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Web Exclusive: Bisphosphonates May Increase the Risk of Jaw Disease in Cancer Patients

BY THE NATIONAL CANCER INSTITUTE

Cancer patients taking bisphosphonate drugs for the prevention of fractures appear more likely to develop jaw disease than patients who do not take the drugs, according to an analysis of records from a large medical database.

Bones are constantly remodeled by the body—broken down and rebuilt in response to everyday stress and occasional damage. Cancer cells that spread (metastasize) to the bones can interfere with this process and cause pain and discomfort to patients.

Bisphosphonates are a kind of drug now frequently given to cancer patients whose disease has spread to the bones. When injected into a vein (intravenous) or taken by mouth (oral), bisphosphonates can slow the breakdown of bone and lower the rate of bone fractures.

However, intravenous bisphosphonates have been associated with osteonecrosis (bone death) in the jaws of some patients. Researchers believe that osteonecrosis may develop when bisphosphonates prevent the body from repairing microscopic damage to the jawbone, as can occur during routine dental procedures or from everyday wear and tear.

But it remains unclear how widespread this problem may be or what factors may put some patients at more risk. The study described below used a large database representing the population of the United States to estimate the incidence of osteonecrosis among cancer patients taking bisphosphonates.

The Study

The study's investigators used records from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which collects

information on cancer incidence and survival in 18 geographic regions that encompass approximately 26 percent of the U.S. population. SEER records can be linked to Medicare data to provide additional information on treatment received by patients aged 65 and older.

The researchers identified people diagnosed with cancer between 1986 and 2002 who had received at least one injection of the bisphosphonates pamidronate disodium (Aredia) or zoledronic acid (Zometa). They then matched each bisphosphonate user to two cancer patients diagnosed during the same years who had not received bisphosphonates (non-users) but who were otherwise largely similar in key respects (for example, type of cancer, age, sex, and risk factors for osteonecrosis).

Ultimately, investigators matched 14,349 bisphosphonate users with 28,698 non-users. Users were more likely to have bone metastases and require intravenous steroid drugs for their cancer, but in all other measured respects, users were similar to non-users.

The SEER-Medicare database did not have a specific code to designate osteonecrosis of the jaw. Instead, the investigators looked for cases of jaw inflammation as well as jaw or facial bone operations, outcomes that occasionally occur as a result of osteonecrosis. The investigators also estimated the total dose of bisphosphonates received by each user. The study's lead author was Gregg S. Wilkinson, PhD, of the University of Texas Medical Branch in Galveston.

Results

Starting at 18 months after they first received bisphosphonates, users were significantly more likely than non-users to be diagnosed with jaw inflammation or to have undergone jaw or facial surgery. This likelihood did not vary by age, sex, type of cancer, or other variables examined by the investigators.

The difference between users and non-users became more pronounced over time -- at six years of follow-up, 5.48 percent of those treated with bisphosphonates had been diagnosed with jaw inflammation or had undergone jaw or facial surgery, compared to 0.3 percent of non-users.

Among users, the higher their total (cumulative) dose of bisphosphonate, the greater the likelihood that they would suffer one or the other of the two outcomes occasionally associated with osteonecrosis.

Limitations

The investigators acknowledged that their study is limited because they could not measure the actual incidence of osteonecrosis. "Some misclassification was likely present," explained the investigators, since patients with conditions other than osteonecrosis, including infections acquired during chemotherapy, could have suffered jaw inflammation or undergone jaw or facial surgery.

Another limitation is that only patients 65 and older treated by a physician would

have been recorded in the SEER-Medicare linked database. Younger cancer patients, and those treated by a dentist instead of an oral surgeon, were automatically excluded from this analysis, leading to possible underestimation of the incidence of osteonecrosis.

In an accompanying editorial, Sook-Bin Woo, DMD, MMSc and Daniel Solomon, MD, of Brigham and Women's Hospital in Boston, Mass., noted that “[s]tudies of this nature may both overestimate and underestimate incidence and prevalence.”

In addition, the investigators could not study whether one kind of bisphosphonate was more likely to cause osteonecrosis than another. A database code for zoledronic acid distinct from pamidronate disodium did not exist until 2002, and the Medicare database did not record data on the use of oral bisphosphonates, which are thought to be less likely to cause osteonecrosis than bisphosphonates given intravenously.

Comments

In spite of these shortcomings, state Woo and Solomon in their editorial, “this study adds to the growing body of evidence of the relationship between use of intravenous bisphosphonates and the occurrence of osteonecrosis of the jaw.”

“I think [this study] is a great step,” agreed Lillian Shum, PhD, program director with the National Institute for Dental and Craniofacial Research. Large clinical trials are now needed, she said, in particular to compare the benefits and side effects of different bisphosphonate regimens. Bisphosphonates vary widely in how much they inhibit bone breakdown, and “there is a chance that...individualized treatment using one drug over another can benefit some people and avoid the risk,” she stated.

In the meantime, said the authors, “it is important that patients receiving therapy with both established and new formulations of intravenous bisphosphonates be followed carefully for adverse bone events involving the facial bones that may be indicative of osteonecrosis of the jaw.”

SOURCE: [Journal of the National Cancer Institute, July 4, 2007](#)