LETTER

# Oral Osteonecrosis Associated with the Use of Zoledronic Acid: First Case of a Patient with Advanced Pancreatic Cancer and Bone Metastases

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Dear Sir:

while traditionally associated with radiation therapy for head and neck cancer, osteonecrosis of the jaw has recently been described mainly in breast cancer and multiple myeloma patients undergoing long-term intravenous bisphosphonate treatment [1, 2, 3, 4, 5, 6, 7, 8, 9, 10,11, 12, 13, 14, 15]. Bisphosphonates are used to treat bone metastases, as they decrease bone resorption, primarily through their apoptotic effects on osteoclasts [16]. Studies indicate that zoledronic acid is the most potent bisphosphonate [17]. While there has been some variation in the reported frequency of osteonecrosis of the jaw development in patients treated with i.v. bisphosphonate, a recent large retrospective analysis by Hoff *et al*. reported that 0.72% of these patients ultimately developed osteonecrosis of the jaw [18]. This study also identified several risk factors associated with the development of osteonecrosis of the jaw, including high cumulative doses of bisphosphonates, poor oral health and dental extractions [18]. The high incidence of osteonecrosis of the jaw in patients with breast cancer and multiple myeloma was explained by the significantly higher cumulative dose and significantly longer duration of treatment that these patients receive, compared to patients with other malignancies [18]. A separate smaller analysis of osteonecrosis of the jaw in multiple myeloma patients identified the number of zoledronic acid infusions as the most important risk factor [19].
There has been no report of osteonecrosis of the jaw development in a patient with pancreatic cancer. Given that level of exposure to zoledronic acid has been identified as a significant risk factor, it is probable that the severity of pancreatic adenocarcinoma and the associated shorter duration of survival have prevented these patients from accumulating the required zoledronic acid exposure.

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## Case Report

A 51-year-old Caucasian was diagnosed with Stage III pancreatic adenocarcinoma. He was initially treated on a clinical study with a novel taxane, Genexol-PM® [20]. After 12 cycles (approximately 9 months) on the Genexol-PM® therapy, restaging CT scan suggested new bone metastases. A bone scan was performed which revealed several bone metastases and the regimen was discontinued. The patient was begun on gemcitabine 1,000 mg/m$^2$ weekly for 2 out of 3 weeks, plus oral erlotinib 100 mg/day. Additionally, due to the presence of bone metastases, he was started on zoledronic acid, 4 mg i.v. monthly.
After 17 cycles (approximately 13 months) of gemcitabine plus erlotinib, with monthly zoledronic acid infusions, the patient developed signs of jaw necrosis including severe jaw pain, inflammation, loosening teeth and some numbness of the jaw. The patient had no signs of mucositis associated with the chemotherapy. He was diagnosed with osteonecrosis of the jaw by his orthodontist based on clinical and radiological findings (Figure 1). Treatment with zoledronic acid was discontinued at that point.

## Discussion

With more therapeutic options available, some patients with pancreatic adenocarcinoma are living longer and uncommon sites of metastases, such as bones are found in these patients, and like in our patient, might receive greater cumulative doses of zoledronic acid. As the duration and level of exposure to zoledronic acid have been established as important risk factors for the development of osteonecrosis of the jaw, this exciting increase in longevity in our pancreatic adenocarcinoma

patient, we believe is associated with hitherto unseen side effects of treatment. As this case illustrates, oncologists dealing with pancreatic cancer patients who are being treated with i.v. bisphosphonates should bear in the mind the possibility of osteonecrosis of the jaw development. As studies have highlighted the role of good oral hygiene and regular visits to dental health care professionals in the prevention and management of osteonecrosis of the jaw, it is apparent that there is a need to refer these patients for a baseline dental evaluation and to involve dental health professionals in their future care.

In addition to the duration and degree of exposure to bisphosphonates, the use of corticosteroids and chemotherapy may also play a role in the development of osteonecrosis of the jaw [6, 21, 22, 23, 24]. Many patients who develop osteonecrosis have been additionally exposed to these drug regimes, making it difficult to tease out the principle contributing factor to the development of osteonecrosis of the jaw [6]. Further studies are necessary to determine the degree to which chemotherapeutic agents and corticosteroid use contributes to the development of bisphosphonate-induced osteonecrosis of the jaw.

In many cases a plain dental X-ray can help to diagnose osteonecrosis (Figure 1). Histology is often necessary to distinguish osteonecrosis from neoplastic osteolysis, while a biopsy can contribute to bone damage. In order to avoid invasive procedures, functional imaging by a tracer such as $Tc^{99m}$-sestamibi, when combed to non-tumor specific substances such as FDG-PET, can support the diagnosis of osteonecrosis [25].

Another scintillating part of this issue is that bisphosphonates, which constitute a widely used class of drugs for the treatment of metabolic bone disorders, including tumor-associated bone disease, are also capable of inhibiting p21ras signaling. Third-generation, nitrogen-containing bisphosphonates, such as zoledronic acid, inhibit farnesyldiphosphate synthase, an enzyme involved in the mevalonate pathway, preventing post-translational events of prenylation of small GTP-binding proteins such as p21ras, rab, rho, rac and cdc42, which are required for a variety of biologic functions including signal transduction and cell adhesion. Recent reports have also shown that these compounds induce anti-proliferative and apoptotic effects in multiple myeloma cells *in vitro*, may synergize with chemotherapeutic or biologic agents, and may offer clinical benefits.

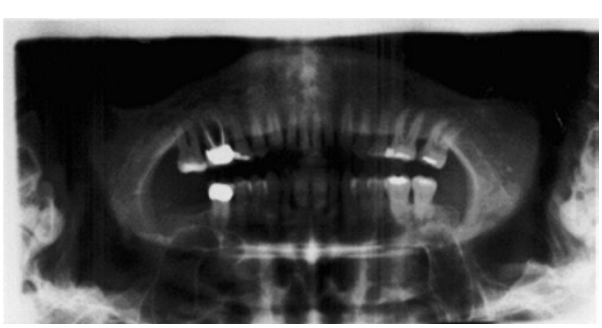

**Figure 1.** Radiological findings of oral osteonecrosis in our patient following zoledronic acid.

Based on preclinical studies, a phase II trial of gemcitabine plus zoledronic acid was conducted in 35 patients with stage i.v. cancer of the pancreas [26]. The patients received gemcitabine 1,000 $mg/m^2$ intravenously on days 1, 8, 15, and 22 in cycle 1 and days 1, 8, and 15 in subsequent cycles. Zoledronic acid 4 mg was given intravenously on day 1 every 4 weeks. To date, there has been 1 partial response. Grade 3 and 4 treatment-related toxicities included: neutropenia (24%); thrombocytopenia, leukopenia, and fatigue (14% each); anemia, nausea, and diarrhea (9.5% each); and vomiting and dehydration (5% each). The combination of zoledronic acid with gemcitabine was well-tolerated. Future genomic testing is proposed for responders.

**Conflict of interest** The authors have no potential conflicts of interest

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