Future ONCOLOGY

REVIEW

Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents

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ABSTRACT Osteonecrosis of the jaws (ONJ) is an adverse side event of bisphosphonates and denosumab, antiresorptive agents that effectively reduce the incidence of skeletal-related events in patients with metastatic bone cancer and multiple myeloma. Available data suggest that 0–27.5% of individuals exposed to antiresorptive agents can develop ONJ. There is increasing evidence that avoidance of surgical trauma and infection to the jawbones can minimize the risk of ONJ, but there are still a significant number of individuals who develop ONJ in the absence of these risk factors. Bone necrosis is almost irreversible and there is no definitive cure for ONJ with the exclusion, in certain cases, of surgical resection. However, most ONJ individuals are affected by advanced incurable cancer and are often managed with minimally invasive nonsurgical interventions in order to control jawbone infections and painful symptoms. This article summarizes current knowledge of ONJ epidemiology, manifestations, risk-reduction and therapeutic strategies. Further research is needed in order to determine individual predisposition to ONJ and clarify the effectiveness of available treatments.

KEYWORDS
• antiresorptive agents
• bisphosphonates
• cancer • denosumab
• epidemiology
• jaw • management
• osteonecrosis • risk

Antiresorptive agents have revolutionized the treatment of cancer in individuals with bone metastases and those with multiple myeloma as they can effectively prevent skeletal complications and relieve bone pain **(Table 1)** [1]. There is now overwhelming evidence that bisphosphonates (BPs) can reduce skeletal morbidity in multiple myeloma and solid tumors affecting bone by 30–50% [2]. Recent studies have shown that the new RANKL inhibitor denosumab can be even more effective than BPs in reducing the incidence of and delaying the time to skeletal-related events [3]. BPs are also useful in preventing cancer treatment-related bone loss in individuals with chemotherapy-related ovarian failure, and those who have been exposed to aromatase inhibitors and androgen deprivation therapy [4]. Further research is required to confirm the suggestion that some antiresorptive agents may also modify the course of the disease and disrupt the metastatic process, thereby reducing the risk of disease progression and prolonging disease-free survival, especially in early-stage cancers [2,4,5].

Although adverse events related to antiresorptive therapy are usually considered to be infrequent and mild, osteonecrosis of the jaw (ONJ) is now established as a clinically significant, potentially painful and debilitating condition that can significantly affect the quality of life of patients with cancer [6]. Of note, it is estimated that the magnitude of its negative effects is equivalent to other side effects associated with cancer treatment, which influences treatment decisions, possibly

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Table 1. Antiresorptive agents used in cancer and myeloma patients.

API	Formulation	Route	Indication and schedule
Alendronic acid (sodium salt)	Tab 70 mg Tab 10 mg	p.o.	Treatment of postmenopausal osteoporosis (70 mg/week) Treatment of osteoporosis in men (70 mg/week) Treatment and prevention of osteoporosis induced by glucocorticoids (70 mg/week)
Alendronic acid + cholecalciferol	Tab 70 mg/5600 UI	p.o.	Treatment of postmenopausal osteoporosis in patients with unsupplemented vitamin D deficit (70 mg/week)
Ibandronic acid (monosodium salt monohydrate)	Tab 50 mg Btl 6 mg/6 ml	p.o. iv.	Prevention of SREs in breast cancer patients with bone metastases (50 mg/day p.o. or 6 mg every 3–4 weeks iv.) Treatment of hypercalcemia of malignancy
	Tab 150 mg Btl 3 mg/3 ml	p.o. iv.	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 Btl 100 mg/8 ml	iv./im. iv.	Osteogenesis imperfecta (2 mg/kg/3 months) Paget's bone disease (different schedules)
Pamidronic acid (disodium salt)	Btl 15 mg/5 ml Btl 30 mg/10 ml Btl 60 mg/10 ml 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) Treatment of hypercalcemia of malignancy
Zoledronic acid (monohydrate)	Btl 4 mg/5 ml	iv.	Prevention of SREs in cancer patients with bone metastases or MM (4 mg every 3–4 weeks) Treatment of hypercalcemia of malignancy
	Btl 5 mg/100 ml	iv.	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) Treatment of bone Paget's disease
Denosumab	Btl 120 mg	sc.	Prevention of SREs in cancer patients with bone metastases (120 mg every 4 weeks) Treatment of hypercalcemia of malignancy
	Btl 60 mg	sc.	Osteoporosis (60 mg sc. every 6 months)

API: Active pharmaceutical ingredient; Btl: Bottle; im. Intramuscular; iv.: Intravenous; MM: Multiple myeloma; p.o.: Orally; sc.: Subcutaneous; SRE: Skeletal-related event; Tab: Tablet.

reducing the potential benefit of antiresorptive agents [6]. Jaw osteonecrosis has been suggested to occur in 0–27% of metastatic bone cancer and myeloma patients receiving nitrogen-containing BP (N-BP) [7] and also denosumab, a novel anti-RANKL antiresorptive agent [8]. Furthermore, ONJ cases have been reported after antiangiogenic treatment, with and without BP therapy [9].

The aim of this article is to summarize current knowledge regarding ONJ associated with antiresorptive therapy in cancer patients and discuss future perspectives regarding prevention and management of this debilitating condition. It is beyond the scope of this work to determine the level of evidence of available literature as the vast majority of current data and procedures remain empirical and based upon expert opinion and experience-based decision-making.

Definition

The first definition of ONJ was introduced by the American Association of Oral and Maxillofacial Surgery (AAOMS) [10] and comprised the following criteria:

- Current or previous treatment with BPs;
- Exposed bone in the maxillofacial region that has persisted for more than 8 weeks and;
- No history of radiation therapy to the jaw.

This definition, which relies heavily upon the presence of clinically evident necrotic bone exposed through the oral mucosa or facial skin, has been adopted by the vast majority of clinical and epidemiological studies, and commonly used in clinical trials for case adjudication. However, several independent reports have recently highlighted that ONJ does not always present with oral mucosa fenestration and necrotic bone exposure [11–17].

The so-called 'nonexposed variant of jaw osteonecrosis', initially reported in 2008, is characterized by a number of other clinical features to the jaw that develop in the absence of frank bone exposure [11–14,18,19]. These include otherwise unexplained jawbone pain, fistula/sinus tract, loose teeth, swelling and, in advanced cases, pathological fracture of the mandible. Of note, diagnosis of nonexposed osteonecrosis is based on excluding common jawbone diseases, such as odontogenic infections and other bone disorders known to cause similar manifestations. It is estimated that the

nonexposed variant can represent up to a third of all ONJ cases [11].

The term 'stage 0' was first used by Mawardi *et al.* to gather suspected ONJ cases presenting with clinical and radiological signs of disease other than oral bone exposure [14]. Eventually, the AAOMS acknowledged the existence of these clinical manifestations and included the nonexposed variant within the 'stage 0 group' of the revised staging system in 2009 [20]. Nevertheless, their case definition was not modified accordingly and it remained focused upon the clinical evidence of long-standing bone exposure. This, therefore, continued to influence entry criteria and case adjudication in clinical studies, leading to a likely underestimate of ONJ incidence. This paradox was highlighted by several authors who called for an urgent change in case definition [16,17]. Lately, attention has been raised regarding the potential role of imaging for the diagnosis and staging of ONJ patients. A combination of clinical and radiological signs, albeit not specific for ONJ, may be more inclusive and representative of the bone disease process [21].

Within this perspective, a refined case definition and severity score system have recently been proposed, both of which are based on the radiological extent of bone involvement rather than intraoral bone exposure alone [22]. Remarkably, in a recent document [23] the American Association of Maxillofacial Surgery also seemed to be more willing to accept the use of imaging techniques for ONJ detection and presurgical evaluation.

Epidemiology

ONJ associated with antiresorptive agents is a relatively new disease. Strangely, ONJ was not detected in initial BP trials and the first cases were reported in 2003 [24–27]. The epidemiology of ONJ remains unclear due to inconsistency and limitations of available studies, including a lack of a specific ICD code, under-reporting in surveillance drug systems, a recent introduction of preventive measures, case adjudication restricted to exposed ONJ, short-term observation and a lack of cumulative long-term incidence rates **(Table 2)** [11,28–48].

A recent review reports a wide-ranging ONJ incidence from 0 to 27.5%, relevant to individuals exposed to intravenous N-BP [7], with a mean incidence of 7%. The high variation in incidence figures is probably related to referral bias, as well as differences in study design and in the provision or risk-reduction dental strategies [7]. A recent meta-analysis reports the mean incidence of ONJ associated with denosumab to be 1.7% [49–52]. Interestingly, the studies reviewed in the meta-analysis reported a similar incidence of N-BP-associated ONJ, which is significantly less than previously reported; this may reflect the systematic adoption of risk-reduction dental strategies, but also differences in study design (e.g., observation time was in all cases less than 5 years and therefore shorter that most previous BP studies).

The oversuppression of osteoclast-mediated bone remodeling and consequent bone sclerosis and ischemia has been suggested to play a major pathogenetic role in ONJ, which was also confirmed by animal studies [53,54]. This would also explain the increased risk of ONJ associated with concomitant use of BP and antiangiogenic agents. A number of local factors have been consistently reported to increase the risk of ONJ development, including surgery to the jawbone and dental infection. It remains unclear however whether infection represents a primary event or simply a colonization of already necrotic ischemic bone. Overall, ONJ pathogenesis is not fully understood and the reason why only a subgroup of patients taking antiresorptive drugs develop ONJ remains unexplained. A detailed list of factors identified in the subgroup of patients developing ONJ is discussed below.

Clinical manifestations

Exposed ONJ, by definition, is characterized by the presence of clinically evident necrotic bone, which is exposed through the oral mucosa or facial skin, tending to affect the mandible more frequently than the maxilla [55]. Common associated manifestations include soft tissue swelling and erythema, pus discharge, fistula/sinus tracts, tooth loss, jaw deformity, pain and sensory disturbances. The dimension of exposed bone in ONJ can vary from a few millimetres to several centimetres. Of note, little is known regarding the true extension of necrotic bone surrounding the superficial exposed areas, as very few studies have reported data from radiographs, computed tomography (CT) or MRI scans [56]. It seems that the vast majority of patients present with localized bone disease, which often is painful and infected [55]. Yet, several patients seem to display clinical

Table 2. Epidemiology of osteonecrosis of the jaw.

Patient population	Odds of ONJ (frequency/incidence/prevalence)	Ref.
BRONJ in metastatic cancer and MM patients	Variable frequency (range: <1 to >20%; from case series and epidemiologic studies) Limitations: different cancer subsets, N-BP type and length of exposure and follow-up Cumulative 2-year risk of ONJ lowers with oral preventive measures in cancer patients on monthly infusions of zoledronate	[28] [30] [111]
BRONJ in metastatic breast cancer patients	Variable frequency (range: 1–8%); higher risk for zoledronate users than pamidronate	[30,58,61]
BRONJ in nonmetastatic breast cancer patients (adjuvant setting)	17 adjudicated ONJ cases (1.1%) and 9 suspected cases among 1686 patients in the largest finalized study (AZURE) on zoledronic acid use 0.52% in all zoledronic acid studies (different schedules and follow-up)	[4] [37]
Denosumab-related ONJ in metastatic breast cancer patients	2% (20 out of 1020) adjudicated ONJ cases (median on-study time: 17 months) in one large trial (vs 1.4% after zoledronic acid)	[51]
BRONJ in metastatic prostate cancer patients	Variable frequency (range: 3–20%); increased frequency (11 out of 55; 20%) in one experimental trial combining zoledronic acid and antiangiogenic agents	[38–40,58]
BRONJ in nonmetastatic prostate cancer patients (adjuvant setting)	3.5% (2 out of 58) ONJ cases after 5 zoledronic acid infusions (every 3 months for 1 year)	[41]
Denosumab-related ONJ in metastatic prostate cancer patients	2% (22 out of 943) adjudicated ONJ cases (median on-study time: 12.2 months) in one large trial (vs 1% after zoledronic acid)	[43]
Denosumab-related ONJ in nonmetastatic prostate cancer patients (adjuvant setting)	5% (33 out of 720) adjudicated ONJ cases (median on-study time: 20 months) in one large trial	[44]
BRONJ in bone metastatic cancer different from breast and prostate	Large variations in case series 1.3% (11 out of 878) adjudicated ONJ cases (median on-study time: 7 months) in one large trial with zoledronic acid	[30] [42]
Denosumab-related ONJ in bone metastatic cancer different from breast and prostate	1.1% (10 out of 878) adjudicated ONJ cases (median on-study time: 7 months) in one large trial with denosumab	[42]
BRONJ in multiple myeloma patients	Variable frequency (range: 0–51%) in case series and reviews (typically 6–16%) Higher frequency with zoledronic acid than with pamidronate, especially at low doses 4% (35 out of 983) adjudicated ONJ cases after zoledronic acid vs 0.3% (3 out of 979) after chlodronate in one large randomized study Lower incidence in zoledronic acid-treated patients with monthly infusions during the first year and then every 3 months	[45,46,58,65] [47] [35] [48]
Denosumab-related ONJ in myeloma patients	Unknown (trials ongoing)	–

BRONJ: Bisphosphonate-related osteonecrosis of the jaw; MM: Multiple myeloma; N-BP: Nitrogen-containing bisphosphonate; ONJ: Osteonecrosis of the jaw.

manifestations of a more severe advanced form of ONJ; this includes an extension of necrosis and infection to the inferior border and ramus of the mandible, sinuses or zygoma in the maxilla, and it leads to severe intractable pain, sinusitis, pathological fracture, and oral-antral/nasal communication [55].

Clinical manifestations of the nonexposed variant of ONJ include otherwise unexplained jawbone pain, fistula/sinus tract, swelling, loose teeth and pathological fractures [11–14,18,19]. Notably, these individuals have no apparent cause for these clinical signs and symptoms, and indeed the diagnosis of nonexposed ONJ is one of exclusion from other possible jawbone disorders (e.g., dental infection and metastases). It has been suggested that nonexposed ONJ can account for approximately a third of all ONJ cases [11], and that only half of the cases progress over time to develop frank bone exposure.

The AAOMS has introduced a classification/staging system of ONJ based on clinical manifestations, which they suggest should also guide treatment [20]. This has been criticized by several authors who have highlighted the need to incorporate all potential manifestations of ONJ, including the nonexposed variant, and add imaging as part of the staging classification/system **(Table 3)** [22].

Systemic risk factors

A number of the systemic risk factors have been associated with increased likelihood of ONJ

development, including drug-related factors, genetic variants and comorbidities **(Table 4)** [57]:

- Administered drugs: in hematological and oncological patients, zoledronic acid (administered to the majority of ONJ patients but also the drug most commonly used, at least after 2002) seems to result in a statistically higher risk of ONJ [58–62] compared with pamidronate, and this is despite the absence of randomized studies. Insufficient data do not allow a definitive comparison with ibandronate, even if the latter appears to be at lower risk [63]. Clodronate (a non-nitrogenous BP, mainly used in patients with myeloma) is associated with a lower risk of ONJ in comparison with zoledronic acid [35], which is probably due to a different mechanism of action, as well as frequency of use.

- Administration route (intravenous vs oral): there is a higher risk for intravenous injection of N-BP but this factor may be closely related to their prevalent use in cancer patients (at significantly higher total doses and durations) [28,63,64].

- Total dose of administered N-BP (cumulative doses): available data indicate a higher risk of developing ONJ with an increase in total N-BP dose, which is intravenously administered monthly to cancer and hematological patients, both for zoledronate and pamidronate [58–60]. As previously reported, there are insufficient follow-up data for intravenous zoledronate and ibandronate in noncancer patients (administered every 3, 6 to 12 months). Regarding cumulative doses and duration of treatment with oral BPs, the majority of cases of ONJ were observed in osteoporotic patients treated for years (usually more than 2–3 years), with an average of 4.6 years, according to the review by Palaska *et al.* [65].

- Duration of treatment with intravenous N-BP: on average, ONJ patients were treated for longer periods than those without ONJ. The duration of intravenous treatment with N-BP is generally correlated with the total dose of drug administered, given the type of monthly administration, continuous and indefinite in time, recommended by major guidelines, at least until 2007 [60,66,67]. In a recent review of the literature [65], the mean/minimum time for the appearance of ONJ were 1.8 years and 10 months, respectively, for zoledronate, and 2.8 and 1.5 years, respectively, for pamidronate, but cases of ONJ appearing after few N-BP infusions are occasionally reported (often after tooth extractions). However, more data are needed, after more recent recommendations [68–70] and preliminary results of randomized trials [71] have indicated the possibility of less prolonged BP treatment (1–2 years, with a subsequent tailoring of therapy). Finally, despite the lack of studies separately analyzing the survival time factor from the duration of treatment with BP, the increasing survival of cancer and hematological patients

Table 3. Clinical and radiological osteonecrosis of the jaw staging system.

Stage	ONJ type
Stage 1†	Focal ONJ Clinical signs and symptoms: bone exposure, sudden dental mobility, nonhealing postextraction socket, mucosal fistula, swelling, abscess formation, trismus and gross mandible deformity hypoesthesia/paraesthesia of the lips CT signs: increased bone density limited to the alveolar bone region (trabecular thickening and focal osteosclerosis), with or without the following signs: markedly thickened and sclerotic lamina dura, persisting alveolar socket and cortical disruption
Stage 2‡	Diffuse ONJ Clinical signs and symptoms: same as stage 1 CT signs: increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal, periosteal reaction, sinusitis, sequestra formation and oro-antral fistula
Stage 3	Complicated ONJ Same as stage 2, with one or more of the following: Clinical signs and symptoms: extra-oral fistula, displaced mandibular stumps and nasal leakage of fluids CT signs: osteosclerosis of adjacent bones (zygoma and hard palate), pathologic mandibular fracture and osteolysis extending to the sinus floor

†Stage 1a: asymptomatic; stage 1b: symptomatic (pain and purulent discharge).
‡Stage 2a: asymptomatic; stage 2b: symptomatic (pain and purulent discharge).
CT: Computed tomography; ONJ: Osteonecrosis of the jaw.
Data taken from [57].

Table 4. Drug-related and systemic risk factors of osteonecrosis of the jaw in the cancer population.

Risk factor	Strength
Drug (BP)	
Product (zoledronate vs others)	+++
Route of administration (iv. vs oral)	++
Cumulative dosage	+++
Duration of treatment	+++
Underlying disease (for which treatment with N-BP is indicated)	
Solid tumors	++
Multiple myeloma	++
Supportive care	
Chemotherapy	-/+
Steroids in cancer patients	-/+
Antiangiogenic drugs (i.e., bevacizumab and sunitinib)	++
Thalidomide	+/-
Erythropoietin stimulation factors	+/-
Lifestyle	
Smoking	+/-
Alcohol	-/+
Obesity	+/-
Individual features	
Sex	+/-
Age	+/-
Genetic factors	+/-
Comorbidity	
Diabetes	+/-
Rheumatoid arthritis	+
Hypocalcemia, hyperparathyroidism	+
Vitamin D deficit, osteomalacia	+
Renal dialysis	+/-
Anemia	+/-

-/+: Occasionally positive data unproven in larger studies; +: Positive data in some studies but still inconclusive; +/-: Positive and negative data, unlikely to be confirmed; ++: Positive data in most studies; +++: Sound and consistent data; BP: Bisphosphonate; iv.: Intravenous; N-BP: Nitrogen-containing bisphosphonate.
Reproduced with permission from [57].

(time between diagnosis of advanced cancer and death) could prove to be [58,66,67,72,73] an additional risk factor responsible for a prolonged exposure to other (known and unknown) risk factors.

- Concurrent treatment with a biological drug: recently, the combined use of latest-generation antiangiogenic agents (i.e., bevacizumab, sunitinib and sorafenib) and N-BP has been associated with an increased risk of developing ONJ **(Table 5)** [9,28,62,74,75].

There is also emerging evidence of an increased incidence of ONJ in cancer patients treated with tyrosine-kinase inhibitors and bevacizumab [76–79]. On the contrary, conflicting data have been published regarding the role of thalidomide [80,81]:

- Individual genetic susceptibility to ONJ development has been investigated in a small number of genome-wide association and candidate gene studies [82–84]. The largest study performed so far (n = 94 ONJ cases) suggests that MHC class II polymorphisms may represent genetic risk factors related to the development of ONJ [85].

- Hypocalcemia, hyperparathyroidism and bone mineralization disorders: a single study demonstrated the possible contributing effect of secondary hyperparathyroidism after administering BP to developing ONJ [86]. Recently, a strong association between osteomalacia and ONJ has been identified [87], and the potential triggering effect of vitamin D deficiency on secondary hyperparathyroidism and bone mineralization defects has been already shown in animal models and is currently under investigation [88].

Other systemic risk factors for ONJ currently under investigation are reported in **Table 4**.

Oral risk factors

A general consensus exists that dentoalveolar surgery and simple dental extraction in particular are the most significant risk factors associated with ONJ in cancer patients taking antiresorptive drugs **(Table 5)** [89]. Dental implant placement is also considered a potential trigger for ONJ to occur in cancer patients, although the true risk has not yet been assessed [90]. Dental and periodontal infection significantly increases the risk of ONJ in cancer patients exposed to antiresorptive therapy [91–94]. Indeed, periodontal disease was diagnosed in 84% of cases in a large sample of patients with ONJ [89]. However, periodontal disease is commonly observed in the general population in individuals >40 years of age, which may represent a confounding factor in assessing epidemiological association [95–98]. Also, early clinical stages of ONJ are known to include nonexposed alveolar bone necrosis that can mimic clinical and radiological manifestations

of periodontitis (tooth mobility, bone loss, loss of attachment and pus discharge), which may lead to misdiagnosis and overestimation of the association between ONJ and periodontitis. Furthermore, a significant correlation has been documented between the use of removable dentures and the development of ONJ in a population of metastatic cancer patients treated with high-dose intravenous N-BP [59,63]. Other oral triggers have been reported in the literature but lack definite validation **(Table 6)**.

Natural history, long-term behavior & prognosis

Little is known regarding the natural history, long-term behavior and overall prognosis of ONJ associated with antiresorptive agents. Jaw osteonecrosis has been traditionally described as a chronic disorder with persisting, sometimes progressing, clinical manifestations with a poor response to curative therapeutic attempts [24,99]. There is currently a paucity of knowledge in the literature detailing the course of ONJ in the absence of therapeutic intervention (natural history). However, anecdotal evidence and clinical experience suggest that a proportion of patients suffer from an aggressive disease that progresses rapidly to cause severe pain with necrosis and infection of large areas of the jawbones whereas in other individuals ONJ may remain localized and minimally symptomatic [100]. Several patients present with asymptomatic forms of exposed ONJ from the beginning, which exfoliate and tend to heal with stable mucosal coverage, without further recurrences. These cases have been considered for a long time and are accordingly grouped as initial and localized forms of ONJ (AAOMS stage 1) based on the clinical signs and symptoms of disease. Recently, a multicenter retrospective study conducted in a large ONJ population (800 patients) and known as MISSION, proved that staging performed using AAOMS criteria, while pooling together patients with similar clinical findings, cannot adequately discriminate the extent of bone disease as determined by CT. In fact, nonspecific CT signs of ONJ are present for all AAOMS disease stages, which are almost indistinguishable, so that every stage contains patients with very different degrees of bone involvement [101].

It is generally agreed that interruption of antiresorptive therapy does not modify the natural history of the disease owing to the long half-life and persistence of these agents within the bone tissue [64]. Indeed there is no robust evidence showing remission of clinical manifestations (e.g., mucosal coverage of areas of previously exposed bone) and/or reduction in pain symptoms on N-BP withdrawal. However, it has been suggested that the natural history of ONJ associated with denosumab may differ from BP-related ONJ due to the shorter half-life of this agent, which may facilitate bone healing and symptom remission after removal of necrotic bone and suspension of therapy [102]. However, there are no studies at the moment supporting this hypothesis.

More evidence, although not robust, is available regarding the long-term behavior of ONJ after or during therapy, as well as the prognosis

Table 5. Main antiangiogenic drugs used in cancer and myeloma patients in combination with nitrogen-containing bisphosphonates, potentially increasing osteonecrosis of the jaw risk.

API	Formulation	Route	Indication and schedule
Bevacizumab	Btl 400 mg 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	p.o.	Renal cell cancer, GISTs and neuroendocrine tumors (50 mg/day for 4 weeks)
Sorafenib	Tab 200 mg	p.o.	Renal cell cancer (800 mg/day)
Pazopanib	Tab 200 mg Tab 400 mg	p.o.	Renal cell cancer (200–800 mg/day)
Thalidomide	Tab 50 mg	p.o.	Myeloma (400 mg/day for 6 weeks)
Lenalidomide	Tab 5, 10, 15 and 25 mg	p.o.	Myeloma (tailored doses)
mTOR inhibitors			
Everolimus	Tab 5 and 10 mg	p.o.	Renal cell cancer, breast cancer (10 mg every day)
Temsirolimus	Btl 30 mg	iv.	Renal cell cancer (25 mg every week)

API: Active pharmaceutical ingredient; Btl: Bottle; GIST: Gastrointestinal stromal tumor; iv.: Intravenous; p.o.: Orally; Tab: Tablet.

Table 6. Oral risk factors of antiresorptive drug-related osteonecrosis of the jaw in the cancer population.

Oral risk factors	Strength
Dental implant surgery	+++
Dental/periodontal infection	++
Removable dentures	+++
Dentoalveolar surgery	
Simple dental extraction	+++
Regenerative bone procedures	++
Endodontic surgery	++
Periodontal surgery	++
Preimplant bone surgery	+++
Anatomical conditions	
Tori and exostosis	+/-
Pronounced mylohyoid ridge	+

+/-: Positive and negative data, unlikely to be confirmed;
+: Positive data in some studies but still inconclusive;
++: Positive data in most studies; +++: Sound and consistent data.
Data taken from [57].

of the overall disease. The terminology used so far to describe the long-term behavior and prognosis of ONJ is unclear and confusing *per se*, which makes interpretation of available literature difficult. Defining the resolution of ONJ, healing, improvement and worsening varies among studies, and these factors remain inconsistent [49,103–106]. Some authors have adopted a more practical terminology and used complete mucosal coverage of a previously exposed jawbone area as a surrogate of disease improvement, resolution or healing [107–109]. However, this is controversial as bone necrosis is an irreversible, ischemic process and complete mucosal coverage does not necessarily indicate that underlying necrotic bone has 'healed' [28]. Indeed, whereas some patients with ongoing necrosis but complete mucosal coverage and no pain may only require monitoring (clinical examination and imaging), others may experience nonexposed disease progression, which may potentially lead to pathological fracture and require surgical treatment. Furthermore, very few studies have used pain as an independent outcome [109–111], although this may well be more relevant to patients than the presence of exposed bone. The variability and inconsistency of therapeutic regimens in the literature are another factor limiting the understanding of the long-term behavior and prognosis of this disorder. Cases of ONJ of mild-to-moderate severity are often managed conservatively with antibiotics, local antimicrobials and the minimally invasive surgical debridement of superficial necrotic bone spicules [28,64,112], whereas more severe cases are often addressed by resection of large portions of maxillofacial bone [20,105,111]. Comparison of these different patient groups has proven very difficult due to significant discrepancies in study objectives, outcome measures and risk factors.

With respect to ONJ prognosis (e.g., pretreatment vs post-treatment disease status), available studies report a rate of 'resolution', 'healing' or 'improvement' (which indicate absence or dimensional reduction of an area of exposed jawbone) ranging from 15 to 80% of affected individuals, with an average of 50% [103–105,107,110–115]. The remaining 50% of ONJ patients is thought to present persistent and/or progressive disease [104]. Those few studies reporting pain as an outcome describe the remission of painful symptoms in approximately 60–75% of patients [109,110]. These figures suggest that pain control can be achieved in the majority of patients, irrespective of the presence of exposed bone.

The long-term behavior of ONJ was studied in a small cohort of 30 patients by O'Ryan *et al.*, who reported that osteonecrosis can have a recurrent and refractory course in approximately a third of cases, especially when it is triggered by dental extractions and associated with comorbidities [113]. Moretti *et al.* state that the course of ONJ is usually characterized by a progressive reduction in the dimension of bone exposure and painful symptoms in the majority of affected individuals, irrespective of the therapeutic regimen [116].

Risk-reduction strategies & the safety of dental procedures

Risk-reduction strategies are suggested to represent an effective means of reducing the incidence of ONJ associated with antiresorptive agents in the cancer population [28,117,118]. In the absence of randomized controlled trials testing the efficacy of different treatments in patients at risk of ONJ development, the best level of evidence for risk-reduction strategies comes from observational studies (type III evidence). Recently, the Joint Committee of the Italian Societies of Maxillofacial Surgery and Oral Pathology and Medicine launched a critical path analysis of the known risk-reduction strategies for ONJ, introducing a flow-chart of dental measures aimed at reducing the risk of ONJ in individuals exposed to/due to

start antiresorptive agents [57]. Despite different care professionals being involved in the design of these pathways, large gaps in knowledge persist among both physicians and dentists [119], as well as deficiencies in the information provided to the patient [120].

It is the responsibility of prescribing physicians to provide cancer patients who are about to start therapy with BP or other antiresorptive drugs with adequate information regarding the risk of developing ONJ, and refer them for a thorough dental and oral examination prior to therapy commencement. Conversely, it is the responsibility of the dental care provider to implement preventive measures and inform patients about the need for continuing dental care during treatment with antiresorptive agents.

Patients must be informed that a significant risk of ONJ occurrence remains despite the adoption of specific preventive protocols. This is because ONJ has been described to develop in absence of frank dental trauma or infection, and also because there are a number of minor factors that cannot be easily controlled (e.g., hard food trauma to areas of thin mucosa, including mylohyoid ridge and tori). Patients should also be told about the possible clinical manifestations of ONJ in order to promptly alert the oncologist/dental practitioner and anticipate a final diagnosis [120]. A rational, preventive approach should consider drug- and dental-related issues. The aim of prevention is to remove any possible dental and periodontal infection foci and to maintain patients' oral health over time. Whether therapy with antiresorptive agents has already been commenced or not makes a clear difference in the adoption of specific preventive measures, in addition to the presence of dental and periodontal disease. Preventive dentistry may reduce the prevalence of ONJ in those receiving denosumab as it has in those receiving BPs [121]. In cases where the administration of N-BP or antiresorptive agents has been planned but not yet initiated, the oral cavity of the patient must be carefully checked clinically and should be imaged for any pathological condition (e.g., tooth caries, periodontal diseases, pressure sores caused by incongruous removable prostheses and teeth with questionable prognosis), and then treated according to standard dental practice. It is critical to delay the initiation of antiresorptive agents until a definite healing of the oral mucosa has been obtained [122,123].

In cases where the administration of antiresorptive agents has been already commenced, the oral cavity of the patient must be carefully inspected for dental and periodontal diseases and then treated according to specific protocols **(Table 7)**. While several dental therapies can be performed in cancer patients undergoing antiresorptive agents without increasing the risk of ONJ, dental extractions and oral surgery should be always avoided where possible. Clearly dental extractions do not always trigger ONJ in patients exposed to antiresorptive agents, which shows how little we know regarding individual and personalized risk assessment. In the absence of better evidence, all patients exposed to antiresorptive medications should be advised to avoid surgical procedures to the jawbones where possible. In cases where dental surgical procedures cannot be avoided, the use of minimally invasive surgery has been suggested to improve bone healing, which includes careful shaving of sharp edges of the extraction socket and tight primary soft tissue closure with mucoperiosteal flaps [100,124–126]. There remains, of course, cases where intravenous N-BP therapy needs to be initiated immediately and therefore risk-reduction dental strategies would have to be omitted [127].

Once started on antiresorptive regimens, cancer patients should be included in a protocol of dental and periodontal infection prevention and supportive periodontal therapy on a 4-month follow-up basis [96]. The use of ill-fitting dentures should be also investigated at each visit for the presence of oral mucosal injuries and the dentures relined accordingly. The positive correlation between the duration of exposure to BPs or antiresorptive agents and the risk of ONJ has been documented in the literature [24] and explains the need for apparently frequent recall visits.

While the antiresorptive activity of denosumab is reversible and time dependent, the effects of N-BPs and zoledronate in particular are long lasting, even after a single infusion. Indeed, it has been shown that these molecules inhibit bone remodeling for several years after incorporation into bone [128]. For these reasons, overall agreement exists that elective oral surgery and periodontal surgery, including bone grafts and insertion of dental implants, are contraindicated in multiple myeloma and metastatic cancer patients who are on or have been exposed to N-BP infusions. A temporary cessation of antiresorptive therapy ('drug holiday') has been suggested among risk-reduction

Table 7. Dental treatment warnings for cancer patients at risk of antiresorptive drug-related osteonecrosis of the jaw.

Dental treatments	Malignancies	
	Before antiresorptive therapy	*During & after antiresorptive therapy*
Dentoalveolar surgery and preimplant bone surgery	Indicated: simple tooth extraction[†] Contraindicated: preimplant bone surgery Necessary await until complete wound healing (4–6 weeks) before start of antiresorptive therapy	Indicated: surgical tooth extraction[‡] Contraindicated: preimplant bone surgery Advisable: 1-month temporary withdrawal of antiresorptive drug (in agreement with prescribers) to facilitate wound healing (4–6 weeks)
Dental implant surgery	Contraindicated	Contraindicated
Cosmetic and restorative dentistry	Indicated	Indicated
Endodontic treatment	Indicated	Indicated
Orthodontic treatment	Possible	Possible
Periodontology: oral hygiene and nonsurgical treatments	Indicated	Indicated (every 4 months)
Periodontal/endodontic surgery	Indicated[‡§]	Indicated[‡§] Advisable: 1-month temporary withdrawal of antiresorptive drug (in agreement with prescribers) to facilitate wound healing (4–6 weeks)
Fixed dentures	Possible	Possible (maintenance of biologic width)
Removable dentures	Possible	Possible (frequent denture reline advisable)

Dental procedures are classified as follows: indicated (none or low risk, or, in turn, when the benefit derived from the treatment far exceeds the risk of osteonecrosis of the jaw); possible: low risk without specific contraindications, but the benefits of the treatment have to be outweighed case by case; contraindicated: the risk of osteonecrosis of the jaw associated with the procedure is high and the benefits for the patient are insubstantial.
[†]If antiresorptive therapy cannot be further delayed, dental surgery is advisable.
[‡]Warrant airtight closure of the surgical site with the use of mucoperiosteal flaps.
[§]Only if aimed at treating significant ongoing inflammatory-infective processes not otherwise curable.
Reproduced with permission from [57].

strategies. Although it is possible that the healing potential of bone and the oral mucosa could progressively improve following cessation of antiresorptive drugs [129], there remains no study demonstrating significant benefits from drug holidays in this setting. Some authors have suggested that temporary withdrawal of N-BP therapy may allow better soft tissue healing [130] following tooth extraction [124] and also surgical resection [111] by reducing drug accumulation into the operated site. However, there is no robust evidence to support this theory. The choice to discontinue N-BP should always be taken together with the oncologist and then maintained until completion of the healing process [124].

A rational, preventive approach must also take into account dental-related issues and specifically the feasibility of elective and therapeutic procedures.

Two possible scenarios exist: first, a cancer patient with maintained oral health, for whom only preventive dental/periodontal measures or elective procedures are necessary and, second, a cancer patient with existing dental, periodontal or perimplant disease and/or mucosal lesions of a traumatic nature, for whom suitable therapeutic strategies are needed.

In general, each elective nonsurgical procedure (restorative dentistry, prosthodontics, periodontics, endodontics and orthodontics), including professional hygiene, can be safely carried out, based on the treatment protocols normally used for the general population. However, elective surgical procedures (e.g., implant surgery, preimplant bone surgery and periodontal surgery) need to be carefully evaluated and should be avoided when the administration of BP/antiresorptive agents has been already commenced.

Medical management of ONJ

Managing ONJ has proven to be difficult and it remains a major challenge for clinicians.

Robust evidence from well-designed clinical trials is scarce, and the most available treatment recommendations reflect expert opinions and are, therefore, characterized by a low level of evidence [7,20,30,131,132]. In addition, such recommendations have been developed for use in BP-related ONJs exclusively. At present, little information is accessible on the treatment of ONJ caused by denosumab. Denosumab-related osteonecrosis theoretically differs from bisphosphonate-related osteonecrosis of the jaw in that the drug-induced suppression of bone turnover is transient and

the disease process may have more favorable outcomes once the drug has been waived, thus requiring less invasive management [52]. However, in the absence of a specific treatment protocol for denosumab-associated ONJ, it seems reasonable to adopt those developed for the treatment of bisphosphonate-related osteonecrosis of the jaw.

The nonsurgical management of ONJ is aimed at improving the stage of the disease and avoiding its progression. It includes the use of antimicrobial mouth rinses (0.2% chlorhexidine digluconate), local disinfection/cleaning of exposed bone and fistula, pain control, and the administration of antibiotics and nutritional support when required. In the presence of exposed bone, superficial debridement may be useful to reduce sharp edges and relieve soft tissue irritation [20,23,110,116,131–134]. Broad-spectrum antibiotics (amoxicillin/clavulanic acid, ampicillin/sulbactam, metronidazole or clindamycin) are the first-line drugs to be used in combination although the use of other antibiotics (such as erythromycin, ciprofloxacin and doxycycline) has also been documented in the literature [20,132,134]. Systemic antibiotics are recommended in the presence of overt infection (e.g., suppuration and abscess formation) and local inflammation, with or without pain [20]. Ten days to a 3-week course with oral antibiotic therapy has been suggested, but there is little research available that indicates the most efficient drug and course duration.

In refractory and severe cases of ONJ, intravenous antibiotic therapy may be required [20]. Patients with nonspecific clinical findings and symptoms (e.g., intraoral sinus tract or jaw pain), but in the absence of clinically exposed bone (AAOMS stage 0), may also benefit from systemic antibiotic therapy, in association with chronic pain medication when indicated [20]. The medical treatment of ONJ may also be indicated for patients with a poor prognosis of the underlying neoplastic disease, who would not benefit from extensive radical surgery [20,134].

It has been suggested that a reduction in the intraoral bacterial load plays an important role in ONJ management as it may minimize the risk of exposed bone infection and disease progression. ONJ patients should be carefully educated towards maintenance of good oral hygiene, routine dental examinations and preventive dental care. This is particularly relevant in cancer patients who may suffer from a number of adverse side effects to the oral cavity associated with the use of antineoplastic therapy, including oral mucositis, xerostomia and oral graft-versus-host disease [135]. These side effects, particularly in cases of ONJ, significantly affect patients' quality of life and cause chronic pain, eating discomfort, aesthetic concerns and decreased life satisfaction [6]. Optimal oral hygiene requires appropriate motivation, adequate tools (toothbrush, dental floss and tape, interproximal brushes, woodsticks, single-tufted brushes, a tongue cleaner and disclosing solution to identify dental plaque) and professional oral hygiene instructions. Preventive care includes the removal of supra- and sub-gingival plaque and calculus (scaling and root planning).

In addition to infection and pain control, a number of therapeutic strategies have been suggested to be of potential benefit to patients with ONJ. Systemic low-dose recombinant human parathyroid hormone (i.e., teriparatide) has been reported to induce a resolution of clinical signs and the symptoms of ONJ in a noncancer setting. However, the evidence is weak due to the uncontrolled design and small size of relevant studies [131,136–139]. Hyperbaric oxygen therapy was suggested to increase the effectiveness of medical and/or surgical treatment of ONJ [111,140] but concerns remain regarding its cost–effectiveness, the impact on quality of life and the overall clinical benefit [141,142]. Finally, limited evidence is available to support the use of low-intensity laser and medical ozone therapy [103,143,144].

It is widely agreed that suspension of antiresorptive therapy would provide little benefit, if any, to ONJ prognosis due to the long half-life of N-BP and because the risk of a malignant disease progression largely exceeds the potential benefits in most cases [20,26,28,70,145–153]. In the absence of conclusive evidence, it seems sensible not to withdraw N-BP therapy in individuals who have developed ONJ [20,26,28,70,145–153]. Denosumab has a significantly shorter half-life than N-BPs and its effects of bone turnover are more rapidly reversible; therefore, ONJ related to denosumab may be less likely to recur once the necrotic bone has exfoliated or has been surgically removed and the antiresorptive treatment has been suspended [20,26,28,70,145–153].

Surgical management of ONJ

The benefits of surgical management of ONJ have been extensively debated in the available literature. The surgical resection of necrotic jawbone

has been traditionally considered palliative rather than curative, as it has been offered mainly to patients with advanced disease not responding to medical treatment [7,154,155]. There is now enough evidence to suggest that nonsurgical treatment often fails to provide positive outcomes in ONJ patients with advanced disease [7,112], whereas radical surgery seems to offer more predictable and curative results [7,20,27,64,66,131,156–164]. However, the surgical treatment of early-stage ONJ remains controversial [34,103,159–161,163,165,166].

Kuhl *et al.* found that the negative results of previous studies were probably biased by the fact that surgery is often performed in patients with poor health and extensive necrosis [7]. Indeed, when medical and surgical treatments were compared in terms of clinical healing and resolution of pain, surgery has been demonstrated to perform better for all disease stages [7,105,106]. On the basis of this increasing evidence, the AAOMS has recently highlighted the role of resective surgery [23] in restoring form and/or function as opposed to controlling symptoms and delaying the progression of the disease. Standardized terminology has been adopted in the literature to categorize resective surgical procedures for ONJ patients (i.e., marginal and segmental resection) [111,158], whereas there is less clarity regarding conservative surgical treatments.

The Joint Committee of the Italian Societies of Maxillofacial Surgery and of Oral Pathology and Medicine has recently proposed a classification of surgical procedures based on their invasiveness and recommended their allocation to ONJ patients on the basis of the radiological extent of disease, as seen on CT **(Table 8)** [22 ,132]. Conservative surgical treatments (i.e., debridement or bone curettage, and sequestrectomy) differ from surgical resection in that the removal and curettage of necrotic bone is performed without the intention of including a margin of normal surrounding bone [158,167]. When using conservative surgical treatments, the boundary between normal and diseased bone is usually based on the intraoperative identification of areas of vascularized 'bleeding' bone at the margins of necrotic avascular ischemic bone [157,161,163,168]. However, this approach is not advisable in patients with advanced bone disease as it has been associated with a high recurrence rate of ONJ [56]. Of note, methods to aid identification of healthy bone margins are currently being investigated, including tetracycline bone labeling [169–171] and more detailed preoperative CT-based surgical planning [111]. Clinical judgment alone often underestimates the amount of diseased bone at the time of surgery, thus leaving in place diseased, albeit vascularized, bone, that may later become evident as 'new' foci of ONJ, even at distant sites. In this way, new foci may actually be 'recurrent' foci and this possibility has to be taken into account when interpreting the available studies. New foci of ONJ should always be proved by imaging, showing the absence of a connection with the operated site.

Although some authors advocate direct vascular impairment of the oral mucosa caused by N-BP accumulation in the pathogenesis of ONJ [130,172], it is well understood that the oral mucosa can be safely spared during ONJ surgery and the same can also be used to obtain stable mucosal coverage of the operated site, once the necrotic bone has been fully removed [111,158,173,174].

Some reports suggest the use of less invasive instruments, such as low-level laser therapy and piezoelectric surgery, which may minimize

Table 8. Management of drug-related osteonecrosis of the jaw in metastatic cancer and multiple myeloma patients.

SICMF-SIPMO	Surgical therapy†‡§¶	Medical therapy#
Stage 1 (focal ONJ)	Dentoalveolar surgery: curettage and bone sequestrectomy; marginal resection for recurrent disease Perioperative topical disinfection (clorexidine 0.2%) iv. perioperative antibiotic therapy (7–14 days long)	Oral disinfectants Systemic antibiotic therapy (7–14 day long) (to be done monthly or in case of recurrent pain and suppuration)
Stage 2 (diffuse ONJ) and stage 3 (complicated ONJ)	Segmental resection (bone reconstruction if indicated) iv. perioperative antibiotic therapy (7–14 days long) Perioperative topical disinfection (clorexidine 0.2%)	Accessories: biostimulation (ozone or laser therapy); hyperbaric oxygen therapy Aims: symptomatic (palliation); spontaneous sequestration of necrotic bone; remission

†Stable mucosal coverage of the operated site should be always achieved irrespective of the surgical technique adopted.
‡Accessories: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to bone.
§1-month postoperative withdrawal of antiresorptive agent is advisable to reduce its excessive accumulation at the surgical site that could hamper the healing process.
¶Postoperative clinical follow-up at 1, 3, 6 and 12 months. CT scans at 6 and 12 months after surgery.
#Suitable for early-stage disease, systemically compromised patients for whom surgical therapy is contraindicated, or in case of patient's refusal of surgery.
iv.: Intravenous; ONJ: Osteonecrosis of the jaw; SICMF: Italian Societies of Maxillofacial Surgery; SIMPO: Italian Societies of Oral Pathology and Medicine.
Data taken from [57].

vascular damage to the bone and promote a faster and pain-free healing of soft and bone tissues [175]. However, there remains little robust evidence to support their superiority to traditional bone-cutting equipment. Similarly, the real benefit of combining bone resection with autologous platelet-rich plasma remains unclear [176].

One controversial aspect of the aforementioned surgical literature relies on the definition of outcomes and related time points. The current definition of healing indicates the clinical evidence of stable oral mucosal coverage and it has been adopted by the vast majority of surgical studies [158,161]; however, mucosal coverage does not necessarily reflect the absence of underlying necrotic bone. Likewise, it is still uncertain how long the oral mucosa should remain intact to confirm stable healing. Despite several authors believing a 6-month clinical follow-up to be sufficient to confirm a definite cure [167,171,177], there is increasing evidence that ONJ may recur 1 year or more after the completion of surgery [111,158,161,163]. In addition, the radiological signs of ONJ recurrence may manifest themselves well before the onset of any clinical sign or symptom. It would, therefore, seem sensible to monitor ONJ patients for at least 1 year and perform CT imaging at 6-month intervals in order to evaluate the long-term outcomes of surgical treatment.

Perioperative, antibiotic therapy and topical disinfection with chlorhexidine mouthwash, until complete soft tissue healing is achieved, are recommended in the vast majority of surgical protocols. The potential benefit of temporary postoperative interruption of N-BP has been suggested but supporting evidence remains inconclusive [111]. It seems reasonable to speculate that in the future the combination of medical treatments (i.e., pain control, local disinfection and antibiotics) and surgical therapy could become the leading strategy where complete and successful healing is achievable. Single-modality medical

EXECUTIVE SUMMARY

- Osteonecrosis of the jaw (ONJ) represents a clinically significant, potentially painful and debilitating condition that can significantly affect the quality of life of cancer patients. Its occurrence is related to current or previous treatment with antiresorptive agents (bisphosphonates [BPs] and denosumab).
- The incidence of BP-related ONJ widely ranged from 0 to 27.5% (mean: 7%) due to inconsistency and limitations of available studies. A meta-analysis of few recent studies reports a mean incidence of 1.7% for ONJ associated with denosumab, with no statistical differences when directly compared with zoledronic acid.
- The oversuppression of osteoclast-mediated bone remodeling and consequent bone sclerosis and ischemia has been suggested to play a major pathogenetic role in ONJ.
- Exposed ONJ is characterized by the presence of clinically evident necrotic bone, affecting the mandible more frequently than the maxilla. Common associated manifestations include soft tissue swelling and erythema, pus discharge, fistula/sinus tracts, tooth loss, jaw deformity, pain and sensory disturbances.
- ONJ does not always present with oral mucosa fenestration and necrotic bone exposure, but it may occur as otherwise unexplained jawbone pain, fistula/sinus tract, swelling, loose teeth and pathological fractures.
- Dentoalveolar surgery and simple dental extraction are the most significant risk factors associated with ONJ.
- The natural history of ONJ associated with denosumab may differ from BP-related ONJ due to the shorter half-life of this agent.
- Risk-reduction strategies are suggested to represent an effective way of reducing the incidence of ONJ. These strategies include the removal of any possible dental and periodontal infection foci, and the maintenance of patients' oral health over time.
- The nonsurgical management of ONJ is aimed at improving the stage of the disease and avoiding its progression. It includes the use of antimicrobial mouth rinses (0.2% chlorhexidine digluconate), local disinfection/cleaning of exposed bone and fistula, pain control and the administration of antibiotics and nutritional support when required. In the presence of exposed bone, superficial debridement may be useful to reduce sharp edges and relieve soft tissue irritation.
- The nonsurgical treatment often fails to provide positive outcomes in ONJ patients with advanced disease, whereas radical surgery seems to offer more predictable and curative results. However, the surgical treatment of early-stage ONJ remains controversial.

treatment could be adopted either in early ONJ or to treat patients with low performance status and high risk of surgical complications.

Conclusion

ONJ is a clinically significant, adverse effect of antiresorptive agents. Although ONJ epidemiology and pathogenesis remain unclear, significant improvements have been made with respect to definition, diagnosis and staging, as well as risk-reduction strategies and treatment. A substantial effort to disseminate available knowledge within the medical community and, in particular, among cancer and oral health specialists is warranted.

Future perspective

Epidemiology and pathogenesis of ONJ remains unclear, due to its refined definition, introduction of further antiresorptive agents (e.g., denosumab) and/or antiangiogenic drugs (e.g., bevacizumab, sunitinib) with different pharmacodynamics, and the increasing adoption of some preventive measures all over the world. Future perspectives of concerns are also related to the risk reduction and management of this debilitating condition, particularly to the true utility of a drug holiday and to a number of issues regarding the antibiotic therapy, including the most efficient drug, if any, and course duration. The use of imaging techniques for ONJ detection and presurgical evaluation is also a significant field of future investigation. Moreover, the effectiveness of a number of therapeutic strategies needs to be better assessed, such as teriparatide, hyperbaric oxygen therapy, use of low-intensity laser and medical ozone therapy. Finally, the comparative effectiveness of radical versus conservative surgical treatments will be the primary aim of the clinical research in the next 5–10 years.

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