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Complications of Treatment

Drug induced osteonecrosis of the jaw

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ABSTRACT

Despite the widespread use of bisphosphonates and their unequivocal efficacy for the treatment of various disease states, osteonecrosis of the jaw remains one of the most feared complications associated with their use. Current evidence, however, suggests that there is also a relationship between occurrence of osteonecrosis of the jaw and use of other classes of pharmacotherapies namely RANKL inhibitors as well as angiogenesis inhibitors. Although these drugs have different mechanisms of action than bisphosphonates, they all seem to interfere with the bone remodeling process i.e. alter the balance between bone resorption and bone formation which may be the most plausible explanation for pathogenesis of osteonecrosis of the jaw. The main objective of this review is to introduce the readership to a number of relatively new medications that may cause osteonecrosis of the jaw. Accordingly, we will summarize latest findings from clinical studies, meta analyses and case reports published in medical literature on this topic. For some of these medications, the evidence may not appear as robust as that for bisphosphonates; yet, the possibility of this adverse event occurring with these non bisphosphonate drugs should never be precluded unless proven otherwise. Thus, it is imperative that health care providers implement preventive measures so as to circumvent the incidence of osteonecrosis of the jaw. In this day of age where medical care is becoming personalized, we will highlight some of significant findings from studies seeking to identify genetic markers that may potentially play a role in development of osteonecrosis of the jaw.

Introduction

Osteonecrosis of the jaw (ONJ) is a rare but serious disease of the jaw namely the maxilla and mandible. As the name suggests (osteo = bone and necrosis = death), ONJ manifests as lesions of necrotic and exposed bone in the oral cavity that persist for at least 8 weeks. Other accompanying symptoms include pain, mucosal swelling, loose teeth, erythema, and/or infections. Although more than a decade has passed since the first case report of ONJ, the exact pathophysiology of the disease has not been completely elucidated; however several theories have been proposed. ONJ was first introduced in 2003 by Marx RE [1] when he reported 36 cases of ONJ subsequent to the use of intravenous bisphosphonates (zoledronate and pamidronate) for the treatment of hypercalcemia related to multiple myeloma and metastatic breast cancer. The widespread use of bisphosphonates and the seriousness of this condition which adversely impacts the patient's quality of life, prompted Novartis (the manufacturing company of zoledronate and pamidronate) in 2004 to revise the package insert for both drugs so as to alert health care providers about the possibility of the incidence of ONJ with the use of these agents. Moreover, in 2005, this warning was broadened to include oral bisphosphonates indicating that this adverse event is rather a drug class effect. Hence, the term bisphosphonate related osteonecrosis of the jaw (BRONJ) came to light so as to distinguish ONJ caused by bisphosphonates from ONJ of other etiologies. Recently, several case reports have emerged implicating drugs belonging to different therapeutic classes in the pathogenesis of ONJ. Accordingly, the term BRONJ has become obsolete and is no longer restricted to bisphosphonate use. In their latest update of the 2009 position paper on BRONJ [2,3], the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended that the term BRONJ be replaced with the new terminology "Medication Related Osteonecrosis of the Jaw" (MRONJ) subsequent to this emerging body of evidence. Based on this new position paper, a definitive diagnosis of MRONJ can be made if all of the criteria listed in Table 1 are met. Once identified, the current guidelines provide treatment recommendations on the basis of the severity or stage of the disease (Table 2).

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Table 1
Criteria for diagnosis of medication related osteonecrosis of jaw.

Diagnostic criteria based on AAOMS recommendations
1. Current or previous treatment with drugs known to cause ONJ (antiresorptive agents, RANKL inhibitors, VEGFR inhibitors, etc...)
2. Exposed bone in the maxillofacial region that has persisted for at least 8 weeks
3. No previous history of radiation to the jaws

Table 2
Staging and treatment strategies.

Medication related osteonecrosis of jaw (MRONJ) staging		Recommended treatment approach
Stage 0	No clinical evidence of ONJ due to nonspecific symptoms, radiographic changes or clinical findings	Pain medication and/or antibiotics
Stage 1	Presence of exposed and necrotic bone in patients with no symptoms or evidence of infection	Antibacterial mouth wash Clinical follow up on a quarterly basis
Stage 2	Presence of exposed and necrotic bone accompanied by pain, erythema and/or purulent drainage	Antibacterial mouth wash, oral antibiotics and pain medications Debridement to relieve soft tissue irritation and infection control
Stage 3	Presence of exposed and necrotic bone	Antibacterial mouth wash, oral antibiotics and pain medications Surgical debridement for linger term palliation of infection and pain

With the continued advent of new and complex therapies, the list of drugs associated with ONJ will most likely continue to grow (Table 3). Because staying abreast of drug related complications can be quite daunting, we felt that there is a need for a review paper that recapitulates the most current findings published in the medical literature about this topic. Hence, in this review, we will not only list the drugs implicated in ONJ development, but also describe the possible underlying mechanisms by which they induce ONJ. It is a known fact that ONJ is a debilitating condition, yet it is preventable if appropriate measures are instituted. Accordingly, we will highlight the latest recommendations put forth by medical societies so as to reduce the occurrence of ONJ in patients receiving those drugs.

Proposed mechanisms of BP induced ONJ

Bisphosphonates are structurally related to inorganic pyrophosphate where the O atom that links the two phosphate moieties together in pyrophosphate is replaced by a C atom, thereby conferring stability and resistance to degradation by osteolytic enzymes

Table 3
Drugs associated with ONJ.

Drug	Mode of action	Half life	Dose	Route	Approved indication
Alendronate	Inhibition of FPS*	At least 10 years	5–10 mg daily 35–70 mg weekly	Oral	Treatment and prevention of osteoporosis
Risendronate	Inhibition of FPS*	480–561 h	5 mg daily 35 mg weekly 150 mg monthly	Oral	Treatment and prevention of osteoporosis
Ibandronate	Inhibition of FPS*	IV: 5–25 h Oral: 37–157 h	150 mg monthly 3 mg every 3 months	Oral IV	Treatment and prevention of osteoporosis
Pamidronate	Inhibition of FPS*	21–35 h	60–90 mg every 3–4 weeks	IV	Prevention of SRE Hypercalcemia of malignancy Paget disease
Zolendronate	Inhibition of PFS*	167 h	5 mg yearly 4 mg every 3–4 weeks	IV	Osteoporosis Prevention of SRE Hypercalcemia of malignancy Paget disease
Denosumab	Inhibition of bone remodeling by blocking RANKL	25–28 days	60 mg every 6 months 120 mg every 3–4 weeks	SC	Osteoporosis Prevention of SRE Hypercalcemia of malignancy
Bevacizumab	Inhibition of angiogenesis by blocking action of VEGF	11–50 days	5–10 mg every 2 weeks 15 mg every 3 weeks	IV	Metastatic colorectal carcinoma Glioblastoma Metastatic NSCLC Metastatic renal carcinoma
Sunitinib	Inhibition of tyrosine kinase of VEGFR, PDGFR, FLT3, c-kit	40–60 h	50 mg daily for 4 weeks of a 6 week cycle	Oral	GIST Metastatic renal cell carcinoma Neuroendocrine tumors
Sorafenib	Inhibition of tyrosine kinase of VEGFR, PDGFR, FLT3, c-kit, BRAF	25–48 h	400 mg twice daily	Oral	Metastatic hepatic carcinoma Metastatic renal cell carcinoma
Everolimus	Inhibition of mTOR	30 h	0.75–1 mg twice daily 10 mg daily	Oral	Kidney and liver transplant Hormone receptor positive breast cancer Metastatic renal cell carcinoma
Temsirolimus	Inhibition of mTOR	17 h	25 mg weekly	IV	Metastatic renal cell carcinoma
Cabozantinib	Inhibition of tyrosine kinase of VEGFR, MET, RET	55 h	140 mg daily	Oral	Metastatic medullary thyroid cancer

* FPS: farnesyl pyrophosphate synthase.