Bisphosphonates in Prostate Cancer: Where Are We and Where Should We Go?

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Bone metastases are frequent occurrences in prostate cancer. The discovery that prostate cancer is a hormone-dependent cancer has substantially altered strategies for treating this disease. Hormone therapy has since become the focus of much of the therapeutic improvement in the management of advanced prostate cancer. The use of hormone therapy prior to the appearance of metastases has resulted in improved survival in randomized studies and has led to the widespread use of early, as well as adjuvant, hormone therapy. One of the drawbacks of long-term hormone therapy has been reported in recent studies on the effects of androgen-deprivation therapy on bone metabolism.

We now realize that bone loss is evident over time and that men who receive such therapy have an increased risk of osteoporotic fractures (1).

The class of compounds known as bisphosphonates have generated interest as therapeutic agents for prostate cancer because of evidence that they reduce the risk of fracture among postmenopausal women with osteoporosis (2). However, only a few studies have examined the effects of various bisphosphonates on preventing bone loss among men undergoing androgen-deprivation therapy. For example, pamidronate, given intravenously every 3 months, was recently shown to prevent bone loss in men undergoing medical castration for prostate cancer (3). A subsequent study (3) reported that zoledronic acid, used intravenously every 3 months to treat men undergoing medical castration, was associated with an increase in bone mineral density over 1 year. No study to date has shown that either of these agents reduces the risk of fractures in a similar group of patients.

Bisphosphonates have been shown to be effective in reducing bone complications in patients with osteolytic bone metastases due to multiple myeloma and breast cancer (4). It was long felt that prostate cancer, which produces osteoblastic metastases, would not be responsive to bisphosphonates because these agents primarily inhibit osteoclast function. However, results of a recent study (5) have revealed that bone resorption in metastatic prostate cancer is very high, reflecting substantial osteoclastic activity. Therefore, there is biologic rationale for the use of bisphosphonates in prostate cancer to treat both the metastases and the ongoing bone loss due to androgen deprivation. Unfortunately, early-generation bisphosphonates had not been shown to statistically significantly improve the outcomes of men with metastatic prostate cancer (6). In a recent report (7), the third-generation bisphosphonate zoledronic acid was shown to statistically significantly reduce the proportion of patients with hormone-refractory prostate cancer and bone metastases who experienced a skeletal-related event (SRE), including fractures, over 15 months. A statistically significant delay in the onset of the first SRE and a reduction in the overall rate of SREs over time were also observed.

In this issue of the Journal, Dearnaley et al. (8) report on 311 men with hormone-sensitive metastatic prostate cancer who were randomly assigned to receive oral clodronate (a first-generation bisphosphonate) or placebo for 3 years. This was a very well-planned study with adequate follow-up to reach conclusions about the efficacy of this bisphosphonate. The primary endpoint was symptomatic bone progression–free survival. Secondary endpoints included overall survival and toxicity. The authors report a reduction in symptomatic bone progression–free survival in the clodronate group that did not reach statistical significance. Survival was better in the clodronate group than in the placebo group but did not reach statistical significance. The authors note, however, that statistically significantly more patients in the clodronate group than in the placebo group experienced drug-related toxicity that required a reduction in drug dose. Results of a subgroup analysis appear to indicate that patients who began therapy when their cancer was at an earlier stage of metastasis had better outcomes than patients who began therapy when their cancer was at a later stage of metastasis.

The inability to demonstrate a statistically significant benefit using clodronate in metastatic prostate cancer may be due to several factors. First, the bioavailability of oral bisphosphonates through the gastrointestinal tract is limited. Therefore, the amount of drug that reaches the bone may be insufficient to obtain the necessary effect in a bone environment that is severely damaged by both the effects of metastases and bone loss resulting from androgen deprivation. Drug tolerability is also limited by the gastrointestinal toxicity related to this class of drugs and therefore limits dosage. A second factor that could limit the efficacy of clodronate is the potency of the drug itself. A trial done by the National Cancer Institute (9) that also used clodronate (but in this case, intravenously) did not show a statistically significant benefit in patients with hormone-refractory prostate cancer receiving chemotherapy. Another placebo-controlled trial [reported in (5)] in hormone-refractory prostate cancer also reported that the second-generation bisphosphonate, pamidronate IV, showed no statistically significant benefit. Here again, potency of the drug may have been the limiting factor.

The study by Dearnaley et al. (8) provides at least some evidence that starting bisphosphonates earlier in the metastatic state may give better results. In addition, the authors suggest that using more potent, newer-generation bisphosphonates may eventually lead to even better control of complications related to metastatic prostate cancer. The challenge will be to identify patients that are most at risk and therefore most likely to benefit. Research into the usefulness of markers of bone turnover, for example, may help to identify patients at higher risk of experiencing bone complications and help to limit costs related to treatment. For now, the main risk factor for complications is the presence of bone metastases in patients with hormone-refractory disease. These patients are at very high risk for bone complica-

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tions and should be considered for bisphosphonate therapy. To date, the only regimen that has proven to be effective in treating such patients is intravenous zoledronic acid. Research into the earlier use of bisphosphonates in metastatic prostate cancer as well as into the potential of bisphosphonates to actually prevent metastases is ongoing. With a better understanding of the role of bisphosphonates in treatment-induced bone loss, prevention and treatment of metastases, and antitumor effects, it is most likely that the role they play will expand in the management of advanced prostate cancer.

REFERENCES