News and Views from the Literature

Prostate Cancer

Bisphosphonates in Metastatic Prostate Cancer

Reviewed by Masood A. Khan, MD, Alan W. Partin, MD, PhD
Department of Urology, Johns Hopkins School of Medicine, Baltimore, MD

[*Rev Urol*. 2003;5(3):204–206]

Bone is the most common, and frequently the only, site for prostate cancer metastases; bone metastases occur in 80% of men with advanced prostate cancer.[1] Bone metastases result in substantial morbidity, including pain, spinal cord compression, and pathologic fractures.[2]

Hormonal therapy that results in the suppression of androgen activity with either surgical or medical castration (using luteinizing hormone-releasing hormone analogues), with or without antiandrogens, is regarded as the optimal first-line therapy for patients with metastatic prostate cancer.[3] Unfortunately, hormonal therapy is only initially successful in 70% to 80% of cases, with a median duration of response of 12 to 24 months.[3] In addition, long-term use of androgen blockade has been shown to result in osteoporosis, thereby further contributing to bone fragility.[4]

Treatment of advanced, hormone-resistant prostate cancer primarily involves relief of symptoms and improvement in quality of life. Bisphosphonates have been shown to decrease the level of pain experienced and reduce the risk of skeletal events (eg, pathologic fractures, hypercalcemia, and the need for radiotherapy or surgery) in patients with bony metastases secondary to breast cancer[5] and multiple myeloma.[6] Bisphosphonates act predominantly by inhibiting bone-resorbing osteoclasts that are associated with the formation of osteolytic bone lesions. Prostate cancer is associated with osteoblastic (not osteoclastic) bone lesions that result in the deposition of calcium in new bone. The rationale for the use of bisphosphonates in the treatment of prostate cancer is that biochemical and histomorphometric studies have indicated that osteolysis may also be present in prostate cancer bone metastases.[2,7,8] The following recently published studies report on the impact of bisphosphonates in patients with metastatic prostate cancer.

A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients with Hormone-Refractory Metastatic Prostate Carcinoma

Saad F, Gleason DM, Murray R, et al.
J Natl Cancer Inst. 2002;94:1458–1468.

In a randomized, placebo-controlled, phase III trial, the authors evaluated the ability of zoledronic acid, a new nitrogen-containing bisphosphonate, to reduce skeletal-

related events associated with metastatic bone disease in patients with hormone-refractory prostate cancer. A total of 643 patients were randomly assigned to receive either intravenous infusions of placebo or zoledronic acid (4 mg or 8 mg over 15 minutes) every 3 weeks for up to 15 months. Proportions of patients with skeletal-related events, time to the first skeletal-related event, skeletal morbidity rate, pain and analgesic scores, disease progression, and drug safety were assessed. Because of suspicion that the 8-mg infusion dose of zoledronic acid might be associated with renal dysfunction, all patients in this treatment arm subsequently received the 4-mg infusion dose of zoledronic acid. The results of the study showed that a significantly greater proportion of patients from the placebo group had skeletal events than those who received zoledronic acid, 4 mg (43.2% vs 33.2%, respectively; $P < .03$). Similarly, the median time to the first skeletal-related event was significantly shorter in the placebo group than in the patients who received zoledronic acid, 4 mg (363 days vs 420 days, respectively; $P < .02$). Pain scores and the use of analgesics increased more in patients who received placebo than in patients who received zoledronic acid, but there were no differences in disease progression, performance status, or quality-of-life scores between the groups. The authors concluded that zoledronic acid, 4 mg, was well tolerated and reduced skeletal-related events in prostate cancer patients with bone metastases.

A significantly greater proportion of patients from the placebo group had skeletal events than those who received zoledronic acid, 4 mg.

Caution needs to be applied in interpreting these data for the routine introduction of zoledronic acid as a treatment option for patients with metastatic prostate cancer. Although the authors comment that zoledronic acid was well tolerated, the incidence of fatigue, anemia, myalgia, fever, and lower-limb edema were all higher (by at least 5%) in patients who received zoledronic acid. This may account for the lack of improvement in quality-of-life among the patients who received zoledronic acid, even though they experienced fewer skeletal-related events. Furthermore, fewer than 40% of the patients who received zoledronic acid completed the study. The 2 major causes for discontinuation from the study, accounting for approximately 60% of the causes, were adverse drug-related events and withdrawal of consent. In addition, zoledronic acid did not influence disease progression.

The Placorhen Study: A Double-Blind, Placebo-Controlled, Randomized Radionuclide Study with ^{186}Re-Etidronate in Hormone-Resistant Prostate Cancer Patients with Painful Bone Metastases. Placebo Controlled Rhenium Study

Han SH, de Klerk JMH, Tan S, et al.
J Nucl Med. 2002;43:1150–1156.

Although local-field, external-beam radiotherapy can be effective in treating focal bone metastasis, synchronous multiple bone metastases are less suitable for such treatment. Alternatively, systemic radionuclide therapy using bone-seeking agents—with the advantage that all affected areas are treated simultaneously, with relative sparing of the surrounding tissue—can be considered for painful metastases. In a double-blind, randomized, placebo-controlled study, using a computer-assisted, standardized, objective method of pain assessment, these authors evaluated the efficacy of ^{186}Re-etidronate for the treatment of painful bone metastases in patients with androgen-independent prostate cancer. A positive “pain response day" was defined as a day on which pain intensity was reduced by 25% or greater compared with the baseline value and the medication index and daily activities were at least constant, or a day on which pain intensity was reduced less than 25% and the medication index or daily activities improved by 25% or greater. The total response (%) was defined as the number of positive response days divided by the number of days of follow-up.

Systemic radionuclide therapy using bone-seeking agents can be considered for painful metastases.

Of the 111 patients enrolled, 79 were evaluable (43 received ^{186}Re-etidronate and 36 received placebo). The total response of the patients who received ^{186}Re-etidronate varied from 0% to 96% (mean, 27%) and was significantly greater ($P < .05$) than the response in the placebo group (0%–80%; mean, 13%). In addition, the number of patients who required radiotherapy was higher in the placebo group than among the patients who received ^{186}Re-etidronate (67% vs 44%, respectively). This, however, did not reach statistical significance ($P < .07$). There was no difference in the survival interval between the 2 groups. The results of this study are encouraging for the use of ^{186}Re-etidronate for the management of bone pain from metastatic prostate cancer. However, the authors reported on a relatively short posttreatment follow-up period of 12 weeks. Longer follow-up data are required.

High Activity Rhenium-186 HEDP with Autologous Peripheral Blood Stem Cell Rescue: A Phase I Study in Progressive Hormone Refractory Prostate Cancer Metastatic to Bone

O'Sullivan JM, McCready VR, Flux G, et al.
Br J Cancer. 2002;86:1715–1720.

Rhenium-186 (^{186}Re) combined with the bisphosphonate hydroxyethylidene diphosphonate (HEDP) has previously been shown to produce response rates ranging from 30% to 80%, with a mean duration of response of 7 weeks, in patients with bone pain secondary to metastatic prostate cancer.[9] These study authors postulated that by increasing the administered activity of ^{186}Re-HEDP, palliation benefits may be maximized. In order to prevent major bone marrow toxicity, autologous peripheral blood stem cell rescue (PBSCR) was used in all patients. The feasibility and toxicity of high activities of ^{186}Re-HEDP (2500–5000 MBq) followed 14 days later by the return of PBSCR was tested in a phase I trial that enrolled 25 patients with androgen-independent prostate cancer metastatic to bone. Activity-limiting toxicity (grade 3/4 hematologic toxicity) occurred in 2 of the 6 patients who received 5000 MBq. A prostate-specific antigen (PSA) reduction of 50% or greater lasting at least 4 weeks was demonstrated in 20% of the patients (n = 5), and the actuarial survival at 1 year was 54%. These results are encouraging in that the authors have shown that administered activities of 5000 MBq of ^{186}Re-HEDP with PBSCR are feasible and produce a PSA response (mean duration, 3.5 months). The authors have commenced a phase II trial to further evaluate the response rates. ■

References

1. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer.* 2000;88:2989–2994.
2. Scher HI, Chung LW. Bone metastases: improving the therapeutic index. *Semin Oncol.* 1994;21:630–656.
3. Gotkas S, Crawford ED. Optimal hormonal therapy for advanced prostatic carcinoma. *Semin Oncol.* 1999;26:162–173.
4. Diamond T, Campbell J, Bryant C, Lynch W. The effects of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma. *Cancer.* 1998;83:1561–1566.
5. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med.* 1996;335:1785–1791.
6. Djulbegovic B, Wheatley K, Ross J, et al. Bisphosphonates in multiple myeloma. *Cochrane Database Syst Rev.* 2002;(3):CD003188.
7. Clarke NW, McClure J, George NJ. Morphometric evidence for bone resorption and replacement in prostate cancer. *Br J Urol.* 1991;68:74–80.
8. Garnero P, Buchs N, Zekri J, et al. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. *Br J Cancer.* 2000;82:858–864.
9. Maxon HR 3rd, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. *J Nucl Med.* 1991;32:1877–1881.

Hormonal Therapy

Androgen Replacement and Quality of Life

Reviewed by Jacob Rajfer, MD
The David Geffen School of Medicine at UCLA and Division of Urology, Harbor-UCLA Medical Center, Los Angeles, CA

[*Rev Urol.* 2003;5(3):206–207]

Considerable attention is being paid to the quality of life as men age—and why not? As men age, they still want to remain productive, active and, of course, healthy. Unfortunately, it seems that nature is cruel. For men, this cruelty starts immediately after college, when they begin to notice, ever so subtly, that the refractory period between their erectile events increases. As men enter their forties, they begin to notice that their erections have started to change, such that the erections may not be as rigid as they once were or do not seem to last as long. Some men even begin to lose that "every moment's interest in sex" that seems to define their persona during youth. This change in sexuality, coupled with the other phenotypic evidence of aging, such as losing one's hair and increasing one's waistline, begs the question—what's next? As most men who have already traveled that road know so well, it does not get any better. What men also have to look forward to with aging is an increasing sense of lethargy, occasional bouts of memory failure, recognition of no longer being a Samson, and, sometimes, depression. Yes, they can become grumpy, overweight, old men.

These aforementioned symptoms and signs are referred to as andropause or androgen deficiency of the aging man (ADAM). As men age, their testosterone levels—particularly their free testosterone levels—decrease. There are many reasons for this but, suffice it to say, this does occur in many men. If these symptoms of aging result from a decrease in testosterone levels, it makes sense that such men may benefit from exogenous androgen treatment. Many men opt for this treatment when confronted with their midlife changes because the evidence suggests that many of these afflictions of aging are ameliorated with androgen replacement.