Use of Bisphosphonates in the Treatment of Prostate Cancer

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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.

Bisphosphonates are potent inhibitors of bone resorption. There are marked differences in their antiresorptive potency based on the structure of their side chains. Recent large double-blind, placebo-controlled studies have shown the benefit of monthly intravenous pamidronate (Aredia) in reducing skeletal complications among patients with osteolytic bone metastases from breast cancer or multiple myeloma. These studies also demonstrated the benefits of intravenous pamidronate in palliating symptoms, reducing analgesic requirements, and preventing deterioration of quality of life.

Although studies of oral bisphosphonates confirmed some possible benefit, the results were less consistent than those observed in studies evaluating intravenous pamidronate. Given the poor absorption as well as gastrointestinal side effects of oral bisphosphonates, these results were not unexpected and have led to a consensus statement by the American Society of Clinical Oncology. The Society recommends intravenous pamidronate 90 mg every 3 to 4 weeks in breast cancer patients with osteolytic bone disease.

Similar large double-blind placebo-controlled trials have not been completed in patients with prostate cancer, despite the frequent spread to bone of this cancer. Bisphosphonates have been shown to reduce bone resorption, and thus, researchers put an early emphasis on evaluating these agents in patients with osteolytic rather than osteoblastic involvement. However, a number of recent studies have shown enhanced bone resorption in prostate cancer patients with bone involvement.

Another possible rationale for the use of bisphosphonates in prostate cancer patients is the enhanced bone loss associated with androgen blockade. Although some data suggest improvement in bone density among chemotherapy-treated breast cancer patients who receive bisphosphonates, there are currently no studies to show this benefit in prostate cancer patients subjected to androgen blockade.

Previous Results in Prostate Cancer Patients

The results of previously published clinical trials evaluating these agents in prostate cancer patients with metastatic bone involvement have been difficult to interpret. A number of clinical trials with complex study designs and short follow-up have evaluated the weaker first-generation bisphosphonates clodronate and etidronate (Didronel). In several of these trials, patients were also treated with chemotherapy or hormonal therapy.

The primary end point of these studies was pain relief rather than prevention of skeletal complications or new metastatic bone disease. None of these trials demonstrated a clear benefit for the use of the bisphosphonate. Because it took researchers longer to determine the benefits of monthly intravenous pamidronate in breast cancer patients receiving hormonal therapy compared to those treated with chemotherapy, it may also be important to evaluate bisphosphonates in prostate cancer patients with a longer follow-up. A recent study suggested that bone loss may be increased in patients who receive oral clodronate for advanced prostate cancer.

Another more potent aminobisphosphonate, olpandronate, was evaluated in 28 patients who received the drug intravenously for 5 days, with 16 continuing to receive daily oral drug. Most patients experienced pain relief accompanied by a reduction in analgesic use, but this was an open-label study.

Newer Bisphosphonates

The more potent third-generation agents ibandronate and zoledronic acid have been evaluated in several randomized trials, but the completed studies have primarily involved patients with breast cancer, multiple myeloma, or tumor-induced hypercalcemia. The greater efficacy of intravenous zoledronic acid compared to pamidronate is clearly demonstrated by the improvement in reversal of cancer-induced hypercalcemia with this newer bisphosphonate, compared to...
pamidronate.[13] However, its potential for preventing skeletal complications or new bone metastases is unknown, and is the subject of ongoing large randomized clinical trials (in populations that include prostate cancer patients).

Oral daily ibandronate markedly inhibited bone resorption markers in one study involving a heterogeneous group of patients with metastatic bone disease.[14] Monthly intravenous ibandronate has been shown to be superior to placebo in preventing skeletal complications in women with breast cancer metastasized to bone,[15] although the results in patients with myeloma were disappointing.[16] Whether this new agent will be effective in prostate cancer is unknown.

**Antitumor Effects of Bisphosphonates**

Recent studies suggest that bisphosphonates not only inhibit bone resorption but also have antitumor effects.[17] These agents thwarted the ability of prostate and breast cancer cells to adhere to bone extracellular matrix. In addition, pretreatment of prostate and breast cancer cells with bisphosphonates greatly inhibited their invasion and blocked the proteolytic activity of matrix metalloproteinases. These drugs have also been shown to directly induce apoptosis of tumor cells in vitro and reduce the production of growth-promoting cytokines in the bone microenvironment. Importantly, all of these observed potential antitumor effects occurred in both a dose-dependent and potency-related manner. In addition, recent studies have shown that the more potent bisphosphonates induce a significant antiangiogenic effect.

In vivo models provided support for the potential clinical antitumor effect of these agents. For example, risedronate treatment of nude mice injected with a human breast cancer cell line inhibited the development of bone metastases. SCID-hu mice with human myeloma showed a paraprotein reduction in the presence of pamidronate.

Limited clinical data suggest that these agents may have antitumor activity in patients with metastatic bone disease. In the placebo-controlled study of intravenous pamidronate in myeloma patients, survival was prolonged among patients who were on salvage chemotherapy and received pamidronate, compared to placebo.[4] In addition, a retrospective analysis of the randomized intravenous pamidronate breast cancer trials demonstrated a survival advantage in patients less than 50 years old who received the bisphosphonate.[18]

In the adjuvant setting, conflicting results exist regarding the antitumor effects of oral clodronate. The Diehl study showed a reduction in both osseous and nonosseous metastatic disease as well as an overall survival advantage among breast cancer patients with micrometastatic bone marrow involvement who received clodronate as opposed to placebo.[19] However, in a recent placebo-controlled study by Saarto and coworkers, the clodronate-treated group not only failed to show any reduction in bone metastases but also had more nonskeletal metastases and a worse overall survival.[20]

**Potential Uses of Bisphosphonates in Prostate Cancer Patients**

Thus, bisphosphonate therapy has potential benefit for patients with prostate cancer in a number of clinical settings. These include: (1) prevention of bone loss for patients receiving androgen blockade, (2) treatment of patients with metastatic bone involvement, (3) treatment of prostate cancer patients with rising prostate-specific antigen without obvious metastatic disease, and (4) prevention of metastatic disease among patients with localized disease. Ongoing double-blind, placebo-controlled clinical trials will more clearly determine the usefulness of these agents in all of these clinical settings.

**References:**


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