BoneKEy-Osteovision. 2006 September;3(9):24-27
http://www.bonekey-ibms.org/cgi/content/full/ibmske;3/9/24
DOI: 10.1138/20060230

COMMENTARIES

Bisphosphonates for Metastatic Bone Disease — Too Much of a Good Thing?

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Commentary on: Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006 May 16;144(10):753-61.

Bisphosphonates are an important part of the supportive care of many patients with cancer. Potent intravenous bisphosphonates are the standard of care for hypercalcemia of malignancy and reduce the risk of skeletal complications, including fractures and spinal cord compression, in patients with bone metastases resulting from a broad spectrum of primary tumor types, including breast, prostate, and lung cancer. For patients with metastatic bone disease, bisphosphonates are approved at cumulative doses many-fold higher than those recommended to treat benign bone disease. Zoledronic acid, for example, is approved to treat patients with bone metastases at the dose and schedule of 4 milligrams every 3-4 weeks. In contrast, zoledronic acid 5 milligrams once every 12 months is in development for the treatment of postmenopausal osteoporosis. Osteonecrosis of the jaw (ONJ) has emerged as an adverse effect of bisphosphonate therapy, primarily in patients receiving bisphosphonates for metastatic bone disease. These observations raise the question of whether the current dose and schedule for metastatic bone disease represent too much of a good thing. A recent review on ONJ provides insight into this important controversy.

The review by Woo *et al*. (1) observes that most of the reported cases of ONJ have been in patients with multiple myeloma or breast cancer who had received treatment with pamidronate, zoledronic acid, or both drugs. The relationship between bisphosphonates and ONJ appears dependent on time and dose. Most cases occur after dental surgery. Woo *et al*. emphasize that little is known about the pathophysiology of ONJ but conclude that the mechanism of ONJ is probably " severe suppression of bone turnover." If correct, the latter observation suggests that ONJ is a potential adverse effect of any potent osteoclast-targeted therapy.

Dose and Schedule Considerations

The currently recommended dose and schedule of zoledronic acid (4 milligrams every 3-4 weeks) for treatment of bone metastases arose from two phase I dose ranging studies (2;3). In the first, 44 patients with bone metastases from a variety of primary tumor types were treated with a single intravenous injection of zoledronic acid (1, 2, 4, 8, or 16 milligrams) (2). Zoledronic acid at doses ≥ 2 milligrams suppressed urinary NTx by > 50% for up to 8 weeks with no discernable dose-effect at higher dose levels. Zoledronic acid at 1 milligram achieved less marked and less durable marker suppression. In a second phase I study, 59 patients with bone metastases from a variety of primary tumor types were treated with monthly intravenous injections of zoledronic acid (0.1, 0.2, 0.4, 0.8, 1.5, 2, 4, or 8 milligrams) for three months (3). A dose-dependent decrease in all markers of bone resorption was

observed, although the dose-response curve was flat for doses ≥ 0.8 milligrams/month. Based on the results of these studies, zoledronic acid (4 and 8 milligrams every 3-4 weeks) was selected for development in the pivotal randomized controlled trials. The 8-milligram dose was subsequently discontinued because of excess renal toxicity.

Should the recommended dose and schedule of bisphosphonate therapy for patients with metastatic bone disease be revisited based on recent recognition of ONJ as an adverse effect of bisphosphonate therapy?

Only large prospective clinical trials can provide the definitive answers about safety and efficacy of alternative doses and schedules. Recent retrospective analyses of the relationship between biochemical markers of osteoclast activity and clinical outcomes, however, may provide some valuable guidance. Using data from subjects with bone metastases from prostate cancer and other solid tumors assigned to the placebo-arm of two pivotal studies of zoledronic acid, Brown *et al*. reported that elevated levels of urinary NTx are associated with shorter time to skeletal-related events, skeletal disease progression, and death (4). In subjects assigned to zoledronic acid in the three pivotal studies for bone metastases, higher levels of urinary NTx during treatment are also associated with shorter time to skeletal-related events, disease progression, and death (5). Notably, baseline urinary NTx was elevated (>50 nmol/mmol creatinine) in approximately 80% of subjects in the pivotal studies of zoledronic acid. During treatment with zoledronic acid, urinary NTx was elevated (>50 nmol/mmol creatinine) in about 20% of subjects with breast or prostate cancer and markedly elevated (>100 nmol/mmol creatinine) in about 10% of these subjects.

Taken together, these observations that (1) elevated NTx is associated with adverse clinical outcomes, and (2) urinary NTx is persistently elevated in a substantial subset of patients during bisphosphonate treatment suggest that lower doses and/or a less frequent schedule in unselected patients is likely to decrease efficacy. The substantial interpatient variations in baseline markers of osteoclast activity and response to bisphosphonate treatment raise the question of whether individualized bisphosphonate therapy represents an effective strategy to improve safety, cost, and convenience. In the BISMARK (BISphosphonate MARKer) study recently launched in the United Kingdom, 1400 women with metastatic breast cancer will be randomly assigned to either zoledronic acid at the standard dose and schedule or zoledronic acid at a less frequent schedule based on levels of urinary NTx. The primary endpoint will be skeletal-related events. Secondary endpoints include survival, quality of life, and cost.

Duration of Therapy

There is limited information about the optimal duration of bisphosphonate treatment to prevent disease-related skeletal complications in cancer patients. In the completed randomized controlled trials of pamidronate and zoledronic acid in patients with bone metastases, the duration of study treatment was only 12 to 24 months. An ongoing, industry-initiated, randomized controlled trial will help determine the optimal duration of bisphosphonate treatment and the potential role of alternate maintenance schedules in metastatic breast cancer, although the expected results of this study are many years away and may not be applicable to other cancer types.

The current American Society of Clinical Oncology (ASCO) guidelines for bisphosphonates in multiple myeloma and metastatic breast cancer recommend that once initiated, intravenous bisphosphonates “should be continued until substantial decline in a patient’s general performance status” (6;7). Notably, these guidelines were developed prior to the first reports linking bisphosphonates to ONJ in 2003. The recent emergence of ONJ as a potential risk from long-term bisphosphonate exposure, however, suggests that the recommended duration of bisphosphonate treatment should be revisited. A recent consensus statement from the Mayo Clinic for use of

bisphosphonates in multiple myeloma, for example, recommended discontinuation of bisphosphonates after two years for patients with complete responses or plateau phase and less frequent treatment (every 3 months) for patients with active myeloma (8). Prospective studies will be required to determine the effect of shortened treatment duration and/or less frequent maintenance schedules on safety and efficacy.

The life expectancy for patients with bone metastases from solid tumors is short. The median overall survival for men with hormone-refractory metastatic prostate cancer, for example, is only 15-18 months. The median overall survival for patients with bone metastases from lung cancer is even shorter. Accordingly, the challenging risk-benefit considerations about treatment duration are relevant only for the small subset of patients with indolent metastatic disease or particularly durable responses to systemic treatment.

Future Directions

In addition to marker-directed treatment with bisphosphonates, newer bone-targeted agents may hold the promise for improving the therapeutic index in the management of metastatic and benign bone disease. Denosumab is a fully human monoclonal antibody against RANKL in development for the treatment of benign and malignant bone disease. Denosumab achieves rapid and sustained inhibition of osteoclast activity in postmenopausal women and patients with multiple myeloma or bone metastases from breast cancer (9;10). In contrast to bisphosphonates, denosumab does not accumulate in bone and achieves sustained osteoclast inhibition due at least in part to a long circulatory half-life (>30 days). Will the distinct mechanism of action and pharmacokinetics of denosumab prevent ONJ? Or is sustained osteoclast inhibition sufficient to increase the risk of ONJ regardless of pharmacokinetics and mechanism of action? These questions are now being put to the test in head-to-head randomized controlled trials of zoledronic acid and denosumab in metastatic bone disease.

Conflict of Interest: The author reports that he receives research support and consulting fees from Novartis Oncology and Amgen.

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