Osteonecrosis Of The Jaw In A Patient Receiving Cabozantinib.

OSTEONECROSIS OF THE JAW IN A PATIENT RECEIVING CABOZANTINIB

ABSTRACT

Since the discovery of bisphosphonate-related osteonecrosis of the jaw, there has been increasing evidence in recent years of osteonecrosis induced by drugs other than bisphosphonates, mainly agents with antiangiogenic and antiosteoclastic activity. Mandibular osteonecrosis was observed in a 51-year-old woman with medullary thyroid cancer receiving cabozantinib, a new tyrosine kinase inhibitor having antiangiogenic activity. The bone necrosis appeared after a dental extraction. The clinical, radiographic and histologic picture of a chronic nonhealing extraction socket was consistent with drug-induced osteonecrosis of the jaw. Healing was achieved by segmental ostectomy. The osteonecrosis was likely associated with a vascular endothelial growth factor (VEGF) pathway inhibition, implying inhibition of angiogenesis and hampering of the local host defence mechanisms.

Key words: antiangiogenic drugs, cabozantinib, medullary thyroid cancer, osteonecrosis of the jaw, VEGF inhibition.

Running title: Cabozantinib-related osteonecrosis of the jaw.

INTRODUCTION

Osteonecrosis of the jaw (ONJ), presenting as necrotic bone usually associated with a chronic, nonhealing and painful wound, may be the result of radiotherapy, chemotherapy or a complication of osteomyelitis[1]. Oral surgical intervention and oral mucosal breakdown are the main local predisposing factors for ONJ development, which is a unique phenomenon of the jawbones. After the description of bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) in 2003[2, 3], there has been a growing clinical and basic research interest in drug-related ONJ[4], with several issues being suspected of increasing the risk of developing necrosis[5]. Moreover, several drugs other than BP have been claimed to potentially induce osteonecrosis, for example, as a result of antiangiogenic activity. We herewith describe a patient, having been treated with cabozantinib for progressive metastatic medullary thyroid cancer (MTC), who developed osteonecrosis of the mandible with no history of BP treatment.

CASE REPORT

A 51-year-old woman was referred by her dentist for a longstanding, asymptomatic, nonhealing socket in the left mandible 3 months after a dental extraction due to deep caries. The oral administration of amoxicillin clavulanate and the use of a 0.2% chlorhexidine mouthwash resulted in no improvement. Fourteen years before, the patient had been diagnosed with medullary thyroid cancer and she had undergone thyroidectomy (pT4aN1), followed by adjuvant chemotherapy (5-fluorouracil and dacarbazine). Four years later, she developed locoregional recurrences. Therefore, she again underwent surgery followed by adjuvant radiation therapy (55 Gy, with an irradiation field not involving the mandibular alveolar bone). Nevertheless, control of the disease was not achieved: 3 years later, metastases appeared first in the liver (segment VII) and then in the axillary and abdominal lymph nodes. Thirteen years after the onset of the oncological disease, the patient entered a double-blind, phase III trial testing the effectiveness of orally administered cabozantinib (175 mg per day)[6]; during treatment she suffered such adverse effects as diarrhoea, hand–foot syndrome and fatigue. At the time of the extraction, she was being treated with levothyroxine, calcitriol, vitamin D3, duloxetin, propranolol, lansoprazole and loperamide. She had never been treated with BPs.

Three months after the initial intake of cabozantinib, the mandibular left first molar was extracted because of deep caries but, as previously described, no healing of the socket was achieved. Intraoral examination revealed local signs of inflammation and infection, with slight purulent exudation (Figure 1A).

On admission, an orthopantomogram was performed, revealing incomplete bone remodelling of the mandibular left first molar socket (Figure 2). Further assessment by CT scan showed irregularity of the alveolar cortical margin and a sclerotic reaction (Figure 3). These signs were consistent with bone necrosis. Cabozantinib was not discontinued, nor were other prescriptions changed. Surgical debridement of the socket and antibiotic therapy did not achieve clinical improvement; therefore, a segmental ostectomy was performed along with the extracting the mandibular left second molar and maintaining the antibiotic and antiseptic therapy (oral amoxicillin clavulanate and chlorhexidine 0.2% mouthwash) until mucosal healing had been achieved. Histological assessment of the specimen confirmed the presence of atypical bone necrosis. At the 4-year follow-up, the patient remains free of lesions and symptoms (Figure 1B).

DISCUSSION

MTC is a rare malignancy originating from calcitonin-producing parafollicular C cells of the thyroid[7]. MTC constitutes 4% of all thyroid cancers, with an incidence of 0.1/100,000 in the US. If MTC is confined to the thyroid gland, surgical therapy leads to complete remission in 75%–90% of cases; such ratio lowers to 20%–30% in the presence of nodal involvement or distant metastases. The 10-year mortality rate is 30%–40%. The onset of MTC is almost always a result of a mutation or rearrangement of the proto-oncogene RET[8], which encodes a membrane tyrosine-kinase (TK) which, in turn, behaves as a receptor for growth factors. In addition to RET, the hepatocyte growth factor receptor MET and vascular endothelial growth factor receptor 2 (VEGFR2) signalling pathways can**[AU: does this edit preserve your meaning?]** be upregulated; they have been

implicated in the pathogenesis of MTC through promotion of proinvasive and proangiogenic phenotypes[9]. RET, MET and VEGFRs are oncogenes that encode tyrosine kinases and play an important role in cell growth and angiogenesis[9]. Cytotoxic chemotherapy or radiotherapy have limited, transient activity in patients with unresectable or metastatic MTC[10]. Cabozantinib is an orally bioavailable TK inhibitor with activity against MET and VEGF[11], recently approved in the United States for the treatment of progressive MTC[6, 12]. Phase I studies demonstrated that cabozantinib inhibits TK receptors, thus inhibiting cellular growth and angiogenesis. In the double-blind, phase III trial, cabozantinib (140 mg/day) achieved a statistically significant improvement of progression-free survival in patients with progressive metastatic MTC, and it represents an important new treatment option for patients with this rare disease[7, 10, 11].

BPs have been reported as mainly responsible for ONJ, because of their combined effects on bone remodelling and angiogenesis. Nevertheless, only 5 years after the first papers describing BRONJ were published, several reports started to highlight the development of ONJ in patients treated with angiogenesis inhibitor alone, without any BP[13]. For the past 5 years there has been growing evidence of bone necrosis occurring in patients recently treated with agents having antiangiogenic and antiosteoclastic activity[14], so that use of the terms “drug-related osteonecrosis of the jaws[15]” or “medication-related osteonecrosis of the jaw (MRONJ)[1]” have been suggested. In the present case, the patient was taking several drugs at time of the extraction that were not likely to act negatively on bone turnover (Table 1). Calcitriol and vitamin D could

adversely[**AU: does this edit preserve your meaning?]** act on osteoblasts, causing them to release receptor activator of nuclear factor kappa-B ligand, which in turn activates osteoclasts. Neither of the drugs administered during the previous course of chemotherapy had long-term side effects on bone metabolism.

Ten years before the extraction, the patient underwent radiation therapy, but the irradiation field involved only a scatter dose to the mandibular alveolar bone that did not exceed 15 Gy, while loss of osteocyte vitality can be found in doses exceeding 30–35 Gy. Therefore, in the present case, given the long period elapsed and the low dose, the effect of radiation therapy can be considered negligible. Even if the pathogenesis of bone necrosis remains poorly understood, several mechanisms have been suggested for BRONJ: cessation of bone turnover by the osteoclast-inhibiting effect of BP, inhibition of capillary neoangiogenesis, direct toxicity on soft tissues and impaired immune reactions. Cabozantinib has no recognised role in inhibiting osteoclasts. So in this case, the onset of osteonecrosis is likely associated with the VEGF pathway inhibition, implying inhibition of angiogenesis with hampering effects on wound healing and possibly bone remodelling. Moreover, given the role of VEGF in monocyte/macrophage differentiation and chemotaxis, cabozantinib could also hamper the local host defence mechanisms[13].

The patient described in the present report participated in the clinical trial, which reported several cabozantinib-related adverse effects associated with the VEGF pathway inhibition, mainly hypertension and haemorrhage[6]. Nevertheless, there were three cases of osteonecrosis reported for the same trial, corresponding to 1.4% of patients taking cabozantinib[6]. These data are consistent with other reports highlighting

the important role of antiangiogenic drugs that act directly on VEGF (e.g., bevacizumab) in predisposing patients to ONJ, regardless of their association with BPs[13, 14, 16]. Such growing evidence for the role of antiangiogenic drugs as predisposing factors of ONJ and the lack of reliable markers to identify susceptible hosts supports the need for oncologists and dentists to be aware of the potential for developing ONJ. Even if further investigation is needed to determine the relationship of ONJ to antiangiogenic drugs, this growing evidence suggests the need for close monitoring of oral health and to be aware of the possibility that patients undergoing cancer chemotherapy with antiangiogenic drugs are at risk of acquiring BP-related ONJ**.[AU: Editing OK?]** When the present patient was treated with cabozantinib, bone necrosis was not a recognised adverse effect, so that drug administration was not ceased. Nevertheless, the ostectomy that followed brought healing. Evidence on the effectiveness of a drug holiday are sparse. The present case is part of the current debate on the need for drug discontinuance in the presence of MRONJ and, even within the intrinsic limitations of a case report, this information could be useful in adding knowledge to the issue. Moreover, it might be useful to point out that antiangiogenic agents are more likely to represent a temporary and reversible predisposing factor, are more closely related to drug assumption and are potentially more easily managed by clinicians than are BPs.

Given the emerging evidence on the possible role of antineoplastic drugs on the jaw bone, dentists need to be fully aware of all the drugs that patients are taking, with specific reference to antiresorptive and antiangiogenic agents.

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TABLE

Table 1. Action and side effects of drugs assumed during previous course of chemotherapy and at time of dental extraction

Drug	Action	Side effects during use	Long term side effects
Fluorouracil	antimetabolite	nausea, vomiting, diarrhoea, mucositis, headache, myelosuppression, alopecia, photosensitivity, hand–foot syndrome, maculopapular eruption, itch, cardiotoxicity, persistent hiccups, mood disorders	Not reported
Dacarbazine	alkylating agent	haematopoietic depression, anorexia, nausea, vomiting,	Not reported
Levothyroxine	synthetic thyroid hormone	effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism (narrow therapeutic index)	cardiac side-effects and decreases in bone mineral density (due to long-term suppression of TSH values)
Calcitriol	hormonally active metabolite of vitamin D	hypercalcaemia	Not reported
Duloxetin	serotonin-norepinephrine reuptake inhibitor	nausea, somnolence, insomnia, dizziness,), dry mouth, headache, sexual dysfunction	Not reported

Propranolol	sympatholytic nonselective beta blocker	nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, alopecia, abnormal vision, hallucinations, insomnia, nightmares, sexual dysfunction	Not reported
Lansoprazole	proton-pump inhibitor	dry mouth, insomnia, drowsiness, blurred vision, rash, pruritus	Not reported
Loperamide	opioid-receptor agonist	constipation, dizziness, nausea, abdominal cramps	Not reported

FIGURE CAPTIONS

Figure 1: left lower gingiva showing slight pus exudation in the site of dental extraction (A) and healing after segmental ostectomy (B)

Figure 2: orthopantomogram revealing incomplete bone remodelling of the left lower first molar socket

Figure 3: computed tomography scan showing irregularity of the alveolar cortical margin and sclerotic reaction