomatitis grade 4% |
|---|---|---|---|---|---|---|---|---|---|
| (1) | Cho et al. [45] | 2013 | Advanced hepatocellular carcinoma<br>A: sorafenib 400 mg twice daily | A: 99 | A: 4 (4%) | Not reported | | Not reported | |
| (2) | Chrisoulidou et al. [46] | 2015 | Refractory thyroid cancer<br>Sorafenib 400 mg was given orally twice daily continuously, sunitinib 50 mg was given once daily on a 4 weeks of treatment followed by 2-week intervals without therapy, and vandetanib 300 mg was given once daily | A: 24 | A: 13 (54%) | A: 12 (50%) | | A: 1 (4.16%) | |
| (3) | Grignani et al. [47] | 2015 | Unresectable high-grade osteosarcoma progressing after standard treatment<br>400 mg sorafenib twice a day together with 5 mg everolimus once a day | A: 38 | A: 20 (52.63%) | Not reported | | Not reported | |
| (4) | Hainsworth et al. [48] | 2015 | Stage III/IV epithelial ovarian cancer<br>A: paclitaxel 175 mg/m2, 1–3 h IV infusion/carboplatin AUC 6.0, 20 min IV infusion/sorafenib 400 mg PO BID | A: 43 | A: 16 (37%) | Oral mucositis<br>A: 16 (37%) | | A: 0 | |
| (5) | Hainsworth et al. [49] | 2013 | Phase II<br>Sorafenib 200 mg PO BID and everolimus 35 mg PO once weekly | A: 75 | A: 10 (13.3%) | Mucositis/stomatitis: 10/14%<br>Mucositis/stomatitis: 2/3% | | Mucositis/stomatitis: 0<br>Mucositis/stomatitis: 0 | |
| (6) | Lee et al. [6] | 2009 | Retrospective study<br>A: sorafenib 400 mg twice daily for RCC and HCC<br>B: sunitinib 50 mg daily, consisting of 4 weeks of treatment followed by a 2-week rest period in cycles of 6 weeks for RCC and GIST | A: 109<br>B: 119 | A: 28 (26%)<br>B: 43 (36%) | Not reported | | Not reported | |

Table 2: Continued.

| | Authors | Year | Neoplasia | Cases number | Stomatitis (%) | Stomatitis grade 1% | Stomatitis grade 2% | Stomatitis grade 3% | Stomatitis grade 4% |
|---|---|---|---|---|---|---|---|---|---|
| (7) | Marschner et al. [33] | 2017 | mRCC<br>A: sorafenib<br>B: sunitinib | A: 25<br>B: 152 | A: 3 (12.0%)<br>B: 29 (23.2%) | A: 2 (8%)<br>B: 27 (17.7%) | | A: 1 (4.0%)<br>B: 2 (1.6%) | |
| (8) | Meyer et al. [50] | 2017 | Unresectable HCC<br>A: sorafenib 660 mg | A: 157 | A: 41 (26%) | A: 36 (23%) | | A: 5 (3%) | |
| (9) | Porta et al. [51] | 2011 | mRCC<br>A: sunitinib<br>B: sorafenib | A: 85<br>B: 60 | A: 50 (58.8%)<br>B: 16 (26.7%) | A: 48 (56.4%)<br>B: 16 (26.7%) | | A: 2 (2.4%)<br>B: 0 | |
| (10) | Richly et al. [52] | 2006 | Refractory solid tumors<br>A: sorafenib 100 mg + doxorubicin<br>B: sorafenib 200 mg + doxorubicin<br>C: sorafenib 400 mg + doxorubicin<br>D: sorafenib 400 mg + doxorubicin | A: 6<br>B: 6<br>C: 12<br>D: 10 | TOT 11 (32%) | Not reported | | A: 3 (50%)<br>B: -<br>C: 6 (50%)<br>D: 2 (20%) | |
| (11) | Schwartzberg et al. [53] | 2013 | Advanced breast cancer<br>A: sorafenib (400 mg, twice daily) | A: 79 | A: 27 (34.1%) | A: 17 (21.5%) | | A: 10 (12.65%) | |
| (12) | Shacham-Shmueli et al. [54] | 2012 | Advanced solid tumors<br>A: sorafenib 100 mg BID (50 mg tablets) + infusion regimen<br>B: sorafenib 200 mg BID (50 mg tablets) + infusion regimen<br>C: sorafenib 400 mg BID (50 mg tablets) + infusion regimen<br>D: sorafenib 400 mg BID (50 mg tablets) + bolus A regimen<br>E: sorafenib 400 mg BID (200 mg tablets) + infusion regimen<br>F: sorafenib 400 mg BID (200 mg tablets) + bolus B regimen | A: 10<br>B: 7<br>C: 6<br>D: 9<br>E: 6<br>F: 9 | A: -<br>B: -<br>C: -<br>D: 3 (33%)<br>E: -<br>F: - | Not reported | | A: -<br>B: -<br>C: -<br>D: 3 (33%)<br>E: -<br>F: - | |
| (13) | Sho et al. [55] | 2017 | Advanced hepatocellular carcinoma<br>A: 250 mg/m$^2$ of 5-FU and sorafenib 800 mg daily<br>B: 350 mg/m$^2$ of 5-FU and sorafenib 800 mg daily<br>C: 450 mg/m$^2$ of 5-FU and sorafenib 800 mg daily | A: 3<br>B: 3<br>C: 6 | A: 0<br>B: 1<br>C: 3 | A: 0<br>B: 1<br>C: 2 | | A: -<br>B: -<br>C: 1 | |

Table 2: Continued.

| | Authors | Year | Neoplasia | Cases number | Stomatitis (%) | Stomatitis grade 1% | Stomatitis grade 2% | Stomatitis grade 3% | Stomatitis grade 4% |
|---|---|---|---|---|---|---|---|---|---|
| (14) | Ueda et al. [56] | 2013 | Metastatic renal cell carcinoma<br>A: axitinib<br>B: sorafenib | A: 359<br>B: 355 | A: 54 (15.04%)<br>B: 44 (12.39%) | A: 49 (13.64%)<br>B: 43 (12.11%) | | A: 5 (1.39%)<br>B: 1 (0.28%) | |
| (15) | Williamson et al. [57] | 2010 | Advanced and metastatic squamous cell carcinoma of the head and neck<br>A: sorafenib orally at 400 mg twice daily on continuous basis in 28-day cycles | A: 41 | A: 2 (4.9%) | Not reported | | A: 2 | |
| (16) | Zhao et al. [44] | 2013 | Locally advanced clear cell renal carcinoma<br>A: sorafenib 400 mg orally twice daily for 4-week cycle<br>B: sunitinib 50 mg orally daily for a 6-week cycle | A: 20<br>B: 23 | A: 8 (40%)<br>B: 7 (30%) | Not reported | | Not reported | |
| Total | | | | 1218 | 250 (20.52%) | | | | |
| Total with grade | | | | 830 | 174 (20.96%) | 155 (18.67%) | | 19 (2,28%) | |
| Total not reporting grade* | | | | 266 | 60 (22.55%) | Not reported | | Not reported | |
| Total reporting only grade >2** | | | | 122 | 16 (13.11%) | Not reported | | 16 (13.11%) | |

*Note*. *Cho et al. (2013) [45], Grignani et al. (2015) [47], Lee et al. (2009) [6], and Zhao et al. (2013) [44] did not report the grade of stomatitis; **Richly et al. (2006) [52], Shacham-Shmueli et al. (2012) [54], and Williamson et al. (2010) [57] reported the incidence rates limited to grade 3 and grade 4 treatment-related toxicities; for this reason, data about cases of stomatitis and stomatitis grades 1 and 2 are lower than real.

Table 3: Report on all papers about axitinib and stomatitis.

| | Authors | Year | Neoplasia | Number of cases | Stomatitis number | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| (1) | Rugo et al. [58] | 2005 | Phase I study<br>Advanced solid tumors<br>A: AG-013736<br>Axitinib 5–30 mg in 28-day cycle | A: 36 | A: 4 (11%) | A: 2 (6%) | | A: 2 (6%) | |
| (2) | Ueda et al. [56] | 2013 | Metastatic renal cell carcinoma<br>A: axitinib<br>B: sorafenib | A: 359<br>B: 355 | A: 54 (15.04%)<br>B: 44 (12.39%) | A: 49 (13.64%)<br>B: 43 (12.11%) | | A: 5 (1.39%)<br>B: 1 (0.28%) | |
| (3) | Karam et al. [59] | 2014 | Phase II trial of locally advanced nonmetastatic clear cell renal carcinoma<br>A: axitinib 5 mg for up to 12 weeks | A: 24 | A: 17 (70.8%) | A: 16 (67%) | | A: 1 (4.2%) | |
| (4) | Oh et al. [60] | 2015 | Phase I study: previously untreated advanced gastric cancer<br>A: axitinib 5 mg twice a day (days 1 to 21) with cisplatin 80 mg/m$^2$ (day 1) and capecitabine 1,000 mg/m$^2$ twice a day (days 1 to 14) in 21-day cycles | A: 22 | A: 16 (72.7%) | A: 12 (54.5%) | | A: 4 (18.2%) | |
| *Total* | | | | *441* | *91 (20.63%)* | *79 (17.91%)* | | *12 (2.72%)* | |

Table 4: Report on all papers about cabozantinib and stomatitis.

| | Authors | Year | Neoplasia | nNumber of cases | Stomatitis total | Stomatitis grade 1 | Stomatitis grade 2 | Stomatitis grade 3 | Stomatitis grade 4 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Neal et al. [61] | 2016 | Phase II trial for EGFR wild-type non-small-cell lung cancer<br>A: erlotinib<br>B: cabozantinib<br>C: erlotinib + cabozantinib | A: 40<br>B: 40<br>C: 39 | A: 2 (5%)<br>B: 17 (43%)<br>C: 9 (24%) | A: 2 (5%)<br>B: 13 (33%)<br>C: 8 (21%) | | A: 0<br>B: 4 (10%)<br>C: 1 (3%) | A: 0<br>B: 0<br>C: 0 |
| 2 | Tolaney et al. [62] | 2017 | Phase II metastatic triple negative breast cancer<br>A: oral dosing of cabozantinib at 60 mg daily over a 21-day cycle | A: 35 | A: 13 (37%) | A: 11 | A: 2 | A: 0 | A: 0 |
| | *Total* | | | *114* | *39 (34.21%)* | *34 (29.82%)* | | *5 (4.38%)* | |

This method allows reaching a preferential localization of a drug in the region of disease, thus achieving an increase in local concentration. VEGFR TKI drugs work by inhibiting neoangiogenesis in the tumor.

The cloning of vascular endothelial growth factor in 1989 was a major step in understanding of tumor angiogenesis. Angiogenesis inhibitors are a class of drugs that include monoclonal antibodies and tyrosine kinase inhibitors.

In this review, we focused on oral side effects provoked by tyrosine kinase inhibitors. Small molecule inhibitors of VEGFR2 were first reported in 1996. This type of therapy is based on the fact that tumor cells can obtain the necessary oxygen and nutrients for survival by passive diffusion for tumor size <1-2 mm, but angiogenesis is necessary for tumor growth beyond the size of 100–300 cells [68]. The mRNAs for both VEGFR1 and VEGFR2 are reported to be upregulated in tumor-associated endothelial cells in comparison to the vasculature of the surrounding normal tissue. Moreover, recent studies highlighted that VEGF and VEGFR-1 and VEGFR-2 not only drive tumor angiogenesis but also directly stimulate tumor growth and the formation of metastases [69].

Overexpression of both VEGF and VEGFR is reported for many human solid cancers, including cancers of the gastrointestinal tract [70, 71], pancreas [72], breast [73, 74], stomach [75], cervix [76, 77], bladder [78, 79], kidney [78], prostate [80], ovaries [81, 82], endometrium [83], lung [84], brain [85, 86], and melanoma [87] and squamous cell carcinoma of the head and neck [88].

The main oral side effects reported in the studies include nonspecific stomatitis, dysgeusia, and xerostomia. These toxicities may occur alone or in combination.

Results of analysis of the literature showed that the incidence rate of overall stomatitis is higher in patients treated with sunitinib (40.08%) compared to sorafenib (22.55%), axitinib (20.63%), and cabozantinib (34.21%). Although it was not possible to carry out an accurate analysis of stomatitis by grade, it can be noted that most of the studies included in the review showed a high rate of minor stomatitis (G1-G2), while the onset of severe stomatitis (G3-G4) was lower. Indeed, in patients treated with sunitinib, the rate of incidence of low-grade stomatitis was 35.73%, while the rate of incidence of high-grade stomatitis was 5.35%; in patients treated with sorafenib, the rate of incidence of low-grade stomatitis was 18.67%, while the rate of incidence of high-grade stomatitis was 2.28%; in patients treated with axitinib, the rate of incidence of low-grade stomatitis was 17.91%, while the incidence of high-grade stomatitis was 2.72%; in patients treated with cabozantinib, the rate of incidence of low-grade stomatitis was 29.82%, while the rate of incidence of high-grade stomatitis was 4.38%. These results differ from those reported in literature about mucositis provoked by conventional chemotherapy in which mucositis is often a severe and dose-limiting toxicity.

The stomatitis caused by this kind of targeted therapy presents as a diffuse mucosal hypersensitivity/dysesthesia which can be associated with moderate erythema or inflammation of the oral mucosa. The symptoms appear in the first week of treatment and then gradually disappear [67, 89]. The literature reports that sunitinib and sorafenib may cause linear lingual ulcers of the nonkeratinized mucosa. Other typical oral side effects caused by treatment with VEGFR TKI are dysgeusia reported after treatment with cabozantinib and sunitinib and benign migratory glossitis which can be moderately painful and usually does not require any treatment modification or specific local treatment [90].

The changes in vascular permeability caused by the inhibition of VEGF can also induce mucocutaneous bleeding [91] and a delay in wound healing. Moreover, an oral screening for patients should be considered before undergoing therapy with antiangiogenic treatment. Treatment with tyrosine kinase inhibitors should end at least 1 week before oral surgery.

## 5. Conclusion

In conclusion, the targeted therapy has not kept the initial promises, as it determines several side effects, even if it is often lower than traditional chemotherapy. Regarding the

oral cavity, the main side effect remains stomatitis, present in 20–30% of patients. The major advantage is that stomatitis is predominantly grade 1-2 in patients treated with targeted therapy while the effects of conventional chemotherapy are predominantly grades 3 and 4.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

## References


[1] D. M. K. Keefe and E. H. Bateman, "Tumor control versus adverse events with targeted anticancer therapies," *Nature Reviews Clinical Oncology*, vol. 9, no. 2, pp. 98–109, 2012.

[2] J. B. Epstein, J. Thariat, R.-J. Bensadoun et al., "Oral complications of cancer and cancer therapy: from cancer treatment to survivorship," *CA: A Cancer Journal for Clinicians*, vol. 62, no. 6, pp. 400–422, 2012.

[3] W. Bensinger, M. Schubert, K. Ang, D. Brizel et al., "NCCN Task Force Report. prevention and management of mucositis in cancer care," *Journal of the National Comprehensive Cancer Network*, vol. 6, supplement 1, pp. S1–S21, 2008, quiz S22-S24.

[4] R. J. Motzer and R. M. Bukowski, "Targeted therapy for metastatic renal cell carcinoma," *Journal of Clinical Oncology*, vol. 24, no. 35, pp. 5601–5608, 2006.

[5] R. J. Motzer, S. Hoosen, C. L. Bello, and J. G. Christensen, "Sunitinib malate for the treatment of solid tumours: A review of current clinical data," *Expert Opinion on Investigational Drugs*, vol. 15, no. 5, pp. 553–561, 2006.

[6] W. J. Lee, J. L. Lee, S. E. Chang et al., "Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib," *British Journal of Dermatology*, vol. 161, no. 5, pp. 1045–1051, 2009.

[7] J. Dengjel, I. Kratchmarova, and B. Blagoev, "Receptor tyrosine kinase signaling: A view from quantitative proteomics," *Molecular BioSystems*, vol. 5, no. 10, pp. 1112–1121, 2009.

[8] R. J. Motzer, T. E. Hutson, P. Tomczak et al., "Sunitinib versus interferon alfa in metastatic renal-cell carcinoma," *The New England Journal of Medicine*, vol. 356, pp. 115–124, 2007.

[9] G. Sonpavde and T. E. Hutson, "Pazopanib: A novel multitargeted tyrosine kinase inhibitor," *Current Oncology Reports*, vol. 9, no. 2, pp. 115–119, 2007.

[10] S. Faivre, C. Delbaldo, K. Vera et al., "Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer," *Journal of Clinical Oncology*, vol. 24, no. 1, pp. 25–35, 2006.

[11] R. M. Bukowski, "Third generation tyrosine kinase inhibitors and their development in advanced renal cell carcinoma," *Frontiers in Oncology*, vol. 2, Article ID 00013, 2012.

[12] B. Escudier, T. Eisen, W. M. Stadler, C. Szczylik et al., "Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial," *Journal of Clinical Oncology*, vol. 27, no. 20, pp. 3312–3318, 2009.

[13] A. M. Pick and K. K. Nystrom, "Pazopanib for the treatment of metastatic renal cell carcinoma," *Clinical Therapeutics*, vol. 34, no. 3, pp. 511–520, 2012.

[14] G. D. Demetri, "Differential properties of current tyrosine kinase inhibitors in gastrointestinal stromal tumors," *Seminars in Oncology*, vol. 38, no. 1, pp. S10–S19, 2011.

[15] D. C. Smith, M. R. Smith, and C. Sweeney, "Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial," *Journal of Clinical Oncology*, vol. 31, no. 4, pp. 412–419, 2013.

[16] U. Vaishampayan, "Cabozantinib as a novel therapy for renal cell carcinoma," *Current Oncology Reports*, vol. 15, no. 2, pp. 76–82, 2013.

[17] K. Traynor, "Cabozantinib approved for advanced medullary thyroid cancer," *American Journal of Health-System Pharmacy*, vol. 70, no. 2, p. 88, 2013.

[18] M. Arakawa-Todo, T. Yoshizawa, K. Zennami, G. Nishikawa et al., "Management of adverse events in patients with metastatic renal cell carcinoma treated with sunitinib and clinical outcomes," *Anticancer Research*, vol. 33, no. 11, pp. 5043–5050, 2013.

[19] A. J. Armstrong, S. Halabi, T. Eisen et al., "Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicentre, open-label, randomised phase 2 trial," *The Lancet Oncology*, vol. 17, no. 3, pp. 378–388, 2016.

[20] Y.-J. Bang, Y.-K. Kang, W. K. Kang et al., "Phase II study of sunitinib as second-line treatment for advanced gastric cancer," *Investigational New Drugs*, vol. 29, no. 6, pp. 1449–1458, 2011.

[21] F. Cardoso, J.-L. Canon, D. Amadori et al., "An exploratory study of sunitinib in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive metastatic breast cancer," *The Breast*, vol. 21, no. 6, pp. 716–723, 2012.

[22] A. Carrato, A. Swieboda-Sadlej, M. Staszewska-Skurczynska et al., "Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer: A randomized, phase III trial," *Journal of Clinical Oncology*, vol. 31, no. 10, pp. 1341–1347, 2013.

[23] A. Dirican, Y. Kucukzeybek, C. Erten et al., "Prognostic and predictive value of hematologic parameters in patients with metastatic renal cell carcinoma: Second line sunitinib treatment following IFN-alpha," *Asian Pacific Journal of Cancer Prevention*, vol. 14, no. 3, pp. 2101–2105, 2013.

[24] M. Domagala-Haduch, I. Cedrych, M. Jasiówka, M. Niemiec, and P. Skotnicki, "Analysis of adverse events of sunitinib in patients treated for advanced renal cell carcinoma," *Archives of Medical Science*, vol. 12, no. 2, pp. 360–364, 2016.

[25] V. L. Goodman, E. P. Rock, R. Dagher et al., "Approval summary: Sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma," *Clinical Cancer Research*, vol. 13, no. 5, pp. 1367–1373, 2007.

[26] V. Grünwald, I. M. E. Desar, J. Haanen et al., "A Phase I study of recombinant human interleukin-21 (rIL-21) in combination with sunitinib in patients with metastatic renal cell carcinoma (RCC)," *Acta Oncologica*, vol. 50, no. 1, pp. 121–126, 2011.

[27] M. H. Hong, H. S. Kim, C. Kim et al., "Treatment outcomes of sunitinib treatment in advanced renal cell carcinoma patients: a single cancer center experience in Korea," *Cancer Research and Treatment*, vol. 41, no. 2, pp. 67–72, 2009.

[28] P. H. O'Donnell, "Efficacy and toxicity of sunitinib in patients with metastatic renal cell carcinoma with severe renal impairment or on haemodialysis," *BJU International*, vol. 108, no. 8, pp. 1284-1285, 2011.

[29] K. H. Kim, H. Y. Kim, H. R. Kim et al., "Efficacy and toxicity of sunitinib in patients with metastatic renal cell carcinoma with

renal insufficiency," *European Journal of Cancer*, vol. 50, no. 4, pp. 746–752, 2014.

[30] J. H. Lee, S.-G. Chang, S. H. Jeon, G. E. Min, and K. H. Yoo, "Comparative analysis between immunochemotherapy and target therapy for metastatic renal cell carcinoma: Overview of treatment-related adverse events and the dropout rate in Korea," *Korean Journal of Urology*, vol. 51, no. 6, pp. 379–385, 2010.

[31] J. L. Lee, M. K. Kim, I. Park et al., "RandomizEd phase II trial of Sunitinib four weeks on and two weeks off versus Two weeks on and One week off in metastatic clear-cell type REnal cell carcinoma: RESTORE trial," *Annals of Oncology*, vol. 26, no. 11, Article ID mdv357, pp. 2300–2305, 2015.

[32] K.-W. Lee, S. R. Park, D.-Y. Oh et al., "Phase I study of sunitinib plus capecitabine/cisplatin or capecitabine/oxaliplatin in advanced gastric cancer," *Investigational New Drugs*, vol. 31, no. 6, pp. 1547–1558, 2013.

[33] N. Marschner, L. Müller, A. Münch, K. Blumenstengel, U. Hutzschenreuter, and S. Busies, "Adverse reactions in mRCC patients documented in routine practice by German office-based oncologists and uro-oncologists," *Journal of Oncology Pharmacy Practice*, vol. 23, no. 4, pp. 288–295, 2017.

[34] M. H. Mir, K. H. Changal, S. A. Aziz, G. M. Bhat, and A. R. Lone, "Sunitinib in metastatic renal cell carcinoma (mRCC): a developing country experience. Do our patients behave differently than the Western patients?" *International Urology and Nephrology*, vol. 48, no. 11, pp. 1811–1816, 2016.

[35] P. H. Patel, P. L. Senico, R. E. Curiel, and R. J. Motzer, "Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma," *Clinical Genitourinary Cancer*, vol. 7, no. 1, pp. 24–27, 2009.

[36] C. Porta, S. Osanto, A. Ravaud et al., "Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma," *European Journal of Cancer*, vol. 47, no. 9, pp. 1287–1298, 2011.

[37] E. P. Rock, V. Goodman, J. X. Jiang et al., "Food and Drug Administration drug approval summary: sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma," *The Oncologist*, vol. 12, no. 1, pp. 107–113, 2007.

[38] M. A. Socinski, S. Novello, J. R. Brahmer et al., "Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 26, no. 4, pp. 650–656, 2008.

[39] G. Sonpavde, P. O. Periman, D. Bernold et al., "Sunitinib malate for metastatic castration-resistant: Prostate cancer following docetaxel-based: Chemotherapy," *Annals of Oncology*, vol. 21, no. 2, pp. 319–324, 2010.

[40] C. N. Sternberg, F. Calabrò, S. Bracarda et al., "Safety and efficacy of sunitinib in patients from Italy with metastatic renal cell carcinoma: Final results from an expanded-access trial," *Oncology*, vol. 88, no. 5, pp. 273–280, 2015.

[41] A. A. M. Van Der Veldt, E. Boven, H. H. Helgason et al., "Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer," *British Journal of Cancer*, vol. 99, no. 2, pp. 259–265, 2008.

[42] I. Yildiz, F. Sen, M. Basaran et al., "Response rates and adverse effects of continuous once-daily sunitinib in patients with advanced renal cell carcinoma: A single-center study in Turkey," *Japanese Journal of Clinical Oncology*, vol. 41, no. 12, Article ID hyr151, pp. 1380–1387, 2011.

[43] C. Yoo, J. E. Kim, J.-L. Lee et al., "The efficacy and safety of sunitinib in Korean patients with advanced renal cell carcinoma: High incidence of toxicity leads to frequent dose reduction," *Japanese Journal of Clinical Oncology*, vol. 40, no. 10, Article ID hyq073, pp. 980–985, 2010.

[44] J. Zhao, Y. Zhu, C. Zhang et al., "Sorafenib or sunitinib as postoperative adjuvant therapy for Chinese patients with locally advanced clear cell renal cell carcinoma at high risk for disease recurrence," *Urologic Oncology: Seminars and Original Investigations*, vol. 31, no. 8, pp. 1800–1805, 2013.

[45] J.-Y. Cho, Y.-H. Paik, H. Y. Lim et al., "Clinical parameters predictive of outcomes in sorafenib-treated patients with advanced hepatocellular carcinoma," *Liver International*, vol. 33, no. 6, pp. 950–957, 2013.

[46] A. Chrisoulidou, S. Mandanas, E. Margaritidou et al., "Treatment compliance and severe adverse events limit the use of tyrosine kinase inhibitors in refractory thyroid cancer," *OncoTargets and Therapy*, vol. 8, pp. 2435–2442, 2015.

[47] G. Grignani, E. Palmerini, V. Ferraresi et al., "Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial," *The Lancet Oncology*, vol. 16, no. 1, pp. 98–107, 2015.

[48] J. D. Hainsworth, D. S. Thompson, J. A. Bismayer et al., "Paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer: A randomized phase II study of the Sarah Cannon Research Institute," *Cancer Medicine*, vol. 4, no. 5, pp. 673–681, 2015.

[49] J. D. Hainsworth, D. M. Waterhouse, W. C. Penley et al., "Sorafenib and everolimus in advanced clear cell renal carcinoma: A phase I/II trial of the SCRI oncology research consortium," *Cancer Investigation*, vol. 31, no. 5, pp. 323–329, 2013.

[50] T. Meyer, R. Fox, Y. Ma, P. Ross et al., "Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial," *The Lancet Gastroenterology and Hepatology*, vol. 2, no. 8, pp. 565–575, 2017.

[51] C. Porta, C. Paglino, I. Imarisio et al., "Safety and treatment patterns of multikinase inhibitors in patients with metastatic renal cell carcinoma at a tertiary oncology center in Italy," *BMC Cancer*, vol. 11, article 105, 2011.

[52] H. Richly, B. F. Henning, P. Kupsch et al., "Results of a Phase I trial of sorafenib (BAY 43-9006) in combination with doxorubicin in patients with refractory solid tumors," *Annals of Oncology*, vol. 17, no. 5, pp. 866–873, 2006.

[53] L. S. Schwartzberg, K. W. Tauer, R. C. Hermann et al., "Sorafenib or placebo with either gemcitabine or capecitabine in patients with HER-2-negative advanced breast cancer that progressed during or after bevacizumab," *Clinical Cancer Research*, vol. 19, no. 10, pp. 2745–2754, 2013.

[54] E. Shacham-Shmueli, R. Geva, A. Figer et al., "Phase I trial of sorafenib in combination with 5-fluorouracil/leucovorin in advanced solid tumors," *Clinical Pharmacology and Therapeutics*, vol. 52, no. 5, pp. 656–669, 2012.

[55] T. Sho, M. Nakanishi, K. Morikawa et al., "A phase I study of combination therapy with sorafenib and 5-fluorouracil in patients with advanced hepatocellular carcinoma," *Drugs in R&D*, vol. 17, no. 3, pp. 381–388, 2017.

[56] T. Ueda, H. Uemura, Y. Tomita et al., "Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma:

Subgroup analysis of Japanese patients from the global randomized phase 3 AXIS trial," *Japanese Journal of Clinical Oncology*, vol. 43, no. 6, Article ID hyt054, pp. 616–628, 2013.

[57] S. K. Williamson, J. Moon, C. H. Huang et al., "Phase II evaluation of sorafenib in advanced and metastatic squamous cell carcinoma of the head and neck: southwest oncology group study S0420," *Journal of Clinical Oncology*, vol. 28, no. 20, pp. 3330–3335, 2010.

[58] H. S. Rugo, R. S. Herbst, G. Liu et al., "Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: Pharmacokinetic and clinical results," *Journal of Clinical Oncology*, vol. 23, no. 24, pp. 5474–5483, 2005.

[59] J. A. Karam, C. E. Devine, D. L. Urbauer et al., "Phase 2 trial of neoadjuvant axitinib in patients with locally advanced non-metastatic clear cell renal cell carcinoma," *European Urology*, vol. 66, no. 5, pp. 874–880, 2014.

[60] D.-Y. Oh, T. Doi, K. Shirao et al., "Phase I study of axitinib in combination with cisplatin and capecitabine in patients with previously untreated advanced gastric cancer," *Cancer Research and Treatment*, vol. 47, no. 4, pp. 687–696, 2015.

[61] J. W. Neal, S. E. Dahlberg, H. A. Wakelee et al., "Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial," *The Lancet Oncology*, vol. 17, no. 12, pp. 1661–1671, 2016.

[62] S. M. Tolaney, D. R. Ziehr, H. Guo et al., "Phase II and biomarker study of cabozantinib in metastatic triple-negative breast cancer patients," *The Oncologist*, vol. 22, no. 1, pp. 25–32, 2017.

[63] N. Bhojani, C. Jeldres, J.-J. Patard et al., "Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma," *European Urology*, vol. 53, no. 5, pp. 917–930, 2008.

[64] J. Desai, L. Yassa, E. Marqusee et al., "Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors," *Annals of Internal Medicine*, vol. 145, no. 9, pp. 660–664, 2006.

[65] P. Suwattee, S. Chow, B. C. Berg, and E. M. Warshaw, "Sunitinib: a cause of bullous palmoplantar erythrodysesthesia, periungual erythema, and mucositis," *JAMA Dermatology*, vol. 144, no. 1, pp. 123–125, 2008.

[66] M. E. Lacouture, L. M. Reilly, P. Gerami, and J. Guitart, "Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib," *Annals of Oncology*, vol. 19, no. 11, pp. 1955–1961, 2008.

[67] A. Yuan, S. L. Kurtz, C. M. Barysauskas, A. P. Pilotte, A. J. Wagner, and N. S. Treister, "Oral adverse events in cancer patients treated with VEGFR-directed multitargeted tyrosine kinase inhibitors," *Oral Oncology*, vol. 51, no. 11, pp. 1026–1033, 2015.

[68] R. S. Kerbel, "Tumor angiogenesis: past, present and the near future," *Carcinogenesis*, vol. 21, no. 3, pp. 505–515, 2000.

[69] P. W. Manley, G. Martiny-Baron, J.-M. Schlaeppi, and J. M. Wood, "Therapies directed at vascular endothelial growth factor," *Expert Opinion on Investigational Drugs*, vol. 11, no. 12, pp. 1715–1736, 2002.

[70] L. F. Brown, B. Berse, R. W. Jackman et al., "Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract," *Cancer Research*, vol. 53, no. 19, pp. 4727–4735, 1993.

[71] G. Lindmark, B. Gerdin, C. Sundberg, L. Påhlman, R. Bergström, and B. Glimelius, "Prognostic significance of the microvascular count in colorectal cancer," *Journal of Clinical Oncology*, vol. 14, no. 2, pp. 461–466, 1996.

[72] J. Itakura, T. Ishiwata, B. Shen, M. Kornmann, and M. Korc, "Concomitant over-expression of vascular endothelial growth factor and its receptors in pancreatic cancer," *International Journal of Cancer*, vol. 85, no. 1, pp. 27–34, 2000.

[73] L. F. Brown, B. Berse, R. W. Jackman et al., "Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer," *Human Pathology*, vol. 26, no. 1, pp. 86–91, 1995.

[74] N. Weidner, J. P. Semple, W. R. Welch, and J. Folkman, "Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma," *The New England Journal of Medicine*, vol. 324, no. 1, pp. 1–8, 1991.

[75] N. Tanigawa, H. Amaya, M. Matsumura, T. Shimomatsuya et al., "Extent of tumor vascularization correlates with prognosis and hematogenous metastasis in gastric carcinomas," *Cancer Research*, vol. 56, no. 11, pp. 2671–2676, 1996.

[76] A. J. Guidi, G. Abu-Jawdeh, B. Berse et al., "Vascular permeability factor (vascular endothelial growth factor) expression and angiogenesis in cervical neoplasia," *Journal of the National Cancer Institute*, vol. 87, no. 16, pp. 1237–1245, 1995.

[77] F. Sillman, J. Boyce, and R. Fruchter, "The significance of atypical vessels and neovascularization in cervical neoplasia," *American Journal of Obstetrics & Gynecology*, vol. 139, no. 2, pp. 154–159, 1981.

[78] L. F. Brown, B. Berse, R. W. Jackman, and K. Tognazzi, "Increased expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in kidney and bladder carcinomas," *American Journal of Pathology*, vol. 143, no. 5, pp. 1255–1262, 1993.

[79] B. H. Bochner, R. J. Cote, N. Weidner et al., "Angiogenesis in bladder cancer: Relationship between microvessel density and tumor prognosis," *Journal of the National Cancer Institute*, vol. 87, no. 21, pp. 1603–1612, 1995.

[80] S. A. Bigler, R. E. Deering, and M. K. Brawer, "Comparison of microscopic vascularity in benign and malignant prostate tissue," *Human Pathology*, vol. 24, no. 2, pp. 220–226, 1993.

[81] T. A. Olson, D. Mohanraj, L. F. Carson, and S. Ramakrishnan, "Vascular permeability factor gene expression in normal and neoplastic human ovaries," *Cancer Research*, vol. 54, no. 1, pp. 276–280, 1994.

[82] G. Gasparini, E. Bonoldi, G. Viale et al., "Prognostic and predictive value of tumour angiogenesis in ovarian carcinomas," *International Journal of Cancer*, vol. 69, no. 3, pp. 205–211, 1996.

[83] A. J. Guidi, G. Abu-Jawdeh, K. Tognazzi, H. F. Dvorak, and L. F. Brown, "Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in endometrial carcinoma," *Cancer*, vol. 78, no. 3, pp. 454–460, 1996.

[84] P. Macchiarini, G. Fontanini, F. Squartini, C. A. Angeletti, and M. J. Hardin, "Relation of neovascularisation to metastasis of non-small-cell lung cancer," *The Lancet*, vol. 340, no. 8812, pp. 145-146, 1992.

[85] K. H. Plate, G. Breier, H. A. Weich, and W. Risau, "Vascular endothelial growth factor is a potential tumour angiogenssis factor in human gliomas in vivo," *Nature*, vol. 359, no. 6398, pp. 845–848, 1992.

[86] V. W. Li, C. Yu AB, J. Folkman et al., "Microvessel count and cerebrospinal fluid basic fibroblast growth factor in children

with brain tumours," *The Lancet*, vol. 344, no. 8915, pp. 82–86, 1994.

[87] R. L. Barnhill, K. Fandrey, M. A. Levy, M. C. Mihm Jr., and B. Hyman, "Angiogenesis and tumor progression of melanoma: Quantification of vascularity in melanocytic nevi and cutaneous malignant melanoma," *Laboratory Investigation*, vol. 67, no. 3, pp. 331–337, 1992.

[88] G. Gasparini, N. Weidner, S. Maluta et al., "Intratumoral microvessel density and L53 protein: Correlation with metastasis in head-and-neck squamous-cell carcinoma," *International Journal of Cancer*, vol. 55, no. 5, pp. 739–744, 1993.

[89] V. Sibaud, F. Boralevi, E. Vigarios, and J.-C. Fricain, "Oral toxicity of targeted anticancer therapies," *Annales de Dermatologie et de Venereologie*, vol. 141, no. 5, pp. 354–363, 2014.

[90] E. Vigarios, J. B. Epstein, and V. Sibaud, "Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors," *Supportive Care in Cancer*, vol. 25, no. 5, pp. 1713–1739, 2017.

[91] L. Thomas, S. Y. Lai, W. Dong et al., "Sorafenib in metastatic thyroid cancer: a systematic review," *The Oncologist*, vol. 19, no. 3, pp. 251–258, 2014.

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*Review Article*

# Osteonecrosis of the Jaw Associated with Antiangiogenics in Antiresorptive-Naïve Patient: A Comprehensive Review of the Literature

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*Objectives*. To review the available literature on medication-related osteonecrosis of the jaw (MRONJ) associated with antiangiogenics in antiresorptive-naïve individuals. *Methods*. A literature search was performed using MEDLINE via PubMed, EMBASE, and Web of Science in December 2017. *Results*. We identified reports describing a total of 35 antiresorptive drugs-naïve patients who developed antiangiogenic-related MRONJ. The mean age of these patients was 59.06 years and the F : M ratio was 4 : 5. The most common underlying disease was metastatic renal cell cancer. Pain to the mandible was the most common complaint (34.29%) and the majority of patients presented with bone exposure. The mean duration of intravenous and oral antiangiogenics before MRONJ development was 6.5 and 16.72 months, respectively. The most common additional risk factor was dental extraction (37.14%). Almost half of the MRONJ patients (48.57%) received surgical treatment. 18 patients (62.06%) were reported to have disease resolution within an average time of 6.75 months. *Conclusion.* MRONJ associated with antiangiogenic therapy in antiresorptive-naïve patients is a rare but potentially serious adverse effect. Available data suggests that there might be notable differences between MRONJ associated with antiangiogenics and antiresorptives; however, further prospective well-designed studies are required.

## 1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon and potentially serious adverse side effect of antiresorptive and antiangiogenic agents [1]. It can cause chronic pain, infection, dysfunction, and disfigurement and can affect the quality of life of affected individuals [2, 3]. The vast majority of cases of MRONJ are associated with antiresorptive agents including bisphosphonates, denosumab, and more recently romosozumab [4–7]. A notably smaller number of cases are associated with the use of antiangiogenic agents, both in individuals who also take antiresorptive drugs and in those who are antiresorptive drugs-naïve [8]. MRONJ can develop in approximately 7% of cancer patients taking high-potency bisphosphonates or high-dose denosumab and about 0.01–0.1% of those with osteoporosis using low-potency oral bisphosphonates or low-dosage denosumab [1, 9–12]. The use of antiangiogenic agents in combination with antiresorptive drugs is known to increase the risk of MRONJ development [13]; however, little is known regarding the incidence and prevalence of antiangiogenic-related MRONJ in antiresorptive drugs-naïve individuals. Antiangiogenic inhibitors have been increasingly used in the management of a range of malignancies including ovarian cancer, metastatic renal cell cancer, breast cancer, colorectal cancer, non-small-cell lung cancer (NSCLC), and glioblastoma multiforme [14]. Antiangiogenic inhibitors can be categorised into three major groups based on their mechanism of action: anti-VEGF monoclonal antibody (e.g., bevacizumab), VEGF decoy receptors or VEGF-Trap (e.g.,

aflibercept), and small molecule tyrosine kinase inhibitors (TKI) that block the VEGF receptors downstream signaling pathways (e.g., sunitinib, cabozantinib, and sorafenib) [15] (Table 1). Additionally, the mammalian target of rapamycin (mTOR) inhibitors also seems to have antiangiogenic effects by inhibiting the production of VEGF and platelet-derived growth factors (PDGF) [16–18].

The number of patients developing MRONJ associated with antiangiogenic inhibitors or a combination of antiangiogenics and antiresorptive drugs has been growing over the last few years [8, 13, 19, 20]. The purpose of the present study is to provide a comprehensive review of the published reports of MRONJ associated with antiangiogenic agents in patients with no history of antiresorptive therapies.

## 2. Materials and Methods

*2.1. Literature Search Strategy.* A literature search was conducted to identify clinical trials, case reports, and case series on MRONJ associated with antiangiogenic treatment in antiresorptive drugs-naïve individuals using MEDLINE via PubMed (up to December 2017), EMBASE (from 1980 to December 2017), and Web of Science (from 1900 to December 2017). The search strategy used the following keywords: "osteonecrosis," "jaw osteonecrosis," "jaw bone necrosis," "oral osteonecrosis," "antiangiogenic," "angiogenesis inhibitors," "antineoplastic agents," "antiangiogenic activity," "antiangiogenic therapy," "chemotherapy," and "targeted therapy." The references of retrieved articles were manually searched in order to identify additional relevant articles and abstracts. The search included articles published in English and other languages. Inclusion criteria were patients developing MRONJ associated with antiangiogenic agents based on the definition of MRONJ proposed by the special committee on MRONJ of the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014 [1]. Patients with history of radiotherapy involving the jaw bones and patients having previous history or concurrent use of antiresorptive therapy were excluded.

## 3. Results

*3.1. Search Results.* A total of 4,597 articles were retrieved by the initial search, including literature reviews, duplicate articles, clinical trials, and case reports with bisphosphonates and antiangiogenic treatment. The flow chart of review process to identify studies included and excluded is shown in Figure 1. Following screening the articles, we identified 28 articles describing 35 cases of MRONJ meeting the aforementioned inclusion criteria. Of these 28 publications, 26 papers were published in English, one was published in Italian, and one was published in Japanese. These 35 reported MRONJ cases were related to previous history of treatment with bevacizumab (14 cases), aflibercept (5 cases), sunitinib (3 cases), cabozantinib (2 cases), sorafenib (1 case), temsirolimus (1 case), everolimus (1 case), dasatinib (1 case), and multiple antiangiogenic agents (7 cases) (Table 2).

All 35 patients were reported to have developed MRONJ associated with at least one antiangiogenic agent and without a history of treatment with antiresorptive drugs. There were 19 males (54.29%) and 14 males (40%). The mean age of patients was 59.06 years (range: 33–80 years). The underlying diseases that required treatment with antiangiogenic agents included metastatic renal cell cancer (10 patients, 28.57%) followed by metastatic colorectal cancer (6 patients, 17.14%), metastatic breast cancer (5 patients, 14.29%), and other cancers (14 patients, 40%).

The most common presenting symptom was pain to the mandible/maxilla (12 patients, 34.29%) whereas 8 individuals (22.86%) reported no notable symptoms. The remaining patients had a variety of presenting complaints including mild discomfort to the mandible (1 patient, 2.86%), spontaneous teeth loss (1 patient, 2.86%), gingival bleeding (1 patient, 2.86%), and limited mouth opening together with submandibular swelling (1 patient, 2.86%). Moreover, there were 6 patients (17.14%) presenting with multiple symptoms including pain to the jaw, halitosis, spontaneous tooth loss, ulceration, difficulty in chewing, and paraesthesia. Regarding clinical characteristics of MRONJ, 32 patients (91.43%) had intraoral frank bone exposure, while the other three patients had nonexposed MRONJ. Mandible was the most common area of MRONJ development (29 patients, 82.86%), whereas four patients (11.43%) developed MRONJ in the maxilla.

Fourteen patients (40%) were exposed to bevacizumab, followed by aflibercept (5 patients, 14.29%), sunitinib (3 patients, 8.57%), cabozantinib (2 patients, 5.71%), sorafenib (1 patient, 2.86%), temsirolimus (1 patient, 2.86%), everolimus (1 patient, 2.86%), dasatinib (1 patient, 2.86%), and multiple antiangiogenic agents (7 patients, 20%). Regarding the routes of drug administration, antiangiogenic medications were administered intravenously in 21 patients (60.00%), while 12 patients (34.29%) were given antiangiogenic therapy orally. Two patients (5.71%) were given the combination of intravenous administration and oral administration. The mean duration of intravenous and oral antiangiogenic therapy before MRONJ development was 6.49 months (range: 0.23–36; SD = 1.82; 95% CI: 2.67–10.30) and 16.72 months (range: 1–60; SD = 6.42; 95% CI: 2.59–30.84), respectively. Patients with MRONJ also received a variety of concomitant medications including chemotherapy, hormone therapy, corticosteroids, antihypertensive drugs, antidepressants, and gastrointestinal medications.

Additional risk factors for MRONJ were reported in 21 patients, with dental extraction being the most prominent factor (13 patients, 37.14%). Other factors included history of mucosal trauma from dentures, chronic infection/inflammation to the tooth-bearing alveolar bone (periodontal disease), and insertion of osteointegrated dental implants (8 patients, 22.86%). The mean time to MRONJ diagnosis after tooth extraction was 3.09 months (range: 0.23–8; SD = 1.13; 95% CI: 0.40–5.77).

Regarding the management of MRONJ, seventeen patients (48.57%) were managed with surgical procedures alone or combined with medications (antibiotic therapy, antimicrobial mouthwash) and interruption of antiangiogenic agents. 16 patients did not receive surgery (45.71%), with antiangiogenic agents being discontinued in 7 cases. There was no active intervention reported in

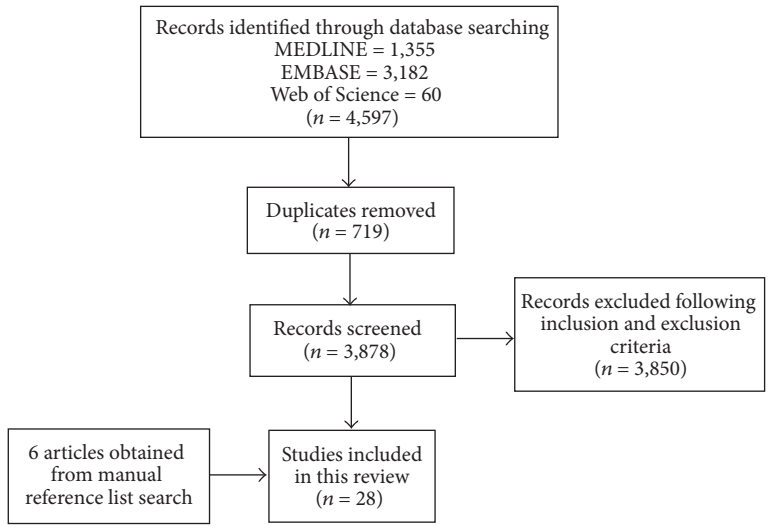


Figure 1: Flow chart of the study selection process.

one patient. Most surgical interventions (11 patients) were minimally invasive procedures including smoothening of exposed bone, local flap coverage, removal of superficial necrotic bone, soft tissue debridement, and bone curettage, whereas 6 patients underwent major surgery such as bone decortication, resection of necrotic bone with local flap coverage, segmental osteotomy, and block resection. The outcomes of therapy were reported for 29 patients (82.8%), whereas no information was provided for the other 6 cases. 18 patients out of these 29 (62%) were reported to have disease resolution, while 11 patients showed persistent bone exposure. Disease resolution was described as complete mucosal coverage/no evidence of exposed bone in 13 cases, whereas no clear description was provided for the remaining 5 cases. Of note, one patient who experienced disease resolution to the left side of the mandible eventually developed a new area of MRONJ to the right mandible. The mean time from MRONJ diagnosis to complete healing was 6.75 months (range months: 1.84–22; SD = 2.47; 95% CI: 0.90–12.59). The data of 35 reported cases with MRONJ associated with antiangiogenics are summarised in Table 3.

## 4. Discussion

The present study is the first comprehensive review upon MRONJ in patients treated with antiangiogenics in the absence of bone-modulating therapy.

We present data from 35 patients with different metastatic cancers who developed MRONJ following antiangiogenic treatments. All individuals were antiresorptive drugs-naïve. We have identified a number of differences between MRONJ associated with antiangiogenic agents and MRONJ associated with antiresorptive drugs. Our data showed a sex ratio of 4 : 5 (F : M) and an age range of 33–80 years (mean: 59.06 years), compared to sex ratio of 3 : 2 and age range of 42–90 years (mean 66 years) reported for antiresorptive drugs-associated MRONJ [50–52]. There also seem to be differences in the prevalence of MRONJ in these two populations. The reported prevalence of MRONJ in patients who had been treated with intravenous bevacizumab alone for the treatment of advanced breast cancer was 0.2%, which was lower than that of MRONJ associated with intravenous antiresorptive agents (7%) [11, 19]. However, it is important to note that the prevalence of MRONJ related to antiangiogenic agents may also depend on the epidemiology of underlying malignancies that require antiangiogenic therapy.

The clinical presentations of MRONJ associated with antiangiogenics also seem to be different from MRONJ due to antiresorptive agents. Approximately up to 25% of MRONJ cases related to antiresorptive medications can present without frank bone exposure [53], whereas most of the patients in the present review had clear evidence of bone exposure (91.43%). However, the number of patients with nonexposed MRONJ might be underestimated, since until 2014 MRONJ could only be diagnosed in individuals with clinical evidence of exposed bone as per AAOMS definition [53, 54].

With respect to the presenting complaints and location, they appear to be similar in two populations. The majority of patients with antiangiogenic-related MRONJ in this study experienced pain to the jaw, which is also the most common complaint in patients with MRONJ associated with antiresorptive agents [51, 55]. In the present study, most MRONJ cases associated with antiangiogenic therapy tended to occur in the mandible more frequently than in the maxilla, similar to those with antiresorptive drugs-induced MRONJ [50, 52].

A number of additional risk factors were identified in the present review including dental extraction, the use of denture, periodontal infection, and dental implant. Almost 40% of reported cases in this study were predominantly preceded by tooth extraction, which is similar to those with antiresorptive drugs-related MRONJ [50, 56].

There is a slight difference with respect to underlying malignancies between two populations. Patients with antiresorptive drugs-associated MRONJ showed the previous history of multiple myeloma, metastatic breast cancer, and metastatic prostate cancer, whereas those with MRONJ

Table 1: Approved antiangiogenic medications [14, 15, 21, 22].

| Approved antiangiogenic drugs | |
|---|---|
| *Anti-VEGF monoclonal antibody* | *Indications for use* |
| Bevacizumab | Metastatic colorectal cancer |
| | Non-small-cell lung cancer |
| | Glioblastoma multiforme |
| | Metastatic renal cell cancer |
| | Macular degeneration |
| | Metastatic HER2 negative breast cancer |
| | Persistent, recurrent, and metastatic cervical cancer |
| | Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer |
| *VEGF decoy receptor (VEGF-Trap)* | *Indications for use* |
| Aflibercept | Metastatic colorectal cancer |
| *Tyrosine kinase inhibitors* | *Indications for use* |
| Sorafenib | Metastatic renal cell cancer |
| | Hepatic cancer (hepatocellular carcinoma) |
| Sunitinib | Metastatic renal cell carcinoma |
| | Gastrointestinal stromal tumour |
| | Pancreatic neuroendocrine tumour |
| Cabozantinib | Medullary thyroid cancer |
| Erlotinib | Non-small-cell lung cancer |
| | Pancreatic cancer |
| Axitinib | Metastatic renal cell cancer |
| Pegaptanib | Macular degeneration |
| Ranibizumab | Macular degeneration |
| Pazopanib | Metastatic renal cell cancer |
| | Soft tissue sarcoma |
| Vandetanib | Medullary thyroid cancer |
| Regorafenib | Metastatic colorectal cancer |
| | Gastrointestinal stromal tumour |
| Imatinib | Chronic myeloid leukemia |
| | Renal cell cancer |
| | Gastrointestinal stromal tumour |
| Dasatinib | Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) |
| | Chronic phase Ph+ CML |
| | Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (Ph+ ALL) |
| *Mammalian target of rapamycin inhibitors (mTOR inhibitors)* | *Indications for use* |
| Temsirolimus | Renal cell cancer |
| Everolimus | Advanced breast cancer |
| | Advanced renal cell cancer |
| | Pancreatic neuroendocrine tumour |
| | Tuberous sclerosis complex |
| | Subependymal giant cell astrocytoma |

related to antiangiogenic medications in our review were mainly diagnosed with metastatic renal cell cancer, followed by metastatic colorectal cancer and metastatic breast cancer as demonstrated in Table 3 [52].

Although there was no consistent pattern in the time to MRONJ development in this review, the average time for developing MRONJ among patients with either intravenous or oral antiangiogenics was shorter than the average time to

Table 2: Previously reported cases of MRONJ associated with antiangiogenic medications ($n$ = 35).

| Number | Authors | Age | Sex | Diagnosis of cancer | Treatment and concurrent medications | Antiangiogenic agents | Symptoms | Clinical presentation | Site of MRONJ | Time to MRONJ | Predisposing factors | Management of MRONJ | Outcomes | Definition of disease resolution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) | Estilo et al. [23] | 51 | F | Metastatic breast cancer | Mastectomy<br>Chest wall resection<br>Chest wall radiation<br>Doxorubicin<br>Cyclophosphamide<br>Letrozole<br>Paclitaxel<br>Capecitabine | Bevacizumab<br>15 mg/kg<br>every 3 weeks<br>(total 8 doses) | Jaw discomfort | Bone exposure | Mandible | 18 weeks after starting bevacizumab | None | Surgical treatment (smoothen exposed bone)<br>Chlorhexidine mouthwash 0.12%<br>Interruption of bevacizumab | Disease resolution (few weeks)<br>Developed new MRONJ lesion (right mandible) | Complete mucosal coverage |
| (2) | Estilo et al. [23] | 33 | F | Glioblastoma multiforme | Surgical resection<br>Radiotherapy<br>Temozolomide | Bevacizumab<br>15 mg/kg<br>every 2 weeks | Jaw pain (gingival pain) | Bone exposure | Mandible | 11 weeks after starting bevacizumab | None | None | Persistent bone exposure (3 months) | — |
| (3) | Greuter et al. [24] | 63 | F | Metastatic breast cancer | Liposomal-doxorubicin | Bevacizumab | Maxillary pain | Bone exposure | Maxilla | 2 months after starting bevacizumab | Extraction due to dental infection (1 month) | Surgical treatment | Disease resolution | Not specified |
| (4) | Serra et al. [25] | 64 | M | Metastatic non-small-cell lung cancer | Pneumectomy<br>Lymph node ablation<br>Cisplatin<br>Gemcitabine | Bevacizumab<br>7.5 mg/kg | Jaw pain | Bone exposure | Mandible | 1 week after starting bevacizumab | Extraction (1 week) | Surgical treatment (local flap coverage)<br>Amoxicillin with clavulanate<br>Chlorhexidine mouthwash 0.2% | Persistent bone exposure (3.5 months) | — |
| (5) | Guarneri et al. [19] | NA | NA | Metastatic breast cancer | Docetaxel | Bevacizumab<br>7.5 mg/kg or<br>15 mg/kg every 3 weeks | NA | Bone exposure | Mandible | 7 months after starting bevacizumab | None | Surgical treatment (mandible decortication, tooth extraction)<br>Interruption of bevacizumab | Disease resolution (6 months) | Complete mucosal coverage |
| (6) | Guarneri et al. [19] | NA | NA | Metastatic breast cancer | Docetaxel | Bevacizumab<br>7.5 mg/kg or<br>15 mg/kg every 3 weeks | NA | Bone exposure | NA | 2 months after starting bevacizumab | None | NA | NA | — |
| (7) | Brunamonti Binello et al. [26] | 47 | M | Adenocarcinoma of parotid gland | Surgical treatment<br>Epirubicin<br>Cisplatin | Bevacizumab<br>15 mg/kg<br>(total 8 doses in 6 months) | Jaw pain, paraesthesia | Bone exposure | Mandible | 16 months after starting bevacizumab | Symptomatic eruption of lower third molar | Surgical treatment (removed necrotic bone)<br>Amoxicillin with clavulanate<br>Metronidazole | Persistent bone exposure (7 months) | — |
| (8) | Bettini et al. [27] | 57 | F | Metastatic non-small-cell lung cancer | Gemcitabine<br>Cisplatin<br>Corticosteroid | Bevacizumab<br>945 mg/21 days<br>4 cycles | Jaw pain, halitosis, tooth loss | Bone exposure | Mandible | 2 months after starting bevacizumab | Periodontal infection | Amoxicillin with clavulanate<br>Lincomycin (for 7 days) | Disease resolution | Complete mucosal coverage |

Table 2: Continued.

| Number | Authors | Age | Sex | Diagnosis of cancer | Treatment and concurrent medications | Antiangiogenic agents | Symptoms | Clinical presentation | Site of MRONJ | Time to MRONJ | Predisposing factors | Management of MRONJ | Outcomes | Definition of disease resolution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (9) | Dişel et al. [28] | 51 | M | Metastatic colon cancer | 5-Fluorouracil Leucovorin Oxaliplatin | Bevacizumab 5 mg/kg every 2 weeks | Jaw pain, ulcer, difficulty in chewing | Bone exposure | Mandible | NA | None | Surgical treatment (bone curettage) | NA | — |
| (10) | Sato et al. [29] | 67 | M | Metastatic sigmoid colon cancer | Surgical treatment Oxaliplatin Leucovorin Irinotecan 5-Fluorouracil | Bevacizumab | Jaw pain | Nonexposed MRONJ | Maxilla | 3 months after starting bevacizumab | Extraction (1 month) | Surgical treatment (removal of necrotic tissue) Antibiotics | Disease resolution | Complete mucosal coverage |
| (11) | Fusco et al. [30] | 60 | M | Metastatic rectal cancer | Surgical treatment Radiotherapy 5-Fluorouracil Leucovorin Irinotecan Oxaliplatin | Bevacizumab | Jaw pain | Bone exposure | Mandible | 9 months after starting bevacizumab | Extraction (8 months) | Antibiotics Chlorhexidine mouthwash | NA | — |
| (12) | Tzermpos et al. [31] | 69 | M | Metastatic non-small-cell lung cancer | Carboplatin Docetaxel Cortisone | Bevacizumab 15 mg/kg every 3 weeks | Jaw pain, discomfort, paraesthesia | Bone exposure | Mandible | 3 years after starting bevacizumab | Denture | Surgical treatment (surgical debridement) Amoxicillin Metronidazole Chlorhexidine mouthwash 0.12% Interruption of bevacizumab | Disease resolution (8 weeks) | Complete mucosal coverage |
| (13) | Abel Mahedi Mohamed et al. [32] | 55 | F | Non-small-cell lung cancer | Corticosteroids | Bevacizumab | Asymptomatic | Bone exposure | Maxilla | 1.5 months after starting bevacizumab | Extraction | Conservative treatment | Disease resolution | Not specified |
| (14) | Abel Mahedi Mohamed et al. [32] | 66 | M | Glioblastoma multiforme | Corticosteroids | Bevacizumab | Pain | Nonexposed MRONJ | Mandible | 1.5 months after starting bevacizumab | Trauma | Conservative treatment (antibiotic treatment) | Disease resolution | Not specified |
| (15) | Ponzetti et al. [33] | 64 | F | Metastatic colorectal cancer | 5-Fluorouracil Irinotecan | Aflibercept | Spontaneous teeth loss with purulent discharge | Bone exposure | Mandible | 22 weeks after starting aflibercept | Periodontal infection | Laser treatment | Persistent bone exposure | — |
| (16) | Mawardi et al. [34] | 43 | M | Metastatic colorectal cancer | 5-Fluorouracil Leucovorin Irinotecan | Aflibercept | Jaw pain | Bone exposure | Mandible | 32 weeks after starting aflibercept | None | Amoxicillin Chlorhexidine mouthwash | Persistent bone exposure (1.5 months) | — |
| (17) | Mawardi et al. [34] | 63 | M | Metastatic carcinoid cancer | NA | Aflibercept | Asymptomatic | Bone exposure | Mandible | 46 weeks after starting aflibercept | None | Amoxicillin with clavulanate Chlorhexidine mouthwash | Persistent bone exposure (2.5 months) | — |
| (18) | Mawardi et al. [34] | 51 | M | Metastatic esophageal cancer | 5-Fluorouracil Leucovorin Oxaliplatin | Aflibercept | Jaw pain | Bone exposure | Mandible | 14 weeks after starting aflibercept | Extraction (2 weeks) | Amoxicillin Chlorhexidine mouthwash Nonsurgical sequestrectomy | Persistent bone exposure (2 months) | - |

Table 2: Continued.

| Number | Authors | Age | Sex | Diagnosis of cancer | Treatment and concurrent medications | Antiangiogenic agents | Symptoms | Clinical presentation | Site of MRONJ | Time to MRONJ | Predisposing factors | Management of MRONJ | Outcomes | Definition of disease resolution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (19) | Zarringhalam et al. [35] | 47 | M | Metastatic colorectal, peritoneum, liver, and pelvic cancer | None | Aflibercept | Asymptomatic | Bone exposure | Mandible | 4 weeks after starting aflibercept | None | Surgical treatment (smoothen sharp exposed bone) | Persistent bone exposure (12 weeks) | — |
| (20) | Nicolatou-Galitis et al. [36] | 64 | F | Metastatic renal cell cancer | Nephrectomy<br>T4 replacement therapy<br>Prednisolone (50 mg/day) | Sunitinib 50 mg/day for 4 weeks on and 2 weeks off (for 4 years) | Jaw pain | Bone exposure | Mandible | 4 years after starting sunitinib | Denture | Amoxicillin<br>Chlorhexidine mouthwash<br>Azithromycin<br>Interruption of sunitinib | Disease resolution (3 months) | Complete mucosal coverage |
| (21) | Fleissig et al. [37] | 58 | F | Metastatic renal cell cancer | Nephrectomy<br>Thyroxin sodium | Sunitinib 50 mg/day for 4 weeks on and 2 weeks off | Limited mouth opening, submandibular swelling, pain | Bone exposure | Mandible | 10 months after starting sunitinib | Extraction (8 months) | Amoxicillin with clavulanate (IV)<br>PenG (IV) for 6 weeks and oral amoxicillin for 6 weeks<br>Interruption of sunitinib | Disease resolution (18 weeks) | Complete mucosal coverage |
| (22) | Melloni et al. [38] | 62 | M | Metastatic renal cell cancer | NA | Sunitinib 50 mg/day for 4 weeks on and 2 weeks off | Jaw pain and infected lesion to the cutaneous side of the jaw | Bone exposure | Mandible | 5 years after starting sunitinib | None | Surgical treatment (surgical sequestrectomy, ablation of necrotic bone, and local flap coverage)<br>Amoxicillin with clavulanate<br>Ofloxacin<br>Interruption of sunitinib | Disease resolution (12 months) | Complete mucosal coverage |
| (23) | Tempia Valenta et al. [39] | 51 | F | Medullary thyroid cancer | NA | Cabozantinib | NA | Bone exposure | Mandible | 6 months after starting cabozantinib | Extraction | Surgical treatment (surgical debridement)<br>Amoxicillin and clavulanate<br>Chlorhexidine mouthwash 0.2% | Disease resolution (22 months) | Not specified |
| (24) | Marino et al. [40] | 51 | F | Medullary thyroid cancer | Thyroidectomy<br>5-Fluorouracil<br>Dacarbazine<br>Radiotherapy<br>Levothyroxine<br>Calcitriol<br>Vitamin D3<br>Duloxetine<br>Propranolol<br>Lansoprazole<br>Loperamide | Cabozantinib (175 mg/day) | Asymptomatic | Bone exposure | Mandible | 3 months after starting cabozantinib | Extraction due to dental infection (3 months) | Surgical treatment (segmental ostectomy and tooth extraction)<br>Amoxicillin and clavulanate<br>Chlorhexidine mouthwash 0.2% | Disease resolution | Complete mucosal coverage |
| (25) | Garuti et al. [41] | 74 | M | Metastatic hepatocellular carcinoma | Furosemide<br>Potassium canrenoate<br>Bisoprolol<br>Allopurinol<br>Tamsulosin<br>Hydroxychloroquine<br>Vitamin D<br>Sertraline | Sorafenib 400 mg/day | Asymptomatic | Nonexposed MRONJ | Mandible | 3 months after starting sorafenib | None | Interruption of sorafenib | Persistent bone exposure (3 months) | — |

Table 2: Continued.

| Number | Authors | Age | Sex | Diagnosis of cancer | Treatment and concurrent medications | Antiangiogenic agents | Symptoms | Clinical presentation | Site of MRONJ | Time to MRONJ | Predisposing factors | Management of MRONJ | Outcomes | Definition of disease resolution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (26) | Abel Mahedi Mohamed et al. [32] | 53 | F | Acute lymphoblastic leukemia | Corticosteroids | Dasatinib | Pain | Bone exposure | Mandible | 5 months after starting dasatinib | Extraction | Surgical treatment (block resection) | Disease resolution | Not specified |
| (27) | Parti et al. [42] | 60 | M | Metastatic renal cell cancer | Nephrectomy Prostatectomy | Temsirolimus 25 mg every week | NA | Bone exposure | Mandible | 3 months after starting temsirolimus | Extraction (3 months) | Interruption of temsirolimus | NA | — |
| (28) | Yamamoto et al. [43] | 80 | F | Metastatic breast cancer | Capecitabine Tamoxifen Fulvestrant Exemestane | Everolimus | Jaw pain, localised heat, tenderness | Bone exposure | Mandible | 2 months after starting everolimus | None | Interruption of everolimus | Persistent bone exposure (2 months) | — |
| (29) | Agostino et al. [44] | 73 | M | Metastatic renal cell cancer | Nephrectomy | (1) Sunitinib 50 mg/day for 4 weeks of 6-week cycle (2) Temsirolimus 25 mg every week (3) Bevacizumab 10 mg/kg every two weeks | NA | NA | NA | 12 months after starting bevacizumab | NA | Interruption of bevacizumab | NA | — |
| (30) | Koch et al. [45] | 59 | M | Metastatic renal cell cancer | Nephrectomy Interferon Vinblastine Ramipril Hydrochlorothiazide Metoprolol I-Thyroxin | (1) Sorafenib (2) Sunitinib 50 mg/day for 4 weeks and then sunitinib 37.5 mg/day | Asymptomatic | Bone exposure | Mandible | 51 months after starting sunitinib | Extraction (2 months) | Surgical treatment (ablation of necrosis and local flap coverage) | Disease resolution | Complete mucosal coverage |
| (31) | Santos-Silva et al. [46] | 61 | M | Metastatic renal cell cancer | Nephrectomy Hydrochlorothiazide Captopril | (1) Bevacizumab 10 mg/kg every 2 weeks (2) Temsirolimus 25 mg every week | Jaw pain | Bone exposure | Mandible | 55 weeks after starting bevacizumab and temsirolimus | None | Chlorhexidine mouthwash 0.12% Interruption of bevacizumab and temsirolimus | Disease resolution (3 months) | The absence of exposed necrotic bone |
| (32) | Pakosch et al. [47] | 53 | F | Pancreatic cancer | Surgical treatment Gemcitabine Leucovorin 5-Fluorouracil Oxaliplatin Paclitaxel Erlotinib | (1) Bevacizumab (2) Sorafenib | Jaw pain | Bone exposure | Mandible | 4 months after starting bevacizumab and sorafenib | Denture | Surgical treatment (decortication), Amoxicillin with clavulanate Chlorhexidine mouthwash Solcoseryl Interruption of bevacizumab and chemotherapy | Disease resolution (2 months) | Complete mucosal coverage |
| (33) | Jung [48] | 62 | F | Renal cell cancer | Nephrectomy | (1) Pazopanib (2) Everolimus | Gingival bleeding and sore gum | Bone exposure | Mandible | 7 weeks after starting everolimus | Dental implant | Cephalosporin Surgical treatment (sequestrectomy and internal fixation) | Disease resolution | Complete mucosal coverage |

Table 2: Continued.

| Number | Authors | Age | Sex | Diagnosis of cancer | Treatment and concurrent medications | Antiangiogenic agents | Symptoms | Clinical presentation | Site of MRONJ | Time to MRONJ | Predisposing factors | Management of MRONJ | Outcomes | Definition of disease resolution |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (34) | Patel et al. [49] | 67 | M | Metastatic renal cell cancer | Nivolumab<br>Amlodipine<br>Ramipril<br>Levetiracetam<br>Dexamethasone<br>Lansoprazole<br>Morphine<br>Metoclopramide<br>Amiodarone<br>Cholecalciferol | (1) Pazopanib<br>(2) Axitinib | Asymptomatic | Bone exposure | Maxilla | 1 months after starting axitinib | None | Hydrogen peroxide mouthwash | NA | — |
| (35) | Abel Mahedi Mohamed et al. [32] | 70 | M | Renal cell cancer | Corticosteroids | (1) Sunitinib<br>(2) Everolimus | Asymptomatic | Bone exposure | Mandible | 10 months after starting sunitinib, everolimus was commenced | Extraction | Conservative treatment | Persistent bone exposure | — |

NA: not available.

Table 3: Summary of data of reported cases of antiangiogenic-related MRONJ ($n = 35$).

| | |
|---|---|
| Age (years, range) | |
| Mean | 59.06 (33–80) |
| Gender (*n*, %) | |
| Male | 19 (54.29%) |
| Female | 14 (40.00%) |
| NA | 2 (5.71%) |
| Diagnosis of cancers (*n*, %) | |
| Metastatic renal cell cancer | 10 (28.57%) |
| Metastatic colorectal cancer | 6 (17.14%) |
| Metastatic breast cancer | 5 (14.29%) |
| Other cancers | 14 (40.00%) |
| Metastatic non-small-cell lung cancer | 4 |
| Glioblastoma multiforme | 2 |
| Medullary thyroid cancer | 2 |
| Malignant parotid tumour | 1 |
| Pancreatic cancer | 1 |
| Metastatic hepatocellular carcinoma | 1 |
| Metastatic carcinoid cancer | 1 |
| Metastatic oesophageal cancer | 1 |
| Presenting complaints (*n*, %) | |
| Jaw pain | 12 (34.29%) |
| Jaw pain with other complaints | 6 (17.14%) |
| Asymptomatic | 8 (22.86%) |
| Jaw discomfort | 1 (2.86%) |
| Spontaneous teeth loss | 1 (2.86%) |
| Limited mouth opening and submandibular area swelling | 1 (2.86%) |
| Gingival bleeding | 1 (2.86%) |
| NA | 5 (14.29%) |
| Clinical presentation (*n*, %) | |
| Bone exposure MRONJ | 32 (91.43%) |
| Nonexposed MRONJ | 3 (8.57%) |
| Location | |
| Mandible | 29 (82.86%) |
| Maxilla | 4 (11.43%) |
| NA | 2 (6.67%) |
| Types of antiangiogenic agents (*n*, %) | |
| Bevacizumab | 14 (40%) |
| Aflibercept | 5 (14.29%) |
| Sunitinib | 3 (8.57%) |
| Cabozantinib | 2 (5.71%) |
| Sorafenib | 1 (2.86%) |
| Temsirolimus | 1 (2.86%) |
| Everolimus | 1 (2.86%) |
| Dasatinib | 1 (2.86%) |
| Multiple antiangiogenic agents | 7 (20.00%) |
| Route of antiangiogenic administrations (*n*, %) | |
| Intravenous administration | 21 (60.00%) |
| Oral administration | 12 (34.29%) |
| Combination of intravenous administration and oral administration | 2 (5.71%) |
| Time to MRONJ (months, 95% CI) | |
| Intravenous antiangiogenics | 6.49 (2.67–10.30) |
| Oral antiangiogenics | 16.72 (2.59–30.84) |
| Predisposing factors (*n*, %) | |
| Extraction | 13 (37.14%) |
| Periodontal disease | 3 (8.57%) |
| Minor trauma from use of denture | 4 (11.43%) |
| Dental implant | 1 (2.86%) |
| Mean time to MRONJ after extraction (months, 95% CI) | 3.09 (0.40–5.77) |
| Management of MRONJ (*n*, %) | |
| Surgical treatment | 17 (48.57%) |
| Minimally invasive surgical procedures | 11 |
| Major surgical procedures | 6 |
| Nonsurgical treatment | 16 (45.71%) |
| No treatment | 1 (2.86%) |
| NA | 1 (2.86%) |
| Treatment outcomes (*n*, %) | |
| Disease resolution | 18 (62.06%) |
| Mean time to resolution (months, 95% CI) | 6.75 (0.90–12.59) |
| Incomplete resolution | 11 (37.93%) |
| NA | 6 |

NA: not available.

MRONJ onset in those treated with antiresorptive drugs. The mean time to event for intravenous and oral antiangiogenic agents in this study was 6.5 and 16.71 months, respectively, while it was reported to be approximately 1.8 and 3 years for bisphosphonate therapy [12, 57].

Patients with metastatic malignancy may receive a number of anticancer drugs simultaneously. In this review, we found that seven of the reported cases received more than one antiangiogenic agent in their treatment history [32, 44–49]. Of these patients, some were given different antiangiogenics at the same time, while others received these agents at different time points. The development of MRONJ is usually associated with the latest antiangiogenic agent used by the patient; however, one cannot exclude the fact that the antiangiogenic agents previously used by these patients might have contributed to it.

We included in this review two cases of MRONJ associated with new TKIs, namely, pazopanib in combination with axitinib ($n = 1$) and dasatinib ($n = 1$) [32, 49]. According to the Food and Drug Administration's Adverse Event Reporting System (FAERS), pazopanib and axitinib have been associated with the development of MRONJ in 10 and 9 individuals, respectively; however, as data regarding concurrent or previous medication were not available in FAERS documentation [58], it is difficult to conclude whether these individuals were indeed antiresorptive drugs-naïve. Therefore, we decided not to include these 19 cases in our review.

With regard to the management of MRONJ, approximately half of the individuals with MRONJ associated with antiangiogenics (48.57%) were managed surgically, which is similar to those with bisphosphonate-related MRONJ [11, 52].

However, the prognosis of antiangiogenic-related MRONJ appears to be better than that of individuals developing MRONJ associated with antiresorptive agents. We observed a 62% rate of disease resolution in those where outcomes were reported as opposed to approximately 50% reported in the literature for MRONJ associated with antiresorptive agents [56, 59, 60]. It is possible that the higher rate of disease resolution might be related to the shorter half-life of antiangiogenics [61, 62], as well as the lower cumulative dosages [63]. Moreover, the average time to resolution for MRONJ associated with antiangiogenics appears to be shorter than antiresorptive drugs-induced MRONJ (6.75 months, range: 1.84–22 months versus 8.2 months, range: 0.2–25.6 months) [55].

In this comprehensive review, we excluded a number of potential antiangiogenic-related MRONJ cases due to a lack of adequate clinical information. For example, the 2012 report on aflibercept by the US Food and Drug Administration (FDA) described 3 aflibercept-treated bisphosphonate-naïve patients who developed MRONJ; however, none of these patients were added to the present review as one had jaw bone exposure for less than 8 weeks and no information was provided for the other two cases [64]. Furthermore, in a pivotal BOLERO-2 trial, MRONJ has been described in 2 patients in the experimental arm (everolimus-exemestane) and 1 patient in the control arm (exemestane), with one of three patients to receive bisphosphonate treatment [65]. However, there was no evidence to show whether the patient with a history of bisphosphonate treatment was in the experimental arm or control arm. More recently, Antonuzzo et al. [66] reported the first case with MRONJ potentially associated with regorafenib, one of the tyrosine kinase inhibitors, in an antiresorptive drugs-naïve individual. Although MRONJ appeared 22 months after regorafenib treatment, Fusco et al. [67] have noted that some details such as the use of other medications prior to regorafenib treatment, dosing, and the time on medication are still missing. This medication is usually used as a third or further line of treatment of metastatic colorectal cancer. Therefore, it is also worth knowing whether this patient has received other well-documented antiangiogenic medications such as bevacizumab and aflibercept prior to regorafenib. If this is the case, bevacizumab or aflibercept possibly might contribute to the development of MRONJ rather than regorafenib alone. Another patient with gastrointestinal stromal tumours (GISTs) receiving imatinib monotherapy presented with pain and exposed bone at lower right mandible after having the tooth removed for 5 weeks. The patient was treated with debridement of necrotic bone and antibiotic and then was discharged. Unfortunately, there was no further information about this patient [68]. The duration of persistent bone exposure in this case was not mentioned if it was longer than 8 weeks. Therefore, available data seems not to be enough to classify this case as MRONJ according to the definition of MRONJ [1] and to confirm the association between MRONJ and imatinib. In addition to the above reported cases, Hopp et al. [69] reported one patient with necrotic bone exposure after the 2-year intravitreal injections of bevacizumab for treatment of retinal vascular thrombosis without notable dental risk factors or use of bisphosphonates. After the patient experienced pain to the mandible, the lesion was completely healed by antibiotics treatment within 8 weeks. Therefore, this case seems not to be correlated with the definition of MRONJ formulated by the AAOMS in 2014 [1].

It is important to highlight that another case of oral soft tissues complication associated with bevacizumab was also reported by Magremanne et al. [70]. Although this case was included in previous reviews regarding cases of MRONJ associated with antiangiogenic agents, there was no evidence of osteonecrosis of the jaw and also the necrotic area seemed to be limited only to oral soft tissues. This reported case does not meet the definition of MRONJ and hence it was excluded from this review.

## 5. Conclusion

There remains incomplete information regarding the cases of antiangiogenic-related MRONJ in antiresorptive-naïve individuals reported in the literature. It is therefore difficult to draw any conclusion regarding the epidemiology and the characteristics of MRONJ in this patient population. Within the limitation of available data, we have identified a number of differences between MRONJ associated with antiangiogenics and MRONJ related to antiresorptive drugs including demographic characteristics, prevalence, the underlying malignant disease, time to the onset, and time to resolution. Considering that the list of antiangiogenic inhibitors that have potential to increase the risk of MRONJ development is increasing, further prospective and well-designed research is warranted to confirm our findings and increase knowledge and understanding of the disease.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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## References

[1] S. L. Ruggiero, T. B. Dodson, and J. Fantasia, "American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update," *Journal of Oral and Maxillofacial Surgery*, vol. 72, no. 10, pp. 1938–1956, 2014.

[2] N. V. Hinchy, V. Jayaprakash, R. A. Rossitto et al., "Osteonecrosis of the jaw - Prevention and treatment strategies for oral health professionals," *Oral Oncology*, vol. 49, no. 9, pp. 878–886, 2013.

[3] M. Capocci, U. Romeo, F. Guerra et al., "Medication-related osteonecrosis of the jaws (MRONJ) and quality of life evaluation: A pilot study," *La Clinica Terapeutica*, vol. 168, no. 4, pp. e253–e257, 2017.

[4] R. E. Marx, "Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic," *Journal of Oral and Maxillofacial Surgery*, vol. 61, no. 9, pp. 1115–1117, 2003.

[5] A. T. Stopeck, A. Lipton, J. Body et al., "Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study," *Journal of Clinical Oncology*, vol. 28, no. 35, pp. 5132–5139, 2010.

[6] J. Uyanne, C. C. Calhoun, and A. D. Le, "Antiresorptive drug-related osteonecrosis of the jaw," *Dental Clinics of North America*, vol. 58, no. 2, pp. 369–384, 2014.

[7] F. Cosman, D. B. Crittenden, J. D. Adachi et al., "Romosozumab treatment in postmenopausal women with osteoporosis," *The New England Journal of Medicine*, vol. 375, no. 16, pp. 1532–1543, 2016.

[8] I. S. Hamadeh, B. A. Ngwa, and Y. Gong, "Drug induced osteonecrosis of the jaw," *Cancer Treatment Reviews*, vol. 41, no. 5, pp. 455–464, 2015.

[9] J. Bagan, C. Scully, V. Sabater, and Y. Jimenez, "Osteonecrosis of the jaws in patients treated with intravenous bisphosphonates (BRONJ): A concise update," *Oral Oncology*, vol. 45, no. 7, pp. 551–554, 2009.

[10] I. R. Reid, "Osteonecrosis of the jaw—who gets it, and why?" *Bone*, vol. 44, no. 1, pp. 4–10, 2009.

[11] S. Kühl, C. Walter, S. Acham, R. Pfeffer, and J. T. Lambrecht, "Bisphosphonate-related osteonecrosis of the jaws—a review," *Oral Oncology*, vol. 48, no. 10, pp. 938–947, 2012.

[12] N. Malden and V. Lopes, "An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence," *Journal of Bone and Mineral Metabolism*, vol. 30, no. 2, pp. 171–182, 2012.

[13] V. Fusco, C. Porta, G. Saia et al., "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," *Clinical Genitourinary Cancer*, vol. 13, no. 4, pp. 287–294, 2015.

[14] S. De Falco, "Antiangiogenesis therapy: an update after the first decade," *Korean Journal of Internal Medicine*, vol. 29, no. 1, pp. 1–11, 2014.

[15] B. Al-Husein, M. Abdalla, M. Trepte, D. L. DeRemer, and P. R. Somanath, "Antiangiogenic therapy for cancer: an update," *Pharmacotherapy*, vol. 32, no. 12, pp. 1095–1111, 2012.

[16] D. Del Bufalo, L. Ciuffreda, D. Trisciuoglio et al., "Antiangiogenic potential of the mammalian target of rapamycin inhibitor temsirolimus," *Cancer Research*, vol. 66, no. 11, pp. 5549–5554, 2006.

[17] R. Yuan, A. Kay, W. J. Berg, and D. Lebwohl, "Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy," *Journal of Hematology & Oncology*, vol. 2, article 45, 2009.

[18] M. Moriya, T. Yamada, M. Tamura et al., "Antitumor effect and antiangiogenic potential of the mTOR inhibitor temsirolimus against malignant pleural mesothelioma," *Oncology Reports*, vol. 31, no. 3, pp. 1109–1115, 2014.

[19] V. Guarneri, D. Miles, N. Robert et al., "Bevacizumab and osteonecrosis of the jaw: Incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer," *Breast Cancer Research and Treatment*, vol. 122, no. 1, pp. 181–188, 2010.

[20] R. L. Wynn, "Bevacizumab (Avastin): An anti-angiogenic drug associated with osteonecrosis of the jaw," *General dentistry*, vol. 59, no. 6, pp. 410–413, 2011.

[21] S. Y. Yoo and S. M. Kwon, "Angiogenesis and its therapeutic opportunities," *Mediators of Inflammation*, vol. 2013, Article ID 127170, 11 pages, 2013.

[22] "The U.S. Food and Drug Administration. FDA approved drug products," 2017, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021986.

[23] C. L. Estilo, M. Fornier, A. Farooki, D. Carlson, G. Bohle III, and J. M. Huryn, "Osteonecrosis of the jaw related to bevacizumab," *Journal of Clinical Oncology*, vol. 26, no. 24, pp. 4037-4038, 2008.

[24] S. Greuter, F. Schmid, T. Ruhstaller, and B. Thuerlimann, "Bevacizumab-associated osteonecrosis of the jaw," *Annals of Oncology*, vol. 19, no. 12, pp. 2091-2092, 2008.

[25] E. Serra, M. Paolantonio, G. Spoto, F. Mastrangelo, S. Tetè, and M. Dolci, "Bevacizumab-related osteneocrosis of the jaw," *International Journal of Immunopathology and Pharmacology*, vol. 22, no. 4, pp. 1121–1123, 2009.

[26] P. Brunamonti Binello, R. Bandelloni, M. Labanca, B. Buffoli, R. Rezzani, and L. F. Rodella, "Osteonecrosis of the jaws and bevacizumab therapy: A case report," *International Journal of Immunopathology and Pharmacology*, vol. 25, no. 3, pp. 789–791, 2012.

[27] G. Bettini, S. Blandamura, G. Saia, and A. Bedogni, "Bevacizumab-related osteonecrosis of the mandible is a self-limiting disease process," *BMJ Case Reports*, vol. 2012, 2012.

[28] U. Dişel, A. A. Beşen, Ö. Özyilkan, E. Er, and T. Canpolat, "A case report of bevacizumab-related osteonecrosis of the jaw: Old problem, new culprit," *Oral Oncology*, vol. 48, no. 2, p. -e3, 2012.

[29] M. Sato, F. Ono, A. Yamamura, and S. Onochi, "A case of osteonecrosis of the jaw during treatment by bevacizumab for sigmoid colon cancer," *Journal of Japanese Society of Gastroenterology*, vol. 110, no. 4, pp. 655–659, 2013.

[30] V. Fusco, A. Fasciolo, R. Gaino et al., "Bevacizumab-related osteonecrosis of jaw in a rectal cancer patient never treated with bisphosphonates," *Ann Stomatol*, vol. 5, 2, p. 31, 2014.

[31] F. Tzermpos, A. Ismail, M. Pavli, and K. I. Tosios, "Osteonecrosis of the mandible in a patient with lung adenocarcinoma undergoing anti-angiogenic therapy with bevacizumab," *Oral Surgery*, vol. 9, no. 1, pp. 40–46, 2016.

[32] H. Abel Mahedi Mohamed, C. E. Nielsen, and M. Schiodt, "Medication related osteonecrosis of the jaws associated with targeted therapy as monotherapy and in combination with antiresorptives. A report of 7 cases from the Copenhagen Cohort," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 125, no. 2, pp. 157–163, 2018.

[33] A. Ponzetti, F. Pinta, R. Spadi et al., "Jaw osteonecrosis associated with aflibercept, irinotecan and fluorouracil: Attention to oral district," *TUMORI*, vol. 102, pp. S74–S77, 2016.

[34] H. Mawardi, P. Enzinger, N. McCleary et al., "Osteonecrosis of the jaw associated with ziv-aflibercept," *Journal of Gastrointestinal Oncology*, vol. 7, no. 6, pp. E81–E87, 2016.

[35] P. Zarringhalam, E. Brizman, and K. Shakib, "Medication-related osteonecrosis of the jaw associated with aflibercept," *British Journal of Oral and Maxillofacial Surgery*, vol. 55, no. 3, pp. 314-315, 2017.

[36] O. Nicolatou-Galitis, M. Migkou, A. Psyrri et al., "Gingival bleeding and jaw bone necrosis in patients with metastatic renal cell carcinoma receiving sunitinib: Report of 2 cases with clinical implications," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 113, no. 2, pp. 234–238, 2012.

[37] Y. Fleissig, E. Regev, and H. Lehman, "Sunitinib related osteonecrosis of jaw: a case report," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 113, no. 3, pp. e1–e3, 2012.

[38] C. Melloni, A. Tuttolomondo, A. Anfosso, C. Calamia, F. D. Clemente, and A. Cordova, "Sunitinib related osteonecrosis of the jaw (SURONJ): a rare occurrence?" *European Journal of Plastic Surgery*, vol. 39, no. 2, pp. 161-162, 2016.

[39] G. Tempia Valenta, R. Marino, F. Erovigni, M. Pentenero, and S. Gandolfo, *Mandibular osteonecrosis related to cabozantinib*, Abstracts of the 11th Biennial Congress of the European Association of Oral Medicine, 1:40, 2012.

[40] R. Marino, F. Orlandi, F. Arecco, S. Gandolfo, and M. Pentenero, "Osteonecrosis of the jaw in a patient receiving cabozantinib," *Australian Dental Journal*, vol. 60, no. 4, pp. 528–531, 2015.

[41] F. Garuti, V. Camelli, L. Spinardi, L. Bucci, and F. Trevisani, "Osteonecrosis of the jaw during sorafenib therapy for hepatocellular carcinoma," *TUMORI*, vol. 102, pp. S69–S70, 2016.

[42] V. Parti, C. Ortega, and M. Aglietta, *Caso clinico di Osteonecrosi da inibitore di m-TOR*, Abstract Convegno Osteonecrosi dei mascellari (ONJ): ruolo della Rete Oncologica del Piemonte e della Valle d'Aosta.

[43] D. Yamamoto, Y. Tsubota, T. Utsunomiya et al., "Osteonecrosis of the jaw associated with everolimus: A case report," *Molecular and Clinical Oncology*, vol. 6, no. 2, pp. 255–257, 2017.

[44] N. M. Agostino, R. Gingrich, and J. J. Drabick, "Bevacizumab demonstrates prolonged disease stabilization in patients with heavily pretreated metastatic renal cell carcinoma: A case series and review of the literature," *Advances in Urology*, Article ID 687043, 2010.

[45] F. P. Koch, C. Walter, T. Hansen, E. Jäger, and W. Wagner, "Osteonecrosis of the jaw related to sunitinib," *Journal of Oral and Maxillofacial Surgery*, vol. 15, no. 1, pp. 63–66, 2011.

[46] A. R. Santos-Silva, G. A. Belizário Rosa, G. D. Castro Júnior, R. B. Dias, A. C. Prado Ribeiro, and T. B. Brandão, "Osteonecrosis of the mandible associated with bevacizumab therapy," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, vol. 115, no. 6, pp. e32–e36, 2013.

[47] D. Pakosch, D. Papadimas, J. Munding, D. Kawa, and M. S. Kriwalsky, "Osteonecrosis of the mandible due to anti-angiogenic agent, bevacizumab," *Journal of Oral and Maxillofacial Surgery*, vol. 17, no. 4, pp. 303–306, 2013.

[48] T.-Y. Jung, "Osteonecrosis of jaw after antiangiogenic agent administration in a renal cell carcinoma patient," *Oral and Maxillofacial Surgery Cases*, vol. 3, no. 2, pp. 27–33, 2017.

[49] V. Patel, C. Sproat, J. Kwok, and N. Tanna, "Axitinib-related osteonecrosis of the jaw," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 2017.

[50] S. B. Woo, J. W. Hellstein, and J. R. Kalmar, "Systematic review: bisphosphonates and osteonecrosis of the jaws," *Annals of Internal Medicine*, vol. 144, no. 10, pp. 753–756, 2006.

[51] S. Otto, C. Schreyer, S. Hafner et al., "Bisphosphonate-related osteonecrosis of the jaws - Characteristics, risk factors, clinical features, localization and impact on oncological treatment," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 40, no. 4, pp. 303–309, 2012.

[52] O. Filleul, E. Crompot, and S. Saussez, "Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases," *Journal of Cancer Research and Clinical Oncology*, vol. 136, no. 8, pp. 1117–1124, 2010.

[53] S. Fedele, G. Bedogni, and M. Scoletta, "Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed," *British Journal of Oral and Maxillofacial Surgery*, 2014.

[54] S. L. Ruggiero, T. B. Dodson, L. A. Assael, R. Landesberg, R. E. Marx, and B. Mehrotra, "American association of oral and maxillofacial surgeons postion paper on bisphosphonate-related osteonecrosis of the jaws," *Journal of Oral and Maxillofacial Surgery*, vol. 67, no. 5, supplement 1, pp. 2–12, 2009.

[55] F. Saad, J. E. Brown, C. Van Poznak 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," *Annals of Oncology*, vol. 23, no. 5, pp. 1341–1347, 2012.

[56] G. Campisi, S. Fedele, V. Fusco, G. Pizzo, O. Di Fede, and A. Bedogni, "Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents," *Future Oncology*, vol. 10, no. 2, pp. 257–275, 2014.

[57] P. K. Palaska, V. Cartsos, and A. I. Zavras, "Bisphosphonates and time to osteonecrosis development," *The Oncologist*, vol. 14, no. 11, pp. 1154–1166, 2009.

[58] X. Zhang, I. S. Hamadeh, S. Song et al., "Osteonecrosis of the Jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS)," *Journal of Bone and Mineral Research*, vol. 31, no. 2, pp. 336–340, 2016.

[59] T. van den Wyngaert, T. Claeys, M. T. Huizing, J. B. Vermorken, and E. Fossion, "Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome," *Annals of Oncology*, vol. 20, no. 2, pp. 331–336, 2009.

[60] T. S. Lazarovici, R. Yahalom, S. Taicher, S. Elad, I. Hardan, and N. Yarom, "Bisphosphonate-realted osteonecrosis of the jaws: a single-center study of 101 patients," *Journal of Oral and Maxillofacial Surgery*, vol. 67, no. 4, pp. 850–855, 2009.

[61] M. S. Gordon, K. Margolin, M. Talpaz et al., "Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer," *Journal of Clinical Oncology*, vol. 19, no. 3, pp. 843–850, 2001.

[62] S. Oudard, B. Beuselinck, J. Decoene, and P. Albers, "Sunitinib for the treatment of metastatic renal cell carcinoma," *Cancer Treatment Reviews*, vol. 37, no. 3, pp. 178–184, 2011.

[63] V. Fusco, D. Santini, G. Armento, G. Tonini, and G. Campisi, "Osteonecrosis of jaw beyond antiresorptive (bone-targeted) agents: new horizons in oncology," *Expert Opinion on Drug Safety*, vol. 15, no. 7, pp. 925–935, 2016.

[64] FDA report, "FDA report on aflibercept: Center for drug evaluation and research," Tech. Rep. 100, Clin Rev. Aflibercept/Zaltrap., 141, 2012, Application number 125418Orig1s000, p. 99.

[65] M. Gnant, J. Baselga, H. S. Rugo et al., "Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2," *Journal of the National Cancer Institute*, vol. 105, no. 9, pp. 654–663, 2013.

[66] L. Antonuzzo, A. Lunghi, E. Giommoni, M. Brugia, and F. Di Costanzo, "Regorafenib also can cause osteonecrosis of the jaw," *Journal of the National Cancer Institute*, vol. 108, no. 4, Article ID djw002, 2016.

[67] V. Fusco, G. Campisi, G. Numico, C. A. Migliorati, D. Santini, and A. Bedogni, "RE: Regorafenib Also Can Cause Osteonecrosis of the Jaw," *Journal of the National Cancer Institute*, vol. 108, no. 9, Article ID djw155, 2016.

[68] M. Viviano, M. Rossi, and S. Cocca, "A rare case of osteonecrosis of the jaw related to imatinib," *Journal of the Korean Association of Oral and Maxillofacial Surgeons*, vol. 43, no. 2, p. 120, 2017.

[69] R. N. Hopp, J. Pucci, A. R. Santos-Silva, and J. Jorge, "Osteonecrosis after administration of intravitreous bevacizumab," *Journal of Oral and Maxillofacial Surgery*, vol. 70, no. 3, pp. 632–635, 2012.

[70] M. Magremanne, M. Lahon, J. De Ceulaer, and H. Reychler, "Unusual bevacizumab-related complication of an oral infection," *Journal of Oral and Maxillofacial Surgery*, vol. 71, no. 1, pp. 53–55, 2013.