Use of Bisphosphonates in the Treatment of Prostate Cancer

Review Article [1] | September 01, 2000
By Karin B. Olson, PA-C [2] and Kenneth J. Pienta, MD [3]

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.

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. This brief review summarizes the known data in this area. The main points made in the discussion are highlighted in previews appearing at the beginning of each section of the article.

Preview: Bisphosphonates inhibit bone destruction by osteoclasts. They are not very effective in inhibiting osteoblasts, which build bone and are the main cause of metastatic prostate cancer lesions.

Although tumor cells may directly destroy bone, most tumor-related bone destruction appears to be due to substances released by the tumor that stimulate osteoclasts. Bisphosphonates effectively inhibit bone resorption by interfering with osteoclast activity through multiple mechanisms, some of which are still not clearly understood. These drugs have a high affinity for calcium and, once administered, bind to hydroxyapatite in areas of exposed bone mineral where active bone remodeling is occurring, making the bone surfaces less available to osteoclastic resorption. Bisphosphonates prevent the migration of osteoclasts toward bone and inhibit the recruitment of osteoclastic precursors at the bone marrow level, thus decreasing osteoclast numbers. They may also induce osteoclastic apoptosis.[1,2]

Several bisphosphonates have been used successfully to treat conditions associated with abnormal osteoclastic activity, such as hypercalcemia, Paget's disease, and osteolytic skeletal metastases. In these populations, bisphosphonate treatment is associated with decreased pain scores, improved performance status, better quality of life, and a significant decrease in skeletal events, such as fractures, spinal cord compressions, and bony pain requiring palliative radiation.[1-4]

Preview: In breast cancer patients, bisphosphonates have been shown to decrease pain at metastatic sites. One bisphosphonate, pamidronate (Aredia), reduced skeletal complications from 64% to 51% over 2 years when compared with placebo but showed no effect on survival or quality of life. Breast cancer patients often have both osteolytic and osteoblastic lesions.

Several recent trials of bisphosphonates in breast cancer patients have shown statistically significant decreases in bone pain and skeletal complications (fractures, spinal cord compression, and the need for palliative external-beam radiation).[3,4] Long-term follow-up data were recently published from two large, multicenter, randomized, double-blind, placebo-controlled trials comparing the efficacy of pamidronate plus antineoplastic treatment with antineoplastic treatment alone in women with advanced breast cancer.[5]

A total of 751 patients receiving either endocrine therapy (protocol 18) or chemotherapy (protocol 19) at study enrollment were randomized to receive either pamidronate, 90 mg IV every 3 to 4 weeks, or placebo in addition to their primary treatment. All patients were allowed to change their anticancer treatment at any time during the study. The primary end point was the skeletal morbidity rate, defined as the number of skeletal complications divided by the time on the trial. Secondary end points were bone pain scores, analgesic use, quality of life, and performance status.

Both mean and individual skeletal morbidity rates were significantly better in the pamidronate group after 24 cycles: Mean skeletal morbidity rate (including hypercalcemia) was 2.5 skeletal complications per year in the pamidronate group vs 4.0 in the placebo group. Median times from study entry to first skeletal complication were 7.0 and 12.7 months in the placebo and pamidronate groups, respectively. Median time to new pathologic fracture was 12.8 months in the placebo group and 25.2 in the pamidronate group. Median time to palliative bone radiation was 16.0 months in the placebo group and had not yet been reached in the pamidronate group.

Although mean pain and analgesia scores had declined by the last study visit in both groups, the...
magnitude of the decline was significantly less in the pamidronate group. Eastern Cooperative Oncology Group (ECOG) performance status and quality of life decreased from baseline to last study visit in both groups, and there was no difference in survival between the two groups. It should also be noted that 69.5% of patients in the pamidronate arm and 75.7% of those in the placebo arm were removed from the study without completing the planned 24 months of treatment because of adverse events, unsatisfactory response, death, refusal of therapy, or other reasons. Based on these results, the authors concluded that the addition of pamidronate to antineoplastic therapy is more effective than antineoplastic therapy alone in preventing skeletal complications and palliating symptoms in breast cancer patients with osteolytic bone metastases.

A recent consensus statement developed by the American Society of Clinical Oncology (ASCO) recommends the use of intravenous pamidronate (90 mg IV every 3 to 4 weeks) in patients with metastatic breast cancer who are receiving systemic anticancer therapy (hormonal or chemotherapy) and who have clear evidence of osteolytic bone destruction.[6] The guidelines specifically do not recommend bisphosphonate therapy for breast cancer patients with no evidence of bone metastases or for patients with positive bone scans but no evidence of either bone destruction or localized bone pain.

Based on these results, the authors concluded that the addition of pamidronate to antineoplastic therapy is more effective than antineoplastic therapy alone in preventing skeletal complications and palliating symptoms in breast cancer patients with osteolytic bone metastases.

Another recent study demonstrated that, despite its efficacy in reducing skeletal events, pamidronate therapy is associated with substantial cost per avoided skeletal event.[7] We certainly do not advocate that any patient be denied bisphosphonate treatment on the basis of cost. Rather, we merely wish to call attention to the fact that this is an expensive treatment option that should not be used indiscriminately in situations where there is no clear evidence of potential benefit to patients.

**Preview:** Theoretically, bisphosphonates could affect the formation of prostate cancer metastases since both osteoclastic and osteoblastic activity appears to be necessary for the formation of metastatic osteoblastic bone disease.

Since bisphosphonates relieve bone pain by inhibiting osteolysis, it seems surprising that they should have an effect on bone pain in advanced prostate cancer, which is primarily osteoblastic. Studies suggest, however, that there is a symbiotic relationship between osteoclasts and osteoblasts in most metastatic bone disease, although one type generally predominates. Although the majority of metastatic lesions in prostate cancer are osteoblastic, there is histologic and biochemical evidence of synchronous osteoclastic bone resorption in these lesions.[8,9] Hence, a decrease in osteoclastic activity could conceivably have an effect on primarily sclerotic prostate cancer bone lesions. In fact, studies have shown that bisphosphonates decrease indices of bone resorption, which are above the normal range in 50% to 80% of prostate cancer patients.[10] Furthermore, research in tumor cell lines indicates that these drugs may also inhibit the adhesion of tumor cells to bone, thereby preventing or delaying the development of new bony metastatic lesions.[11]

**Preview:** Clinical studies evaluating the use of bisphosphonates to treat bone pain in patients with prostate cancer have yielded conflicting results.

Clinical studies of the bisphosphonates in patients with metastatic prostate cancer have produced contradictory results: Some have shown durable improvements in bone pain and quality of life, some have demonstrated only transient improvement, and others have found no effect at all.[12-14] The two bisphosphonates used most commonly in prostate cancer to date are clodronate (which is not currently available in the United States) and pamidronate. Because these drugs have very poor oral bioavailability, they are most effective when given as intravenous infusions, although some studies have followed initial infusional therapy with high-dose oral maintenance.

Pamidronate is administered in doses ranging from 30 to 60 mg weekly to 90 to 120 mg every 3 or 4 weeks; in general, this agent has been shown to reduce pain in 50% of patients with painful metastatic bone lesions.[15,16] Duration of response ranges from 4 to 24 weeks, and patients can be safely re-treated with additional intravenous doses when pain symptoms recur. All trials seem to suggest the importance of continued bisphosphonate treatment to maintain low levels of osteoclastic activity, either through repeated infusions or with oral maintenance.

A randomized, double-blind study of another bisphosphonate, etidronate (Didronel), randomized 57 patients to one of four treatment arms: IV etidronate (7.5 mg/kg for 3 days) followed by oral etidronate (400 mg/d); IV etidronate followed by oral placebo; IV placebo followed by oral etidronate; or IV and oral placebo.[17] Although follow-up was only 1 month, none of the etidronate regimens showed a significant effect on analgesic use or symptom relief.

As mentioned above, all of the bisphosphonates have poor oral bioavailability, with only 0.5% to 4%...
of an oral dose being absorbed.[18,19] Furthermore, the high doses of drug required in oral regimens are associated with a host of potential gastrointestinal side effects, including nausea, vomiting, abdominal cramping, bloating, diarrhea, and esophagitis.

Although intravenous bisphosphonates are generally well tolerated, approximately 10% of patients treated with intravenous pamidronate experience pain flares 24 to 48 hours after administration, which may last for days or weeks. Transient fever also has been reported in approximately 25% to 30% of patients treated with the intravenous formulation of this drug; it occurs 12 to 24 hours after administration and is self-limited.

Pamidronate is not metabolized by the human body, and approximately 25% to 40% of the intravenously administered dose is excreted by the kidneys. Although animal studies have shown that pamidronate can cause renal damage, several studies of patients with normal renal function have failed to demonstrate the development of renal impairment with weekly pamidronate doses given over either 1 or 2 hours.[20,21]

Several new, more potent bisphosphonates that are currently undergoing clinical investigation show promising potential. Olpadronate was recently tested in 28 patients with prostate cancer and painful bony metastases. All patients received 4 mg/d intravenously for 5 days; the first 12 received no further treatment, and the last 16 received oral maintenance doses of 200 mg/d. Overall, 76% of patients reported a decrease in pain after the infusion; this response was still evident at 3 months in those who were receiving oral maintenance.[22] Ongoing trials are assessing the efficacy of a single 20-mg intravenous dose of olpadronate.

Zoledronate, a bisphosphonate 100 times more potent than pamidronate, is being tested at low doses of 0.1 to 8.0 mg in 5-minute infusions and appears to be well tolerated. Although none of the newer bisphosphonates is currently available on the US market, trials of these agents may provide important evidence regarding the efficacy of bisphosphonates in the treatment of painful bony metastases in prostate cancer patients.

**Preview: Evidence regarding the role of bisphosphonates in preventing the development of bone metastases is currently unavailable.**

Existing data suggest that treatment with bisphosphonates is most effective in palliating symptoms and decreasing skeletal events in patients with osteolytic bone metastases. The question of whether bisphosphonates are effective in preventing or delaying the development of bony metastatic disease is also of great interest to oncologists. Unfortunately, relatively few published studies have used prevention of new metastatic bone disease as a primary end point. The results of two small studies in women with breast cancer suggested that clodronate reduced the incidence of subsequent bone metastases, but another study showed an opposite effect, with more metastatic bone disease developing in the clodronate-treated group.[23-25]

Although studies of bisphosphonates in prostate cancer patients with metastatic bone lesions have shown some benefit in terms of pain relief, to date very few data support the use of bisphosphonates in prostate cancer patients who show no evidence of bony metastasis. Such use is still considered experimental. Although ongoing trials are examining bisphosphonate prophylaxis in patients with breast cancer, further research needs to be done to determine the risks and benefits of using bisphosphonates in the early stages of prostate cancer.

**Conclusions**

Bisphosphonates have been shown to effectively reduce the incidence of skeletal events in breast cancer patients with destructive bone metastases. However, the data supporting their use to prevent further metastases in breast cancer patients are inconclusive. These agents have not been shown to increase patient survival or quality of life. Although, theoretically, prostate cancer metastases involve both osteoclasts and osteoblasts, one would predict that bisphosphonates would have a lesser effect in the advanced prostate cancer patient than has been observed in the breast cancer patient, whose metastases involve predominantly osteoclasts.

Therefore, although the bisphosphonates are safe and have only mild side effects in the majority of men, at present, no data are available to support their use to prevent the development of future metastasis. Since trials to test this hypothesis are underway and the answer will not be known for several years, the individual patient and physician must decide whether this is a worthwhile avenue of treatment.

**References:**


Source URL:
http://www.psychiatrictimes.com/review-article/use-bisphosphonates-treatment-prostate-cancer

Links: