Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment

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A comparison of the CBCT findings in MRONJ related to denosumab versus bisphosphonates: an observational pilot study.

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ABSTRACT

INTRODUCTION

The aim of this study was to compare the radiographic abnormalities on cone beam computed tomography (CBCT) in patients with medication-related osteonecrosis of the jaws (MRONJ) related to denosumab use versus bisphosphonate use.

METHODS

The study included 34 consecutive patients with MRONJ who had a history of exclusive use of denosumab (n = 17) or bisphosphonates (n = 17) and had undergone CBCT for determination of extent of disease. Demographic data of the patients were collected. Differences in radiologic characteristics between patients with denosumab-related osteonecrosis of the jaws (DRONJ) and those with bisphosphonate-related osteonecrosis of the jaws (BRONJ) were scored and studied on CBCT.

RESULTS

In patients with DRONJ, sequestra (P = .015) and lysis of the cortical border of the jaw (P = .033) were significantly less common than in patients with BRONJ. Subperiosteal bone formation did not differ between the groups (P = .545). There was no association between stage of disease and duration of drug therapy or duration of symptoms for either medication group.

CONCLUSIONS

The radiologic features of DRONJ may be different from those of BRONJ with regard to the presence of sequestra and cortical lysis and might, therefore, be improperly diagnosed. Underestimation and undertreatment of DRONJ may potentially lead to progression of disease and, thus, make treatment more difficult.

INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) is a serious condition that causes severe morbidity. MRONJ is the collective term that includes necrosis of the jaws related to all forms of anti-resorptive medications including bisphosphonates (BRONJ)[1, 2] and Denosumab (DRONJ),[3-5] as well as anti-angiogenic medications such as Sunitimib and Bevacuzimab[6].

There is an ongoing debate on the etiology and best treatment for MRONJ[2, 7-9]. When diagnosing[2, 6] MRONJ, the first diagnostic procedure performed in daily clinical practice is usually a panoramic radiograph (PR). This provides an immediate view of the lesion, its location, and its size. A disadvantage of PR is that minor lytic lesions in bone can be undetected[10, 11]. Cone beam computed tomography (CBCT) is frequently used to determine the extent of the disease. It provides more detailed information regarding the size of the lesion and exposes the patient to less radiation than multidetector CT. Radiological features on CBCT for BRONJ have been well described and include thickened lamina dura, sclerosis, subperiosteal bone formation, sequestra, a visible inferior alveolar canal, and lysis of the cortical border of the jaw(s)[12-21]. Some of these findings, in particular sequestra, subperiosteal bone formation, and lysis of the cortical border, are decisive for the diagnosis of MRONJ. The remaining features such as thickened lamina dura or visibility of the inferior alveolar canal provide information regarding the effect of the anti-resorptive medication on the bone in general[6, 9].

Denosumab is another anti-resorptive agent used to treat osteoporosis (e.g., Prolia 60 mg every 6 months) or to treat or prevent skeletal complications in malignancies (e.g., Xgeva 120 mg up to every month). Denosumab has been shown to lead to clinical features comparable to BRONJ.

The specific radiological findings in DRONJ are less well described than in BRONJ. There is only one study reporting on differences between these 2 medications. A significant difference was reported in the presence of subperiosteal bone and the size of sequestra in DRONJ[22]. However, there was no significant presence of sequestra in DRONJ. A difference in mechanism of action between both drugs may cause a different radiographic presentation. Both anti-resorptive drugs have effect on osteoclasts, but on different levels.

Bisphosphonates inhibit bone resorption. The nitrogen-chain will form a covalent bond with bone mineral. Due to the attachment to bone, bisphosphonates have a long half-life and will stay active for years after administration. When an osteoclast, which is responsible for resorption of bone, ingests a bisphosphonate, the osteoclast will malfunction and eventually go into apoptosis. Bisphosphonates lead to a decrease in osteoclast number and function and will thus inhibit bone resorption[23].

Denosumab is a RANK-L inhibitor. RANK-L, when binding to the osteoclast cell membrane, activates osteoclasts and leads to maturation of preosteoclasts to osteoclasts. Denosumab binds

RANK-L, causing immediate cessation of the osteoclast function and preosteoclast differentiation and thereby inhibits of bone resorption[24, 25]. Unlike bisphosphonates, the effect is temporary[6]; after six months osteoclast activity will start over.

This underlying difference in mechanism of action may cause a difference in radiological features. Therefore the objective of this pilot study was to compare the frequency and/or severity of the most relevant radiological features detected on CBCT examinations in patients with osteonecrosis of the jaws who had taken denosumab versus those who had taken bisphosphonates. The null hypothesis stated that there are no differences in frequency or severity between the two groups of patients for any of the radiological features.

METHODS

Patients

MRONJ patients, classified according to the criteria of the American Association of Oral and Maxillofacial Surgeons (AAOMS)[6] into 4 stages of the disease as listed in Table I, who presented between January 2012 and January 2018 at the outpatient clinic of Oral & Maxillofacial Surgery

Table I: Criteria and Classification Stages MRONJ and recommendations adapted from Ruggiero et al., 2014 (AAOMS)[6]

Criteria MRONJ
-Current or previous treatment with antiresorptive or antiangiogenic agents
-Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
-No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

MRONJ stage	Description	Treatment strategies
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic therapies including pain medications and antibiotics
Stage I	No symptomatic lesions or bone exposure in the absence of signs of infection	Topical antiseptic therapy Follow-up
Stage II	Bone exposure with pain, infection, and swelling in the area of the lesion	Oral antibiotics, antibacterial mouth rinse, pain control Superficial debridement to relieve soft tissue irritation
Stage III	Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas, and pathological fractures	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

were included in the present study. Only patients exclusively using bisphosphonates (BRONJ-group) or denosumab (DRONJ-group) were included. Patients with a recent or previous combination of anti-resorptive drugs were excluded.

Demographic data and clinical features including sex, age, indication for drug therapy, anti-resorptive medication regimen, duration of drug therapy, duration of symptoms, and stage of the disease, were collected for patient characterization.

CBCT

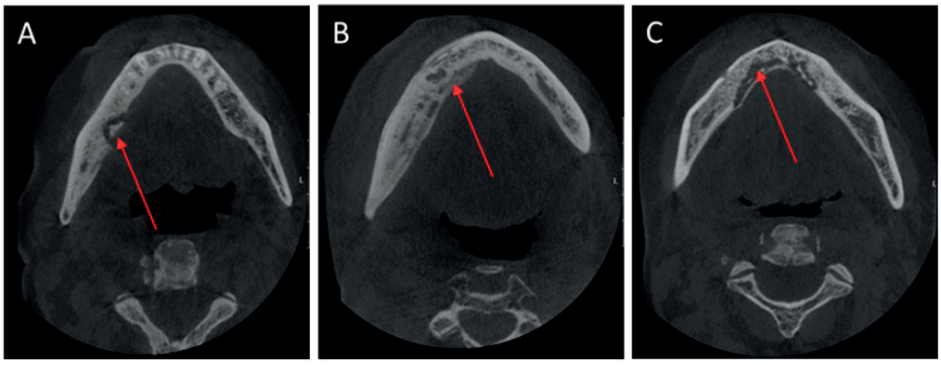
In our center all newly presenting MRONJ patients undergo PR and CBCT. For all patients, the Promax 3D Planmeca cone beam CT scanner was used (Promax® 3D Max, Planmeca USA, Roselle, IL), with exposure parameters of 96 kV, 5.6 mA, 12 s exposure time, FOV 13 x 5.5 cm, voxel size 200µm. The scan volumes were exported in Digital Imaging and Communications in Medicine (DICOM) format and imported into Planmeca Romexis 5.1.1.1dental imaging software (Planmeca, Helsinki, Finland).

Radiological features

CBCT scans were examined for osseous abnormalities previously reported in BRONJ: sequestra, subperiosteal bone formation, and lysis of the cortical border of the jaw(s).

These variables were classified as “present” or “absent” with a 2-point-scale: 0= not present, 1= present (Figure 1).

Figure 1 MRONJ changes on axial view CBCT



A=sequestrum
B=subperiosteal bone formation
C=lysis of the cortical border

All CBCT scans were examined and scored according to this classification by 2 experienced oral and maxillofacial surgeons together, who were blinded to the patients’ clinical status and anti-resorptive medication use. Differences were resolved by consensus, so the Kappa statistic for interexaminer agreement could not be calculated.

Statistics

For continuous variables (duration of drug therapy and duration of symptoms), median and range were calculated. Statistical analysis to evaluate categorical data for group differences was performed with the chi-squared test for sex, indication for drug therapy, stage of the disease, and scores for the presence of sequestra, subperiosteal bone formation, and lysis of the cortical border of the jaws. A logistic regression model was used to assess the effect of the duration of the drug therapy on the duration of symptoms, stage of the disease, and the radiological features; and to assess the relation between the duration of drug therapy and stage. Statistical analysis was performed in SPSS software for Windows (Version 23; SPSS Inc., Chicago, IL). A p-value <0.05 was considered significant.

RESULTS

Patient characteristics (Table II)

From 2012 to 2018, 50 new patients with MRONJ presented to our outpatient clinic, of whom 34 fulfilled the inclusion criteria. The median age was 69 (range 49-86) years. Of the included patients, there were 21 females and 13 males. Denosumab and bisphosphonates were each exclusively used by 17 patients.

Thirteen patients were treated for osteoporosis, and the rest was treated for malignancies: ten for breast cancer, ten for prostate cancer and one for lung cancer. In the Denosumab group only 1 out of 17 patients used the drug for osteoporosis versus 11 in the bisphosphonate group, ($p<0.001$), meaning more widespread anti-osteoporotic drug use in the bisphosphonate group. Five patients had intravenous use of bisphosphonates for malignancies. The remaining twelve patients had osteoporosis and used either oral bisphosphonates (n=10) or received a yearly intravenous dose (n=2). The regimens for Denosumab and bisphosphonates are summarized in the table.

Median duration of therapy before developing MRONJ was shorter in the Denosumab group (18 months, with a range from 8-48) then in the bisphosphonate group (42 months, with a range of 18-240). Because the data were not normally distributed, statistics were not performed. The median duration of symptoms was 6 months with Denosumab and 8 with Bisphosphonates. The duration of symptoms were also not normally distributed, therefore further statistical analysis was not performed either. Disease severity as indicated by stage was equally distributed between the groups ($p=0.169$) with 16 patients and 18 patients classified in stage II and III, respectively.

Table II Clinical features

	Denosumab	Bisphosphonates	Total	p-value
Age	69 (52-83)	69 (49-86)		
Gender				0.078[C]
Female	8	13	21	
Male	9	4	13	
Indication				<0.001*[C]
Osteoporosis	1	12	13	
Cancer	16	5	21	
Breast cancer	7	3		
Prostate cancer	8	2		
Lung cancer	1			
Duration of medication (months)	18 (8-48)	42 (18-240)		
Anti-resorptive medication				
Bisphosphonates			17	
Intravenous use		7		
Zolendronic acid monthly		4		
Zolendronic acid yearly		2		
Pamidronic acid monthly		1		
Oral use		10		
Alendronic acid 70mg weekly		9		
Risedronic acid 35 mg weekly		1		
Denosumab			17	
Xgeva 120mg monthly	16			
Prolia 60mg every 6 months	1			
Stage[1]				0.169[C]
II	10	6	16	
III	7	11	18	
Duration of symptoms (months)	6 (2-16)	8 (2-39)		

[C]=Chi-square-test
[I]=Independent T-sample test
*p<0.05 was considered statistical significant
[1]=staging according to definition MRONJ AAOMS (Ruggiero et al 2014)

Radiologic characteristics (Tables III and IV)

The CBCT scans of 17 consecutive DRONJ patients were compared to 17 consecutive BRONJ-patients.The DRONJ group had a significantly lower frequency of sequestra (70.6%) than the BRONJ patients, all of whom exhibited sequestra (p=0.015). Subperiosteal bone formation was present in 94.1% in the DRONJ-group. This was not significantly different from the incidence in of 93.3% in the patients taking bisphosphonates (p=0.545). Lysis of the cortical border was present in 76.5% of the patients treated with denosumab compared to 100% of patients treated with bisphosphonates, which was significantly different (p=0.033).

Table III Group results for radiological features

Medication	Sequestra scores (Cumulative percentage)	Subperiosteal bone formation scores (Cumulative percentage	Lysis of the cortical border of the jaw(s) (Cumulative percentage)
Denosumab	0=29.4% 1=70.6%	0=5.9% 1=94.1%	0=23.5% 1=76.5%
Bisphosphonate	0=0% 1=100%	0=6.7% 1=93.3%	0=0% 1=100%
Chi-square test	p=0.015*	p=0.545	p=0.033*

*p<0.05 was considered statistically significant

Statistics

Logistic regression showed no association between stage of the disease and duration of drug therapy for denosumab (p=0.813) or bisphosphonates (p=0.867). Nor for duration of symptoms and stage of the disease an association was found for denosumab (p=0.824) or bisphosphonates (p=0.501)

Additional analyses for the separate radiological characteristics of MRONJ (sequestra, subperiosteal bone formation, lysis of the cortical border) were not possible due to the small number of patients in the groups.

Table IV Logistic regression models

	Denosumab			Bisphosphonates		
Stage of disease	p-value*	OR	CI	p-value*	OR	CI
Duration of drug therapy	0.813	1.012	(0.919;1.114)	0.867	1.001	(0.985;1.018)
Duration of symptoms	0.824	1.028	(0.805;1.314)	0.501	1.041	(0.927;1.169)

*p<0.05 was considered statistical significant
OR=Odds Ratio
CI=confidence interval (95%)

DISCUSSION

The aim of this study was to analyse the most relevant radiologic abnormalities detected on CBCT between DRONJ and BRONJ. We observed that 2 characteristics of BRONJ, sequestra and cortical lysis, were significantly less prevalent in DRONJ patients. Another radiological characteristic often identified in BRONJ, subperiosteal bone formation, did not differ in prevalence between groups. Based on these results DRONJ may be unintentionally underdiagnosed, thereby leading to an unnecessary delay in treatment.

Radiologic features of BRONJ are clearly described in literature[6, 12, 14-21]. As mentioned, these include bone sclerosis, thickening of the lamina dura, lysis of the cortical border, prominence of the inferior alveolar nerve canals, and pathological fracture, in addition to the features of

sequestra, subperiosteal bone formation, and lysis of the cortical border of the jaw(s) that were examined in this research. In the clinical setting of MRONJ, these 3 radiological features are considered pathognomic for the diagnosis of osteonecrosis of the jaws. Some differences between the specific medications have been reported by Baba et al, who reported CT imaging findings of 64 BRONJ patients compared to 10 DRONJ patients[22]. The results revealed that the presence of sequestra in the DRONJ group was not significantly different in frequency between the 2 groups but the sequestra were significantly larger. However, the small patient group of DRONJ was a limitation that made it difficult to interpret and generalize the results. Furthermore, the study showed absence of subperiosteal bone formation in BRONJ patients. This is in contrast to other reports in the literature in which subperiosteal bone formation is considered a relevant clinical and radiological feature for BRONJ[6, 9, 10].

The study, however, revealed that sequestra and cortical bone lysis were up to 30% less frequent in DRONJ patients than BRONJ patients. This may lead to underdiagnosis of DRONJ. If there are no visible sequestra or subperiosteal bone formation, a surgeon might inappropriately decide to delay treatment.

The different mechanism of action between Denosumab and bisphosphonates could be a possible explanation for these findings. Since osteoclasts are responsible for sequestra formation and lysis of the cortical border, the observed difference may lie in the fact that Denosumab is a more powerful inhibitor of osteoclast formation and activation then bisphosphonates[24, 25]. Therefore, the radiological features between BRONJ and DRONJ patients may differ. This is also extremely relevant for the treatment of DRONJ patients since in BRONJ the evident sequestration of bone demarcates the healthy bone margins. Without evident sequestration it is sometimes difficult to find the margins of viable bone, possibly leading to insufficient treatment in DRONJ cases.

As a small observational study in an academic referral center, this investigation has several limitations. In the DRONJ-group nearly all patients had an oncological indication for anti-resorptive use. Due to the absolute difference in dosing, monthly administration of Xgeva (120mg) compared to a half yearly dose of Prolia (60mg) for osteoporosis, one could argue that this is the cause of the observed differences. However, correction for treatment indications in the analyses' observed radiological differences is not possible due to the sample size. In addition, stage did not differ between groups, as were their total duration of anti-resorptive treatment. There was no association between stage and the duration of symptoms, but the present study did not have sufficient power to generalize this outcome. Since MRONJ is a condition of progressive nature, early detection in symptomatic patients remains of upmost importance. Despite these limitations, we believe the differences are clinically relevant and may hold implications for clinical daily practice. Whenever possible, a CBCT scan should be routinely done. Considering our observations, this would be of additional value, especially for stage 2 and stage 3 DRONJ patients, in diagnosing and treating DRONJ. CBCT is readily available and should be added to panoramic radiography to get more insight into the different clinical aspects of the disease in 3 dimensions[17,21,22].

The absence of sequestra and/or cortical bone lysis may unintentionally imply that there is no necrosis. This could potentially lead to the choice of a conservative treatment, which could lead to serious deterioration of the DRONJ[23-26] and then to a more difficult treatment.

CONCLUSION

This study indicated that Denosumab-related necrosis may present clinical and radiological features that differ from bisphosphonate necrosis. Sequestra and cortical bone destruction seems to be significantly less common in the Denosumab group versus the bisphosphonate group. This is an important finding, since underestimation and undertreatment of DRONJ potentially leads to deterioration of the disease and thus a more complicated clinical outcome.

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