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Denosumab-related osteonecrosis of the jaw: A retrospective study

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Background: Osteonecrosis of the jaw is a very delicate side effect of Denosumab. The aim of this retrospective study was to assess the occurrence rate of Denosumab-related osteonecrosis of the jaw (DRONJ) at the Cancer Institute of Lorraine (ICL) and to highlight necrosis risk factors.

Methods: To that purpose, we analyzed the medical records of 249 consecutive patients treated with Denosumab at the ICL during the past 5 years. Patients who received orofacial radiotherapy or a previous treatment with a bisphosphonate were excluded. The *P*-value was set at .005.

Results: A total of 141 patients treated at the ICL between January 2010 and December 2015 were included. All patients were treated with XGEVA®. Of the 141 patients included in the study, 10 developed DRONJ. The incidence of DRONJ increases with the duration of follow-up as follows: 3% at 1 year, 7% at 2 years, and 8% from 30 months on. No risk factor for necrosis could be identified except the realization of prior dental extraction ($P = .025$).

Conclusion: Our results raise important questions about the dental management of these patients, in particular, concerning the healing period between dental extractions and the initiation of Denosumab.

KEYWORDS
Denosumab, dental management, Oncology, osteonecrosis of the jaw, retrospective, side effect

1 | INTRODUCTION

Denosumab is a monoclonal antibody which has two commercial presentations in France: Prolia® (Amgen Inc, Thousand Oaks, CA, USA, for benign pathologies) and XGEVA® (Amgen Inc, for malignant diseases).

It acts by inhibiting the formation, function, and survival of osteoclasts to decrease bone resorption. For that, it targets the RANK/RANK-L complex. It prevents the RANK activation by binding to the pre-osteoclast RANK-L and creates a saturation of osteoclast receptors.

Denosumab is indicated in cases of osteoporosis, Paget's disease (bone disease, localized and with slow progression), bone giant cell tumors, and bone metastases. It is a second-line agent for Paget's disease if bisphosphonates are contraindicated. Denosumab is prescribed in almost the same indications as bisphosphonates and is gradually supplanting the latter because of its advantages. In fact, it is interesting to note that XGEVA® has a much shorter half-life than bisphosphonates (28 days) and a shorter duration of action too (6 months vs 5-10 years for bisphosphonates) while having a higher efficiency than zoledronic acid on bone metastases development.[1,2]

Nevertheless, Denosumab and bisphosphonates have common side effects such as hypocalcaemia, hypersensitivity to products (skin allergic reactions, hypotension, dyspnea, and angioedema) but also an atypical femur fracture or an osteonecrosis of the jaw.[3]

The American Association of Oral and Maxillofacial Surgeons described the medication-related osteonecrosis of the jaw (MRONJ) as a mucosal lesion of the maxillofacial region with necrotic bone

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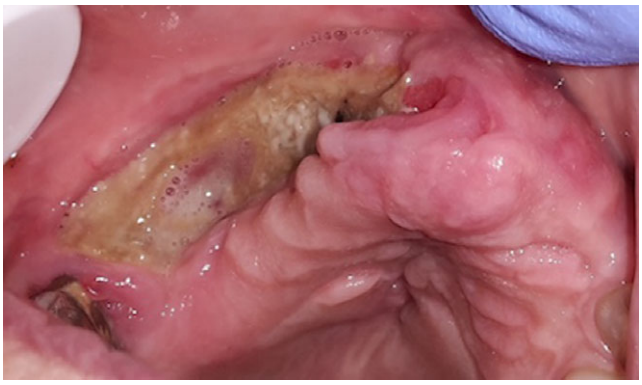

FIGURE 1 Intra-oral appearance of maxillary Denosumab-related osteonecrosis of the jaw

exposure (Figure 1).[4,5] This exposure should be at least 8 weeks old and occur in patients receiving bisphosphonates or Denosumab. It must be in an area free of radiotherapy and bone metastases to be linked to medications. This definition describes both necroses related to the use of bisphosphonates and those related to the intake of Denosumab.

The management of MRONJ is mainly preventive with a dental consultation before prescription. During this consultation, it is important to explain to the patient the risk of necrosis and also to give him advice regarding dental hygiene. It is also important to have a regular dental follow-up (4 times a year). In case of confirmed MRONJ, medication will be suspended in accordance with the prescribing physician. Despite all this, healing an osteonecrosis is long and sometimes complete cure can be obtained.[6]

Surgery is sometimes necessary to have a perfect eviction of all the necrotic bone area and/or to eliminate a bony sequestrum. Some more severe forms require the use of more invasive surgeries such as mandibulectomy. Finally, in case of infection of the necrotic area, the use of antibiotic is necessary and a regular monitoring will be established.[7]

Thus, Denosumab-related osteonecrosis of the jaw (DRONJ) is a very delicate side effect of Denosumab. Indeed, the resolution of DRONJ is often long and complex. That is why the objectives of this study were to assess the occurrence rate of DRONJ at the Cancer Institute of Lorraine (Institut de Cancérologie de Lorraine, Vandoeuvre, ICL) and to highlight necrosis risk factors.

2 | MATERIALS AND METHODS

A retrospective monocentric study was conducted at the ICL by analyzing the medical records of 249 consecutive patients treated with Denosumab at the ICL during the past 5 years. Patients who received orofacial radiotherapy or a previous treatment with a bisphosphonate were excluded. The patients only followed at the ICL's dental service and with an oncological follow-up performed in another center were also excluded from this study. The data recorded were as follows: the existence of a necrosis of the jaw, the patients' age, the type of cancer, an active tobacco use, an alcohol intoxication, a glucocorticoid or anti-angiogenic therapy, an ongoing chemotherapy, the existence of diabetes, pre-therapeutic dental consultation and realization of preventive dental extractions (performed before treatment initiation), and the existence of denture pressure sores. In fact, the type of cancer, a tobacco use, an alcohol intoxication, a glucocorticoid or anti-angiogenic therapy, an ongoing chemotherapy, or diabetes are among the main risk factors for MRONJ. All the patients who benefited from a dental consultation at the ICL received a complete information about the risk of MRONJ and the necessity of a trimestrial dental follow-up.

This retrospective study was approved by our institutional research ethics committee and by the French Data Protection Authority ("Commission Nationale de l'informatique et des Liberté" (CNIL)). It is also in accordance with the Helsinki Declaration.

The quantitative parameters were described by the median and range, and the qualitative parameters by the frequency and the percentage. The incidence of DRONJ was described by the Kaplan-Meier method. The date of origin was the date of introduction of Denosumab. The prognostic factors were tested in univariate analyses by a Cox proportional hazard model. The results are expressed by the hazard ratio and the 95% confidence interval. The level of significance was set at 0.05. Statistical analyses were performed using the SAS software (SAS Institute, Cary, NC 25513, version 9.3).

3 | RESULTS

A total of 141 patients treated at the ICL between January 2010 and December 2015 were included. One hundred and thirty-eight were treated with Denosumab following the appearance of bone metastases and 3 for primary bone tumors.

All patients were treated with XGEVA®. Included patients' characteristics are described in Table 1. The median follow-up time was 25 months (from 5 to 43 months).

A total of 90 patients (63.9%), that is to say all patients with a dental consultation at the ICL, were informed about the risk of DRONJ during their dental consultation and they all received the prevention tips.

Of the 141 patients included in the study, 9 developed DRONJ. Necrosis was related to tooth extraction in 4 cases (development of DRONJ at avulsion sites, radiological persistence of non-healed alveoli), to prosthetic injury in 3 cases (it is also interesting to note that only 3 patients with necrosis carried a dental prosthesis), and finally, 2 spontaneous DRONJ (without local injury found). The mean time between extraction and Denosumab initiation for patients with DRONJ was 4 months (from 2 weeks to 15 months).

Only, 2 cases of DRONJ occurred in patients who did not have any dental consultation and also no prevention. The incidence increased with the duration of follow-up as follows: 3% at 1 year, 7% at 2 years, and 8% from 30 months on. In June 2016, 4 patients had a complete cure of their necrosis. Only, the 36 patients (25.5%) who benefited from dental extractions were checked every month

TABLE 1 Patient's characteristics

Characteristics	
Age at initiation of Denosumab, Median [Range]	58.9 [26;85]
Age at DRONJ' diagnosis, Median [Range]	61.4 [61;80]
Localization of the primary tumor, No. (%)	
Unknown	3 (2.1%)
Breast	70 (49.6%)
Prostate	12 (8.5%)
Lung	20 (14.2%)
Renal	11 (7.8%)
Bone	4 (2.8%)
Head and neck	15 (10.6%)
Digestive	6 (4.4%)
Metastases, *No. (%)*	138 (97.9%)
Risk factors, No. (%) Non-exclusive	
Corticosteroids	83 (58.9%)
Tobacco	42 (29.8%)
Alcohol	11 (7.8%)
Diabetes	15 (10.7%)
Chemotherapy	119 (84.4%)
Targeted therapies	70 (49.6%)
Anti-angiogenic	10 (7.1%)
Pretreatment dental consultation, *No. (%)*	
ICL*	72 (51.1%)
Another dentist	18 (12.8%)
None	51 (36.1%)
Patients with avulsion before treatment	36 (25.5%)
Tooth extraction before treatment (number of teeth). Mean [Range]	2 [0;30]
Duration of treatment with Denosumab (months). Mean [Range]	24 [0;39.6]

Results presented with median and range or frequency (No.) and percentage (%).
*ICL Cancer Institute of Lorraine.

for 6 months by our dental service after Denosumab initiation. Patients who did not require dental treatment before Denosumab continued their follow-up with their treating dentist (4 times a year).

Among patients with DRONJ, no one showed alcohol consumption or anti-angiogenic therapy so no conclusions can be drawn from these data. It is also important to note that among these 9 patients, 5 also benefited from concomitant chemotherapy and 2 from concomitant targeted therapy. None of them underwent tooth extraction after initiation of Denosumab. No risk factor for necrosis could be identified except the realization of dental extraction before treatment initiation ($P = .025$) (Table 2): at 36 months, the incidence of necrosis was 15.5% in the subgroup of patients (corresponding 5 patients) with prior dental extraction vs 5.4% for patients without avulsion (corresponding 4 patients). The time interval between avulsion and necrosis was 15 months (from 2 to 29 months).

TABLE 2 Predictive factors of DRONJ in univariate Cox analyses

Parameters	Hazard ratio and 95% confidence interval	*P*-value
Denosumab initiation		
Before 60 years	1	
After 60 years	0.77 [0.21;2.87]	.699
Cancer localization		
Breast	1	.129
Others	3.38 [0.70;16.27]	
Tobacco		
Non- or ex-smoker	1	.062
Active smoker	3.50 [0.94;13.06]	
Corticosteroids		
No	1	.338
Yes	0.053 [0.14;1.96]	
Diabetes		
No	1	.921
Yes	1.11 [0.14;9.04]	
Chemotherapy		
No	1	.672
Yes	1.57 [0.20;12.53]	
Pretreatment dental consultation		
No	1	.281
Yes	2.38 [0.49;11.48]	
Tooth extraction before treatment		
No	1	**.025**
Yes	4.51 [1.21;16.86]	

Significant factors ($P < .05$) in univariate analyses.

4 | DISCUSSION

In this study, we obtained a DRONJ rate of 1% from beginning to 6 months of treatment and of 8% until 30 months of treatment. From 12 months of treatment, the rate reached 3% and then exceeded the average rates frequently reported in the literature (between 1% and 2%).[8-13] However, cross-study comparisons are complex, due to the variability of many factors as follows: the number of patients included in the study, duration of follow-up (often less than 24 months), and the various potentially aggravating factors which are not always taken into account or do not appear in the publication.

If the statistical analyses have not been significant for risk factors, it is certainly due to the low number of DRONJ studied and also because the patients with DRONJ in this study had no other comorbidities.

Moreover, DRONJ is still a rare effect of Denosumab. To increase the relevance of our results, it would have been necessary to increase the number of patients in particular by conducting a multicentered study. Another difficulty limiting the number of data is that it is a retrospective study, and therefore, a large number of

patients could not be included because of missing data or inaccuracy. Moreover, the fact that we decided to exclude patients formerly treated with bisphosphonates also reduced our number of cases. However, in our view, this exclusion was essential because it was demonstrated that the risk of necrosis was greatly increased in patients treated with bisphosphonates and then with Denosumab.[14] Moreover, it is then difficult to attribute DRONJ only to Denosumab.[15] Now, it would be interesting to continue this work by a prospective study.

Only 36 patients (25.5%) received regular dental follow-up (1 times per month for 6 months) at the ICL. For the others, we do not know if they had a regular dental follow-up. This could be a point of improvement in our care of these patients.

In this study, only the realization of pretreatment tooth extraction was found to be a risk factor for DRONJ and not a protective one. In addition, DRONJ was mostly reported in the territories where the teeth had been extracted.

The total mucosal healing had always been achieved before treatment initiation (checked and validated by a dentist, at least 6 weeks after tooth extraction). We did not find this type of event when we applied the same protocol before initiating bisphosphonate therapy. Nevertheless, it would seem that a complete bone healing is essential. This raises many questions about our management of these patients. Indeed, a complete bone healing requires 120 days in a healthy patient and here we frequently faced immunocompromised patients because of concomitant chemotherapy. In fact, 5 of the patients presenting DRONJ were undergoing chemotherapy at the time of extraction and 2 a targeted therapy. Thus, this period of cicatrization of 120 days would be a minimum because we are facing patients with delayed healing. However, it is rarely possible to delay the starting of treatment with Denosumab. So, it seems necessary to discuss each case with prescribing doctors and adapt our management to the possible healing time.

We could describe two scenarios. In the first case, the treatment initiation may be delayed and so all compromised teeth (symptomatic or not) could be avulsed. In the second case, where a minimum of 120 days cannot be met, dental extraction should be kept to a minimum and only concern symptomatic teeth. The existence of a potential infection site shall not involve tooth extraction in this second case. In all cases, dental close monitoring will be necessary after introduction of Denosumab.

In this study, we could not identify the existence of a prosthetic injury as a risk factor for DRONJ due to a lack of data. Nevertheless, it is important to note that a prosthetic injury is the cause of 3 of the 9 cases of DRONJ found (that is to say 1/3 of the cases of necrosis). The American Association of Oral and Maxillofacial Surgeons identifies prosthodontic treatments as an important risk factor of MRONJ.[5] Khan et al[16] indicated that wearing a denture involved a twofold increased risk of MRONJ. This risk must therefore be an important message in our preventive measures.

A recent publication of the American Association of Oral and Maxillofacial Surgeons recognizes that DRONJ can occur without bone exposure[4] which constitutes a real diagnostic challenge. This should make us consider our definition of DRONJ. In fact, with the Denosumab, we are increasingly confronted with this type of necrosis evolving without clinical signs.[17]

5 | CONCLUSION

As we have seen previously, Denosumab has great benefits for the patient in terms of carcinology. But, it also involves a risk of DRONJ that increases strongly with time and more and more often it confronts us with DRONJ without bone exposure.

Our results raise important questions about the dental management of these patients who seem to need to be treated differently from patients going to benefit from treatment with bisphosphonates. A questioning concerning indications of treatment with Denosumab also seems necessary.

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CONFLICT OF INTEREST

None.

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