Use of Bisphosphonates in the Treatment of Prostate Cancer

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By Richard Theriault, DO, MBA [1]

Recently, there has been much controversy over whether patients with prostate cancer should be treated with bisphosphonates not only to decrease pain, but to prevent metastasis.

The review of bisphosphonate therapy by Drs. Olson and Pienta is timely. Bisphosphonates have become among the most widely prescribed pharmaceutical agents for malignant and nonmalignant bone disease related to the excessive activity of osteoclasts. Metastatic disease to the bone causes perturbations in bone remodeling, which may manifest as pure osteolytic activity (as seen in multiple myeloma) or various degrees of osteolytic/osteoblastic activity that produce distinct radiographic appearances. Despite the osteotropism common to both prostate and breast cancer, the clinical course and radiographic appearance of bone metastases in these two diseases often differ.

The frequency of skeletal events in breast cancer patients has been amply documented in reports describing the use of pamidronate (Aredia) in osteolytic disease.[1,2] It is unclear whether metastases to bone from two different disease sites with differing radiographic appearances and clinical courses indicate inherent biological differences in the tumor cells, a tumor cell–bone microenvironment interaction, or differences in the relationship of tumor cells to the osteoclast/osteoblast interaction. The exact mechanism of communication between the osteoblast and osteoclast has recently been elucidated, however, and it is now known that osteoprotegerin produced by the osteoblast acts as an osteoclast differentiator and activator.[3,4]

Primarily Pain Relief
The role of metastatic disease cells in the production and regulation of osteoprotegerin is unclear. Nevertheless, osteolysis remains a functional component of prostate cancer. Bisphosphonates primarily relieve pain from metastatic bone disease associated with prostatic malignancy. Randomized trials have demonstrated substantial clinical relief of pain in patients so treated; however, an impact on the progression of bone disease and survival has not yet been demonstrated. Drs. Olson and Pienta present a lucid review of the genesis of osteolytic disease and its relationship to osteoclastic resorption of bone, osteoclast activation by tumor cells, and other bone microenvironmental factors. They also highlight potential beneficial effects on osteoclast activity, including the inhibition of recruitment and differentiation of osteoclastic precursors from cells of the monocyte-macrophage cell line, and the inhibition of osteoclastic resorption caused by bisphosphonate effects on lysosomal pumps and the adherence of osteoclasts to resorption sites. The cost-effectiveness of bisphosphonate use in breast cancer has been a consideration for clinicians, and a recent study by Hillner suggested that the use of pamidronate in metastatic breast cancer is not cost-effective.[5] However, a cost-utility analysis by Dranitsaris and Hsu indicated that prophylactic pamidronate provides a substantial quality-adjusted survival benefit in metastatic breast cancer patients, when considered using Canadian Health Care System criteria.[6]

Renewed Interest in Bone Metastases
The routine use of bisphosphonates in prostate cancer is not recommended, although such therapy may offer substantial improvement in bone pain as well as quality of life for individual patients. The use of more potent bisphosphonates, such as zoledronate, may provide additional benefit in the clinical setting if osteoclast inhibition is the mechanism of this benefit. However, for both the cancer patient and clinical oncologist, the most important aspect of bisphosphonate use in bone disease may be the renewal of interest in researching the metastatic process in bone. Indeed, the growing use of bisphosphonates has led a number of investigators to review the mechanisms and treatment of bone metastasis in experimental animal models.[7,8] The addition of bisphosphonates to other metastatic inhibitors, such as matrix metalloproteinase blockers, has successfully inhibited bone metastasis development.[8] As demonstrated in murine tumor models, the use of bisphosphonates in high-risk patients may prevent the development of metastases.[7,8] Thus, multiple clinical trials are scheduled to begin examining the clinical benefit of
bisphosphonates in women with primary breast cancer who are at high-risk of developing metastasis.

**Issues for Clinical Trials**

The article by Drs. Olson and Pienta also points out some of the weaknesses of the clinical studies of bisphosphonate use in cancer. Among the issues that need to be addressed are the best route of administration, the frequency of administration, drug dose, size and power of the study to detect clinical benefit or differences, and a fundamental lack of long-term measures of bone destruction and remodeling in the cancer patient.

End points such as fracture, surgery to bone, and spinal-cord compression, while clinically relevant, occur late in the disease process. Better measures of osteolytic activity may provide a more rational approach to the use of bisphosphonates in the clinical setting.[9,10]

The major impetus for the use of the bisphosphonates in osteolytic disease associated with breast cancer or myeloma has been the prevention of skeletal events such as fracture, spinal cord compression, the need for radiation therapy, and hypercalcemia of malignancy. However, substantial pain relief and improved quality of life may warrant the use of bisphosphonates in particular patients with prostate metastases. In this situation, the dose, schedule, and frequency of administration become a matter of empiric clinical application.

**References:**


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