Drug-induced osteonecrosis of the jaw

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With the increasing use of intravenous bisphosphonates in oncological settings, osteonecrosis of the jaw is now a more common and often devastating complication which, in an advanced stage, significantly impacts the quality of life. Since management and therapy of osteonecrosis present major challenges, more attention should be focused on the assessment of risk and preventive measures. In recent years bisphosphonate treatment, especially its intravenous application, has been identified as the main cause of osteonecrosis of the jaw. However, denosumab, a novel and promising agent in treating metastatic bone disease and osteoporosis, also increases risks. With coincidental trigger factors such as dental extractions and antiresorptive therapy with either intravenous bisphosphonate or denosumab there is an estimated one to ten per cent risk of subsequently developing osteonecrosis of the jaw. Although several theoretical concepts on the pathogenesis and natural history of bisphosphonate-related osteonecrosis have been presented, a definitive cause-and-effect relationship is missing. Bisphosphonates have effects on immune function, bone remodelling, wound healing and angiogenesis. These mechanisms, in combination with the jaw's vulnerability, might explain its inability to deal with mucosal or bone damage. With a clearer understanding and increasing awareness in the oncology community several other drugs, especially the anti-angiogenic agents bevacizumab and sunitinib are being seriously suspected of inducing osteonecrosis, or at least increasing the risk, in combination or following therapies with bisphosphonates or denosumab.

Keywords: Bisphosphonates, denosumab, osteonecrosis of the jaw, risk factors, staging and treatment.

Introduction

Since the late 1970s bisphosphonates have been part of oncological therapy, with the benefits of a significant reduction of

bone pain and skeletal-related events (SRE) in patients with metastatic bone disease secondary to multiple myeloma, breast cancer or prostate cancer. Skeletal-related events include any secondary complication from the presence of bone metastases such as radiation therapy to reduce pain or prevent fracture, bone surgery to treat or prevent fractures, and pathologic fracture or spinal cord compression that can result in paraesthesias, incontinence, and paralysis [1, 2]. Over the past few years, because of growing positive clinical evidence, the use of bisphosphonates dramatically increased, especially in cases of osteoporosis and of course also in patients with bone metastases of all cancer types. In 2003 the first cases of osteonecrosis of the jaw (ONJ) were published and identified as an adverse effect of the bisphosphonate therapy, mainly occurring during or after intravenous bisphosphonate therapy with the more potent agents pamidronate and zoledronate [3, 4].

In spite of the great number of patients receiving bisphosphonates, osteonecrosis of the jaw is a rather rare complication. But if exclusively the intravenous applications are focused on, the risk of ONJ appears quite high, especially when particular trigger factors are involved. Once patients are suffering from osteonecrosis, therapeutic management can be very challenging and advanced disease significantly impacts the quality of life. Numerous clinical trials are running as shown in Table 1 to identify and evaluate risk or trigger factors as well as to develop evidence based therapeutic approaches.

The first case of osteonecrosis of the jaw in our oncological department was a patient with multiple myeloma and long-term intravenous bisphosphonate treatment. Figure 1 is an impressive 3D reconstruction of CT images of the cranium of this patient with the osteonecrotic lesion in the maxilla and the destructed anterior wall of left maxillary sinus.

Risk factors

Until recently osteonecrosis of the jaw was seen solely in its relationship to bisphosphonate therapy. Its influence on wound healing and bone remodelling, along with its anti-angiogenic properties, conclusively explained the pathophysiological aspects of the inability to deal with mucosal or bone damage. Lately, denosumab, a human monoclonal antibody

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Tab. 1: Clinical trials with search for “osteonecrosis of the jaw” on <http://clinicaltrials.gov>, retrieved 14 Nov. 2011

	Status	Study
1	Recruiting	Osteonecrosis of the jaw in patients with cancer receiving zoledronic acid for bone metastases
2	Completed	CONDOR study of osteonecrosis of the jaws (TMJ)
3	Enrolling by invitation	Genetic risk of osteonecrosis of the jaw (ONJ) in patients with metastatic cancer
4	Completed	DPBRN retrospective cohort study of osteonecrosis of the jaw
5	Recruiting	Genetic risk of osteonecrosis of the jaw (ONJ) in patients with metastatic cancer: concordance study
6	Completed	Long term efficacy and safety of zoledronic acid treatment in patients with bone metastases
7	Active, not recruiting	Randomized controlled trial of hyperbaric oxygen in patients who have taken bisphosphonates
8	Active, not recruiting	Proposal for the development of a well defined database for patients with oral bisphosphonate-related osteonecrosis
9	Recruiting	Zoledronic acid in treating patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma with bone involvement
10	Active, not recruiting	Bisphosphonate-associated jaw osteonecrosis and PET imaging
11	Recruiting	Duration of suppression of bone turnover following treatment with zoledronic acid in men with metastatic castration resistant prostate cancer
12	Completed	Total temporomandibular joint replacement system post approval study
13	Unknown	Alendronate in the prevention of collapse of femoral head in non-traumatic osteonecrosis
14	Recruiting	Safety and effectiveness of oral alendronate therapy on bone mineral density in HIV-infected children and adolescents with low bone mineral density

inhibiting the receptor activator of nuclear factor κ B ligand (RANKL), has proven to be at least noninferior to zoledronic acid in delaying or preventing skeletal-related events. Three similarly designed prospective trials including more than 5,700 patients suffering from bone metastases secondary to different cancer types have shown quite similar rates of overall adverse events, with a comparatively low incidence of 1.0 to 2.0 per cent ONJ but a higher risk by trend for denosumab therapy [5–7].

Fig. 1: 3D reconstruction of ONJ lesion (maxilla, anterior wall of left maxillary sinus) from CT images in a myeloma patient with intravenous bisphosphonate treatment (courtesy of M. Cejna, Department of Radiology, Academic Teaching Hospital Feldkirch, 2005)

Osteonecrosis of the jaw usually commences in the alveolar bone and then spreads into the jaws [8]. With an approximate ratio of 2 to 1, osteonecrotic lesions more commonly appear in the mandible than in the maxilla. Individual cases are reported with osteonecrosis of the skull base or the auditory canal [9, 10], but to date there is no evidence for any manifestation outside of the craniofacial area. There are some reports of atypical femoral fractures in long term bisphosphonate therapy in patients with osteoporosis [11]. This raises the question as to whether there are structural differences or special conditions which promote osteonecrosis in these preferred locations.

First of all, bone turnover is reported to be up to ten times higher in the alveolar bone than in other bones. As we know that bisphosphonates persist for years in the skeleton and are mainly stored in bones with a high turnover rate, we can assume that the concentration within the jaws is much higher than that in the limbs and vertebrae. Also the greater vascularisation of the jaws may have an impact on the described accumulation. Another peculiarity is that the alveolar bones have only a slight mucoperiosteal cover, whereas other bones are protected by a deep covering of soft tissue. Furthermore, bone cells in other localisation are different from those in the alveolar bone, e.g. osteoblasts located in the alveolar region divide significantly faster than osteoblasts in other bones [12]. In addition, many authors assume an influence of the oral microenvironment; some interesting data exist for actinomyces. Many actinomyces species are opportunistic pathogens. Hansen et al. analyzed 45 cases of actinomycosis of the jaw and identified in a vast majority of the patients osteonecrotic bone lesions (ONJ in 58.7%, infected osteoradionecrosis in 35.6%). Actinomycosis of the jaw seems to be a rare condition in patients without any anti-tumor therapy (only three patients out of 45, 6.7%), so that a strong connection between this infection and the bone lesions can be

Tab. 2: Local trigger factors: dentoalveolar surgery [20]

1	Dental extractions
2	Dental implant replacement
3	Periapical surgery
4	Periodontal surgery involving osseous injury

presumed [13]. Whether actinomycosis facilitates the development of osteonecrosis or has to be considered as an opportunistic infection needs further investigation.

Looking at the differences between mandible and maxilla, there is an interesting aspect regarding vascularisation. The maxilla, mainly consisting of spongiosa, has a better blood supply than the mandible, with its very strong corticalis in relation to the whole structure. This could explain the higher incidence of ONJ in the mandible and also the often more complicated courses of disease [14, 15].

Several additional factors have been identified which may potentiate the risk of developing ONJ. As drug-related factors, bisphosphonate potency and duration of therapy have a big influence. Also local risk factors, including dentoalveolar surgery (Tab. 2), the already mentioned anatomical specialities of alveolar bone and concomitant oral disease - for example, periodontal and dental abscesses - have to be mentioned. Furthermore, demographic and systemic factors such as age (several studies report increasing age as consistently associated with ONJ) [16, 17], race (Caucasians more than African Americans) [17, 18] and cancer diagnosis, as well as epigenetic associations [19] may influence the risk of osteonecrosis. Life style and behavioural factors (obesity, tobacco, alcohol) are also proposed to play a role [16]. The probably most important risk factors for ONJ are intravenous bisphosphonate exposure and dentoalveolar procedures [20, 21].

Role of bisphosphonates

Bisphosphonates play a major role in the treatment of metastatic bone disease as well as in osteoporosis. They accumulate in bones, and once integrated into the bone matrix they can persist for years. Several theories exist which attempt to explain the pathogenesis of bisphosphonate-related ONJ, but a definitive cause-and-effect relationship is still missing. Probably it is a multifactorial process: Of primary significance is the jaw's susceptibility in combination with the oral micro-environment, as described above; then the anti-osteoclast activity of bisphosphonates; and additionally anti-angiogenic effects caused by the depression of blood flow and decrease of VEGF [14, 22–24]. Bisphosphonate treatment generally also leads to an inability of the bone to respond to injury, and to a slowdown of the natural bone remodelling process. The theory of slowed remodelling as the main cause of osteonecrosis is discussed highly controversial at the moment as there is compelling evidence that bone turnover is not reduced within ONJ lesions. Furthermore other clinical conditions with reduced bone turnover such as hypoparathyroidism are not associated with development of osteonecrosis [25].

The estimated risk of contracting ONJ depends on the type of bisphosphonate therapy. In osteoporotic patients

(mainly women) on oral bisphosphonates the risk varies from 1 in 10,000 to 1 in 100,000 [21]. The risk increases with the above-mentioned triggering factors, with dental extraction as the most important, to 1 in 300 to 1,000. With intravenous bisphosphonate treatment 1 to 10 per cent of patients who have had a dental extraction develop ONJ [26].

Role of denosumab

In the last few years denosumab, a fully human monoclonal antibody against RANK ligand, was evaluated in three similarly designed randomized double-blinded phase III trials and compared to zoledronic acid, the bisphosphonate most often used in metastatic bone disease. Whereas the standard therapy with intravenous bisphosphonate has some notable side effects, such as renal impairment and acute flu-like symptoms, denosumab usually is well tolerated, not requiring renal monitoring or dose adjustment.

In breast cancer patients with bone metastases denosumab therapy showed a statistically significant delay of time to first on-study SRE (HR 0.82, CI 0.71 to 0.95, $p=0.01$), to subsequent on-study SREs (rate ratio 0.77, CI 0.66 to 0.89, $p=0.001$) and also a greater reduction in bone turnover markers compared to zoledronic acid, and it was therefore estimated superior to the standard therapy [5]. In a second clinical trial with a quite similar setting, comparing monthly denosumab therapy to zoledronic acid in patients with bone metastases from solid tumours (except prostate cancer and breast cancer) or multiple myeloma, denosumab was at least noninferior, and drug safety was quite similar. Because of a higher mortality under denosumab treatment (HR 2.26; 95% CI 1.13 to 4.50) in a subgroup analysis of 180 myeloma patients [6], the US Food and Drug Administration (FDA) and also the European Medicines Agency (EMA) approved the RANKL-inhibitor only for patients with bone metastases from solid tumors but not multiple myeloma.

A third trial, published in Lancet in February 2011, which included 1,904 men with castration-resistant prostate cancer, also showed a significant reduction of SREs with monthly denosumab [7].

In the above prospective trials the safety profile was very interesting. Both therapy arms showed quite similar rates of overall adverse events. Whereas hypocalcaemia more often occurred under the antibody therapy, acute-phase reactions were more common with zoledronic acid. In spite of the routine dose adaption of zoledronic acid in patients with renal insufficiency there was a trend towards more renal adverse events with zoledronic acid. In the breast cancer trial adverse events associated with renal toxicity were statistically significantly more frequent in the zoledronic acid therapy arm. Risk of ONJ as the probably most important side-effect of the two medications was 1 to 2 per cent, and statistically there was no difference in the incidence, although in two trials there was at least a trend towards more osteonecrotic lesions under denosumab [5–7]. Median time on study was between seven months (multiple myeloma or advanced cancer excluding breast and prostate cancer) and 17 months (breast cancer). As a traceable argument Fusco et al. refer to the quite short follow-up in the trials mentioned and therefore assume an underestimation of ONJ in both therapy arms [27].

Post marketing further investigation is needed to show which bone remodelling drug more increases the risk for ONJ in clinical practice. Before Amgen's clinical trial program for denosumab somebody could argue that ONJ is a specific toxicity related to the presence of bisphosphonate in bone. However, with the more or less equal rates of osteonecrosis in both treatment arms this theory has failed.

Immunosuppression and anti-angiogenic treatment

Diabetes mellitus, with its impact on wound healing and periodontal disease, as well as the associated immune deficiency, is a discussed risk factor for developing ONJ. Microvascular ischemia, decreased bone turnover and endothelial cell dysfunction are other possible interrelated factors.

Severely suppressed bone turnover, also described as bone freezing, is a situation defined as very low bone turnover with normally progressing mineralisation. This destabilization probably causes atypical fractures for example in the femoral shaft such as seen in patients on long-term bisphosphonate treatment [28] and perhaps also affects ONJ development.

Khamaisi et al. showed a significantly higher proportion of diabetes patients in a group of 31 consecutive ONJ patients (58%) than in the general population (14%) or in an oncological control group without ONJ under bisphosphonate treatment [29]. But with only one retrospective analysis up until now, there is actually insufficient evidence to prove this relationship.

Chemotherapy and the subsequent immunosuppression are further potential risk factors, although it is very difficult to estimate its influence because of the mostly simultaneous application of bisphosphonates. Prospective data analyzing the role of chemotherapy in ONJ are not available. In preclinical models bisphosphonates are able to stimulate other than bone cells, especially immune-modulating cells, such as bone marrow monocytes and dendritic cells [30, 31]. Therefore further investigation is needed to evaluate the influence of immunosuppression on the risk of osteonecrosis. Corticosteroids, a common co-medication in oncological patients and one of the significant risk factors for osteoporosis when used as a long-term therapy, lead to an increased susceptibility to infection and delayed wound healing. Steroid-induced osteonecrosis is a common adverse event, especially in the femoral head, but occasionally also affecting

other bone sites. As is the case with ONJ, its aetiology and pathophysiology are not sufficiently understood.

Bi et al. developed the first mouse model of bisphosphonate-associated osteonecrosis of the jaw, showing that the development of osteonecrotic lesions and impaired soft tissue healing is one long-term side effect not only of the use of high-dose bisphosphonates, but also of immunosuppressive and chemotherapy drugs, as well as mechanical trauma. The authors are confident that this mouse model will lead to a better understanding of the aetiology of ONJ and the relevance of the discussed risk factors [32].

Estilo et al. recently presented a case report of ONJ with exposed and necrotic bone lesions in two patients without histories of oral or intravenous bisphosphonates. Both had been treated with bevacizumab as part of their oncological therapies. One of them, a 51-year-old woman with a history of breast cancer and chest wall recurrence, had been given eight doses of bevacizumab in combination with capecitabine. The other, a 33-year-old woman, was treated with bevacizumab after subtotal resection of glioblastoma multiforme, followed by simultaneous radiochemotherapy [33].

There is now increasing evidence that bevacizumab as well as sunitinib, both affecting angiogenesis by inhibiting the action of the vascular endothelial growth factor (VEGF), may independently increase or contribute to the risk of ONJ [34–36].

Staging and treatment

In 2006 the American Association of Oral and Maxillofacial Surgeons (AAOMS) developed a position paper to pool the proven knowledge and make it available to interested clinicians. The initial 2006 recommendations were revised and published in a 2009 update [20]. The AAOMS proposes that patients should be considered to have bisphosphonate-related osteonecrosis of the jaw if all of the following three conditions apply:

- current or previous treatment with bisphosphonates;
- exposed, necrotic bone in the maxillofacial region persisting for more than eight weeks;
- no history of radiation therapy of the jaws.

Several other professional associations have defined the clinical term “osteonecrosis of the jaw”, and although they have some differences in detail, all involve a mucosal wound with exposed bone that fails to heal in six to eight weeks and all exclude a history of head and neck radiation [37, 38].

Tab. 3: Recommendation for staging of ONJ (modified according to AAOMS position paper on bisphosphonate-related ONJ [20])

Stage	Characteristics
At risk category	Patients on or after treatment with either oral or intravenous bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings or symptoms
Stage 1	Exposed and necrotic bone in asymptomatic patients
Stage 2	Exposed and necrotic bone associated with infection (pain and erythema in the region of exposed bone)
Stage 3	Stage 2 patients and one of the following: <ul style="list-style-type: none"> – bone lesion extending beyond the region of alveolar bone, resulting in pathologic fracture, extra-oral fistula or oral-antral/oral-nasal communication – osteolysis extending to the inferior border of the mandible of sinus floor

Furthermore the AAOMS has developed staging (Tab. 3) and treatment strategies.

Patients at risk during or after bisphosphonate medication who present with unspecific symptoms such as pain, tooth mobility, mucosal swelling, erythema or ulceration have per definition stage 0 osteonecrosis of the jaw, and therefore symptomatic treatment and sometimes systemic pain medication or antibiotics are necessary [20].

Once suffering from osteonecrosis with exposed and necrotic bone lesions, therapeutic management can be very challenging, and advanced disease significantly impacts quality of life. Stopping intravenous bisphosphonate treatment has no short-term benefits because of the prolonged bone half-life, but it may help control the problem in the long-term. Regarding denosumab evidence and guidelines are missing, but in our opinion drug holiday or discontinuation of treatment of course must be considered.

Probably the main treatment goal is to preserve quality of life by reducing pain, managing infection and preventing the extension of the bone lesion and development of new areas of necrosis [20, 22]. Different treatment strategies depend on the stage of osteonecrosis and the disease burden, and range from patient education and antibacterial mouth rinse to systemic management including oral antibiotics and pain medication. In an advanced state of disease, surgical debridement or resection of necrotic lesions is helpful in long-term control [15, 20–22, 39].

Eckhardt et al. from Department of Cranio-Maxillofacial Surgery of Hannover Medical School evaluated 142 Patients suffering from ONJ, of whom 86% required surgical treatment. Depending on the clinical situation transoral sequestrectomy, marginal bone resection or in case of extensive osteonecrosis or pathologic fracture of the mandible, a continuity resection of the involved mandible and fixation with titanium reconstruction plates were performed. If tension-free soft-tissue closure is not possible, a myofascial flap from the mylohyoid muscle was the method of choice to close the soft-tissue defects [40]. Recently Nocini et al. demonstrated that microsurgical reconstruction of the mandible is a feasible strategy in extensive mandibular osteonecrosis [41].

There is plenty of room for innovative therapy approaches. For example an interesting case report of Cheung and Seeman in 2010 showed healing of an osteonecrotic mandibular lesion after 8 weeks of teriparatide treatment [42], a recombinant human parathyroid hormone which is currently evaluated as antiresorptive agent in glucocorticoid-induced osteoporosis. Of course this is only a case report, and one has to argue that metastatic bone disease and also for example radiotherapy of the skeleton are contraindications to the use of teriparatide. Furthermore there are safety concerns regarding osteosarcoma [43, 44].

Prevention

However, because of the all in all disappointing therapeutic possibilities we should especially focus on avoiding the development of osteonecrosis. It is widely accepted that preventive dental treatment significantly reduces risk [45, 46]. Therefore AAOMS recommends dental evaluations and completing of necessary treatment before initiating intravenous bisphosphonate therapy. Another important pre-condition is

waiting for the complete healing of mucosal wounds. In addition, patients with dentures should undergo frequent examinations for areas of mucosal damage, and proper education of the patients is very important [20]. Good oral health and routine dental care are recommended for all patients with antiresorptive therapy. Because of the long bisphosphonate half-lives once they are incorporated into the bones, many consensus statements recommend a discontinuation of medication, or at least an extension of dosing-intervals, after two years of monthly bisphosphonate treatment [37, 47]. While waiting for more denosumab data similar prevention strategies appear appropriate for each antiresorptive therapy [48].

Specific serum tests like morning fasting C-terminal telopeptide bone suppression marker (CTX) are currently evaluated as possible predictor of ONJ risk but there is not enough evidence yet to adapt or interrupt antiresorptive therapy because of low CTX serum values in daily clinical practice [48].

Prospects

Animal models and new study approaches should lead to a better understanding of the mechanisms of ONJ, thus enabling us to define all important risk factors and their specific influences on its development. This can help researchers develop risk-adapted treatment strategies in metastatic bone disease. Further investigations are necessary to answer the remaining questions, for example whether alternative dosing schedules with lower doses or extended interval dosing either of bisphosphonates or denosumab could increase drug safety. In daily practice frequent and standardized monitoring of patients at risk is very important. Some guidelines and recommendations accept bisphosphonates and denosumab as comparable options for antiresorptive treatment in metastatic bone disease secondary to solid tumors. In case of renal insufficiency denosumab shortly will displace the bisphosphonates. But in our opinion the efficacy and safety of denosumab must be evaluated in a long-term clinical setting before this new drug will be widely accepted to replace the bisphosphonates as a standard therapy in metastatic bone disease.

Take-home message

Osteonecrosis of the jaw is a severe complication in oncological settings which significantly impacts the quality of life. Patients at risk should be monitored frequently because beside bisphosphonates several other drugs are under suspicion of inducing osteonecrosis or at least potentiating the risk in combination with bisphosphonates. Preventive dental treatment significantly reduces risk.

Conflict of interest

The authors declare that there is no conflict of interest.

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