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Cancer

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Cardiovascular Diseases

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Case Report

Life threatening bleeding from an osteonecrosis of the jaw: Are bisphosphonates safe in irradiated head and neck cancer patients?

Tarek Assi1,2, Ralph Chebib2, Sara Lakiss2, Joseph Kattan2

1Gustave Roussy, Université Paris–Saclay, Département de Medecine Oncologique, France
2Hotel Dieu de France University Hospital, Department of Medical Oncology, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

Abstract
Osteonecrosis of the jaw is a significant complication secondary to radiation therapy or drug therapy, most commonly bisphosphonates. Safety data regarding the administration of bisphosphonates in bone metastatic head and neck cancer patients with history of jaw irradiation are almost non-existent. In this paper, we report the case of a Head and Neck (HNC) patient, with history of radiation therapy to the mandible region, treated with intravenous bisphosphonates for bone metastases that resulted in gross, life threatening mouth hemorrhage secondary to advanced, locally invasive ONJ.

Keywords: osteoradionecrosis; osteonecrosis of the jaw; bisphosphonates; head and neck cancer; radiotherapy.

Introduction
Bisphosphonates are one of the most prescribed drugs in cancer patients with bone metastases to reduce the skeletal–related events (1). However, a subset of patients develop a significant complication of these drugs with deep repercussions called “osteonecrosis of the jaw” (2). Medication–related osteonecrosis of the jaw (MRONJ) is the new term recommended by the American Association of Oral and Maxillofacial Surgeons (AAOMS) to describe patients with ONJ related to drugs. More recently, the list of incriminated drugs has been growing with the recent addition of the anti-resorptive agents such as Denosumab or antiangiogenic agents (bevacizumab, sunitinib or everolimus) to the family of bisphosphonates(2,3). Patients treated with intravenous bisphosphonates have an increased risk of ONJ ranging from 0.2 – 12% (4). Nevertheless, this risk may be increased in head and neck cancer (HNC) patients who are at grave risks of developing severe ONJ, especially with the local side effects of radiotherapy that remains one of the main pillars in this type of tumors (5).

Osteoradionecrosis (ORN) is one of the most feared and chronic complications of conventional radiotherapy to the head and neck region, with incidence rates ranging from 2 to 22% (5). The most recent and sophisticated techniques such as intensity–modulated radiation therapy (IMRT) have been associated with a reduced risk of ORN (5.1%) (6). Data concerning the safety of the use of bisphosphonates in previously irradiated mandible region are lacking in the literature despite the risk of occurrence of devastating, life threatening complications. In this paper, we report the case of a HNC patient, with history of radiation therapy to the mandible region, treated with intravenous bisphosphonates for bone metastases that resulted in gross, life threatening mouth hemorrhage secondary to advanced, locally invasive ONJ.

Case presentation
A 70–year–old heavy smoker male was successfully treated with concurrent chemoradiotherapy in 2009 for a locally advanced, moderately differentiated squamous cell carcinoma of the right tonsil. The treatment plan consisted of radiotherapy (66 Gy in 33 sessions) given concurrently with weekly Cetuximab. He remained in complete remission until July 2013, when he sought medical care for diffuse bone pain that revealed multiple bone metastases in the pelvis and lumbar spine of squamous cell type. The search for the primary tumor did not reveal any metachronous tumors in the lung and head and neck region based on the carcinogenesis field. The metastatic bone spread was considered to be secondary to an unusual late relapse of his primary squamous cell tumor of the tonsil. Chemotherapy including...
capecitabine, carboplatin, cetuximab and zoledronic acid followed by maintenance therapy (Cetuximab and zoledronic acid) was initiated resulting in a transient clinical benefit lasting for one year. In June 2014, salvage therapy based on molecular intelligence profiling was initiated with docetaxel, carboplatin and cetuximab. Zoledronic acid was stopped due to renal insufficiency. The patient demonstrated clinical benefit with complete disappearance of the bone pain as well as signs of bone healing and remodeling on pelvic MRI.

In August 2015, more than a year after the start of the second line therapy, the patient started complaining from a right gingival pain few days after performing a “prohibited” dental extraction. A limited area of osteonecrosis of the jaw at the level of the second molar was detected and conservative measures with antibiotics and adapted oral hygiene were established (Figure 1). One week later, and one year after the last zoledronic acid cycle, the patient presented to the emergency room with extensive hemoptysis, severe hypotension and hypovolemic shock. No deep bleeding or coagulation abnormalities were detected. Radiological and clinical investigation has led to the discovery of an ulcerated lesion in his left lower jaw secondary to an extensive bone and vascular erosion in the previous ONJ region. Embolization of the facial artery successfully controlled the bleeding in the oral cavity after failure of local measures (Figure 2). Unfortunately, further liver and bone progression were detected after the procedure and the patient succumbed to his disease two months later.

**Discussion**

The definite etiology of ONJ in HNC patients is often multifactorial. In this current case with an unusual presentation of ONJ, the patient had a history of irradiation before receiving bisphosphonates, thus contributing to an amplified risk of weakening the osseous component of the mandible. Severe, life-threatening bleeding of the oral cavity secondary to facial artery invasion was never reported in the literature before. Nevertheless, this constitutes a serious matter with heavy consequences because the safety of the zoledronic acid administration in metastatic HNC patients with a history of radiation therapy was rarely addressed.

The definition of MRONJ was updated in 2014 and clearly stated the need for the absence of history of radiation therapy to the jaws in order to prevent diagnostic confusions between MRONJ and ORN (2). The previously reported ORN and MRONJ incidences vary widely between the different studies which could be explained by differences in diagnostic criteria, genetic factors, dental status and patient compliance (2). The underlying pathophysiology of MRONJ is not yet clear with many proposed hypothesis; however, it should always be considered a multifactorial entity. Many studies assessed the systemic and local factors predisposing to MRONJ. Incriminated systemic factors were diabetes, smoking, alcohol and an ongoing immunosuppressive therapy while the involved local factors were trauma, overall poor dental health, bony exostosis and dental procedures (3).

**Table 3.** Literature data on laparoscopic surgical biopsies and their conversion rate in pediatric abdominal malignancy

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**Figure 2.** A) Arterial catheterization showing a false aneurysm within the left facial artery. B) Permeability of the left facial artery after embolization.
ORN usually develops after radiation doses of more than 60 Gy between 4 and 24 months after the start of radiation therapy, but the risk may persist beyond several years \(^7\). Potential risk factors for ORN were history of bone surgery and oral cavity tumors while other studies incriminated dentition status, sex, trauma and RT technique (dose and fractionation) \(^8\). The presented data reflects the ambiguity in definition of both entities and the confusion in the diagnosis when patients receive both bisphosphonates and radiation therapy. Our patient had received radiation therapy with doses higher than 60 Gy, 6 years prior to this complication which was precipitated by dental extraction while on bisphosphonates; all these factors have contributed to the rapid and aggressive ONJ with local destructive manifestations.

Both ORJ and MRONJ can remain asymptomatic for prolonged periods; however, symptoms linked to the local inflammation can arise such as pain, ulceration, paresthesia and anesthesia. Advanced stages, most commonly described in patients with ORN of the jaw, may be associated with pathological bone fractures of the mandible and intra—or extra—oral fistulae often leading to life threatening complications \(^9\). Vascular damage or bleeding complications secondary to ONJ were never reported before. Distinction between the two entities will always remain challenging and patient history with the clinical examination will remain the most sensitive diagnostic tools \(^9\). Available data on the safe use of both modalities in the same patient are almost non—existent. Multiple studies have evaluated the combination of Zoledronic acid to radiation therapy and demonstrated improved anti—resorptive characteristics with synergistic effect between the two therapies in myeloma and prostate cell lines. Also, Zoledronic acid in association to irradiation successfully increased the cytotoxic activity in oral squamous cell carcinoma cell cultures with reduction in the cell migration capacity \(^10\). In fact, this increased cytotoxic activity may be translated into an increased risk of toxicity, and maybe more severe consequences of ONJ.

Finally, the main purpose of this report is to increase the awareness of physicians dealing with these psychologically and physically delicate patients on the potential life threatening vascular and neurological complications of ONJ. In fact, dental preventive measures are most important than the actual treatment of ONJ which include oral hygiene, regular clinical exam, caries control and dental prophylaxis. It is advised that the tooth extraction must be performed at a minimum of 14 to 21 days before start of bisphosphonates or radiation therapy. In this era of personalized medicine, genetic and predisposing factors must be identified to allow better selection of patients at increased risk of developing ONJ. Both retrospective and prospective data can be significantly relevant in generating responses concerning the safety issues raised on the use of bisphosphonates in previously irradiated HNC patients.

**References**


