

Osteonecrosis of the jaw related to everolimus and bisphosphonate: a unique case report?



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Osteonecrosis of the jaw (ONJ) is a rare but serious lesion of the jaw, characterized mainly by exposed necrotic bone; it is related to various drugs, usually used for treating patients with advanced malignancies. Drugs implicated in ONJ are: nitrogen-containing bisphosphonates (NBPs), denosumab, anti-angiogenic drugs (e.g bevacizumab, sunitinib, sorafenib) and the selective mammalian target of rapamycin mTOR, everolimus. Previous data regarding the combining of NBPs with antiangiogenic agents conflict with some reports (indicating a similar risk of ONJ compared with the use of NBPs alone¹); other reports show significantly higher rates (18% vs 1% with NBPs alone) of the incidence of ONJ². The mTOR is a serine/threonine kinase, a component of a complex signaling pathway, involved in cell growth and metabolism, reducing VEGF levels and inhibiting the growth and proliferation of tumor cells, endothelial

cells, fibroblasts and blood vessels. Everolimus has been approved for the treatment of advanced breast cancer, neuroendocrine tumors of pancreatic origin (pNET), and advanced renal cell carcinoma (RCC)³.

This case report may help to explain the temporal relationship between therapy and the occurrence of ONJ with the sequential use of NBPs and mTOR.

A 64-year-old male patient underwent a left, radical nephrectomy in 1992 for clear-cell renal carcinoma. In July 2010 he developed a bone metastasis and he was treated with zoledronic acid 4 mg IV every 4 weeks between 7 July 2010 and 17 August 2012. In February 2011 he had another recurrence, a lung metastasis treated with lobectomy and everolimus 10 mg/die for 6 months from 11 April 2011 to 31 October 2012. In 13 October 2012 the patient showed a facial enlargement and oral fistula in the first quadrant with no history of tooth extraction. A bone scan revealed an ill-defined radiolucency and an orosinus communication. In January 2013 the patient underwent a right and partial left maxillectomy and is currently being followed up to minimize the risk of new adverse reactions.

References

1. Guarneri V, et al. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Res Treat* 2010; 122(1): 181-8.
 2. Christodoulou C, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. *Oncology* 2009; 76(3): 209-11.
 3. Lebowitz D, et al. Development of everolimus, a novel oral mTOR inhibitor, across a spectrum of diseases. *Ann N Y Acad Sci* 2013.
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