

CORRESPONDENCE

Regorafenib Also Can Cause Osteonecrosis of the Jaw

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Osteonecrosis of the jaws (ONJ) is a rare but serious complication that has emerged recently in patients treated with bisphosphonates for bone metastases. The first case of bisphosphonate-related ONJ was reported in 2003 (1). The incidence rates of bisphosphonate-induced ONJ ranged from 0% to 27.5%, with a mean incidence of 7% (2).

Recently, several case reports described the association between ONJ and denosumab, an antireceptor activator of nuclear factor kappa-B ligand monoclonal antibody approved for the prevention of skeletal-related events.

In November 2010, the European Medicine Agency issued safety alert about ONJ risk during sunitinib or bevacizumab treatment (3). This risk becomes amplified if the drug is added to bisphosphonate.

The pathogenesis of ONJ in patients treated with anti-angiogenic drugs is still not completely elucidated; a soft tissue involvement through mucositis, stomatitis, and gingival inflammation added to a decreased angiogenesis caused by these therapies seems to impair host defenses to infection and increases the ONJ risk (4).

Regorafenib is a small-molecule multikinase inhibitor with an anti-angiogenic activity due to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition. It is indicated for the treatment of patients with refractory metastatic colorectal cancer and advanced gastrointestinal stromal tumors (GIST) after progression to imatinib and sunitinib.

In our hospital, we followed a woman age 59 years with heavily pretreated metastatic colorectal cancer who presented a necrotic bone exposed to the oral environment in the upper jaw with pain and soft tissue inflammation after 22 months of regorafenib treatment (160 mg orally once daily 3 weeks on and 1 week off). The lesion persisted for up to eight weeks, and using the criteria of bisphosphonate-related ONJ (exposed bone for 6–8 weeks in absence of radiation to head and neck) (5), a clinical diagnosis of ONJ was made. A CT scan of maxillofacial region showed two clear necrotic bone areas extending beyond the alveolar bone area (Figure 1) to maxillary sinus, and so, according to ESMO guidelines, the

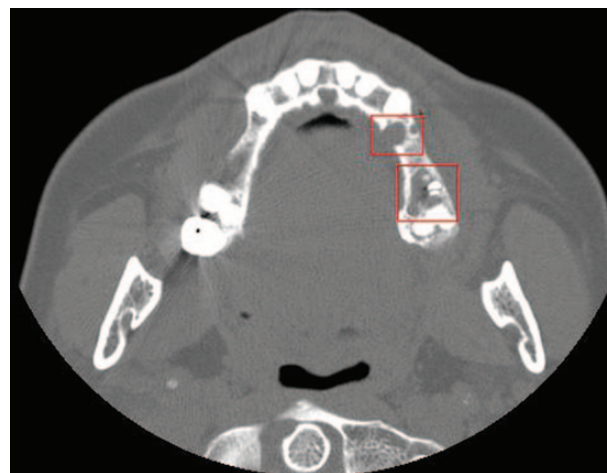


Figure 1. CT scan of maxillofacial region: two areas of osteolysis (6 mm and 11 mm) with interruption of the cortical bone of the left jaw.

stage of ONJ was III (5). The patient didn't receive bisphosphonate anytime.

To the best of our knowledge, this is the first report describing ONJ in patients treated with regorafenib. We would like to alert the scientific community that even regorafenib could cause ONJ.

The increasing number of patients being treated with anti-angiogenic agents underlines also the need for oral screening before treatment with these drugs, and further trials should investigate ONJ-preventive protocols similar to those already existing for patients treated with bisphosphonates.

References

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