Editorial

Osteonecrosis of the Jaw: New Developments in an Old Disease

Over the past century, osteonecrosis of the jaw has been known to occur following head and neck irradiation in cancer patients. This avascular bone necrosis, or dead bone, develops due to inadequate blood supply and historically has been associated with other known risk factors such as chemotherapy, corticosteroid use, local infection, malignancy, or trauma.

In 2003 the first cases of osteonecrosis of the jaw in cancer patients receiving bisphosphonates were reported[1]. Subsequent publications largely in the form of case reports or surveys have demonstrated a temporal relationship between high-dose intravenous (IV) bisphosphonate use and the development of osteonecrosis of the jaw (ONJ)[2-5]. These lesions have affected the mandible as well as the maxilla (unlike osteoradionecrosis) and have presented with painful or painless exposure of the bone in the mandible or maxilla.

Bisphosphonates are valuable agents that have been proven to effectively prevent bone loss and fragility fracture in addition to controlling the skeletal complications of malignancy[6]. As synthetic analogs of pyrophosphate they are potent inhibitors of osteoclast-mediated bone resorption. The aminobisphosphonates (alendronate, ibandronate, pamidronate, risedronate, zoledronate) have a nitrogen-containing side chain that dramatically enhances potency in comparison to the non-nitrogen-containing bisphosphonates (etidronate, clodronate, and tiludronate).

High doses of IV bisphosphonates in the oncology population have been associated with an increased risk of osteonecrosis in published data to date. Durie and colleagues reviewed 1203 patients from a Web-based survey with multiple myeloma or breast cancer, and 75 patients were reported to have ONJ. The likelihood of ONJ appeared to be related to both the potency and duration of therapy[4]. Bamias and colleagues published a case series of 252 patients with bone metastases, and those developing ONJ had received a median of 35 infusions of pamidronate or zoledronic acid, whereas those who were not affected had received a median of 15 infusions ($p < 0.001$)[5]. Duration of therapy appears to be an important risk factor in the development of ONJ in oncology patients.

The true incidence of ONJ in the cancer population receiving high-dose IV therapy is not known, as currently available data are largely limited to case reports and surveys; however, estimates suggest that incidence may range from 6.8% to 9.9% in the myeloma patient population and 2.9% to 4.4% in the breast cancer population[4,5].

Low-dose bisphosphonate therapy is widely used for patients with osteoporosis or Paget's disease. A relationship between low-dose bisphosphonates administered orally or intravenously and ONJ has not been established. Clinical trials in osteoporosis patients to date have not observed an increased risk of ONJ with bisphosphonate use. In the study evaluating IV zoledronate in the prevention of fracture in osteoporosis patients (n = 7765), the incidence of ONJ lesions was similar in the zoledronate and placebo groups, with 1 case in each group developing over a period of 3 years[7]. Both these cases had significant risk factors for osteonecrosis, with one patient receiving prednisone therapy and the other having local dental abscesses. Both these cases healed. Postmarketing data with the orally administered aminobisphosphonates alendronate and risedronate suggest that the condition is rare, with an estimated incidence of less than 1 case per 100,000 patients.

In this issue of *The Journal* the study by Etminan and colleagues evaluated the use of oral bisphosphonates and the risk of aseptic osteonecrosis in elderly patients living in Quebec[8]. Data from RAMQ (Regie de l'Assurance-Maladie du Quebec) as well as the prescription drugs database and the hospitalizations database were evaluated. This retrospective cohort study found an increased relative risk of osteonecrosis at any site among bisphosphonate users, with an adjusted relative risk (RR) of 2.87 for bisphosphonate users (95% CI 1.71–5.05). The adjusted RR for alendronate, etidronate, and risedronate were 2.87, 2.43, and 3.34,

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respectively. The study is of impressive size, with 87,837 subjects. Among limitations to the study, the site of osteonecrosis could not be determined from the available data. It is quite probable that these cases are largely osteonecrosis of the hip, as a significant number had been prescribed corticosteroids.

Etminan and colleagues emphasize the importance of obtaining further prospective data regarding the true incidence of ONJ.

There are currently no published incidence data for ONJ in Canada. An Ontario-wide survey under way is evaluating the incidence of ONJ in the general population as well as in bisphosphonate users. Data are expected to be available in early 2008.

Currently, the incidence of ONJ in the general population is not known. It is probable that low-dose bisphosphonate use in the osteoporosis population may not be a contributing factor to the development of ONJ. However, the relationship between high-dose IV bisphosphonate use in oncology patients and the development of ONJ appears to be significantly stronger. IV bisphosphonates are extremely valuable agents for management of skeletal complications of malignancy. Physicians and patients need to be aware of the potential side-effects and adhere to prevention and management strategies aimed at reducing the risks of ONJ.

It is also important for clinicians and dental specialists to be aware of the benign condition known as lingual mandibular sequestration and ulceration (LMSU). This occurs in healthy people and was reported before the use of aminobisphosphonates in 1993[9]. These osteonecrosis lesions appear similar to bisphosphonate-associated osteonecrosis and can spontaneously present with exposed bone at the mylohyoid ridge. The lesions heal spontaneously within a few days but may take up to 12 weeks for resolution[9]. As the definition of osteonecrosis associated with bisphosphonates requires exposed bone in the maxillofacial area for more than 8 weeks in the absence of head and neck irradiation[10], it is possible that cases of LMSU may be mistaken for bisphosphonate-associated osteonecrosis.

A Canadian task force representing multiple disciplines involved in the diagnosis and management of bisphosphonate-associated ONJ recently completed a systematic review and developed evidence-based guidelines, expected for publication shortly.

The Canadian guidelines address the importance of correcting poor dental hygiene, as periodontal disease is a key risk factor for the development of ONJ. The Canadian guidelines also advise regular dental assessments in keeping with the recommendations of the Canadian Dental Association[11] for all patients including those receiving bisphosphonate therapy. Any area of dental infection should be aggressively treated prior to starting bisphosphonate therapy, particularly in the oncology patient expected to receive high-dose IV therapy. The guidelines also outline pain and infection control strategies in those patients developing ONJ, in addition to medical and surgical management recommendations.

The question arises as to the mechanisms by which bisphosphonates may contribute to the development of ONJ. The underlying pathophysiology resulting in ONJ is currently not fully understood. Proposed mechanisms include the possibility of further reductions in osteoclastic activity in an area of bone that may be relatively hypocellular following previous chemotherapy or radiotherapy. This lack of adequate bone turnover following high-dose IV bisphosphonate therapy could potentially impair the ability of the bone to heal at sites of dental extraction and/or periodontal disease. Other possible mechanisms have been proposed including the potential antiangiogenic effects of aminobisphosphonates[12]. However, other agents known to have antiangiogenic effects such as thalidomide, which are also effective agents in myeloma, have not been associated with the development of ONJ[13]. Reid and colleagues have recently proposed that the aminobisphosphonate may have toxic effects on oral epithelium overlying areas of high bone bisphosphonate concentrations, decreasing the ability of the oral mucosa to heal following local trauma such as a tooth extraction[14]. These theories require further study.

Prospective data are necessary to understand the role of other important risk factors that can lead to the development of ONJ such as diabetes mellitus, peripheral vascular disease, and hyperviscosity syndromes. With the availability of prospective data our understanding of the pathophysiology resulting in osteonecrosis will be greatly advanced, and prevention and management recommendations will be further refined.

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