Patients with multiple myeloma and metastatic cancer to the bones show reduced incidence of skeletal-related events when they are treated with intravenous bisphosphonates such as pamidronate or zoledronic acid (1,2). For many years, the continuous, often monthly, use of bisphosphonates in such patients was not questioned. However, in 2003, an adverse reaction, termed bisphosphonate-associated osteonecrosis of the jaws, was reported in this patient population (3,4). To date, more than 600 cases have been reported, but it is likely that many more exist. The prevalence of osteonecrosis of the jaws in the oncologic population was 6%–11% in small single-center retrospective studies (5–7) and 4% in one web-based survey (8). The risk of development of osteonecrosis of the jaws is dependent on cumulative dose and potency of the agent (6,9). Patients with cancer are more likely than those with osteoporosis to develop osteonecrosis of the jaws because they receive more potent agents and more frequent dosing. Recent recommendations from the Mayo Clinic caution against indefinite use of such agents because of the occurrence of osteonecrosis of the jaws (10). The etiopathogenesis of osteonecrosis of the jaws is unknown, but severe suppression of bone turnover probably plays an important role.

The study by Wilkinson et al. (11) in this issue of the Journal nicely demonstrates the strengths of pharmacoepidemiologic analyses. A large unselected group of patients with cancer, with and without a history of bisphosphonate treatment, was assembled by use of previously collected data through the Surveillance, Epidemiology, and End Results registry. Because these data include patients from referral centers and the wider community, they reduce problems of generalizability that occur in studies that rely heavily on referral populations treated at cancer centers. As well, the study database includes important information regarding comorbid conditions that may confound the relationship between bisphosphonates and jaw pathology. Finally, the use of data from thousands of patients translates into a statistically powerful study conducted relatively quickly without an enormous budget.

The authors found that treatment with intravenous bisphosphonates was associated with an increased risk of jaw or facial bone surgery and an increased risk of being diagnosed with an inflammatory condition or osteomyelitis of the jaw, compared with non-therapy (5.48% versus 0.30%, respectively, at 6 years). The risk rose with increasing cumulative dose. In another epidemiologic study that used claims data from a medical insurer and similar Current Procedural Terminology codes, the odds ratio of jaw surgery among intravenous bisphosphonate users was 4.24 (95% confidence interval = 2.67 to 6.72) (12).

Studies of this nature may both overestimate and underestimate incidence and prevalence. It is unclear what percentage of these inflammatory conditions of the jaw (International Classification of Diseases code 526.4) actually represents osteonecrosis of the jaws. As the authors appropriately acknowledge, osteonecrosis of the jaws has no specific diagnostic codes in administrative claims. Because patients with cancer receiving chemotherapy may experience exacerbation of, or new odontogenic infections as a result of, neutropenia and immunosuppression that may lead to the use of such codes, there may be misattribution. Do bisphosphonates predispose toward inflammatory conditions of the jaw, some of which may or may not be osteonecrosis of the jaws? Or, do patients with metastatic cancer who require bisphosphonate therapy and possibly more chemotherapy and/or experimental therapies because of more advanced disease, experience more episodes of dental infection and therefore require more oral surgical procedures? A review of the medical records of these patients to validate the presence of osteonecrosis of the jaws would have helped to strengthen this study.

Another concern of this administrative claims–based analysis of the potential relationship between bisphosphonates and osteonecrosis of the jaws is detection bias. As clinicians became aware of osteonecrosis of the jaws as a potential oral complication of bisphosphonate use, they are likely to have assessed patients receiving bisphosphonates more closely for osteonecrosis of the jaws than those not receiving bisphosphonates. Because the awareness of this potential relationship increased over time, it would have been useful for the authors to assess for possible detection bias by examining the hazard ratios year by year, stratifying for patients with a similar cumulative exposure. If the hazard ratios increased over time, this increase would support the possibility of detection bias. Furthermore, the Current Procedural Terminology codes that were used included procedures for tumor excision (21015 and 21034) and even impressions for fabrication of dentures (21081) that may have resulted in overestimation of risk.

There may have been underreporting of jaw conditions consistent with osteonecrosis of the jaws since the first cases of bisphosphate-related osteonecrosis of the jaws were reported in 2003, and the study ended in 2003. Because of more awareness of osteonecrosis of the jaws among oncologists and the dental community, the number of cases has increased tremendously in the years since 2003. As well, routine dental claims are not billable to Medicare, and those younger than age 65 years with osteonecrosis of the jaws would not be included in the study database. In spite of shortcomings, this study adds to the growing body of evidence of...
the relationship between use of intravenous bisphosphonates and the occurrence of osteonecrosis of the jaws.

How morbid is this condition and does it impact survival? With the newly introduced staging system (13), it is anticipated that more accurate data on the frequency of occurrence of osteonecrosis of the jaws in each of the stages, their clinical course (progression versus resolution), and morbidity will be obtained.

Bisphosphonates are an important and efficacious drug for managing skeletal-related events in patients with multiple myeloma and metastatic cancer. Although the association between osteonecrosis of the jaws and bisphosphonates had been called into question, the sheer number of cases reported since the widespread use of bisphosphonates began, as well as the mode of action of this class of drugs, lend support to the view that there is a real and probable causal relationship. Many studies are under way to define patient risk factors for osteonecrosis of the jaws, identify biomarkers that may predict osteonecrosis of the jaws and may help monitor progression, and identify radiographic findings that may indicate early bone pathology in the absence of overt osteonecrosis of the jaws. The morbidity of skeletal-related events in patients with cancer compared with the morbidity of patients who develop osteonecrosis of the jaws (of various severities) must be carefully weighed before making decisions to continue or discontinue bisphosphonate use.

References


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