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Rechallenge of denosumab in jaw osteonecrosis of patients with unresectable giant cell tumour of bone: a case series analysis and literature review

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ABSTRACT

Objectives Giant cell tumour of bone (GCTB) is a rare tumour, generally managed with surgery. Treatment of the very rare unresectable advanced/metastatic GCTB is challenging and denosumab is the only current available medical option, an anti-RANKL monoclonal antibody inhibiting osteolysis. An uncommon but severe and treatment-limiting adverse event of denosumab is the osteonecrosis of the jaw (ONJ). The clinical management of GCTB patients stopping denosumab for medication-related (MR)-ONJ and the possible reintroduction of denosumab after MR-ONJ resolution is matter of debate. We performed a retrospective study to describe the incidence, clinical features and outcome of MR-ONJ in unresectable GCTB patients treated with denosumab at our Institution.

Design and setting Retrospective, single-institutional study.

Participants Adult patients receiving denosumab as antineoplastic therapy for GCTB and experiencing MR-ONJ at Fondazione IRCCS Istituto Nazionale Tumori of Milan between January 2008 and July 2019.

Main outcome measures Incidence, time of onset and clinical features of MR-ONJ.

Results 29 patients with locally advanced and/or metastatic GCTB treated with denosumab were identified. At a median follow-up of 70 months (range 1–125), 4 (13.8%) patients experienced MR-ONJ while on treatment, after 125, 119, 85 and 41 months of denosumab, respectively. All patients showed an ongoing tumour stabilisation with denosumab at the MR-ONJ onset and in all cases denosumab was stopped. All four patients were treated with ozone therapy. Two are waiting for surgery, two were already operated on. Both of them experienced disease progression and were thus rechallenged with denosumab. One is still on therapy after 25 months. The other had an MR-ONJ relapse after 39 months and was treated again with ozone therapy and surgery. She is under surveillance, GCTB being currently stable.

Conclusion A clinical algorithm of denosumab rechallenge after complete resolution of MR-ONJ in progressing GCTB patients should be prospectively validated.

Key questions

What is already known about this subject?

- The treatment of the very rare unresectable or advanced/metastatic giant cell tumour of bone (GCTB) is challenging and the only current available medical option is denosumab, an anti-Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) monoclonal antibody inhibiting osteolysis.
- An infrequent but severe and treatment-limiting adverse event of denosumab is the osteonecrosis of the jaw (ONJ).
- The clinical management of GCTB patients stopping denosumab for medication-related ONJ (MR-ONJ) and the possible reintroduction of denosumab after its resolution are a matter of debate.

What does this study add?

- The cases presented in this series confirm that MR-ONJ is a potential severe drug-related treatment-limiting adverse event of denosumab, with a delayed onset, and that it requires an aggressive treatment.
- Denosumab could be restarted in two patients experiencing GCTB progression after the complete resolution of MR-ONJ, with a prolonged disease control.
- A clinical algorithm of denosumab rechallenge after complete resolution of MR-ONJ in progressing GCTB patients should be prospectively validated.

How might this impact on clinical practice?

- The rechallenge of denosumab in patients with advanced GCTB after the resolution of MR-ONJ could be considered, even though the validation of a clinical algorithm should be prospectively validated.

INTRODUCTION

Giant cell tumour of bone (GCTB) accounts for approximately 5% of bone primitive neoplasms and represents a clinicopathologically defined tumour entity characterised by typical radiological, histological and molecular features.[1 2] GCTB is endowed

with a variable clinical behaviour, that is, a benign or a locally aggressive course with a progressively enlarging bone destroying lesion. Local recurrences may occur in a significant number of cases, while metastatic lesions are extraordinarily rare (2%–3% of cases), mainly to the lung.[3 4] GCTB is a tumour predominantly localised in the meta-epiphyseal region of the mature skeleton and is made up of three different cell populations.[5] In details, stromal cells, 'giant cell tumour stroma cells' (GCTSC), represent the real neoplastic and proliferative component, which recruit blood monocytes thanks to inflammatory cytokines, leading to the fusion of 'mononuclear histiocytic cells' into 'osteoclast-like multinucleated giant cells' (MNGC), able to induce osteolysis. This process is determined by the interaction of Receptor Activator of Nuclear Factor Kappa-B (RANK) and RANK ligand (L), expressed by MNGC and GCTSC, respectively, through macrophage colony-stimulating factor as a cofactor.[6] The main treatment of localised GCTB is surgery, but the recurrence rate varies according to the size and location of the tumour, as well as to the extent and the quality of surgery. In addition, in a number of cases, radical surgery is not feasible or is associated with a high morbidity and with a number of sequelae impacting the quality of life.[2] The treatment of unresectable or advanced/metastatic GCTB still represents a clinical challenge for physicians.

Based on the pathogenetic mechanisms underlying the tumourigenesis of GCTB, the potential therapeutic role of bisphosphonates was initially explored, with no benefit. Denosumab is a fully human anti-RANKL monoclonal antibody, which inhibits osteolysis by contrasting the formation and activation of MNGC through the blockade of the RANK–RANKL interaction.[7] The introduction of denosumab has changed the clinical practice for GCTB patients with unresectable or metastatic disease, since it represents the only active medical option currently available.[8] Its safety and efficacy in the setting of advanced/unresectable GCTB were confirmed in an international phase II trial (NCT00680992).[9] One of the most relevant, although infrequent, treatment-limiting denosumab-related adverse events is the osteonecrosis of the jaw (ONJ). In case of medication-related ONJ (MR-ONJ), the current guidelines recommend to promptly interrupt denosumab and to start specific local treatments.[10–14] Nevertheless, data about denosumab reintroduction after the resolution of MR-ONJ and about the oncologic outcome of GCTB patients stopping denosumab are lacking.[15 16]

On this basis, we reviewed our institutional records on all consecutive patients affected by locally advanced/metastatic GCTB and treated with denosumab as an antineoplastic treatment between 2008 and 2019, focusing on the incidence, clinical features and outcome of denosumab-related MR-ONJ.

PATIENTS AND METHODS

In this retrospective, monoinstitutional study, we reviewed the medical records of all consecutive patients affected by locally advanced/metastatic GCTB and treated with denosumab as an antineoplastic treatment at Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale Tumori of Milan between 2008 and 2019.

Denosumab was administered at a standard dose of 120 mg once every 4 weeks as a subcutaneous injection, with additional loading doses at day 8 and 15 during the first cycle. Treatment was continued until the evidence of tumour progression or development of treatment-limiting toxicity.

By institutional policy, all patients treated with denosumab underwent preventive dental screening with a complete oral clinical examination and ortopantomography (OPT) before treatment start, and annually while on therapy. All patients were regularly encouraged to maintain good oral hygiene and oral/oral cavity symptoms were then checked at every visit. In addition, patients were advised to immediately report any oral symptoms and in particular tooth mobility, pain or swelling or mouth sores failing to heal or the presence of secretions and to discuss in advance any dental procedure potentially required.

Data on patient and tumour characteristics, treatment, best response assessed by CT and/or MRI evaluation according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria were retrospectively collected and reviewed. Risk factors for ONJ (local trauma, infection or periodontal diseases, dental extractions or invasive dental procedures, poor oral hygiene and misfitting dentures, prior use of antiresorptive drugs, smoking habit, corticosteroid or chemotherapeutic/antiangiogenic agents and comorbidities such as diabetes mellitus, anaemia, haematological diseases and immunological disorders) were registered at baseline. Data on ONJ clinical presentation were recorded (time of onset, grade according to the clinical classification of Ruggiero *et al*[17], treatments received and their outcome).

Patient informed consent was obtained.

RESULTS

We retrospectively identified 29 adult patients affected by a locally advanced and/or metastatic GCTB, who received a systemic treatment with denosumab at our institution between January 2008 and July 2019.

At a median follow-up of 70 months (range 1–125), 4 of 29 (13.8%) patients developed MR-ONJ while on treatment with denosumab. In details, MR-ONJ was detected after 125, 119, 85 and 41 months of treatment, and in all cases it was clinically diagnosed based on the presence of exposed bone in the maxillofacial region and confirmed by OPT and CT/MRI evaluation. All patients responded to denosumab, showing a prolonged disease stabilisation, and were still responsive at the time of MR-ONJ onset. In all cases, denosumab was stopped. All four patients were

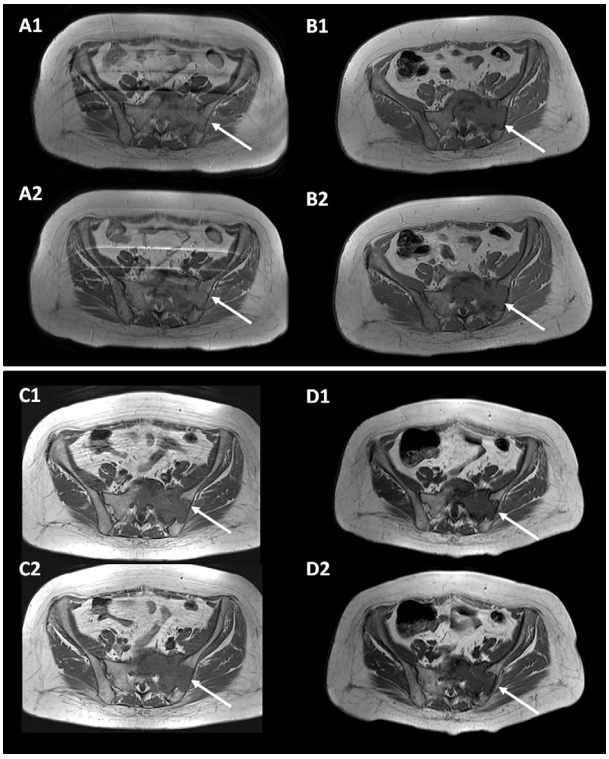

Figure 1 Response to denosumab in a locally advanced GCTB located to the sacrum (case 1). MRI scans (T1 weighted) showed a sacral lesion at baseline (A1–2) and after 3 months of treatment with denosumab (B1–2) with the evidence of a minor reduction in tumour size (stable disease according to RECIST). Disease was stable after 41 months of treatment at the time of ONJ onset. Disease progression was detected 9 months after denosumab interruption (C1–2). A new disease stabilisation was achieved after rechallenging denosumab, as shown by MRI taken 3 months later (D1-2). The white arrows point at the tumour lesion. GCTB, Giant cell tumour of bone; NOJ, osteonecrosis of the jaw.

treated with ozone therapy. Two are waiting for surgery, two were operated on. Both patients resected experienced GCTB progression 9 and 11 months after surgery, respectively, and were thus rechallenged with denosumab. One is still on treatment after 25 months. The other had a relapse of MR-ONJ after 39 months: she was treated again with ozone therapy and surgery and she is under surveillance, with GCTB being currently stable.

These two cases are presented in details hereafter.

CASES PRESENTATIONS

Case 1

This is a 72-year-old woman diagnosed in November 2010 with a 20 cm large GCTB arising from the sacrum. She was symptomatic for lumbar-sacral pain with irradiation to the left lower limb, urinary incontinence and paraplegia. The tumour was deemed resectable only through an en bloc excision of the whole sacrum, refused by the patient. No baseline risk factors for ONJ were identified. In March 2011, she was started on denosumab with mild reduction of the tumour size and a complete resolution of all GCTB-related symptoms (figure 1A and B). The treatment had to be discontinued after 41 months, while the tumour was still responding, for the onset of stage 2 MR-ONJ at the third mandibular quadrant, preceded by oral inflammation at the left part of the lower dental arch for roughly 13 months, which was unresponsive to anti-inflammatory and antibiotic therapy. Oral examination at the time of MR-ONJ showed an erythematous and painful left part of the inferior dental arch, with exposure of the alveolar bone, in absence of fistula or fracture. MR-ONJ was managed with 10 cycles of ozone therapy (twice a week for five consecutive weeks), followed by a surgical toilette of the jaw bone. During surgery an area of devascularised and necrotic bone without clear limitations became evident and it was completely removed up to apparently vital bone. Nine months after denosumab discontinuation, the patient reported a recrudescence of sacral pain and walking impairment. CT scan and fluorodeoxyglucose-positron emission tomography (FDG-PET) showed evidence of local tumour progression. Denosumab was resumed at the standard dose, while under strict control of the oral cavity. Tumour response consisting in a reduction in tumour size with denosumab was achieved again, as shown by both FDG-PET and MRI after 5 and 10 weeks, respectively, from denosumab rechallenge (figure 1C and D). An MR-ONJ relapse was diagnosed at 39 months from denosumab treatment start, localised at the distal margin of the previous surgical area, which extended from the retromolar region to the 3.4–3.5 dental element, and was accompanied by oral inflammation, necrotic fragments and the presence of an oral fistula with purulent secretion (stage 3 ONJ). Denosumab was discontinued and ozone therapy was started, followed by a new surgical procedure of mandibular toilette, showing an osteonecrotic focus in the absence of any well-defined bone sequestration. The necrotic tissue was entirely removed up to vital bone, with complete resolution of MR-ONJ. The disease is currently stable while off-denosumab for 8 months.

Case 2

This is a 40-year-old man, affected by a 4.5 cm large GCTB arising from the clivus, deemed resectable only through en bloc tumour removal together with the involved structures, which the patient refused. No baseline risk factors for ONJ were identified. He was started on denosumab, with dimensional disease stabilisation at MRI and metabolic response at FDG-PET after 2 months. After 6 years of treatment, while the disease was still stable, the patient reported a rapidly increasing oral pain and inflammation to the right part of the upper dental arch, only temporarily benefiting from antibiotic and anti-inflammatory treatment. The dental assessment showed an area of bone exposure of 1.6 dental element, accompanied by an inflammatory reaction, consistent with the diagnosis of stage 2 maxillary ONJ of area 16–17. On this basis, denosumab was interrupted and the patient was managed with

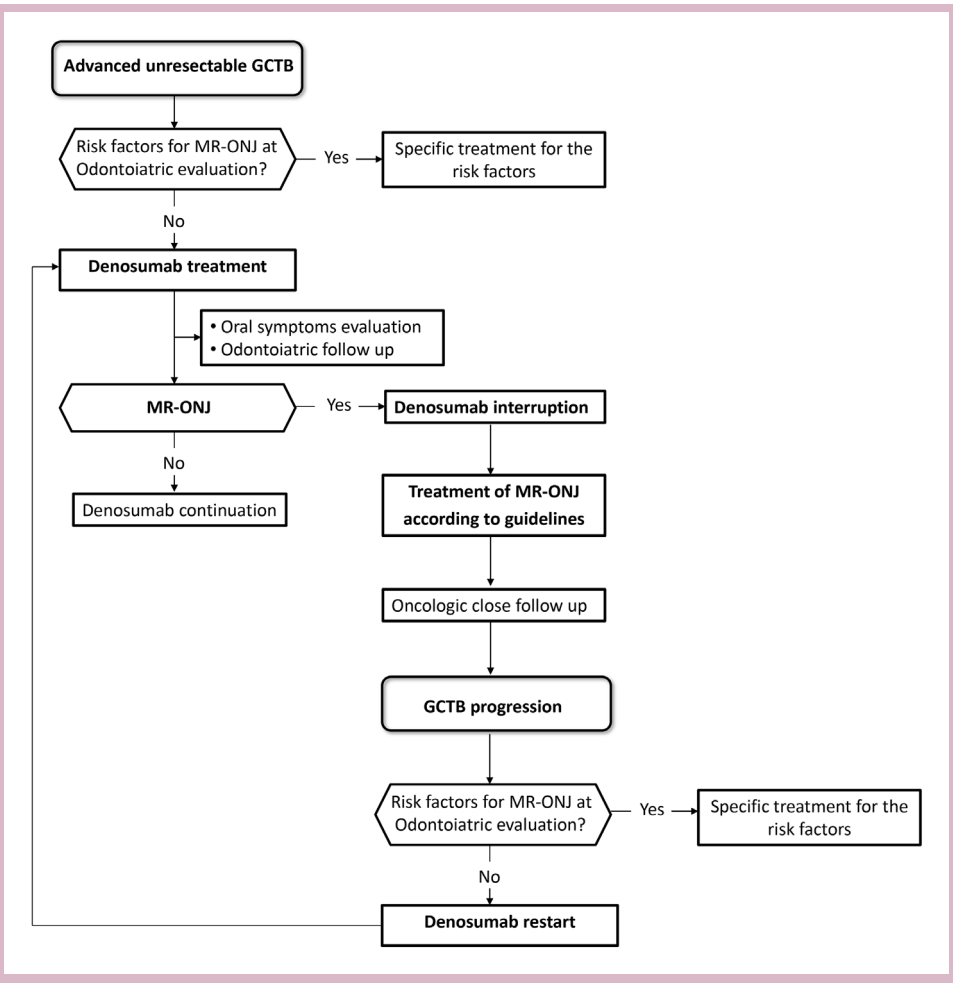

Figure 2 Clinical algorithm for the management of denosumab-related ONJ in advanced giant cell tumour of bone (GCTB) patients treated with denosumab. MR-ONJ, medication-related osteonecrosis of the jaw.

ozone therapy for 10 cycles (twice a week for five consecutive weeks), followed by a surgical partial resection of the right maxillary bone. At the surgical procedure, the necrotic area was well confined and the sequestration was easily removed up to the surrounding vital bone. After 11 months from denosumab interruption, there was radiological evidence of disease local progression. Denosumab was therefore resumed, with a new tumour stabilisation maintained at the last assessment, 25 months later, with no MR-ONJ relapse or additional toxicity.

DISCUSSION AND LITERATURE REVIEW

In this single-institution retrospective case series including 29 cases of unresectable GCTB treated with denosumab, we observed the occurrence of MR-ONJ in more than 10% of patients along ≥5 years of follow-up, always occurring after 3 years or more of therapy. The cases presented herein confirm that ONJ is a potentially severe drug-related treatment-limiting adverse event of denosumab, with a delayed onset, often requiring aggressive treatment. Nevertheless, denosumab could be restarted in two patients at the time of new disease progression and one of them is currently on treatment after more than 2 years. This is particularly relevant since denosumab represents the only active anti-neoplastic treatment for advanced unresectable GCTB.

Our study is endowed with a number of limitations. First of all, this is a retrospective analysis, thus exposed to all potential biases deriving therefrom. Second, it is a single-institution study with a narrow sample size. Nevertheless, no evidence is currently available on this topic, and, to our knowledge, this is the first report on the potential safety and efficacy of denosumab restart after complete resolution of MR-ONJ in GCTB patients.

Denosumab's safety and efficacy were confirmed in an international phase II study (NCT00680992). The interim analysis of this study showed a long-lasting disease control in the vast majority of patients, along with a high response rate and symptomatic improvement.[18 19] The efficacy results have been confirmed in the final analysis.[9] With regard to the safety, which was the primary end-point of the trial, the interim analysis showed an incidence of ONJ of 1% at a median follow-up of 13.0 and 9.2 months in Cohort 1 (unresectable GCTB) and 2 (resectable GCTB with a high-morbidity surgery), respectively,[18 19] while the final study report at a longer median follow-up (65.8

months in cohort 1 and 53.4 in cohort 2) showed only a slightly increased rate of MR-ONJ, detected in 3% of patients.[9] The proportion of patients developing ONJ in our series is instead higher. A possible explanation for this is the longer follow-up of our series, once considered that, in three of the four cases who had an ONJ, the event was observed after 5 years of treatment (ie, at 125, 119, 85 months from denosumab start). In addition, all patients from our series remained on treatment until the evidence of the ONJ, while patients in cohort 2 of the study interrupted denosumab after the surgical resection.

In other cancers, such as breast or prostate cancer, where denosumab is administered for a limited treatment time in patients with bone disease with the aim of reducing the incidence of skeletal-related events,[20–23] the reported incidence of denosumab-related ONJ ranges from 1% to 8.2%. The rates reported in studies including patients with a longer treatment duration or a prolonged follow-up are higher than 5% after 3 years of denosumab.[21 24 25] In unresectable GCTB patients, denosumab is administered up to disease progression, potentially lifelong, and therefore, an increased rate of ONJ may be reasonably expected, in contrast to the limited treatment time scheduled in case of its use as antiresorptive therapy.[21] As a consequence, a long-term odontoiatric follow-up must be ensured, with careful clinical monitoring of the oral cavity, and regular OPT. Consistently, the importance of MR-ONJ prevention is crucial, including assessment of risk factors, maintenance of a proper oral hygiene and, overall, avoidance of invasive odontoiatric procedures during denosumab,[10 11 26] as we reported in one case of our series showing MR-ONJ to the site of a dental extraction.

In details, ONJ is a process characterised by the progressive destruction of the maxillar or mandibular bone potentially leading to severe and debilitating complications,[26–28] caused by the altered dynamics of bone formation and resorption inherent to the mechanism of action of denosumab.[22 23] The clinical presentation of ONJ can be classified in four stages: stage 0, no clinical evidence but non-specific clinical/radiological findings or symptoms; stage 1, exposure of the necrotic bone in absence of clinical symptoms (ie, pain and dysgeusia) or infections; stage 2, presence of symptoms and infection; stage 3, extension of necrosis beyond the alveolar bone to the mandibular inferior border and/or the maxillary sinus or the occurrence of pathological fractures or extraoral fistula.[17] Risk factors for ONJ include: local trauma, infection or periodontal diseases, dental extractions or invasive dental procedures, poor oral hygiene and misfitting dentures, prior use of antiresorptive drugs, smoking habit, corticosteroid or chemotherapeutic or antiangiogenic agents, and comorbidities such as diabetes mellitus, anaemia, haematological diseases and immunological disorders.[29 30] Furthermore, the risk of ONJ increases along with denosumab treatment duration, even though a precise time cut-off has not been defined.[21] In order to minimise the risk of MR-ONJ, it is fundamental to perform an odontoiatric evaluation before the start of treatment with denosumab, aimed at defining the potential risk. In addition, all invasive dental procedures should be performed prior to the beginning of denosumab and avoided while the patient is on treatment.[10 27] Finally, the maintenance of a proper oral hygiene and a close odontoiatric follow-up during treatment is fundamental, as well as the intake of calcium and vitamin D supplements, with regular monitoring of serum calcium levels.[11 26]

Once ONJ develops, current clinical practice guidelines recommend to promptly interrupt denosumab and to start local conservative treatments, such as antibiotic drugs, ozone therapy and superficial debridement, or, in case of failure, to proceed to a surgical toilette of the necrotic area. However, a gold standard for MR-ONJ treatment has not been completely defined[10–14 26]. In our case series, MR-ONJ could be safely managed with denosumab interruption, followed by ozone therapy and surgery. Even though ozone therapy is not a formally validated treatment for MR-ONJ, initial experimental data from a preliminary open label, prospective phase I–II study provided some evidence that it may favour the expulsion of the necrotic bone fragment and the tissue healing.[14] The risk of ONJ recurrence after denosumab rechallenge has not been defined, yet. Interestingly, in our case series, the patient that did not experience MR-ONJ recurrence after denosumab rechallenge had a well-confined bone sequestration which was completely removed after ozone therapy, whereas in the MR-ONJ-relapsing case, ozone therapy failed to induce a control of bone necrosis, namely, a complete demarcation of bone necrosis vis-a-vis vital bone. Though this is just a hypothesis, MR-ONJ relapse could have been favoured by the incomplete resection of necrosis during the first surgery.

Data regarding the reintroduction of denosumab in GCTB patients after the resolution of MR-ONJ are lacking and no evidence-based guidelines on denosumab rechallenge after MR-ONJ are available[15 16] A few papers suggest that denosumab rechallenge may be considered in case of disease progression and/or occurrence of new bone-related symptoms,[29 31] but there are no reports available so far describing clinical cases in which this was tried and their clinical outcome. It was instead reported that restarting bisphosphonates after the complete healing of ONJ in multiple myeloma patients was feasible, although associated with a non-negligible risk of ONJ relapse. Specifically, the authors collected data on multiple myeloma patients developing MR-ONJ and observed that in 12 cases there was a relapse of ONJ, among which six were associated with a rechallenge of bisphosphonates.[32] This topic is of major importance in a tumour in which denosumab is administered for its direct antitumour effect and, most important, denosumab represents so far the only drug potentially active. Denosumab has a clinically cytostatic rather than a true cytotoxic effect, as also suggested by in vitro preclinical studies.[33] Specifically, stromal patients-derived tumour cells from patients treated with denosumab showed a lower proliferation rate

than untreated ones, in parallel with an extreme decrease of the expression of RANKL.[33 34]

It would be worth understanding if a different treatment schedule could reduce or even prevent the onset of ONJ. The recommended treatment schedule in GCTB foresees a loading dose of 120 mg at day 8 and 15 during the first cycle as a subcutaneous injection, followed by 120 mg once every 4 weeks until the evidence of progression or limiting toxicity. In unresectable GCTB, this translated into a chronic therapy lasting for years and no data are available on denosumab efficacy with less intense schedules.[35] An European Organisation for Research and Treatment of Cancer (EORTC) multicentre, open-label, randomised phase II study (NCT03620149) was just started, in order to investigate if a reduced dose of denosumab (120 mg every 12 weeks) in patients affected by unresectable GCTB treated with denosumab at the standard dose of 120 mg every 4 weeks for 12 months is as active as the monthly treatment.

To which extent restarting denosumab after the complete resolution of MR-ONJ remains an open question. In two cases of our series experiencing GCTB progression, we could rechallenge denosumab obtaining a new prolonged tumour control. A clinical algorithm for the management of these patients might be conceived, incorporating a policy of denosumab rechallenge on disease progression (figure 2). Of course, a pretreatment prevention of MR-ONJ should be in place, through the elimination of risk factors and an on-treatment dental strict follow-up. Once diagnosed, MR-ONJ should be aggressively treated following available guidelines.[15 17] After the complete resolution of MR-ONJ, patients should be closely monitored, with the aim of timely detecting GCTB progression. In case of any tumour relapse, treatment with denosumab should be restarted in the absence of dental contraindications and patients should undergo a very close dental monitoring. In case of MR-ONJ reoccurrences, patient management might follow the same algorithm described above (figure 2).

In conclusion, we believe that a prospective effort exploring the feasibility and efficacy of such a clinical algorithm should be envisaged. The creation of a worldwide clinical registry might help. In the end, effective treatment of MR-ONJ could significantly improve the outcome of patients affected by such a rare disease as GCTB.

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