Denosumab and Anti-angiogenetic Drug-related Osteonecrosis of the Jaw: An Uncommon but Potentially Severe Disease

STEFANO SIVOLELLA[1], FRANCO LUMACHI[2], EDOARDO STELLINI[1] and LORENZO FAVERO[1]

Departments of [1]Neurosciences, Section of Dentistry and [2]Surgery, Oncology and Gastroenterology, University of Padua, School of Medicine, Padova, Italy

Abstract. *Osteonecrosis of the jaw (ONJ) is a rare but serious lesion of the jaw characterized by exposed necrotic bone and is related to several drugs usually used for treating patients with advanced malignancies. Common therapies inducing ONJ are nitrogen-containing bisphosphonates (BPs), the human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand denosumab and some anti-angiogenic drugs, alone or in combination with BPs. The real incidence of ONJ is unknown. Several cases of ONJ in patients with cancer who underwent denosumab therapy have been reported and it seems that the overall incidence of denosumab-related ONJ is similar to that for BP-related in this population, ranging between 1-2%. The cell-surface vascular endothelial growth factor (VEGF) receptor plays a major role in cancer progression and can be targeted by drugs inhibiting the tyrosine kinase activator or other second messengers. Most angiogenesis inhibitors, such as the monoclonal antibody bevacizumab and the kinase inhibitor sunitinib, target the VEGF signaling pathway. Unfortunately, cases of bevacizumab-induced ONJ have been reported, especially in patients treated with bevacizumab and BPs in combination. There are only few studies reporting sunitinib-related ONJs. In patients with advanced cancer and malignancy-associated hypercalcemia undergoing BP, denosumab or bevacizumab therapy, enquiry into current dental health and dental examination is mandatory. Good oral hygiene, limiting of alcohol intake and stopping smoking should be suggested for all patients requiring such treatments.*

Osteonecrosis of the jaw (ONJ) is typically described as an unresolved periodontal inflammation leading to necrotic bone exposure in the oral cavity (1). Experimental radio-ONJ was first reported in the 1960s and better-described by Zach *et al*. (2, 3). Currently, ONJ may represent a serious problem in patients irradiated for head and neck carcinomas, but may also be an uncommon complication of cancer chemotherapy (4, 5). Other causes of ONJ are local malignancy, periodontal disease, trauma, and long-term glucocorticoid or bisphosphonate (BP) therapy (6). ONJ is a potentially debilitating disease, which occurs in approximately 5% of patients with myeloma or bone metastases from breast cancer (BC) or prostate cancer receiving high-dose intravenous BPs (7). A high incidence of ONJ has also been reported in patients treated with antiangiogenic drugs, such as bevacizumab and sunitinib, alone or in combination with cytostatic therapy or BPs, and the human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) denosumab, which is involved in the activation and survival of osteoclasts (8, 9).

Diagnosis

According to the American Society of Bone and Mineral Research (ASBMR) BP-associated ONJ is defined as an area of exposed necrotic bone in the maxillofacial region for at least eight weeks in a patient with no history of radiation therapy who was receiving or had been exposed to a BP (10). ONJ occurs more frequently in patients receiving intravenously-administered nitrogen-containing BPs, such as alendronate, ibandronate, pamidronate, risedronate and zoledronic acid, for metastatic bone disease (11, 12). Involvement of the maxilla is less common than that of the mandible and in the majority of patients, bacterial or fungal infection is present, with pain, swelling or purulent discharge (13). Other conditions that can present similarly, including lingual mandibular sequestration and ulceration, should be excluded (6). The lesion is often preceded by a dental surgical procedure, but can also occur spontaneously (14). Fulminant course of the ONJ has been reported in isolated patients with severe chronic diseases, such as rheumatoid arthritis (15).

Correspondence to: Dr. Stefano Sivolella, Department of Neurosciences, Section of Dentistry, University of Padua, School of Medicine, Via Giustiniani 2, 35128 Padova, Italy. Tel: +39 0498218669, Fax: +39 0498070364, e-mail: stefano.sivolella@unipd.it

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Imaging studies of ONJ are essential for surgical planning and minimizing biopsies, to begin correct treatment as soon as possible. 18F-Fluorodeoxyglucose (FDG)-positron-emission tomography/computed tomography (CT) imaging better reveals the extension of the disease compared with both CT alone and contrast-enhanced magnetic resonance imaging, while nuclear medicine imaging is useful in recognizing different causes of ONJ (16, 17).

Epidemiology and Pathophysiology

The true incidence of ONJ is unknown. A 2007 literature review reported that fewer than 1% of patients receiving oral BPs for treating osteoporosis develop ONJ (18). In a prospective study only 0.7% of women with advanced BC treated with BPs developed ONJs, while other studies estimated the incidence at 1.2%-2.4% in patients with BC and myeloma, respectively, with a prevalence of 0.1% (19, 20). In patients treated with BPs and bevacizumab together, the estimated incidence seems to be higher, ranging from 2% to 2.4% (21, 22). The suggested risk factors for ONJs developing are BP potency and longer duration of therapy, age over 60 years, pre-existing oral infection and previous invasive dental treatment (13, 22). Local risk factors include extraction, periapical and periodontal surgery, dental implant placement, anatomic conditions (23).

Several potential mechanisms affecting the risk of ONJ have been proposed, including suppression of bone turnover, immune dysfunction and suppressed angiogenesis (24). ONJ is associated with inhibition of bone remodeling, especially of osteoclast activity, and thus ONJ may occur with all osteoclast-inhibiting therapies, including BPs and denosumab (25). BPs have a direct action on bone cells, cause reduction of bone turnover by inhibiting osteoclast-mediated bone resorption and prevent osteoclast apoptosis and osteolysis. Nitrogen-containing BPs inhibit farnesyl diphosphate synthase, an enzyme in the mevalonate pathway which is essential in the post-transitional farnesylation and geranylgeranylation of small GTPase signaling proteins (26). Loss of bone-resorptive activity and osteoclast apoptosis is due primarily to loss of geranylgeranylated small GTPases (27). In addition, nitrogen-containing BPs, especially zoledronate (Figure 1), induce apoptosis of cancer cells from several origins, including myeloma, BC, prostate carcinoma and osteosarcoma cell lines (28, 29). Cytotoxic therapy-induced immunosuppression, secondary to suppression of the bone marrow and hematopoiesis, should be considered a risk factor for ONJ (24). It has been shown experimentally that both BPs and dexamethasone suppress adaptive regulatory T-cells and activate inflammatory T-helper-producing interleukin-17 cells *in vivo*, thus altering the immune

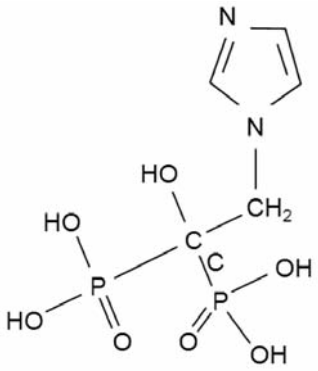

Figure 1. *Chemical structure of zoledronate, a nitrogen-containing bisphosphonate usually given to patients with malignancy-related bone involvement (11).*

system (30). Vitamin D deficiency may increase the risk of BP-related ONJ, but its role is still unclear (31). Data suggest that macrophages may have a central role in allowing the local infection and necrosis, both in BP- and denosumab-related ONJ (32).

Denosumab and Anti-angiogenic drugs

RANKL activates osteoclast precursors and subsequent bone osteolysis, leading to the release of several bone-derived growth factors, including insulin-like growth factor (IGF1) and transforming growth factor-β (TGF-β) (33). The relationship between RANKL, parathyroid hormone-related protein, TGF-β, IGF1, mitogen-activated protein kinase, cancer cells, and bone cells in patients with bone metastasis and malignancy-related hypercalcemia is shown in Figure 2. Denosumab blocks RANKL, mimicking the physiological effects of osteoprotegerin, a tumor necrosis factor family member that prevents differentiation of osteoclasts and promotes their apoptosis, inhibiting bone resorption by depletion of mature osteoclasts (34, 35).

Several cases of ONJ in patients who underwent denosumab therapy have been reported (36, 37). However, a recent review found that the overall incidence of denosumab-related ONJ is similar to that of BP-related ONJ (38). Because the pharmacology of denosumab differs from that of the BPs, denosumab-related ONJ may resolve more rapidly than that related to BPs (39).

Angiogenesis is a critical step in tumor progression and the RANKL system represents the central pathway leading to osteoclast differentiation (35, 40). The cell-surface receptor vascular endothelial growth factor (VEGF) receptor plays a major role in cancer progression and can be targeted by drugs inhibiting tyrosine kinase activator or other second-line messengers, such as extracellular-signal regulated kinases/mitogen-activated protein kinase, and mammalian

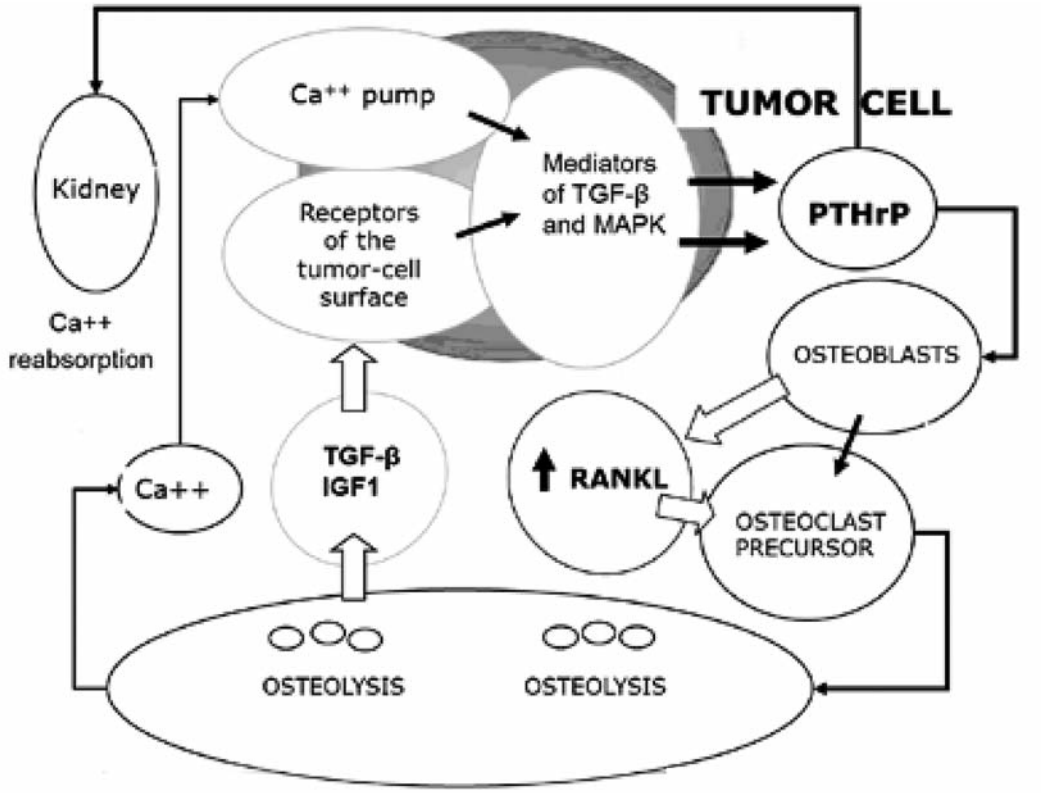

Figure 2. *Relationship between receptor activator of nuclear factor-κB ligand (RANKL) and parathyroid hormone-related protein (PTHrP), transforming growth factor-β (TGF-β), mitogen-activated protein kinase (MAPK), insulin-like growth factor-1 (IGF1), cancer cell and osteoblasts in patients with malignancy-related hypercalcemia. Reproduced, with permission, from (35).*

target of ropamycin (41). Most angiogenesis inhibitors, such as the monoclonal antibody bevacizumab and the kinase inhibitor sunitinib, target the VEGF signaling pathway. Bevacizumab was the first anti-angiogenetic drug approved for clinical use, initially for the treatment of colorectal cancer and currently also for BC and lung cancer (42). It may compromise microvessel integrity, leading to compromise of the osteon at the jaw, and several studies report the risk of ONJ in patients treated with this drug (43-45). A meta-analysis of data from 3,560 patients with advanced BC treated with bevacizumab alone or in combination with BPs showed that the overall incidence of ONJ in this population was 0.2% and 0.9%, respectively (46).

Sunitinib (Figure 3) is a multi-targeted receptor tyrosine kinase (RTK) inhibitor that inhibits cellular signaling by targeting platelet-derived growth factor receptors and VEGF receptors (47, 48). It also inhibits KIT (CD117) and other RTKs, including colony stimulating factor-1 receptor. There are only few studies reporting ONJ in patients treated with sunitinib, and thus the incidence of sunitinib-related ONJ is unknown (49, 50). Cases of ONJ after therapy with BPs and sunitinib together have also been reported (51).

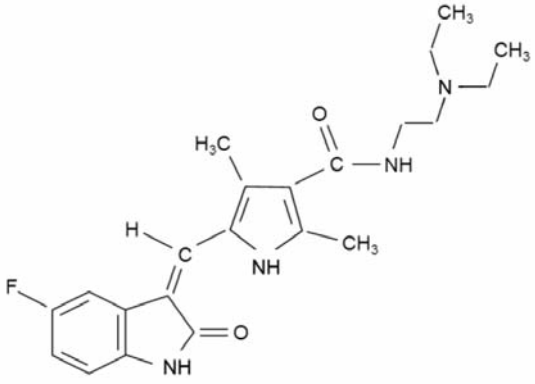

Figure 3. *Chemical structure of sunitinib, a multi-targeted tyrosine kinase inhibitor that blocks vascular endothelial growth factor receptors and platelet-derived growth factor receptors (47).*

Conclusion

ONJ is a rare but serious lesion of the jaw in which there is exposed necrotic bone, due to several drugs usually used in patients with cancer and bone involvement (14). Its etiology

is unknown but preventive dentistry may reduce the prevalence of ONJ, especially in patients receiving BPs or denosumab alone or in combination with antiangiogenic drugs, such as bevacizumab and sunitinib (52). Enquiry into current dental health is mandatory before BP treatment, especially in patients with cancer and the use of BPs must be carefully weighed taking into consideration the severity of malignancy-associated hypercalcemia and other risk factors (53). Good oral hygiene, limiting of alcohol intake and stopping smoking should be requested for all patients requiring such treatment (5). Post-marketing risk-to-benefit studies with these drugs appear warranted, focusing specifically on this rare but potentially disabling disease (37).

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