



# Optimizing Bone Health in Cancer Patients

## IT'S NOT TOO LATE

It's not too late to participate in educational programming on optimizing bone health in cancer patients! Live programs will be conducted through November 2011 and an on line archived webinar is available until May 2012 at [www.optimizingbonehealth.com](http://www.optimizingbonehealth.com). Earlier this year ASHP Advantage embarked on an initiative for pharmacists on optimizing bone health in cancer patients supported by an educational grant from Novartis Oncology. The initiative comprised a series of live educational activities with interactive cases conducted in cooperation with ASHP State Affiliate organizations and an archived case-based webinar. The epidemiology and pathophysiology of skeletal-related events (pathologic bone fractures, spinal cord compression, need for surgery or radiation therapy to bone, and hypercalcemia of malignancy) in patients with cancer was discussed in these programs, and the management of bone metastases and prevention of skeletal-related events (SREs) was illustrated using patient cases.

To participate in an educational activity, pharmacists may choose whichever program format is most convenient: (1) attending one of various scheduled ASHP State Affiliate meetings (go to [www.optimizingbonehealth.com](http://www.optimizingbonehealth.com) for a list of program locations, dates, and times), or (2) participating in a web-based activity on demand at any time at home or in the work place through the initiative Web site ([www.optimizingbonehealth.com/](http://www.optimizingbonehealth.com/)) or the American College of Clinical Pharmacy Web site (<http://www.accp.com/>). One hour of continuing

pharmacy education credit for participating in the program will be available through ASHP. There is no charge, and membership in ASHP is not required to participate in the program. For additional information about the program, go to the initiative Web portal at [www.optimizingbonehealth.com](http://www.optimizingbonehealth.com).

## PRACTICE CHANGES

A post-activity email survey of participants in a live educational webinar on April 14, 2011, *Optimizing Bone Health in Cancer Patients*, was conducted to identify behavior and practice changes that they might implement based on the knowledge acquired by participating in the educational activity and what barriers might interfere with these plans. Most (94%) of the 54 survey respondents indicated that they made or recommended (or intend to make or recommend) a wide variety of changes in practice after participating in the activity. Topping the list of practice changes reported by these respondents are being more aware of monitoring for adverse events (85%), paying more attention to patients with breast or prostate cancer and whether bone-modifying therapy is appropriate (83%), and keeping abreast of ongoing studies, especially those discussed in the presentation (81%). Lack of staff time, knowledge, funds, and physician cooperation were identified as the primary barriers to implementing practice changes. Five respondents indicated that they did not make or recommend any changes at their practice site. Two of these respondents already had established effective measures for bone-modifying therapy in patients with bone metastases or cancer

treatment-induced bone loss (CTIBL) at the institutional and patient-care levels, two respondents were not currently in active practice, one respondent lacked the opportunity to make changes, and one respondent lacked sufficient time to make changes.

Most respondents (79%) would recommend the accredited on-demand Web-based version of the live webinar to their colleagues as a way to establish common ground for working to improve the management of bone-modifying therapies in treating patients with bone metastases or CTIBL in their institution or practice. Three of four respondents would recommend the program to students and residents.

## ANSWERS TO FREQUENTLY ASKED QUESTIONS

Through the TALK TO US feature on the initiative Web site and activity evaluations, pharmacists have the opportunity to ask the faculty for insight on clinical dilemmas and controversial issues. Included here are answers to several frequently asked questions that have been submitted.

**Q** What are the pharmacoeconomic considerations in choosing among currently available bone-modifying medications (i.e., bisphosphonates, denosumab) for patients with bone metastases?

**A** In two large phase III studies of women with metastatic breast cancer and men with castration-recurrent (i.e., hormone-resistant) prostate cancer and bone metastases, denosumab was more effective than intravenous (i.v.) zoledronic acid for delaying the time to a first SRE (a composite of pathologic bone fracture, spinal cord compression, and need for surgery or radiation therapy to bone).<sup>1,2</sup> However, no significant differences were found between the two drugs in overall survival, time to disease progression, or the incidence of serious adverse effects.<sup>1,2</sup> As discussed in the March 2011 issue of this Optimizing Bone Health in Cancer Patients eNewsletter series, insufficient evidence is available to support greater efficacy of zoledronic acid, pamidronate, or denosumab, according to the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer released earlier this year by the American Society of Clinical Oncology (ASCO).<sup>3</sup>

The acquisition cost of denosumab is nearly double

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that of zoledronic acid.<sup>4</sup> Few denosumab pharmacoeconomic data are available in the literature and most data pertain to patients with osteoporosis, not cancer. Pharmacoeconomic data comparing denosumab with currently available i.v. bisphosphonates for prevention of SREs in patients with solid tumors and bone metastases could be helpful to clinicians in selecting bone-modifying therapy for this patient population.

The results of two cost-effectiveness analyses of zoledronic acid versus denosumab for prevention of SREs in patients with metastatic breast cancer or hormone-refractory prostate cancer and bone metastases from

a managed care perspective were presented in poster sessions at the ASCO Annual Meeting in June 2011.<sup>5,6</sup> A model was developed based on published literature to estimate the survival, number of SREs, quality-adjusted life years (QALY) gained, and cost per QALY gained with these therapies over a period of 27-28 months in these two patient populations. The costs of drug acquisition, administration, and monitoring and costs for SREs were taken into consideration. In both patient populations, fewer SREs, more QALYs, and lower costs for SREs were associated with denosumab than zoledronic acid, but drug acquisition costs and total costs (i.e., costs of drug acquisition, administration, and monitoring and costs of SREs) were higher for denosumab than zoledronic acid. The incremental cost per QALY gained by using denosumab instead of zoledronic acid in women with metastatic breast cancer and men with hormone-refractory prostate cancer was \$643,726 and \$1,248,051, respectively, both of which exceed the amount considered reasonable for a medical intervention (\$50,000-\$100,000).

In another financial analysis, the impact of adding denosumab to a managed care formulary that already includes zoledronic acid and providing coverage for denosumab for 1 million members of a health plan was modeled over a 1- to 3-year time frame.<sup>4</sup> The results of the analysis using this model were published in conjunction with the June 2011 ASCO Annual Meeting. Costs for drug acquisition and administration, SREs, and adverse events were taken into consideration. The annual cost of a formulary with only zoledronic acid was \$10.8 million. The cost of a formulary with restricted access to denosumab over 1 year, 2 years, and 3 years was \$11.4 million, \$11.6 million, and \$11.7 million, respectively. The cost of a formulary with open access to denosumab over 1 year, 2 years, and 3 years was \$11.8 million, \$12.3 million, and \$12.8 million, respectively.

Although the available pharmacoeconomic data for bone-modifying agents in patients with bone metastases are limited, these recent pharmacoeconomic analyses illustrate the potential for increased costs if denosumab is used instead of zoledronic acid in this patient population. Clinicians and health plan administrators need to consider whether the incremental costs are worthwhile. Although cost considerations are important to health care providers and systems, patient care benefits should not be overlooked. The convenience of the subcutaneous route of administration is a potential advantage of denosumab over the i.v. route of administration for

bisphosphonates. Other clinical factors also should be considered, including the risk for hypocalcemia in patients receiving denosumab and the need for renal function monitoring in patients receiving bisphosphonates.<sup>7-9</sup> Although the recent pharmacoeconomic analyses provide helpful information, additional comparative pharmacoeconomic data are needed to further define the roles of denosumab and i.v. bisphosphonates in this patient population.

—Chad Barnett, Pharm.D., BCOP

**Q** How often should kidney function be monitored in patients receiving intravenous (i.v.) bisphosphonates?

**A** The bisphosphonates zoledronic acid and pamidronate are excreted intact primarily by the kidneys.<sup>8,9</sup> Patients with renal impairment may be at increased risk for adverse effects, especially renal adverse effects, compared with patients with normal renal function. Deterioration in renal function may occur during bisphosphonate therapy in patients with preexisting renal impairment, especially patients in whom it is severe (creatinine clearance <30 mL/min). Other risk factors for deterioration in renal function include dehydration, the use of multiple cycles of bisphosphonates, and the use of other nephrotoxic drugs.

Zoledronic acid and pamidronate are not recommended for patients with bone metastases and severe renal impairment. Use of the drugs in patients with hypercalcemia of malignancy and severe renal impairment should be considered only after evaluating the risks and benefits of treatment.

According to the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer released earlier this year by ASCO, no adjustment in dosage, infusion time, or interval is required for i.v. bisphosphonates in patients with a creatinine clearance exceeding 60 mL/min, but the serum creatinine concentration should be monitored before each i.v. bisphosphonate dose.<sup>3</sup> The prescribing information for zoledronic acid outlines dosage reductions for patients with a creatinine clearance of 30-60 mL/min.<sup>9</sup> The ASCO clinical practice guideline update did not address patients with solid tumors other than breast cancer or hypercalcemia of malignancy. Because renal function often changes in these patients during the 3- to 4-week interval between

doses, measuring the serum creatinine concentration prior to each i.v. bisphosphonate dose appears warranted. Clinicians should bear in mind that the risks versus benefits of receiving any drug should always be weighed prior to initiating therapy.

—Jane M. Pruemer, Pharm.D., BCOP, FASHP

**Q** In patients with renal impairment, does a creatinine clearance measured using a 24-hour urine collection provide a more accurate indication of renal function than creatinine clearance estimated from a serum creatinine measurement alone?

**A** An estimate of creatinine clearance (mL/min) can be made using the Cockcroft-Gault formula:  $[140 - \text{age (yr)}] \times \text{weight (kg)} \times [0.85 \text{ for female patients}] / [72 \times \text{serum creatinine (mg/dL)}]$ . The Cockcroft-Gault formula for estimating creatinine clearance is based on many assumptions, the most important of which is that the serum creatinine concentration is a true reflection of creatinine clearance. This assumption generally is accurate for young adults, but it is not always accurate for elderly persons in their 60s or beyond because of age-related changes in body mass composition (typically decreased muscle mass and increased fat content). Use of the Cockcroft-Gault formula may over estimate creatinine clearance in elderly cancer patients.

Collecting the urine for 24 hours to determine the amount of creatinine excreted during this period and measuring the serum creatinine concentration at the time of urine collection allows measurement of the true creatinine clearance. This true creatinine clearance is preferred over an estimate obtained using the Cockcroft-Gault formula, especially in elderly cancer patients, because it is a more accurate reflection of renal function.

—Jane M. Pruemer, Pharm.D., BCOP, FASHP

**Q** What is your opinion regarding the need for a baseline dental examination before starting bone-modifying therapy in patients with cancer?

**A** Osteonecrosis of the jaw (ONJ) is a rare but potentially serious adverse effect that occurs primarily in patients with cancer who are receiving bone-modifying agents.<sup>3</sup> Bisphosphonate-associated ONJ is defined as an area of exposed bone in the maxillofacial or mandibular region that persists for more than 8 weeks after identification by a health care provider in a patient who

has been receiving an oral or i.v. bisphosphonate with no prior radiation to the area.<sup>10</sup> The risk for ONJ is increased in patients undergoing dentoalveolar surgery (e.g., dental extraction, dental implant placement) and with the use of high-potency bisphosphonates (e.g., zoledronic acid and to a lesser extent, pamidronate) and a long duration of bisphosphonate therapy. Clinicians are particularly concerned about the risk of ONJ in patients with solid tumors and bone metastases who are receiving bisphosphonates or other bone-modifying agents because therapy often is provided for a long period. The estimated incidence of ONJ is 0.8% to 12% in patients receiving high-potency i.v. bisphosphonates and much lower in patients receiving oral bisphosphonates (0.7 cases per 100,000 person years of exposure for alendronate), although the exact population incidence is unknown due to differing definitions of ONJ and reporting biases.<sup>10</sup>

Denosumab has also been associated with ONJ. In three large phase 3 trials comparing denosumab with zoledronic acid for prevention of SREs in patients with bone metastasis from solid tumors, the incidence of ONJ was similar (1.8% versus 1.3%, respectively).<sup>7</sup>

Treating ONJ can be challenging, so clinicians should focus on minimizing the risk of ONJ by optimizing the dental health of patients with risk factors. All patients should receive a dental examination and appropriate preventive dentistry before initiating bone-modifying therapy and maintain optimal oral health during treatment.<sup>3</sup> Pharmacists can play an important role in avoiding ONJ by counseling patients about the symptoms that may occur prior to clinically-detectable ONJ (e.g., pain, tooth mobility, mucosal swelling, erythema, ulceration), need for a dental examination and preventive dental care prior to initiating bone-modifying therapy, and use of good oral hygiene (e.g., brushing and flossing after meals, use of a fluoride mouth rinse) and avoidance of invasive dental procedures if possible during bone-modifying therapy.<sup>7-9,11</sup> Preventive dentistry has been shown to decrease the risk of ONJ in patients with malignancy receiving i.v. bisphosphonates.<sup>10</sup> Strong evidence-based recommendations for preventive dentistry are lacking for patients receiving oral bisphosphonates. Practically speaking, it would be reasonable to inquire about a patient's dental health prior to starting an oral bisphosphonate and refer the patient to a dentist if the patient has a history of poor dental health.

—Chad Barnett, Pharm.D., BCOP

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