Research Article

New paradigms for dental prevention of medication related osteonecrosis of jaws (MRONJ)

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ONJ-Prevention of local osteonecrosis risk factors should be planned before and during the intake of associated drugs, according to new schedules. Secondary prevention requires a careful clinical oral examination, but also first level X-ray examinations and, when necessary, second level (CT) too. Three main risk factors of ostonecrosis of the jaws (ONJ) are recognised: (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 the paper is to report and summarize the new paradigm recently published (https://www.hindawi.com/journals/bmri/2018/2684924/) by the Italian Society of Oral Pathology and Medicine (SIPMO) on preventive dental management in patients at risk of Medication related osteonecrosis of the jaw (MRONJ), prior to and during/after the administration of the aforementioned ONJ-related drugs.

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Scope

The aim of the paper is to report and summarize the new paradigm recently published by the Italian Society of Oral Pathology and Medicine (SIPMO)[1] on preventive dental management in patients at risk of Medication related osteonecrosis of the jaw (MRONJ), prior to and during/after the administration of the aforementioned ONJ-related drugs.

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Cancer Patients in the Pre-treatment Phase

In the pre-treatment phase, cancer patients in good oral health must be informed and made aware of the risks inherent of MRONJ and the necessity of being enrolled onto a recall 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. [2]

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.

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. [2] 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.

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. [3] [4] [5] 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 indicatedfor cancer patients in-treatment in presence of dental diseases which cannot otherwise be resolved. [2][3]

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. [6] 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.

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). 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). [7] The application of APCs 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.

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. [2]

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.

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. 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.[2] [8]

As a non-invasive dental treatment, orthodontics is classified as an elective treatment and it is thus considered apossible, 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. However, it must be underlined that cancer patient being treated with ONJ-related drugs will rarely request orthodontic treatment. [9][10]

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. 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]

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. [11] [12] 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. 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. [13]

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]

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); 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. [15]

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. [2] These procedures can be performed for non-cancer patients in-treatment in Category A, without applying specific medical and surgical protocols. 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 [16][17]. After removing the sutures, it is of the utmost importance to perform periodic clinical-radiographic check-up (after 1, 3, 6, and 12 months).

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. 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.[17], 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.

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. [2]

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