Review Article

Oral care and the use of bone-targeted agents in patients with metastatic cancers: A practical guide for dental surgeons and oncologists

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ABSTRACT

Background: Bone-targeted agents such as bisphosphonates and the RANKL antibody have revolutionised the care of patients with bone metastases. There has, however, been increasing concern about the oral health of these patients and in particular osteonecrosis of the jaw (ONJ), especially with the increasing use of these agents at higher potencies for greater periods of time.

Methods: A review of the published data in PubMed and meeting abstracts was performed to examine incidence, risk factors, pathogenesis, clinical course and management of osteonecrosis of the jaw with focus on cancer patients treated with bone-targeted agents (BTA) for bone metastases. This manuscript takes the most frequent and pertinent questions raised by oncologists, dentists and oral and maxillofacial surgeons and tries to give a pragmatic overview of the literature.

Results: The incidence of ONJ varies depending on types of bone-targeted agents, duration of treatment and additional risk factors. The causes and pathogenesis of ONJ is not fully elucidated, however bone-targeted therapy induced impaired bone remodelling, microtrauma secondary to jaw activity, and oral bacterial infection seem to be important factors. Since the treatment options for ONJ are limited and not well established, preventive strategies have to be included in patients management.

Conclusions: Many unanswered questions remain about the optimal oral care of patients receiving bone-targeted agents. Prospective data collection will remedy this and help to provide practical guidelines for the management and treatment of those patients that require dental intervention.

1. Background

Few drugs have revolutionised the care of metastatic cancer patients as much as the bisphosphonates. These inhibitors of osteoclast function have undergone extensive clinical development over the last 20 years and have been shown to reduce hypercalcemia, bone pain, fractures, radiotherapy use, spinal cord compression and bone surgery in patients with bone metastases from a range of malignancies. They have also been shown to improve patient quality of life [1]. In addition, oncology patients will frequently receive bisphosphonates for osteoporosis, cancer treatment related bone loss and sometimes as an adjuvant therapy [2]. From an oncologist’s standpoint these therapeutic benefits have been achieved with very few side effects when compared with most other systemic agents used in clinical practice. However, what has become evident is that as these increasingly potent bone-targeted agents are used for longer durations of time, less common side effects such as osteonecrosis of the jaw (ONJ) are presenting challenges not only to oncologists but also to the dental professionals who care for these patients.

This is becoming an increasingly important issue as the use of new agents such as the antibody to Receptor activator of nuclear factor kappa-B ligand (RANKL), denosumab, is also associated with this complication. Given that there is increasing awareness of this complication by oncologists, dental professionals and patients alike, we felt it was timely to offer a practical guide to assist all of us in the care of these patients. This article should not be viewed as a comprehensive review of the literature but more as a practical guide to assimilate the most up to date information.

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2. Definition, diagnosis, incidence and risk factors for osteonecrosis of the jaw

2.1. What is osteonecrosis of the jaw and what other oral conditions can it look like?

While ONJ is also called bisphosphonate-related osteonecrosis of the jaw (BRONJ), in this article we will keep to the term ONJ as clearly BRONJ is a misnomer considering the condition is now described to also result from the use of non-bisphosphonate bone-targeted agents. Some are now calling this condition chemically-mediated ONJ, or chemonoecrosis of the jaw [3,4]. The American Association of Oral and Maxillofacial Surgeons defines BRONJ as “exposed bone in the maxillofacial region that has persisted for more than 8 weeks, together with current or previous treatment with a bisphosphonate and without a history of radiation therapy to the jaw” [5]. This is a relatively rare clinical entity which was first described first in 2003 in cancer patients treated with potent bisphosphonates, following by increasing evidence on incidence, clinical pictures, staging, prophylaxis and treatment options [6]. ONJ can produce significant morbidity in affected patients, decreasing quality of life due to its chronic nature and relatively low recovery rate [7]. Approximately 30% of patients present with exposed bone and pain, and an additional 50% suffer from pain, gingival swelling and purulent discharge. In severe cases (about 20%), some patients can progress to pathologic fracture of the jaw, fistula formation, severe extended bone necrosis and an infection process in the soft tissues [8,9]. Occasionally, pain in the jaw bone or tooth loosening may be the only symptom with no evidence of other clinical or radiological abnormalities [10].

The diagnosis is made by a combination of clinical suspicion, clinical examination and radiological assessment. Clinical suspicion is going to be raised in those patients known to have been receiving treatment with highly potent bone-targeted agents. Clinical examination may reveal exposed jawbone, mucosal swelling, erythema, ulceration and tooth mobility as well as purulent discharge, intra- or extra-oral fistula and necrotic bone in the more advanced cases (Fig. 1). Panoramic and cross-sectional imaging will help determine the extent of necrosis and the presence of a sequestrum or osteomyelitis. Involvement of the mandible is more common than the maxilla, probably due to its more limited blood supply, and has been estimated as being involved in up to 70% of cases [11]. Radiology also helps to exclude other possible aetiologies such as unerupted teeth, bony cysts, sinusitis, temporo-mandibular joint (TMJ) pathology or metastatic disease [12,13] (Table 1).

2.2. Causes and pathogenesis of osteonecrosis of the jaw

The mechanism for the development of ONJ is not fully understood, however, several hypotheses exist. The aetiology appears to be multi-factorial and includes bisphosphonate induced changes, patient related factors and dental surgical procedures.

Mandibular and maxillary bones, particularly the alveolar bone and periodontium, characterize by a high turnover rate throughout life as response to constant mechanical stress, tooth mobilisation, extraction or periodontal infections [14,15]. Bone healing process requires involvement of multiple cytokines and growth factors including platelet-derived growth factors, bone morphogenic proteins, members of the transforming growth factor β superfamily, and members of the insulin-like growth factor family [16]. Human gingival fibroblast (HGF) and human periodontal ligament (HPDL) cells that present in periodontal tissue express RANKL and osteoprotegerin and provide balanced bone remodeling [17]. Bisphosphonate have a high affinity to bone tissue especially at high remodelling sites. Bone-targeted agents clearly interfere with bone remodelling through the osteoclast apoptosis [18,19]. This results in accumulation of dead bone tissue that cannot provide sufficient blood supply to overlying mucosa and lead to bone exposure. In addition, anti-angiogenic properties of bisphosphonates could contribute to vascular impairment [20,21]. Mawardi et al. showed on the mouse bisphosphonate treated model that bacterial infection at the tooth extraction sites causes diminished keratinocyte-growth factor expression in gingival fibroblasts and

Fig. 1. Stages of ONJ (adapted from Bagan et al. [78]) (with permission); (a) an initial stage of osteonecrosis without visible necrotic bone. (b) Osteonecrosis of the upper jaw; stage 1. The patient had no symptoms. (c) Osteonecrosis of the jaw; stage 2. A more extensive area of necrosis and with symptoms. (d) Osteonecrosis of the jaw; stage 3. The patient had an extraoral (cutaneous) fistula.
Table 1
Definition, diagnosis, risk factors of ONJ.

| Question                        | Answer                                                                 | References |
|---------------------------------|------------------------------------------------------------------------|------------|
| What is ONJ?                    | Exposed bone in the maxillofacial region that has persisted for more than 8 weeks, together with current or previous treatment with a bisphosphonate, without a history of radiation therapy to the jaws | [5]        |
| What causes ONJ?                | Bisphosphonate related factors: Impaired bone remodelling and [18,19,77], inhibition angiogenesis [20,21] |            |
|                                  | Patient related factors: Constant microtrauma due to jaw movement [14], Bone trauma due to surgical dental procedures [15], |            |
|                                  | Oral microflora may inhibit healing process and super infect poorly healing wound [23–24] |            |
| Who gets ONJ?                   | Two main factors contribute to development of ONJ: Bone-targeted agent treatment and surgical procedures involving jaw bones that have been surgically or intentionally exposed | [28–30,35–37] |
| Predisposing factors: Immunosuppressive status, increased patient’s age, local oral inflammatory process, chronic corticosteroids use, concurrent chemotherapy, smoking |            |
| How do you diagnose ONJ?        | Symptoms: pain, gingival swelling, purulent discharge, exposed, non-healing bone | [11]       |
| Differential diagnosis of ONJ   | Gingivitis, Mucositis, Infectious osteomyelitis, Sinusitis, Periapical pathology caused by a carious infection, Temporomandibular joint disease, Osteoradionecrosis, Neuralgia-inducing cavitational osteonecrosis (NICO), Bone tumors or metastases | [12,13]   |

Table 2
Incidence of osteonecrosis of the jaw [7,16–20].

| General population | Metastatic breast, prostate cancer | Multiple myeloma |
|--------------------|-----------------------------------|------------------|
| Oral bisphosphonates | 0.00038–0.06% | Single reports | Single reports |
| Pamidronate         | n/a  | 0.5–1% | 1–4% |
| Zoledronic acid     | 0.06% | 1.2–2.9% | 1–10% |
| Denosumab           | 0% in 3 years | 2% | 1.1% |

Therefore leads to a delay in wound-healing process [22]. Colonisation of oral microflora on exposed bone surface and surrounding mucosa might result in development of chronic infection and further impairment of wound healing [23,24] (Table 1).

2.3. Incidence, prevalence and risk factors for osteonecrosis of the jaw

Oral or intravenous bisphosphonates use was found to be the most important risk factor for ONJ [25,26].

Given the heterogeneous nature of the patient population treated by bone-targeted agents, there is considerable variability in the choice of agents, their dose, duration of therapy and schedule, and hence variability in the incidence and prevalence of ONJ. In general however, patients with metastatic bone disease receive considerably more treatment than patients treated for osteoporosis or cancer-treatment related bone loss and therefore it is the advanced cancer population that is more extensively studied. In addition, given the high incidence of bone involvement in metastatic breast, prostate cancers and multiple myeloma patients, together with the frequent use of bone-targeted agents in these patients for many years, it is not surprising that these are the patients at greatest risk for ONJ [27].

While the reported incidence of ONJ varies considerably, it tends to range between 1% and 12% based on results from particular case series, case-controlled and cohort studies [10] (Table 2). There is also variability in incidence across disease sites, with rates of approximately 0–6% in patients with prostate cancer, 1.2–2.9% in breast cancer patients and 2.4–9.9% in multiple myeloma patients. In other malignancies the incidence appears to be about 0–4% [28,29]. It is this variability in incidence between cancer types that provides the greatest clues to risk factors for ONJ. These patients all receive high cumulative doses of potent bone-targeted agents for prolonged periods of time. The importance of potency of the bisphosphonate is reflected through the reported incidence with zoledronic acid (incidence of ONJ of 20% after 3 years of treatment), compared with pamidronate (7% after 4 years treatment), and oral bisphosphonates (0.00038–0.06%) [28–32]. The duration of bisphosphonate exposure is also important with cumulative rates of ONJ of 1% after 12 months of therapy rising to 11% after 4 years of therapy [28].

As mentioned, ONJ is not just a result of bisphosphonate use. Denosumab use has also been associated with cases of ONJ. A recently published meta-analysis of 3 randomised trials compared the efficacy and safety of denosumab versus zoledronic acid in 5723 patients with metastatic breast cancer, prostate cancer or multiple myeloma, and prospectively evaluated the incidence of ONJ. Similar incidences of ONJ were observed with both treatments, with an incidence of 1.3% with zoledronic acid and 1.8% with denosumab. Interestingly the median time of drug exposure before ONJ was the same (14 months) in both groups [33]. However, it is important to realise that patients with any pre-existing dental problem were excluded from participating in the studies included in the meta-analysis and all patients received regular oral examinations. It is therefore likely, given the highly motivated nature of both the patients and the investigators in the trials, that the real world non-trial risks of ONJ would likely be higher.

While spontaneous cases of ONJ are reported, most (up to 80%) are related to recent dento-alveolar trauma, including tooth extractions, dental implant placement, periapical surgery and periodontal procedures involving osseous injury [9,34].

The incidence of ONJ appears to increase for patients when they have additionally undergone an invasive dental procedure, and are approximately 9–50% in patients on intravenous bisphosphonate and 1–8% in patients receiving oral bisphosphonates. These procedures thus appear to result in an increase in the risk of developing ONJ by 5–21-fold [35]. It is important however to note that periodontal disease and bone exostosis (which in themselves
increase the need for dental work) have also been reported to be significant independent risk factors for ONJ [28]. Other predisposing factors include: chronic steroid use in conjunction with bisphosphonates, particularly in the management of patients with multiple myeloma; and an immuno-compromised state secondary to concomitant chemotherapeutic agents and diabetes [25,36–38].

There is a controversy for role of anti-angiogenic therapy on development of ONJ. Some reports support significant increase in ONJ incidence in patients treated with anti-angiogenic agents [39,40]. Moreover, patients receiving anti-angiogenic agents including bevacizumab and sunitinib have doubled the risk of ONJ compared to patients who have not been exposed to such treatment following meta-analysis of denosumab trials [33]. On the other hand analysis of three large prospective trials of bevacizumab in metastatic breast cancer revealed 0.9–2.4% risk of ONJ in patients receiving concomitant bisphosphonates and bevacizumab, which was comparable with those receiving bisphosphonates alone [41]. In general, however, what is clear is that the more risk factors a patient has, the greater the risk of developing ONJ, which can reach 10–20% in patients with more than one risk factor [42].

A systematic review by Migliorati et al. showed variable prevalence of ONJ depending on study type, duration of follow up and type of bisphosphonate. While in studies with documented follow up prevalence was as high as 13.3%, in studies only 0.7%. Analysis of epidemiological studies resulted in prevalence 1.2%. As for type of bisphosphonate the overall prevalence for patients using zoledronic acid was 8.6%, for pamidronate 7.3%, and 21% for both. Prevalence was much higher in cancer patients (89%), and patients with multiple myeloma were affected more frequently than patients with solid cancers [43] (Table 3).

### Table 3
Prevalence of ONJ [43].

| Type of study              | Type of bisphosphonate | Prevalence |
|----------------------------|------------------------|------------|
| Overall prevalence         | Zoledronic acid        | 6.1%       |
| Documented Follow up       | Pamidronate            | 13.3%      |
| No documented follow up    | Both                   | 0.7%       |
| Epidemiologic studies      | Oral BP                | 1.2%       |
|                            |                        | 0.1–4%     |

In this section we will try and address many of the frequently asked questions around preventive and prophylactic measures for patients either starting or already established on bone-targeted therapy (Figs. 2 and 3). In view of the difficulties in treating ONJ, preventive strategies would seem to make the most sense. The efficacy of preventive strategies was investigated in two studies. Authors tried to compare the incidence of ONJ between the investigational group and a control group. The investigational group underwent preventive measures including dental assessment prior to bisphosphonate initiation so that any invasive dental procedures could be completed prior to initiation of bisphosphonate therapy. Bisphosphonate treatment was delayed for 6–8 weeks until complete wound healing after surgical procedures. Whenever possible minor dental interventions with preservation of dental roots, and avoidance of dento-alveolar surgery were preferred over tooth extraction and prophylactic antibiotics were used with invasive procedures. The retrospective control group of patients had received bisphosphonates before implementation of preventive measures. Incidence of ONJ was reduced by two-three times in patients on preventive measures [44,45]. While this data is not from a randomized trial the authors did comment that given the effectiveness of ONJ preventive measures, performing a randomised study with a control group not receiving these measures would likely be considered unethical.

According to these studies and numerous recommendations, patients should be consulted about risk of developing ONJ prior to initiation of bone-targeted treatments and informed about the importance of maintaining their oral hygiene. Patients should be advised to have a dental examination, treatment existing dental problem and extraction of teeth that cannot be restored, preferably by a dental surgeon familiar with the risks of ONJ, prior to starting bisphosphonate therapy. Patients should also avoid dento-alveolar surgical procedures involving the mandibular or maxillary bone while actively receiving intravenous bisphosphonates, or for several months after completion of the therapy [5]. For patients receiving on-going bone-targeted therapies they too should continue to have frequent dental examinations. This allows the identification and early treatment of any dental

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**Fig. 2.** Preventive measures in patients with bone metastases about to start BTAs.
A meta-analysis of seven published single centre, non-randomised studies with a prospective interventional cohort and retrospective control group investigating the efficacy of preventive measures was presented recently at cancer-induced bone disease symposium in Lyon. It showed efficacy of preventive measures with a relative reduction of 68% of ONJ risk (RR 0.32; 95% CI 0.20–0.50; \( p < 0.001 \)).

Given that strategies to avoid ONJ are likely to be more effective than treating the condition once it occurs, it also seems sensible to reduce bisphosphonate exposure as much as possible. This can be accomplished by using less potent agents or less intensive infusion schedules, particularly in those patients who have been on bone-targeted agents for protracted periods of time. In multiple myeloma patients most guidelines recommend stopping bisphosphonates after two years. Recently emerging data in multiple myeloma patients suggests that the incidence of ONJ might be lowered by a reduced dosing schedule without affecting the incidence of skeletal-related events [47]. The risk of ONJ was eight-fold lower with the reduced schedule (monthly injection during the first year and every 3 months thereafter) than with the standard monthly schedule. However, this small retrospective study is not conclusive regarding the efficacy of less frequent dosing or its impact on the development of ONJ. However, a number of ongoing studies are investigating the efficacy of less intensive regimens of bisphosphonates in metastatic bone disease (NCT00320710, NCT00424983). The ZOOM trial, comparing a standard 4 weeks versus 12 weeks schedule of zoledronic acid for the prevention and delay of skeletal related events in metastatic breast cancer patients was presented at the ASCO meeting 2012 and showed equivalent results for these two regimens [48].

**Fig. 3. Prevention of ONJ in patients on established BTAs.**

### 4. How do you manage patients on intravenous bone-targeted agents who require dental work?

For patients who are on IV bisphosphonate therapy and require dento-alveolar procedures there is a suggestion that prophylactic antibiotic use around the procedure may be helpful in reducing ONJ risk [45,49]. A recent study by Lopez-Jornet et al. showed a statistically significant reduction of ONJ with pre and postoperative antibiotics for extraction procedures in an animal model [50]. If a surgical procedure is unavoidable, conservative surgical intervention is preferred in an attempt to minimize trauma to bone tissue. The procedure should be performed by experienced clinicians familiar with ONJ, ensuring that a minimally invasive, efficient procedure be performed with minimal morbidity.

### 5. Should patients on a bone-targeted agent requiring dental work stop their bone-targeted agent?

Recommendations on need of discontinuation of bisphosphonates in patients requiring dental work have not been created yet. Given the very long half-life of bisphosphonates in bone, with a 12-year terminal half-life even for oral agents like alendronate, effects of temporary cessation of the agents is questionable [31,46]. On the other hand, temporary discontinuation of bisphosphonates may remove their acute toxic effect on soft tissue and could facilitate the healing process [5].

AAOMS recommends withholding oral bisphosphonates for up to 3 months before a surgical procedure and for up to 3 months thereafter [5]. This strategy also supported by a correlation of the level of the bone turnover marker, C-terminal telopeptide (CTX) with risk of development of ONJ. According to Marx et al. morning fasting serum CTX levels correlated with the duration of oral bisphosphonate use, with increased values for each month of a drug holiday when the oral bisphosphonate was discontinued, suggesting a recovery of bone remodelling during this time. A rising of CTX was associated with reduced risk of ONJ after surgical dental procedures [51]. On the other hand, other trials failed to show a correlation between level of biochemical markers
(i.e. CTX, N-terminal telopeptide (NTX), or bone specific alkaline phosphatase) and risk of development of ONJ [52–54]. It however must be recognized that inter individual variability, gender, age, physical activity, and seasonal variation exist that can result in difficulty in interpreting these assays, hence more research is needed.

There is no conclusive data that stopping of intravenously given bisphosphonates or denosumab for 2–4-month prior to dental invasive procedure can reduce the risk of ONJ.

6. Management of patients with established osteonecrosis of the jaw

This section will deal with the care of patients on bone-targeted agents who then develop ONJ (Fig. 4). Although a number of clinical guidelines for management of patients with ONJ have been released by various oncology, oral surgical organizations and bisphosphonate manufacturers, there is no established gold standard, since most recommendations are based on case-control studies, retrospective analyses and expert opinions. For patients with established ONJ, treatment objectives are elimination of pain, control of infection in the soft and bone tissue, and minimization of the progression or occurrence of bone necrosis.

In general, patients with ONJ should be evaluated and managed by a team including an oral and maxillofacial surgeon and an oncologist [5,46]. Several staging systems of ONJ have been developed by different dental and oncology organizations to help facilitate treatment decisions. The most useful system had been proposed by Ruggiero and subsequently revised by the American Association of Oral and Maxillofacial Surgeons (Table 4 and Fig. 1). According to this classification, Stage 0 defines patients presenting with non-specific symptoms such as tooth pain, sinus pain, and unexplained tooth mobility but without significant clinical findings on examination. For these patients conservative management with topical mouth rinses (chlorhexidine gluconate or hydrogen peroxide) and analgesia is recommended. This is to decrease and prevent further progression of infection in the exposed bone [5,11].

Among patients with established infection in the bone or surrounding tissue (Stage II) antibiotic penicillin-based therapy in addition to mouthwash may result in healing in patients with minor ONJ lesions. However, a large proportion of cases tend to show chronically infected necrotic process in jaw bones with very limited response to any treatment. Prior to commencement of antimicrobial (penicillin-based) and antifungal therapy, wound and pus culture samples, including those for Actinomyces species should be taken [55,56].

Generally, surgical debridement has been variably effective in eradicating necrotic bone and is not recommended for early stages of ONJ due to the concern of possible exacerbation of the necrotic process [57]. However, in patients with advanced process (Stage III) with pathological fracture, extra oral fistula, osteolysis extending to the base of the jaw or recurrent infections, complete removal of the necrotic bone and where possible immediate reconstruction in addition to systemic antibiotic treatment is indicated [58,59].

Several authors reported successful outcome with surgical treatment of ONJ [9,60,61].

As alternative for conventional conservative surgery, laser applications at low intensity (low level laser therapy—LLLT) have been reported in the literature for the treatment of ONJ with promising results [54,62]. Biostimulatory effects of laser improve reparative processes, increase inorganic matrix of bone and stimulate lymphatic and blood capillary growth, as well as having a bactericidal effect.

**Table 4**

| Stage | Clinical picture |
|-------|------------------|
| Stage 0 | Tooth and jaw pain with no findings on examination, unexplained tooth mobility |
| Stage I | Asymptomatic exposed and necrotic bone without infection |
| Stage II | Exposed and necrotic bone with pain and infection |
| Stage III | Exposed and necrotic bone with pain and infection plus Pathologic fracture or extra-oral fistula/communication or necrosis extending beyond the region of alveolar bone or oro-antral/oro-nasal communication |

*Fig. 4. Management of established ONJ.*
Hyperbaric oxygenation therapy has shown inconsistent results and is now under investigation in an ongoing randomised trial as an addition to surgical or non-surgical treatment [63]. As a result, its use is not presently recommended outside of clinical trials.

Pentoxifylline (blood viscosity reducer agent) and oral vitamin E has shown efficacy in a small case series [64].

Ozone (O3) therapy in the management of bone necrosis or in extractive sites during and after oral surgery in patients treated with bisphosphonate may stimulate cell proliferation and soft tissue healing resulting in alleviation of symptoms [6]. However, several case reports and small uncontrolled studies reported controversial efficacy of O3 gas formulation in addition to conventional in treatment of ONJ [65,66].

In a phase I and II study, medical O3 has been shown to heal ONJ if antibiotic therapy (azithromycin) is administered 10 days prior to O3 oil formulation, where more than half of the patients showing a complete response with radiologic lesion disappearance following reconstruction of the oral tissue [67].

Teriparatide (synthetic peptide that corresponds to the N-terminal residues of human parathyroid hormone) therapy has been recommended to adjust the mechanisms of failed bone remodelling and have anabolic effects on osteoblasts. Teriparatide has been shown to help remove necrotic bone for new healthy bone to be laid down in order to resolve periodontal osseous defects [68]. Subramanian et al. [69] reported on the off-label use of teriparatide for ONJ in 6 patients treated with bisphosphonates for osteoporosis. In this report healing occurred in all cases within 5 months of initiating treatment. In contrast, Narvaez [70] reported a case of lack of response to teriparatide treatment. Of note, teriparatide is contraindicated in patients with osteosarcoma or metastatic bone disease following reports that osteosarcoma has occurred in rats and people who took the drug [71].

Other treatments such as administration of platelet rich plasma, and bone morphogenic proteins have been published as possible procedures in ONJ treatment in small case reports. Clearly the efficacy of these strategies needs to be established in additional prospective studies [72].

7. Should bisphosphonate therapy be discontinued if osteonecrosis of the jaw is present?

Decisions about to continue or stop bisphosphonates in face of established osteonecrosis of the jaw remains controversial.

Although bisphosphonates have not been shown to improve cancer-specific survival patients with metastatic bone disease patients significantly benefits from bisphosphonate treatment through reduced bone pain and a lower incidence of skeletal related events. Their use is therefore recommended in most international guidelines, starting once bone metastases are diagnosed [73–75], however, none give comprehensive recommendations about when to stop treatment.

Recently emerging data suggest that lower frequency of IV bisphosphonates in metastatic breast cancer has the same efficacy as monthly regimen [48]. ONJ on the other hand can be extremely symptomatic with a severely detrimental effect on quality of life.

A case-control study based on risk factors for ONJ confirms that ONJ is associated with the duration of bisphosphonate treatment. A higher risk of ONJ began within 2 years of bisphosphonate treatment and increased four-fold 2 years later, showing that even less potent bisphosphonates remain linked to ONJ after brief treatment therapy [25].

There are several reports that long term discontinuation of IV bisphosphonates in patients with ONJ may be beneficial in stabilizing established sites of osteonecrosis and provide improvement of clinical symptoms [5,46]. However, there have been some cases of spontaneous resolution during ongoing monthly bisphosphonate therapy [28,29]. Moreover, Wilde et al. [60] reported favorable outcome with surgical treatment of ONJ irrespective of whether bisphosphonates were discontinued or not. In another report, the patients who developed ONJ after dental procedures safely restarted bisphosphonate therapy, but those who developed ONJ without a predisposing cause were at increased risk of recurrence after initial healing, especially when these agents were reintroduced [76]. Since bisphosphonates are incorporated into the mineral matrix of bone, it is unknown as to whether or not stopping bisphosphonate therapy would be beneficial in managing ONJ [7]. Nevertheless, stopping the bisphosphonate would remove any acute influences on the periosteum and soft tissues, and could potentially improve the healing process [531].

Therefore decisions around bisphosphonate withdrawal and reintroduction after ONJ are complex and should be made using a multidisciplinary team including oncologist, oral and maxillo-facial surgeon and patient based on weighing the severity of ONJ symptoms against the benefits from ongoing bisphosphonate therapy including patients’ overall prognosis and symptoms of bone metastases [46].

8. Discussion

Bone-targeted agents are established standard of care treatments for patients with metastatic bone disease. Generally they are well tolerated with few side effects, however, in recent years cases of ONJ have been reported as a rare but serious complication of treatment. In light of the palliative intent of bisphosphonate administration on the one hand and the serious implications of ONJ on patient’s well-being and quality of life on the other, it has become an important issue for oncologists, dentists, and oral and maxillofacial surgeons. Given the increasingly widespread use of highly potent bone-targeted agents such as bisphosphonates and inhibitors of RANKL function, the prevalence of ONJ is likely to continue to increase.

We simply have to accept that while there is growing data on incidence and risk factors of ONJ, the current data about the prevention and treatment of ONJ is relatively poor and is based mainly on case reports, case-controlled series, retrospective studies and expert opinions. Ongoing prospective trials in metastatic and adjuvant (D-CARE trial, http://www.clinicaltrials.gov/ct2/show/NCT01077154) settings with accurate ONJ monitoring will help us answer many more questions about the prevention and management of this condition. In particular strategy looking at de-escalating regimens in patients with bone metastases that can reduce exposure of the jaw to bisphosphonates and therefore reduced risk of ONJ and improve patient care [48].

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