

CLINICAL CHALLENGES

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Osteonecrosis of the Jaw in a Patient Receiving Bisphosphonate Therapy

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Case Study

Mr. M, a 66-year-old man, was diagnosed with stage IV hormone-refractory prostate cancer four years ago. At that time, he presented with metastatic disease to the lumbar spine, hip, and pelvic region and received site-specific radiation therapy to alleviate his pain. He initially was treated with leuprolide acetate injections every three months, bicalutamide by mouth daily, and IV bisphosphonate infusions once a month. After six months of hormonal therapy, his prostate-specific antigen (PSA) level began to rise and his treatment was changed to docetaxel and estramustine starting two days prior to receiving docetaxel. He tolerated the regimen very well, with greater than 50% reduction in his PSA. After the fourth cycle of docetaxel and estramustine, the PSA level began to rise and his treatment was changed to paclitaxel, estramustine, and carboplatin (TEC). Monthly infusions of zoledronic acid were continued. Because his PSA level continued to rise following five cycles of TEC, Mr. M agreed to a new treatment plan of docetaxel, carboplatin, estramustine, and zoledronic acid IV.

During a chemotherapy follow-up visit, Mr. M complained of a sudden onset of right lower jaw pain that he described as a "toothache." Zoledronic acid infusions were placed on hold, chlorhexidine 0.12% antiseptic rinse was prescribed, and a dental consult was

ordered. Dental x-rays were negative for any dental abnormalities, and four views of the mandible were unremarkable. The following week, Mr. M complained of persistent right lower jaw pain radiating to his right ear with a new onset of headache, photosensitivity, and occasional dizziness. A neurologic consult was ordered. A computed tomography scan of the brain showed scattered sclerotic lesions to the skull base consistent with blastic metastases. A magnetic resonance imaging (MRI) scan of the brain was normal, but an MRI scan of his cervical spine revealed spondylosis from C4–5 through C6–7 without bony metastases. Temporal arteries and temporomandibular joints were normal. On physical examination, Mr. M had no scalp or sinus tenderness and no oral lesions were noted. The neurologic examination also was normal. The clinical impression was that the patient had trigeminal neuropathic pain, and he was placed on gabapentin.

Mr. M returned two weeks later with painless purulent drainage from the site of a previous tooth extraction on the lower right side of his mouth. A wound culture was obtained, and empiric antibiotic therapy with clindamycin was ordered because the patient was allergic to penicillin. A maxillofacial surgeon was consulted. A maxillofacial computed tomography scan with contrast was performed and revealed osteomyelitis or osteonecrosis of the right mandibular ramus.

What is osteonecrosis of the jaw?

No consensus definition exists for osteonecrosis of the jaw (ONJ), and its pathobiologic mechanisms are not clearly understood (Ruggiero et al., 2006). ONJ is a rare, osseous pathologic complication that causes temporary or permanent loss of blood supply to the jaw bone, resulting in necrosis, or death, of the bone. The incidence of ONJ ranges from 1%–21% in patients treated with bisphosphonates (Assouline-Dayane, Chang, Greenspan, Shoenfeld, & Gershwin, 2002; Bamias et al., 2005). The condition usually is diagnosed clinically, based on visual inspection of the oral cavity and, in some cases, review of radiographic studies (Ruggiero et al.).

What are the risk factors for osteonecrosis of the jaw?

The exact mechanisms that induce necrosis of the jaw remain poorly understood; however, cancer and certain cancer treatments have been linked as risk factors (Assouline-Dayane et al., 2002). ONJ has been reported in the literature since the 19th century (Ruggiero et al., 2006). An increasing body of literature suggests that the use of bisphosphonates, especially IV formulations, may be associated with ONJ (Ruggiero et al.; Woo, Hellstein, & Kalmar, 2006). The most important risk factors for the development of ONJ are the type and total dose of bisphosphonate and history of trauma, dental surgery, or dental infection. Although osteoblastic function is reduced during bisphosphonate therapy, the continuous mineralization process results in hard, brittle bone (Ruggiero et al.; Woo et al.). Zoledronic acid, an aminobisphosphonate,

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not only inhibits osteoclastic activity, but also inhibits tumor cell adhesion to the extracellular matrix, inhibits tumor invasion, and has antiangiogenic properties (Woo et al.; Wood et al., 2002). The risk for ONJ is substantially higher for patients taking zoledronic acid and increases over time, most likely because of the long half-life of bisphosphonate drugs. Women are slightly more predisposed than men in a ratio of 3:2 among all reported cases (Woo et al.).

The oral cavity is constantly under stress from the chewing process. The need for repair and remodeling increases greatly when an infection in the maxilla or mandible exists or an extraction is performed (Hellstein & Marek, 2005). Migliorati, Schubert, Peterson, and Seneda (2005) studied 17 patients with cancer who developed ONJ while undergoing bisphosphonate therapy. Most of the 17 cases of ONJ initially occurred after dental extractions and most lesions were infected secondarily. Migliorati, Schubert, et al. classified risk factors into two categories: local and systemic (see Figure 1).

What is the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw?

The pathogenesis of bisphosphonate-associated osteonecrosis is not well understood and is most likely the result of multiple etiologies (Ruggiero et al., 2006). Bisphosphonate-associated osteonecrosis results from a complex interplay of bone metabolism, local trauma, increased demand for bone repair, infection, and hypovascularity (Migliorati, Casiglia, et al., 2005). In normal bone homeostasis, osteoclastic resorption is tightly balanced against osteoblastic bone deposition. Both functions are necessary for repair of physiologic microdamage that occurs during normal bone use. The balance is altered during bisphosphonate therapy. Woo et al. (2006) suggested that ONJ results from marked suppression of bone metabolism that causes accumulation of physiologic microdamage in the jawbones, compromising biomechanical

properties. Trauma from normal mastication and the presence of oral infections increase the demand for bone repair that exceeds the capacity of the hypodynamic bone, resulting in localized bone necrosis. Antiangiogenic properties of aminobisphosphonates and other antineoplastic medications and the presence of comorbid conditions may promote the risk or persistence of ONJ (Woo et al.).

A common question concerning ONJ is the propensity of the condition to occur in the jawbones rather than other places in the body. Woo et al. (2006) suggested that the jawbones are separated from a trauma-intense and microbiologically diverse oral environment by a fragile, thin (≤ 2 mm) mucosal barrier and periosteum, thus providing easy access for osseous damage and infection that, when combined with the long-term effects of bisphosphonate therapy, lead to necrosis of the jawbones.

Does a correlation exist between the incidence of developing osteonecrosis with the time of exposure and the number of bisphosphonate infusions given?

In a retrospective study conducted by Bamias et al. (2005), a correlation was found between the incidence of developing ONJ and the time of exposure and the number of bisphosphonate infusions that were given. Patients who developed ONJ received a median of 35 infusions with a median time of exposure to bisphosphonates of 39.3 months (range = 11–86 months) compared to those who did not develop osteonecrosis and received a median number of 15 infusions with a median time of exposure to bisphosphonates of 19 months (range = 4–85 months).

Is a cumulative effect present in developing osteonecrosis of the jaw, and is a significant difference found according to the bisphosphonate used?

Bamias et al. (2005) analyzed patients who received bisphosphonate therapy and showed that a cumulative effect existed for developing osteonecrosis with an increased risk of more than 1% after 12 months and as much as 11% after four years of treatment. According to the comparative study, incidence of osteonecrosis was significantly higher in the group of patients who received zoledronic acid. The incidence of ONJ increased by 1% in the first year, rising to 21% at three years, compared to 0% incidence of ONJ in the first two years, increasing to 7% after four years of treatment in patients who received pamidronate alone or with subsequent zoledronic acid. The increased incidence of ONJ with zoledronic acid compared with pamidronate is unknown, but zoledronic acid is believed to have a more potent inhibiting effect on bone turnover than pamidronate, thereby allowing for cell death to occur.

Grade 1

Asymptomatic, radiographic findings only

Grade 2

Symptomatic and interfering with function, but not interfering with activities of daily living (ADL); minimal bone removal indicated (i.e., minor sequestrectomy)

Grade 3

Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated

Grade 4

Disabling

Figure 2. Osteonecrosis of the Jaw: Grading Severity

Note. Based on information from National Cancer Institute, 2006.

Are criteria available for staging the severity and lesion size of osteonecrosis of the jaw?

Figure 2 provides criteria for staging severity of ONJ. Novartis (2006), the manufacturer of zoledronic acid, convened an expert panel of oral surgeons, pathologists, medical oncologists, and orthopedic physicians to develop recommendations for the prevention and treatment of ONJ. The panel updated recommendations for the prevention, diagnosis, and treatment of ONJ that included severity and lesion size staging.

What is the clinical presentation of osteonecrosis of the jaw, and how is it diagnosed?

Patients with ONJ initially present with vague symptoms such as heaviness in the jaw area, numbness in the maxilla or mandible, and various dysesthesias. ONJ can remain asymptomatic for many weeks or months. Because of the unique presentation, healthcare providers must aggressively monitor patients at high risk, perform regular oral inspections, and initiate diagnostic tests when indicated. Most patients notice exposed bone in an area where a tooth was extracted recently. Intra-oral lesions appear as areas of exposed yellow to white, hard bone surface with smooth or jagged edges. Contiguous sinus tracts may be present as well as painful ulceration in soft tissues that are in contact with ragged bony margins (Woo et al., 2006). Patients become symptomatic when trauma occurs to adjacent opposing healthy soft tissue from irregular surfaces of the exposed bone or a secondary infection. Many patients complain that the tongue comes in contact with a sharp edge from exposed bone. Objective signs that may occur before clinical presentation of ONJ are a sudden change in the health of periodontal or mucosal tissues, failure of the oral mucosa to heal, undiagnosed oral pain, loose teeth, or soft tissue infection. If ONJ is suspected, diagnostic evaluation through referral to a dentist

Systemic Risk Factors

- IV use of bisphosphonates (e.g., pamidronate, zoledronic acid)
- Multiple myeloma
- Cancer metastatic to bone

Local Risk Factors

- Dental extractions
- Surgery to bone
- Trauma secondary to denture use
- Presence of oral infection
- Poor oral health

Figure 1. Bisphosphonate-Associated Osteonecrosis Risk Factors

Note. Based on information from Migliorati, Schubert, et al., 2005.

or oral maxillofacial surgeon is recommended to evaluate panoramic and tomographic imaging to rule out other causes such as cysts, impacted teeth, or metastatic disease (Ruggiero et al., 2006). Diagnosing ONJ in the early stages is difficult because radiographic alterations are subtle and minimal changes may not be detectable (Woo et al.). Radiographic presentation of ONJ may be indistinguishable from osteoradionecrosis of the jaw in patients who have had radiation to the head and neck; however, osteoradionecrosis rarely involves the maxilla (Woo et al.). As surface bone degrades over time, radiographs eventually show poorly defined radiolucency, with or without radiopaque sequestra (Ruggiero et al.; Woo et al.).

Is a tissue biopsy recommended?

A tissue biopsy is not recommended unless metastasis to the jaw is suspected. The risk of introducing further bone damage outweighs the benefit of a confirmed biopsy (Ruggiero et al., 2006). However, if a biopsy is performed to rule out metastatic disease, a tissue sample from the affected area and a culture from the biopsy site should be submitted for microbial cultures (aerobic and anaerobic) to identify organisms with the potential to cause secondary infections. *Actinomyces* organisms often are seen microscopically or cultured when ONJ is present (Ruggiero et al.; Woo et al., 2006).

Can any measures be initiated to prevent the occurrence of osteonecrosis of the jaw?

As soon as a treating oncologist prescribes bisphosphonate therapy, the patient should be referred to an experienced dentist or oral and maxillofacial surgeon for an examination prior to starting therapy. The dental consultation should consist of panoramic radiographic examinations with individual periapical films to determine whether invasive procedures such as tooth removal, periodontal surgery, root canal treatment, cavity control, dental restoration, or dentures are needed. Such procedures should be completed prior to starting bisphosphonate therapy. In the absence of dental disease, preventive measures recommended before initiating bisphosphonates include dental prophylaxis with cleanings and caries control. Many patients who have been receiving bisphosphonates for long periods of time may be unaware of recent findings concerning ONJ. Those patients should be referred to a dentist for a thorough examination and advised of the hazards of having dental extractions or invasive procedures during bisphosphonate therapy (Marx, Sawatari, Fortin, & Broumand, 2005; Ruggiero et al., 2006; Woo et al., 2006).

Education regarding oral hygiene, such as daily flossing and brushing and maintaining scheduled dental examinations every three to four months should be stressed. Once patients receive bisphosphonate therapy, any invasive

dental procedures that may cause soft tissue injury should be avoided. Patients who wear dentures should be advised to ensure that their dentures fit properly and are removed each night. Dental infections should be managed aggressively with a nonsurgical approach if possible. Prophylactic antibiotics are not indicated prior to noninvasive dental care but are recommended for any invasive dental procedure. Penicillin remains the drug of choice.

What are the treatment recommendations when osteonecrosis of the jaw is diagnosed?

A consultation with an oral maxillofacial surgeon or dental oncologist is strongly recommended for the treatment of patients with cancer who have developed ONJ. The treatment regimen should be coordinated between the oral surgeon and medical oncologist for optimal therapy of ONJ and the underlying neoplastic disease. Collaboration between the medical oncologist and oral surgeon is crucial, and ongoing communication is imperative to provide an optimal treatment plan and alternative treatment options.

Treatment recommendations (see Table 1) include intermittent antibiotic therapy along with oral antiseptic rinses of chlorhexidine gluconate 0.12% (Peridex®, Zila Pharmaceuticals, Inc., Phoenix, AZ) or minocycline hydrochloride to prevent secondary soft tissue infection, pain, and osteomyelitis. The drug of choice is penicillin VK 500 mg by mouth every six to eight hours for 7–10 days, then twice daily for maintenance. The duration of antibiotic therapy and the benefits of oral antiseptic rinses such as chlorhexidine gluconate 0.12% have not been determined;

in addition, interrupting or discontinuing bisphosphonate therapy has not proven to be beneficial. Improved pain control and mucosal disease control has been observed anecdotally with such a treatment strategy (Ruggiero et al., 2006).

Combination therapy using quinolones and metronidazole or erythromycin and metronidazole has been proven to be effective as an alternative for patients who are allergic to penicillin. Clindamycin alone is not recommended because of its lack of activity against *Actinomyces*, *Eikenella*, *Corrodens*, and similar species that have been found to frequently colonize exposed bone (Marx et al., 2005). Hyperbaric oxygen has not been shown to be effective for treating ONJ and is not recommended (Ruggiero et al., 2006).

No evidence has been published to support or oppose discontinuation of bisphosphonate therapy once ONJ develops or to temporarily interrupt dosing before required dental surgery. The long half-life of bisphosphonates, recovery of normal osteoclast function, and bone turnover after drug withdrawal may be too gradual for temporary dose interruption to have clinical significance. If ONJ has developed and the underlying systemic disease is stable, bisphosphonates can be withdrawn until the area of osteonecrosis heals or disease progression becomes evident (Woo et al., 2006). Zarychanski, Elphee, Walton, and Johnston (2006) suggested that durable resolution of necrotic bone lesions rarely occurs even if the drug is withdrawn. They also cautioned against surgical debridement of necrotic bone.

Nursing Implications

Nurses caring for patients undergoing bisphosphonate therapy must be aware of

Table 1. Anti-Infective Pharmacologic Treatments Recommended for Patients With Osteonecrosis of the Jaw

Treatment	Dose and Schedule
Antibacterials	
Penicillin VK	500 mg every six to eight hours for 7–10 days, then twice daily for maintenance
Amoxicillin	500 mg every eight hours for 7–10 days, then twice daily for maintenance
Patients with penicillin allergy	
Clindamycin	150–300 mg four times per day
Vibramycin	100 mg daily
Erythromycin ethylsuccinate	400 mg three times per day
Azithromycin	500 mg by mouth on day 1; 250 mg by mouth every day on days 2–5
Antifungals (when required)	
Nystatin oral suspension	5–15 ml four times per day or 100,000 IU/ml
Mycelex troches (clotrimazole)	10 mg three times per day for 7–10 days
Fluconazole	200 mg initially, then 100 mg every day
Antivirals	
Acyclovir	400 mg by mouth twice daily
Valacyclovir hydrochloride	500 mg–2 g twice daily

Note. Based on information from Ruggiero et al., 2006.

their risk of ONJ. Reinforcement of patient education concerning dental hygiene and prompt evaluation of any dental or oral lesions is vitally important. Nurses can facilitate referral to a dental oncologist or oral maxillofacial surgeon if a patient reports symptoms of ONJ or examination of the patient's oral cavity reveals signs of inflammation or exposed bone. Patients beginning bisphosphonate therapy should be reminded that a complete oral and dental examination and all invasive procedures must be completed prior to beginning bisphosphonate therapy.

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Clinical Highlights: Osteonecrosis of the Jaw

Definition

Osteonecrosis of the jaw (ONJ) is a rare complication that causes temporary or permanent loss of blood supply to the jawbone, resulting in necrosis, or death, of the bone. The incidence of ONJ ranges from 1%–21% in patients treated with bisphosphonates (Assouline-Dayana, Chang, Greenspan, Shoenfeld, & Gershwin, 2002; Bamias et al., 2005).

Pathophysiology

The pathogenesis of bisphosphonate-associated osteonecrosis is not well understood and is most likely the result of a complex interplay of bone metabolism, local trauma, increased demand for bone repair, infection, and hypovascularity (Migliorati, Schubert, Peterson, & Seneda, 2005; Ruggiero et al., 2006). The homeostatic balance of osteoblastic bone deposition against osteoclastic resorption is altered during bisphosphonate therapy. Antiangiogenic properties of aminobisphosphonates and other antineoplastic medications and the presence of comorbid conditions may promote the risk or persistence of ONJ (Woo, Hellstein, & Kalmar, 2006). A common question concerning ONJ is the propensity of the condition to occur in the jawbones rather than other places in the body. Woo et al. suggested

that the jawbones are separated from a trauma-intense and microbiologically diverse oral environment by a fragile, thin (≤ 2 mm) mucosal barrier and periosteum, thus providing easy access for osseous damage and infection that, when combined with the long-term effects of bisphosphonate therapy, lead to necrosis of the jawbones.

Risk Factors

The following are risk factors for the development of ONJ: IV bisphosphonate therapy, dental extractions, dental procedures involving bone surgery, preexisting periodontal disease, trauma from dentures, oral infections, poor oral hygiene, history of coagulopathies, multiple myeloma, metastatic cancer to the bone (e.g., breast, lung, prostate), head and neck radiation therapy, and immunotherapy.

Women develop ONJ more often than men in a ratio of 3:2 among all reported cases (Woo et al., 2006). The most important risk factors for development of ONJ are the type and total dose of bisphosphonate and history of trauma, dental surgery, or dental infection (Migliorati et al., 2005; Ruggiero et al., 2006; Woo et al.).

Differential Diagnoses

Consider ONJ in the differential diagnosis of any patient who has exposed bone without evidence of healing. Any patient who has a

nonhealing gum or jaw wound after six weeks of treatment and no evidence of metastatic disease can be considered to have ONJ. Differential diagnoses include cysts, impacted teeth, dental caries, trigeminal neuralgia, temporal mandibular joint disease, sinusitis, gingivitis, periodontal disease, osteoradionecrosis, and metastatic disease. A biopsy is contraindicated unless metastasis is suspected. The risk of introducing further bone damage outweighs the benefit of a confirmed biopsy (Ruggiero et al., 2006).

Clinical Presentation

The mandible is affected by ONJ more often than the maxilla (Marx, Sawatari, Fortin, & Broumand, 2005). Clinical presentation ranges from vague subjective symptoms to debilitating objective symptoms. The most common clinical presentation is exposed bone that can occur spontaneously or at the site of a previous tooth extraction and often has sharp edges. Drainage can be present at the site of previous dental surgery. Soft tissue swelling and infection may be present as well as loosening of teeth. Pain can occur spontaneously or when chewing or brushing teeth. Less common symptoms are numbness, a feeling of a heavy jaw,

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and various dysesthesias (impairment in sensitivity to touch). The symptoms may be present for weeks or months prior to a diagnosis of ONJ (Ruggiero et al., 2006). Undiagnosed pain, a change in oral mucosal tissue, and failure of mucosal tissue to heal should prompt a suspicion of ONJ and appropriate dental workup.

Prevention and Education

The optimal goal of patient education is prevention of ONJ. Advise patients that, prior to starting bisphosphonate therapy, they must have a dental consultation. Panoramic x-rays should be performed, and dental prophylaxis should include cleanings, cavity control, and periodic x-rays to compare and evaluate bone breakdown. Education on preventive measures should be reinforced at each visit. Patients should be instructed regarding daily flossing and brushing after meals. Dentures should fit properly and be removed at night. Dental examinations with cleanings are recommended every three to four months.

Patients on IV bisphosphonate therapy should be instructed to continue with their routine dental care. Elective jaw procedures should be avoided during bisphosphonate therapy. Prophylactic antibiotics are recommended only for invasive procedures but are not necessary for routine dental procedures.

Treatment Recommendations

Treatment for ONJ includes oral antibiotics along with oral antiseptic rinses. The preferred treatment is penicillin VK 500 mg by mouth every six to eight hours for 7–10 days, then twice daily for maintenance, or amoxicillin 500 mg by mouth every eight hours for 7–10 days,

then twice daily for maintenance (Ruggiero et al., 2006). Combination therapy using quinolones and metronidazole or erythromycin and metronidazole has been proven to be effective as an alternative for patients who are allergic to penicillin. Clindamycin alone is not recommended (Marx et al., 2005). Use of a concurrent antiseptic oral rinse (e.g., swish and spit 15 cc chlorhexidine 0.12% twice daily) is recommended. Antifungals such as nystatin oral suspension 5–15 ml four times per day or 100,000 IU/ml, clotrimazole troches 10 mg three times per day for 7–10 days, or fluconazole 200 mg by mouth initially, then 100 mg orally daily, may be prescribed if evidence of oral fungal infection exists.

Cessation or Interruption of Bisphosphonate Therapy

No evidence has been published to support or oppose discontinuation of bisphosphonate therapy once ONJ develops or to temporarily hold dosing before required dental surgery. The long half-life of bisphosphonates and recovery of normal osteoclast function and bone turnover after drug withdrawal may be too gradual for temporary dose holds to have clinical significance. If ONJ has developed and the underlying systemic disease is stable, bisphosphonates can be withdrawn until the area of osteonecrosis heals or disease progression becomes evident (Woo et al., 2006). Necrotic bone lesions generally do not resolve during drug withdrawal. Surgical debridement of necrotic bone lesions should be avoided.

Nursing Implications

Nurses caring for patients undergoing bisphosphonate therapy must be aware of their risk of ONJ. Reinforcement of patient education concerning dental hygiene and prompt evaluation of any dental or oral lesions is vitally important. Nurses can

facilitate referral to a dental oncologist or oral maxillofacial surgeon if a patient reports symptoms of ONJ or examination of the patient's oral cavity reveals signs of inflammation or exposed bone. Patients beginning bisphosphonate therapy should be reminded that a complete oral and dental examination and all invasive procedures must be completed prior to beginning bisphosphonate therapy.

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