

New Oncology Drugs and Osteonecrosis of the Jaw (ONJ)

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 EXAM #17

Introduction

Osteonecrosis of the jaw (ONJ) is a name that is immediately associated with bisphosphonate-containing pharmaceuticals. These medications have for several years been used in oncology in patients with metastatic disease to the skeleton and also to treat post-menopausal women with osteoporosis.

Bisphosphonates are potent inhibitors of osteoclastic bone resorption leading to suppression of bone remodeling.¹ With bone resorption suppressed the balance between bone resorption and bone-formation is altered.² Since 2003, oral and intravenous bisphosphonates have been reported to cause ONJ and a recent review in the *Journal of the Tennessee Dental Association* updated the readers on this subject.³ Since the first cases of ONJ were reported in the literature, several issues involving the dental care of patients taking bisphosphonates have been discussed at national and international meetings and in the medical and dental literature. The management of ONJ in the dental office and the provision of dental care for a patient taking a bisphosphonate medication remains controversial. The American Dental Association and other professional organizations have issued guidelines based on expert opinions suggesting to the dental professional ways to manage cancer patients using intravenous bisphosphonates and osteoporosis patients using oral medication.⁴⁻⁸ The prevalence of ONJ in cancer patients using an intravenous bisphosphonate is described in the scientific literature as being between 3 and 12%^{6,9-12} and less than 1% in osteoporosis patients taking oral bisphosphonates.^{5,8} This prevalence is based on retrospective studies and may be biased in the way cases of ONJ were diagnosed.¹¹

There are, to date, no prospective controlled studies that can provide a more exact prevalence for ONJ. Bisphosphonate



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drugs are now in clinical trials for testing for many other applications in oncology and medicine. Furthermore, bisphosphonates are now being used in off-label indications for the treatment of several other pathological bone processes such as giant-cell lesions, giant-cell tumor of bone, osteogenesis imperfecta, fibrous dysplasia, Gaucher's disease, osteomyelitis and as adjunct in orthopedic implants.¹³

Recently, cases of ONJ have been described in cancer patients being treated with other medications, including anti-angiogenics and a newly developed anti-resorptive agent.¹⁴⁻²⁰ These agents are being intensively investigated for their use in oncology and other applications and an increase in their use can be expected in the near future.²¹

This paper has the goal of alerting the readers of the *TDA Journal* about the use of these new agents in oncology and in non-oncological applications, and to discuss the likely possibility that the number of ONJ cases will increase.

Anti-angiogenics

Angiogenesis (formation of new vasculature) inhibition is now being intensively studied in cancer research.²² Some of these agents are called "targeted therapy" because they are designed to bind to specific molecules involved in blood vessel formation, whereas, other agents aim to directly inhibit endothelial cell function or response. Therefore, investigators are using different strategies in the development of these agents, including blocking the ability of endothelial cells to break down tissue

matrix, inhibiting endothelial cells directly, blocking factors that stimulate angiogenesis, or blocking integrin, a molecule present on the surface of endothelial cells. According to the National Cancer Institute, there are about 20 agents in different phases of investigational trials and some are already in clinical use. **Table 1** presents a list of the new agents and indications for use.

Some of the anti-angiogenic agents are already in use including bevacizumab, sunitinib, sorafenib, thalidomide, alpha-interferon and matrix metalloproteinases.²³ They are used in combination with chemotherapy and/or radiation therapy and have application in different types of cancer.²⁴ The following drugs have been reported to cause ONJ.

Bevacizumab: a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor (VEGF), a protein involved in blood vessel formation (angiogenesis). A number of oncologic uses have been approved by the FDA including metastatic colorectal cancer in 2004, lung cancer in 2006, breast cancer in 2008 and metastatic renal cell carcinoma in 2009. Applications in pancreatic and ovarian cancer are being investigated. In addition, this drug has been used in diseases of the eye that develop due to abnormal growth of blood vessels (macular degeneration and diabetic retinopathy). One of the concerns with the use of bevacizumab is that the drug will interfere with normal processes in the body where blood vessel formation is necessary and desired, e.g., wound healing or collateral circulation formation around a blocked artery, and that this therapy could worsen conditions like coronary artery disease or peripheral artery disease.²⁵ Several cases of oral osteonecrosis have already been reported with this medication.^{14,15}

Sunitinib: a small molecule that inhibits a multitargeted receptor tyrosine kinase (RTK). These are high affinity cell surface receptors for several polypeptide

Table 1. New oncologic drugs with potential to cause osteonecrosis of the jaw (ONJ)

| Drug Generic (trade name) | Manufacturer | Indications in Oncology | Mode of Action | Reported to cause ONJ |
|---------------------------|-----------------------------------|--|--|---|
| Denosumab (Prolia®) | Amgen, Inc. | • In clinical trials for advanced cancer. | • Suppression of bone remodeling by Inhibition of RANKL | Yes, in a trial with breast cancer patients |
| Bevacizumab (Avastin®) | Genetech BioOncology | • metastatic colorectal cancer • non-squamous non-small cell lung cancer • metastatic breast cancer • glioblastoma • metastatic renal cell carcinoma | • Inhibition of angiogenesis by blocking the action of vascular endothelial growth factor (VEGF) | Yes |
| Sunitinib (Sutent®) | Pfizer Oncology | • advanced renal cell carcinoma • gastrointestinal stromal tumor (GIST) | • Inhibition of angiogenesis by blocking vascular endothelial growth factor tyrosine-kinase | Yes |
| Sorafenib (Nexavar®) | Bayer Health Care Pharmaceuticals | • renal cell carcinoma • hepatocellular carcinoma | • Inhibition of angiogenesis by blocking vascular endothelial growth factor tyrosine kinase | Potential |

growth factors, cytokines, and hormones. This molecule was approved by the FDA in 2006, for the treatment of renal cell carcinoma and a resistant form of gastrointestinal stromal tumor (GIST). The most common adverse events associated with Sunitinib therapy are fatigue, diarrhea, nausea, anorexia, hypertension, a yellow skin discoloration, hand-foot-skin reaction, and stomatitis.^{26,27} Because of the mechanism of action of inhibition of angiogenesis and also the use of this medication in combination with chemotherapy, there is a potential for the development of oral osteonecrosis.¹⁸

Sorafenib: a small molecule that inhibits RTK and was approved by the FDA in December of 2005, for use in advanced renal cell carcinoma and advanced hepatocellular carcinoma. Side effects of Sorafenib include skin rash, hand-foot-skin reactions, diarrhea, and hypertension. The risk of bleeding has also been investigated and it is considered significant.²¹ Although no cases of oral osteonecrosis have been reported with this medication, the mechanism of action is similar to other anti-angiogenic agents and the potential for the drug to cause oral complications should be considered.

New Antiresorptive Therapy

Denosumab: the first fully human monoclonal antibody. It is in the final stages of clinical development and testing. Osteoclasts and many body cells have surface receptors called receptor activator of nuclear factor k-B (RANK). RANK Ligand (RANKL) is a protein that binds to RANK on the surface of osteoclasts leading to the activation and maturation of osteoclasts for bone resorption; one of the stages of bone remodeling.

Denosumab specifically targets RANKL preventing the maturation of osteoclasts and bone resorption. It has recently been approved by the FDA for the treatment of osteoporosis.²⁸ Clinical trials for prevention of skeletal related events in patients with advanced cancer are ongoing. A recent study that compared Denosumab with zoledronic acid (Zometa®) in 2,046 patients with advanced breast cancer demonstrated the superior efficacy of Denosumab.¹⁷ One of the complications reported in this trial was the development of oral osteonecrosis. Among the 2,046 patients included in the study, there were 20 (2%) cases of osteonecrosis in the Denosumab arm and 14 (1.4%) in the Zometa arm. Other Denosumab trials involving several cancer populations with advanced disease are ongoing and results should be presented soon. Therefore, it is expected that this monoclonal antibody will soon be competing with bisphosphonates in the treatment of osteoporosis and patients with advanced cancer with skeletal metastasis. Thus, this is another medication that can cause oral osteonecrosis in cancer patients, whereas, no cases of osteonecrosis have yet been reported in the osteoporosis studies.

Discussion

This manuscript introduces a number of new medications being used in oncology that have different mechanisms from the bisphosphonates but that can also cause oral osteonecrosis. The scientific information available on this issue is still scanty. Nevertheless, several publications have already reported oral osteonecrosis in patients being treated with Bevacizumab, Sunitinib, and Denosumab. This requires from the

dentist a constant updating on prevention and management alternatives to treat such patients. These agents will have a large role in oncology and their use is going to increase. It is likely, therefore, that the number of patients with oral osteonecrosis will also increase. Because this is such a new problem, there are no specific guidelines addressing the management of patients taking the new antiresorptive or antiangiogenic agents. We recommend colleagues to use the same prevention and management measures used for patients taking bisphosphonates.^{4-6,8,29}

Populations are living longer. Cultural and medical aspects of today's societies imply that individuals can live a healthy life and that it is possible to remain healthy until old age. The increased longevity of people is allowing time for the development of new diseases and today it is not uncommon for a dental professional to have several medically complex patients among their patient pool who need routine dental care. Individuals can now live a fairly normal life and have reasonable quality of life in spite of having several chronic diseases that require the use of multiple medications daily. Therefore, taking complete histories from our patients is a must.

It is well known that medications can be associated with a number of oral complications that require attention from the dentist. Oral osteonecrosis can be a serious oral complication in cancer and osteoporosis patients, independent from the etiology. Dentists usually feel uncomfortable to design a surgical treatment plan in a patient using a bisphosphonate and frequently patients are denied care because of uncertain

outcome projections. This is not an acceptable alternative for a patient who needs dental care and who wants to maintain oral health. Therefore, dental professionals must be current with dental and medical advances, must be alert for new oral complications that their patients may develop and should be up to date with guidelines available for management of medically complex individuals.

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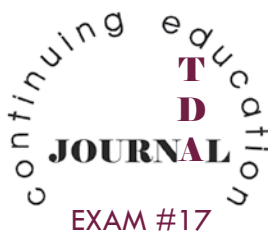
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Questions for Continuing Education Article - CE Exam #17

- Bisphosphonates are potent inhibitors of:
 - menopause
 - metastatic disease
 - hydronephrosis
 - osteoclastic bone resorption
- The prevalence of ONJ in cancer patients using intravenous bisphosphonates is described in the literature as being:
 - 3 and 12%
 - Less than 1%
 - 25%
 - 50%
- Recent cases of ONJ have been described in cancer patients being treated with other medications, including:
 - Anti-spasmodics
 - Antihistamines
 - Anti-hypertensives
 - Anti-angiogenics
- Angiogenesis is the:
 - Formation of new chromosomes
 - Destruction of blood vessels
 - The beginning of angina
 - The formation of new vasculature
- Anti-angiogenesis is used as an attempt to:
 - Deprive the cancer of blood supply
 - Prevent pain
 - Prevent infection
 - Perfuse the cancer with blood
- Thalidomide is:
 - An anti-neoplastic agent.
 - A safe drug for pregnant females during first trimester.
 - Classified as a Bisphosphonate.
 - Classified as an anti-angiogenic.
- VEGF is:
 - Vegetative growth factor
 - Vegetable Foundation
 - Vitamin E Growth Factor
 - Vascular endothelial growth factor
- How does Bevacizumab work?
 - It blocks endorphins
 - It encourages blood vessel formation
 - It blocks VEGF
 - It increases the percentage of macular degeneration
- Sunitinib and Sorafenib are:
 - Soporifics
 - Large molecular anti-angiogenic agents that inhibit RfK
 - Small molecules that inhibit RTK
 - Drugs which cause the largest percentage of osteonecrosis
- Denosumab is the:
 - Drug with the highest percentage of ONJ
 - First drug to attack osteoclasts
 - First fully human monoclonal antibody
 - Drug of choice to treat ONJ

Answer Form for TDA CE Credit Exam #17: New Oncology Drugs and Osteonecrosis of the Jaw (ONJ)

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| 2. a b c d | 7. a b c d |
| 3. a b c d | 8. a b c d |
| 4. a b c d | 9. a b c d |
| 5. a b c d | 10. a b c d |

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