New-generation anticancer drugs and medication-related osteonecrosis of the jaw (MRONJ): review of the literature and single-center experience.

Agostino Guida¹, Antonio Grimaldi¹, Franco Ionna¹, Francesco Perri¹, PAOLO ANTONIO ASCIERTO

¹ Istituto Nazionale Tumori "Fondazione Pascale"

Funding: The author(s) received no specific funding for this work.

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

Since its first association to Zoledronate in 2004, the number of drugs which may induce medication-related osteonecrosis of the jaw (MRONJ) increased annually. Nowadays, novel chemotherapy agents, such as immunotherapy or targeted therapy are increasingly used in the clinical practice. Adopted for Metastatic Melanoma (MM) therapy, immunotherapy and targeted therapy agents are now used in a wide and increasing variety of cancers, such as head & neck, urologic, gynecologic and pulmonary neoplasms, especially in regard to bone metastasis control.

We thus investigated literature to understand a possible impact of such novel cancer therapies on MRONJ. A review of the literature searching PubMed and Scopus was performed. We also report of a case of late MRONJ onset, 3 years after administration of ipilimumab.

As a result, association of immunotherapy and/or chemotherapy and/or targeted therapy, in sequence or as single therapies, may rarely induce osteonecrosis of the jaw. Ipilimumab was associated 3 times in literature to MRONJ, both in single therapy and in association with other drugs. In a paper published by our Institute, Ipilimumab produced late effects, inducing MRONJ 3 years after its administration;
Complete healing was reached with pharmacological therapy. Nivolumab was associated once in literature to MRONJ, both in patients undergoing multiple therapy both in single therapy. Pembrolizumab was related twice to MRONJ in literature, once when in association with epacadostat and once with Denosumab. Interestingly, 5 out of 7 reported cases were triggered by periodontal abscess.

New-generation anti-cancer drugs, such as immunotherapy and targeted therapy agents, seems at low risk of developing MRONJ. Their field of application is widening, and so is the number of patients who are administered with such drugs.

Yet, mechanisms underlying their action are not fully comprehended and, even if they may be considered safe, literature suggests that unexpected events in terms of MRONJ break-out may occur.

Multidisciplinary approach, with dental evaluation prior/during/after chemotherapy, is strongly advised.

Background

Events of nonhealing-exposed bone in the maxillofacial region were initially reported in patients treated with intravenous (IV) bisphosphonates (BP). Pamidronate (Aredia) and zoledronic acid (Zometa)—two IV BPs—were thus labeled as at risk for osteonecrosis of the jaws (ONJ). Consequently, in the following years a warning followed for all BPs to be at risk for ONJ, which was thus renamed as bisphosphonate-related ONJ (BRONJ).

During subsequent years, other BPs and medications belonging to other classes have been related to the development of ONJ, including denosumab (humanized monoclonal antibody blocking the activation of receptors for nuclear factor kB-ligand), bevacizumab (humanized monoclonal antibody), and sunitinib (tyrosine kinase inhibitor).

As sporadic events, case reports have highlighted possible association between ONJ and azacitidine, imatinib, everolimus, zivafibercept, ipilimumab, and tocilizumab. As the number of drug class widened during the years, this condition was then more widely re-named as medication-related osteonecrosis of the jaw (MRONJ).

Both pathogenesis and associated risk factors of this disease are not fully comprehended. Nowadays, novel chemotherapy agents, such as immunotherapy or targeted therapy are increasingly used in the clinical practice. Adopted for Metastatic Melanoma (MM) therapy, immunotherapy and targeted therapy agents are now used in a wide and increasing variety of cancers, such as head & neck, urologic, gynecologic and pulmonary neoplasms, also in regard to bone metastasis control.

We thus investigated literature to understand a possible impact of such novel cancer therapies on MRONJ and report our experience in managing an unusual case of osteonecrosis onset 3 years after the administration of ipilimumab.

Materials & Methods

Literature analysis

Review of the present scientific literature was performed on the research engine SCOPUS and PUBMED. Research query was: "(Ipilimumab OR Nivolumab OR Pembrolizumab OR anti-PD1 OR Dabrafenib OR Trametinib OR Vemurafenib OR
Cobimetinib OR Encorafenib OR Binimetinib OR anti-BRAF OR anti-MEK) AND (MRONJ OR BRONJ OR osteonecrosis), designed to be as wide as possible. The research retrieved 9 results on PUBMED and 49 on Scopus. A first selection was performed through abstract analysis. Exclusion criteria were:

- articles not in English;
- articles off-topic [not reporting case(s) of MRONJ onset as complication of the aforementioned drugs in single/combined therapy];
- reviews of scientific literature;
- duplicates results.

**Personal experience: case report**

During November 2018, a 58-year-old woman affected by BRAF-mutated metastatic melanoma, under treatment at the Immunotherapy Unit of Naples Cancer Institute “G. Pascale”, was referred to the Oral Pathology outpatient clinic. While in follow-up, the patient reported severe pain in the oral cavity, which was ongoing for 4 months, due to a non-healing alveolus after the avulsion of the lower right third molar. Patient referred that she had been treated by her dentist for an alveolar osteitis (AO, dry sockets) with 1-week cycle of amoxicillin + clavulanic acid (2.25 + 0.75 g/d per os) and chlorhexidine 0.2% mouthwash daily/weekly socket irrigation. Such therapies had been repeated three times during those months, continuing chlorhexidine 0.2% home mouthwash daily socket irrigation among the antibiotic cycles. Application of zinc oxide eugenol in the alveolus had also been performed. Every treatment she had undergone had been unsuccessful. She showed no extra-oral sign of swelling nor abscess. Clinically, intraoral inspection showed presence of a non-healed alveolar socket; the bottom and the walls of the alveolus were clearly visible, made of non-vascularized non-suppurated bone, surrounded by swollen mucosa (Figure 1).
Figure 1: Intraoral inspection revealed the nonhealing alveolus.

A 3-day-old orthopantomography (OPT) was exhibited, with radiographic sign of non-healed alveolus (Figure 2).
Anamnesis was carefully harvested. The patient had been diagnosed with cutaneous melanoma in 2009. She thus underwent surgical resection of primary tumour. Lung progression of disease was found in 2015, which lead to treatment with ipilimumab (3 mg/kg mg iv, every 3 weeks for 4 cycles). Complete remission of the disease was reached. In 2017, the patient suffered from hepatic progression; as Melanoma was BRAF-mutated, she underwent dabrafenib + trametinib (300 + 2 mg per os/die). The patient thus suffered from G. 3 toxicity (fever), which lead to treatment stopping and replacement with vemurafenib + cobimetinib (vemurafenib: 1920 per os/die for 3 months, then 1440 mg per os/die; cobimetinib: 60 mg per os/die for 3 weeks then 1-week pause). Such treatment was still ongoing at the time her dental problem. She referred no history of smoking nor head and neck radiation therapy. Ipilimumab was the only medication administered to her that has been related to MRONJ\textsuperscript{12,17}. Her MRONJ was thus evaluated as a “stage 2” according to the AAOMS classification, showing “Exposed and necrotic bone(...) with evidence of infection, (...) symptomatic”\textsuperscript{11}. She was thus administered with amoxicillin + metronidazole (3 + 1.5 g per os/die) and chlorhexidine 0.2% mouth rinse twice a day; paracetamol (1 g per
was prescribed for pain control.

Results

Literature analysis

Seven papers (6 case reports and 1 case series) did not match the exclusion criteria and could be included in our study\textsuperscript{12,17,19-23} (full-texts are added as supplementary data of the present article). From the case series\textsuperscript{17}, 2 cases were traceable to Ipilimumab (one in single and one in multiple therapy), but one was already reported in another study\textsuperscript{12}, so we considered only one additional case. Drugs reported to have caused MRONJ, oncological anamnesis and reported trigger factors are summarised in Table 1.

| Drug(s) | Oncological anamnesis | Trigger factor          |
|---------|-----------------------|-------------------------|
| E+P\textsuperscript{20} | Metastatic Melanoma | Periodontal abscess     |
| D+P\textsuperscript{21} | Lung Cancer           | Peri-implant abscess    |
| I\textsuperscript{12} | Metastatic Melanoma  | Periodontal abscess     |
| I+D\textsuperscript{17} | Not specified         | Not specified           |
| I\textsuperscript{19} (late) | Metastatic Melanoma  | Tooth extraction        |
| B+IL2+Z+D+C+N\textsuperscript{22} | Renal Cancer         | Peri-implant abscess    |
| N\textsuperscript{23} | Metastatic Melanoma  | Periodontal abscess     |

Table 1: Drug(s), oncological anamnesis and trigger factor of MRONJ cases (B: Bevacizumab; C: Cabozantinib; D: Denosumab; E: Epacadostat; I: Ipilimumab; IL-2: Interleukin-2; N: Nivolumab; P: Pembrolizumab; Z: Zolendronate)

Different class groups for drugs identified in our literature research are reported in Table 2.

| Drug (Si,Mu) | Drug class                                    |
|--------------|-----------------------------------------------|
| D (Mu\textsuperscript{*}), I (Si, Mu), N (Si, Mu), P (Mu) | Monoclonal antibodies                         |
| B (Mu)       | Antiangiogenics                               |
| C (Mu)       | Cancer growth inhibitor (CGI)                 |
| E (Mu)       | Inhibitors of indoleamine dioxygenase-1 (IDO-1) |
| IL-2 (Mu)    | Synthetic cytokine                           |
| Z (Mu\textsuperscript{*}) | Biphosphonate                               |

Table 2: Drugs and their class of belonging, specifying if they were identified during single (Si) or multiple (Mu) therapy. (B: Bevacizumab; C: Cabozantinib; D: Denosumab; E: Epacadostat; I: Ipilimumab; IL-2: Interleukin-2; N: Nivolumab; P: Pembrolizumab; Z: Zolendronate). \textsuperscript{*}This drugs were identified during multiple therapy in our reasearch, but are a well-known cause of MRONJ\textsuperscript{1}.

If case reports in which patients were admistered also drugs which are well-known cause of MRONJ\textsuperscript{1} (denosumab, zolendronate, bevacizumab) are excluded, only nivolumab, epacadostat, pembrolizumab and ipilimumab are reported to
have caused MRONJ in single (nivolumab, ipilimumab) or multiple (epacadostat+pembrolizumab) therapy. Only one MRONJ case (ipilimumab, single therapy three years before) onset after tooth extraction; the other cases arose were reported to be in relation to periodontal/peri-implant conditions.

**Personal experience: case report**

At the 2-week follow-up visit, clinical improvement was clearly visible. She referred that a 10 × 5 mm bone sequestrum had been spontaneously ejected after 6 days of therapy and that her symptoms had therefore disappeared; clinically, she still showed incomplete wound healing. Two additional weeks of therapy were thus administered and so the patient reached complete alveolar healing (Figure 3).

![Image of clinical resolution](https://doi.org/10.32388/48DL31)

*Figure 3: Complete clinical resolution after 4 wks of antibiotic/disinfectant therapy (amoxicillin + metronidazole 3 + 1.5 g per os/ die- and chlorhexidine 0.2% mouth rinse).*
No further treatment for MRONJ was prescribed. Patient underwent monthly follow-up. During the 6th month, a new OPT confirmed alveolar healing. (Figure 4).

![Figure 4: Radiographic appearance at OPT after 6 months of follow-up, showing complete bone healing.](image)

**Discussions**

Several new medications have been added to the potential cause of MRONJ drug list during the past years. In addition to well-known medication, as highlighted by our review, MRONJ may be a major adverse reaction to several new-generation anticancer drugs. These drugs may have unexpected mechanisms, being their pharmacodynamic not fully comprehended yet.

Pembrolizumab, a humanized monoclonal antibody targeting the programmed cell death protein 1 (PD-1), has become the standard treatment for metastatic non-small-cell lung cancer (NSCLC) patients since it has been shown to prolong progression-free survival and overall survival of these patients\(^{21}\). In one report\(^{21}\), authors speculate that it may have boosted Denosumab (a humanized monoclonal antibody against receptor activator of NF-kB ligand-RANKL) effect in triggering MRONJ, as both of their molecular pathways results in an anti-osteoclastogenic effects. Similarly, in another case report\(^{20}\), Pembrolizumab effect on bone metabolism through T-Cells modulation may have been reinforced by
Epacadostat, which inhibits IDO1 increasing the efficacy and growth of T-Cells and NK cell growth with increased production of IFNg, which inhibits osteoclastogenesis. Therefore, up until now, there is no evidence that Pembrolizumab or Epacadostat may cause MRONJ in single therapy.

Alongside with Pembrolizumab, Nivolumab is an anti-PD-1 checkpoint inhibitor. Our literature research showed two cases of MRONJ possible related to this drug, one in single therapy\textsuperscript{23} and on in multiple therapy\textsuperscript{22}. In the single therapy case, authors remarked the link between inflammation -deeply influenced by Nivolumab administration- and bone metabolism. Similarly, in the multiple therapy case, authors remark how the administration of various monoclonal antibody may have boosted Zolendronate and Bevacizumab effect.

Ipilimumab is a humanized monoclonal antibody against cytotoxic T lymphocyte–associated antigen-4 (CTLA-4). CTLA-4 is expressed both in activated T cells and in suppressor T-regulatory cells, binding to antigen-presenting cells and therefore diminishing T-cell responses. The block of the CTLA-4 is able to improve the antitumor responses of activated T cells. In a case report\textsuperscript{12} it is indicated as cause of MRONJ through by empowering the number of systemic activated T-cell presence. CTLA4-deficient activated T cells have been shown to be associated with osteonecrosis, as activated T cells may ignite osteoclastogenesis via osteoprotegerin ligand, resulting in bone loss. Such effects is also reported to empower denosumab effect in another case report\textsuperscript{17}.

Interestingly, in the case report we have described in this paper too\textsuperscript{19}, Ipilimumb may have caused MRONJ 3 years after its administration. Ipilimumab is known to have a 14.7-day blood halflife\textsuperscript{19} but the real advantage of the drug is in the long-term efficacy, due to the immune responses induced by checkpoint inhibitors. Similarly like the anticancer effects, side effects such as pruritus, diarrhea, vitiligo, hepatitis, and endocrinopaties may occur many years after administration\textsuperscript{12}. It is conceivable that MRONJ may be also a late side effect under certain circumstances, which may have been co-caused by the ongoing target therapy ( vemurafenib + cobimetinib) of the patient. The effect of BRAF and MEK inhibitors in BRAF-mutant melanoma can lead to an immune-stimulating microenvironment by enhancing expression of immune-stimulating molecules and cytokines, reducing immunosuppressive cell populations, and decreasing immunosuppressive cytokines. The cell damage to the tumor by the target therapy may have induced a tumor-antigen spreading, restimulating T-cell activity whose response had been increased and modulated by the effect of ipilimumab. Moreover, it has been demonstrated that anti-BRAF therapy enhances the reactivity and cytotoxicity of T cells\textsuperscript{19}. The re-activation of such empowered T-cell clones may have lead the patient into a window of time in which she was at risk for MRONJ, similarly to when the patient was on treatment with ipilimumab.

**Conclusions**

- MRONJ pathologic pathways are not fully comprehended. Yet, decreased bone turnover by modulation of osteoclast function, inhibition of angiogenesis, infection, inflammation and soft tissue toxicity have been identified as playing an important role\textsuperscript{24}. It is well acquired in scientific literature that T-Cells may interfere with osteoclasts both with cell-to-cell
contact and the production of different cytokines (CKs). Proinflammatory CKs are pro-osteoclastogenic, while anti-inflammatory CKs inhibit osteoclastogenesis by direct or indirect RANKL inhibition. The immune system is thus involved in bone loss and bone regeneration. Trauma from regular oral activity, oral surgery (eg, tooth extraction) or teeth/periodontal diseases, increasing the demand for bone to mend itself, may result in localized bone necrosis in patients with altered immunologic state due to ongoing/past immunotherapy.

In our literature review, 5 out of 7 MRONJ cases were triggered by periodontal/periimplant abscess/acute inflammatory phase. Periodontal patients are well-known for having altered cytokines productions/immunologic cell function when not treated, as they stay in a local chronic inflammation state, which may also reflect on systemic inflammation state. This may both lead to novel perspective in investigating MRONJ pathologic mechanism, confirming inflammation as a key moment in its comprehension, both underline the necessity of periodontal surveillance for patients undergoing immunotherapy.

New-generation anti-cancer drugs seem at low risk of developing MRONJ, with isolated cases reported in literature. Yet, literature suggests that unexpected events in terms of MRONJ break-out may occur. The authors thus recommend caution and strict vigilance in the dental management of patients treated with chemotherapy interfering with immunological function of the patients. Multidisciplinary evaluation is thus strongly advised prior/during/after chemotherapy. The administration of the prophylactic antibiotic protocol (amoxicillin + metronidazole; 3 + 1.5 g per os/die) in case of oral surgery and/or continous dental surveillance may be arranged in accordance between the dental surgeon and the oncologist, with the best possible evaluation of both oral and systemic conditions. Such cooperation may reduce the occurrence of adverse events which, as we have shown in our review, may result in patient's discomfort, pain and, as reported in one paper, major complications such as mandible fracture.

Further studies are needed on a large number of cases, in order to fully comprehend the relation between new-generation anti-cancer drugs and MRONJ.

References

1. Ruggiero SL, Dodson TB, Fantasia J, et al. American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72:1938-1956.
2. Hohnecker JA. DearDoctor. Precautions Added to the Label of Aredia and Zometa. East Hanover, NJ: Novartis Oncology; 2004:2.
3. United States Food and Drug Administration, Office of Drug Safety: Postmarketing safety review. Bisphosphonates. http://www.fda.gov/ohrms/dockts/ac/05/briefing/20054 095B2_03_04-FDATab3. pdf. Accessed October 09, 2019.
4. Lipton A, Steger GG, Figueroa J, et al. Randomized active controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol. 2007;25:4431-4437.
5. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases.

Qeios ID: 48DL31 · https://doi.org/10.32388/48DL31
in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28:5132-5139.

6. Malan J, Ettinger K, Naumann E, Beirne OR. The relationship of denosumab pharmacology and osteonecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114:671-676.

7. Owosho AA, Blanchard A, Levi L, et al. Osteonecrosis of the jaw in patients treated with denosumab for metastatic tumors to the bone: a series of thirteen patients. J Craniomaxillofac Surg. 2016;44(3):265-270.

8. Fleissig Y, Regev E, Lehman H. Sunitinib related osteonecrosis of jaw: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:e1-e3.

9. Estilo CL, Fornier M, Farooki A, et al. Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol. 2008;26:4037-4038.

10. Nicolatou-Galitis O, Migkou M, Psyrri A, et al. Gingival bleeding and jaw bone necrosis in patients with metastatic renal cell carcinoma receiving sunitinib: report of 2 cases with clinical implications. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:234-238.

11. Kim DW, Jung YS, Park HS, Jung HD. Osteonecrosis of the jaw related to everolimus: a case report. Br J Oral Maxillofac Surg. 2013;51:e302-e304.

12. Owosho AA, Scordo M, Yom SK, et al. Osteonecrosis of the jaw a new complication related to ipilimumab. Oral Oncol. 2015;51:e100-e101.

13. Ponzetti A, Pinta F, Spadi R, et al. Jaw osteonecrosis associated with aflibercept, irinotecan and fluorouracil: attention to oral district. Tumori. 2016;102(suppl.2).

14. Mawardi H, Enzinger P, McCleary N, et al. Osteonecrosis of the jaw associated with zivafibercept. J Gastrointest Oncol. 2016;7:E81-E87.

15. Nicolatou-Galitis O, Galti D, Moschogianni M, et al. Osteonecrosis of the jaw in a patient with acute myeloid leukemia, who received azacitidine. J Cancer Metasta Treat. 2016;2:220-223.

16. Nicolatou-Galitis O, Razis E, Galti D, Vardas E, Tzerbos F, Labropoulos S. Osteonecrosis of the jaw in a patient with chronic myelogenous leukemia receiving imatinib: a case report with clinical implications. Forum Clin Oncol. 2013;4:29-33.

17. Owosho AA, Liang STY, Sax AZ, et al. Medication-related osteonecrosis of the jaw: An update on the memorial sloan kettering cancer center experience and the role of premedication dental evaluation in prevention. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125:440-445.

18. Bennardo F, Buffone C, Giudice A. New therapeutic opportunities for COVID-19 patients with tocilizumab: possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws. Oral Oncol. 2020;106:104659.

19. Guida A, Perri F, Ionna F, Ascierto PA, Grimaldi AM. New-generation anticancer drugs and medication-related osteonecrosis of the jaw (MRONJ): Late onset 3 years after ipilimumab endovenous administration with a possible role of target therapy. Clin Case Rep. 2020 Dec 2;9(1):61-66.

20. Decaux J, Magremanne M. Medication-related osteonecrosis of the jaw related to epacadostat and pembrolizumab. J Stomatol Oral Maxillofac Surg. 2020 Dec;121(6):740-742.

21. Myoken Y, Fujita Y, Kawamoto K, Toratani S. Osteonecrosis of the jaw in a metastatic lung cancer patient with bone metastases undergoing pembrolizumab + denosumab combination therapy: Case report and literature review. Oral
22. Bennardo F, Buffone C, Muraca D, Antonelli A, Giudice A. Medication-Related Osteonecrosis of the Jaw with Spontaneous Hemimaxilla Exfoliation: Report of a Case in Metastatic Renal Cancer Patient under Multidrug Therapy. Case Rep Med. 2020 Oct 22;2020:8093293.

23. Pundole X, Jones AL, Tetzlaff MT, Williams MD, Murphy WA Jr, Otun A, Goepfert RP, Davies MA. Osteonecrosis of the jaw induced by treatment with anti-PD-1 immunotherapy: a case report. Immunotherapy. 2020 Dec;12(17):1213-1219.

24. Chang J, Hakam AE, McCauley LK. Current Understanding of the Pathophysiology of Osteonecrosis of the Jaw. Curr Osteoporos Rep 2018;16:584–95.