The Role of Antiangiogenic Therapy in the Development of Osteonecrosis of the Jaw

John E. Fantasia, DDS

KEYWORDS

• Antiangiogenic therapy • Vascular endothelial growth factor inhibitors • Tyrosine kinase inhibitors
• Mammalian target of rapamycin inhibitors • Nitrogen-containing bisphosphonates
• Receptor activator of nuclear factor-κB ligand inhibitors • Denosumab

KEY POINTS

- Osteonecrosis of the jaw (ONJ) has been linked to the use of various nitrogen-containing bisphosphonates and denosumab.
- Drugs that suppress angiogenesis also play a role in ONJ.
- Patients receiving antiresorptive medications and a medication with antiangiogenic properties are likely at increased risk for ONJ.
- Drugs with antiangiogenic properties include a monoclonal inhibitor of angiogenesis, and certain tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and immunomodulatory agents.

INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) has primarily been associated with antiresorptive medications, specifically nitrogen-containing bisphosphonates (nBP) and the monoclonal inhibitor of the receptor activator of nuclear factor-κB ligand (denosumab). The pathogenesis of osteonecrosis of the jaw (ONJ) is likely multifactorial although impaired bone resorption certainly plays a crucial role, and the vasculature may also play a key role in the pathophysiology.[1] For review, the nBPs include alendronate (Fosamax), risedronate (Actonel, Atelvia), ibandronate (Boniva), pamidronate (Aredia), and zoledronic acid (ZA) (Zometa, Reclast). Denosumab is marketed as Prolia, for osteoporosis; and Xgeva, for prevention of skeletal-related events in patients with bone metastasis from solid tumors. The standard dosing of denosumab (Prolia) for osteoporosis is 60 mg subcutaneous injection every 6 months. The standard dosing of denosumab (Xgeva) for bone metastasis from solid tumors is 120 mg subcutaneous injection every 4 weeks. Recent studies have noted that angiogenesis suppression may play a role in developing ONJ and that serum vascular endothelial growth factor (VEGF) levels may be a predictive marker of ONJ.[2] Both nBPs and denosumab block bone destruction because they inhibit osteoclast-mediated bone resorption. nBPs are also known to inhibit angiogenesis.[3] To date, denosumab has not demonstrated antiangiogenic activity.[4] The development of MRONJ associated with bisphosphonates and denosumab exposure has been well documented.[5–7] In patients with certain cancers, nBP or denosumab is frequently used in

Division of Oral and Maxillofacial Pathology, Department of Dental Medicine, Hofstra North Shore-LIJ School of Medicine, 270-05 76th Avenue, New Hyde Park, NY 11040, USA
E-mail address: fantasia@lij.edu

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combination with medications that have antiangiogenic properties. Many traditional chemotherapeutic agents have antiangiogenic properties.[8] Data are emerging to show that either nBPs or denosumab in combination with targeted antiangiogenic therapies increases the likelihood of MRONJ.[9]

The past decade has seen increasing use of molecular targeted therapies for cancer and other disease processes. Angiogenesis is a rational target for therapy, as tumor growth and metastasis depends on neovascularization. These medications include use of the VEGF-specific antibody (bevacizumab) in combination with chemotherapy. Moreover, tyrosine kinase inhibitors (TKIs) that block the VEGF receptor and other kinases in both endothelial cells and cancer cells have yielded survival benefit in patients with some forms of cancer.[10] Examples of TKIs include sunitinib (Sutent) and sorafenib (Nexavar). There are isolated case reports and cohort studies suggesting an increased risk of ONJ occurring in patients treated with medications used in the treatment of various cancers and conditions that are antiangiogenic or targets of the VEGF pathway. Other classes of cancer drugs can have antiangiogenic properties. The mammalian target of rapamycin (mTOR) inhibitor everolimus has antiangiogenic properties distinct from a VEGF-receptor TKI.[11] Immunomodulatory agents such as thalidomide, which has been used in the treatment of multiple myeloma, also have antiangiogenic properties.[12] Most patients with cancer receive a variety of antineoplastic medications, and cancers with primary skeletal involvement, such as multiple myeloma, and other cancers with skeletal metastasis are treated with antiresorptive medications. This treatment complicates identification of the causative agent or agents responsible for osteonecrosis. There are evolving data to suggest an increased incidence of MRONJ and worsening of the condition in patients who are receiving an antiresorptive and a medication that also influences angiogenesis.[13] Prospective data are needed to help define whether the incidence of osteonecrosis is the same, additive, or synergistic when antiresorptive agents are used in combination with medications with antiangiogenic properties (**Table 1**).

MEDICATION-RELATED OSTEONECROSIS OF THE JAWS IN PATIENTS RECEIVING THE VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITOR BEVACIZUMAB, WITH AND WITHOUT ANTIRESORPTIVE EXPOSURE

Bevacizumab binds VEGF, and prevents the interaction of VEGF to its receptors on the surface of

Table 1
Medications, generic and proprietary names, used in the treatment of various cancers and conditions that are antiangiogenic or targets of the vascular endothelial growth factor pathway

Generic	Brand Name in USA	Form	Indications for Use
Monoclonal Antibody Inhibitor of Angiogenesis			
Bevacizumab	Avastin	IV infusion	mCRC, NSCLC, Glio, mRCC
Tyrosine Kinase Inhibitors (TKIs)			
Sunitinib	Sutent	Capsule	GIST, RCC, pNET
Sorafenib	Nexavar	Tablet	HCC, RCC
Panzopanib	Votrient	Tablet	RCC, STS
Axitinib	Inlyta	Tablet	RCC
Mammalian Target of Rapamycin (mTOR) Pathway Inhibitors			
Everolimus	Afinitor	Tablet	HR+BC, pNET, RCC, TSC, SEGA
Temsirolimus	Toriseliv	Infusion	RCC
Sirolimus	Rapamune	Tablet	Organ rejection in renal transplant
Immunomodulatory Agents			
Thalidomide	Thalomid	Capsule	MM, ENL
Lenalidomide	Revlimid	Capsule	MM, MDS, MCL
Pomalidomide	Pomalyst	Capsule	MM

Abbreviations: ENL, erythema nodosum leprosum; GIST, gastrointestinal stromal tumor; Glio, glioblastoma; HCC, hepatocellular carcinoma; HR+BC, hormone receptor–positive breast carcinoma; IV, intravenous; MCL, mantle cell lymphoma; mCRC, metastatic colorectal carcinoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; mRCC, metastatic renal cell carcinoma; NSCLC, nonsquamous non–small cell lung carcinoma; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; STS, soft tissue sarcoma; TSC, tuberous sclerosis complex.