Managing Metastatic Bone Pain: The Role of Bisphosphonates

Julie Gralow, MD, and Debu Tripathy, MD
University of Washington (J.G.), Seattle, Washington; and University of Texas Southwestern Medical Center (D.T.), Dallas, Texas, USA

Abstract
Approximately two-thirds of patients with bone metastases have severe and debilitating pain. Despite a range of treatments, about 25% of patients with painful bone metastases suffer from uncontrolled pain. Bisphosphonates are the standard care for the reduction of skeletal events associated with bone metastases. We review the efficacy of currently available bisphosphonates in cancer-related bone pain. Oral clodronate, intravenous (i.v.) pamidronate, and i.v. zoledronic acid have shown an analgesic effect in some studies. Both i.v. and oral ibandronate reduced bone pain in breast cancer patients with bone metastases and maintained bone pain scores below baseline levels for up to two years in clinical trials. Pilot studies of intensive i.v. ibandronate dosing show rapid and effective relief from moderate-to-severe bone pain in patients with breast cancer and other tumors. Phase III trials are warranted to compare the efficacy of bisphosphonates in treating bone pain and to confirm the effects of intensive dosing regimens. J Pain Symptom Manage 2007;33:462–472. © 2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Bisphosphonates, bone pain, clodronate, ibandronate, pamidronate, zoledronic acid

Introduction
Bone is a common site of cancer metastasis.1 The incidence of bone metastases depends on the primary tumor, but is particularly high in patients with advanced breast or prostate cancer, developing in up to 80% of these patients.2 Complications of skeletal metastases include fractures, hypercalcemia, and bone pain. Skeletal pain is the most common cause of cancer-related pain and is severe and debilitating in two-thirds of patients.1–3 It has a profound impact on quality of life and leads to impaired mobility; many patients are bedridden, with reduced functional capacity and increased dependency on others.4

Immediate and effective pain management due to bone metastases needs to be integrated with the long-term goal of preventing fractures. Pain relief commonly involves a combination of analgesics and systemic chemotherapy, hormonal therapy, or radiopharmaceuticals, with localized treatments such as radiotherapy and surgery.1 While some patients have adequate and prolonged pain relief with these treatments, many continue to experience some level
of metastatic bone pain and others have refractory or recurrent symptoms.1–3 A recent study suggested that metastatic bone pain is inadequately treated in many patients, even in those taking strong opioids,4 and other strategies are needed for metastatic bone pain that is opioid resistant.6 Physicians who took part in market research in the United States estimated that about a quarter of patients treated for metastatic bone disease suffer uncontrolled pain.7 Analgesic interventions, including opioids, can cause significant side effects, which have a further impact on patients’ quality of life and on health care resources.2,3,8 Other approaches to managing bone pain that are effective and well-tolerated would be welcomed.

Bisphosphonates and Bone Pain

Bisphosphonates are the standard care for the prevention and treatment of skeletal-related complications of bone metastases.9–13 They inhibit osteoclast maturation and function and ultimately cause osteoclast apoptosis.10,14 Because of their direct inhibitory effect on osteoclast-mediated bone resorption, bisphosphonates were initially developed to treat predominantly osteolytic bone metastases, such as those found in multiple myeloma and, to some extent, in breast cancer. However, histomorphometric and biochemical evidence show that osteoblastic lesions also lead to increased osteolysis and bone turnover and that bone resorption markers are significantly raised in patients with advanced prostate cancer, a cancer with predominantly osteoblastic features in the bone.15–18 Bisphosphonates are increasingly used to treat predominantly osteoblastic lesions, such as those in patients with prostate cancer.

This paper reviews data from clinical trials investigating the efficacy of commonly used bisphosphonates in treating metastatic bone pain (including severe and opioid-resistant bone pain) due to various tumors, including breast cancer, multiple myeloma, and urological cancers.

Standard or Low-Dose Bisphosphonate Treatment

Table 1 summarizes clinical trials that have assessed the effect of standard doses of bisphosphonate therapy on metastatic bone pain relief. Lower-than-recommended doses of bisphosphonates have also provided analgesic effects in some patients, as described below.

Clodronate

Several randomized, placebo-controlled trials examined the effect of long-term treatment with the approved dose of clodronate (1,600 mg/day given orally) in preventing and managing skeletal complications, including bone pain. In patients with breast cancer and osteolytic bone metastases receiving chemotherapy or hormonal therapy, up to 12 months of treatment with clodronate significantly reduced both pain intensity (P = 0.01) and use of analgesics (P = 0.02).19 In patients with multiple myeloma, clodronate led to a significantly lower incidence of back pain at 24 months (10.9% vs. 19.9% for patients on placebo, P = 0.05) and poor performance status (18.3% vs. 30.5%, P = 0.03). Pain scores were significantly reduced with short-term clodronate in patients with progressive bone metastases from a variety of tumor types (P = 0.03).20,21 However, in several other randomized studies of patients with breast or prostate cancer, or other neoplasms, clodronate gave no significant pain relief compared to placebo.4

In a short-term study of patients with metastatic bone disease, clodronate was inferior to i.v. pamidronate 90 mg in relieving bone pain (P < 0.01) after three months of treatment.22 Bone pain scores fell below those at baseline in the pamidronate group, but increased from baseline in the clodronate group.

Pamidronate

Pamidronate is routinely given intravenously at a dose of 90 mg, infused over two hours every 3–4 weeks. Two randomized, placebo-controlled trials studied the efficacy of standard-dose pamidronate in reducing skeletal morbidity for up to 24 months in patients with breast cancer and osteolytic bone lesions.23,24 Data were pooled to give a larger cohort of patients (n = 215) for whom data were available at 24 months.25 Mean pain scores and use of analgesics increased in both groups by the last study visit (last measurement at any time within the study), but were significantly less in the pamidronate group than in the placebo group (P < 0.001
<table>
<thead>
<tr>
<th>No. Patients/Primary Cancer</th>
<th>Scheduling</th>
<th>Study</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate</strong></td>
<td></td>
<td></td>
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<tr>
<td>144 breast cancer</td>
<td>1,600 mg/day oral for 1 year</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Significantly reduced pain and analgesic use vs. placebo ($P = 0.01$ and $0.02$, respectively)</td>
<td>19</td>
</tr>
<tr>
<td>55 various neoplasms</td>
<td>1,600 mg/day oral for 1 year</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Decreased pain ($P = 0.03$), no significant difference in analgesic use</td>
<td>21</td>
</tr>
<tr>
<td><strong>Pamidronate</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>382 breast cancer</td>
<td>90 mg i.v. every 3−4 weeks, for up to 2 years</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Significant difference in pain scores at 9 and 14 months ($P \leq 0.05$)</td>
<td>23</td>
</tr>
<tr>
<td>754 breast cancer</td>
<td>90 mg i.v. every 3−4 weeks, for up to 2 years</td>
<td>Double-blind, placebo-controlled trial. (pooled analysis of two trials)</td>
<td>Final bone pain scores were greater than baseline after 2 years ($P = 0.007$). Analgesic use increased more with pamidronate than with placebo</td>
<td>25</td>
</tr>
<tr>
<td>51 breast cancer</td>
<td>90 mg i.v. monthly for 4 months</td>
<td>Controlled trial vs. oral clodronate</td>
<td>Pamidronate significantly ($P = 0.05$) improved pain scores compared with clodronate after 5 months ($P &lt; 0.012$) and 4 months</td>
<td>22</td>
</tr>
<tr>
<td>392 multiple myeloma</td>
<td>90 mg i.v. every 4 weeks for 9 months</td>
<td>Double-blind, placebo-controlled study</td>
<td>Pain scores decreased from baseline, only significant at 7 months ($P \leq 0.05$)</td>
<td>27</td>
</tr>
<tr>
<td>378 prostate cancer</td>
<td>90 mg i.v. every 3 weeks for 27 weeks</td>
<td>Double-blind, placebo-controlled (pooled analysis of two trials)</td>
<td>No significant or sustained effects on pain scores</td>
<td>28</td>
</tr>
<tr>
<td><strong>Zoledronic acid</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1,648 multiple myeloma and breast cancer</td>
<td>4 mg i.v. every 3−4 weeks for 13 months</td>
<td>Multicenter double-blind trial vs. pamidronate 90 mg every 3−4 weeks</td>
<td>Bone pain was below baseline for 13 months. Analgesic scores were unchanged</td>
<td>12</td>
</tr>
<tr>
<td>773 lung and other solid tumors</td>
<td>4 mg i.v. every 3 weeks for 9 months</td>
<td>Multicenter, double-blind, placebo-controlled trial</td>
<td>Bone pain increased from baseline</td>
<td>30</td>
</tr>
<tr>
<td>645 prostate cancer</td>
<td>4 mg i.v. every 3 weeks for 15 months</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Bone pain and analgesic use increased over time</td>
<td>13</td>
</tr>
<tr>
<td>227 breast cancer</td>
<td>4 mg i.v. every 4 weeks for 12 months</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Statistically significant decrease from baseline in mean composite BPI score ($P = 0.0004$). Analgesic scores not different</td>
<td>34</td>
</tr>
<tr>
<td>20 prostate cancer</td>
<td>4 mg i.v. every 3 weeks for 6 months</td>
<td>Nonblinded study</td>
<td>Bone pain significantly reduced after 1 ($P = 0.007$) and 3 months ($P = 0.011$)</td>
<td>32</td>
</tr>
<tr>
<td>604 various primary cancers</td>
<td>4 mg i.v. every 3−4 weeks</td>
<td>Multicenter, prospective single-arm study</td>
<td>Mean VAS pain scores reduced significantly from baseline until treatment end (36 weeks, $P &lt; 0.0001$). Mean analgesic scores also decreased ($P &lt; 0.0001$)</td>
<td>33</td>
</tr>
<tr>
<td>615 multiple myeloma, breast, and prostate cancer</td>
<td>4 mg i.v. every 3−4 weeks</td>
<td>Nonblinded study</td>
<td>Reductions in mean VAS scores from baseline over six study visits. Only statistically significant at visits four and five. Total mean FACT-G quality-of-life score remained constant</td>
<td>37</td>
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(Continued)
for both parameters). For patients with data at 24 months, those in the pamidronate group had a slight decrease in mean pain and analgesic scores from baseline that was significantly different from the increases from baseline in the placebo group ($P = 0.015$ and $P < 0.001$, respectively). However, performance status and quality of life worsened from baseline to last visit and to 24 months and did not differ significantly between the two groups.

An earlier study using pamidronate 45 mg infused every three weeks in metastatic breast cancer found that a significantly higher proportion of patients randomized to pamidronate plus chemotherapy had pain relief than patients given chemotherapy alone (44% vs. 30%, $P = 0.025$). However, the control group did not receive a placebo infusion because of ethical objections in some centers, and this might have influenced the results.

In a multiple myeloma trial, the pain scores of patients given pamidronate 90 mg fell and remained significantly below baseline throughout the nine months of the trial. However, pain scores of patients given placebo also fell below baseline after two months and did not differ significantly from those of patients given pamidronate except at seven months.

Small et al. reported a combined analysis of two placebo-controlled studies of pamidronate 90 mg, given every three weeks for 27 weeks, to relieve bone pain in 378 men with metastatic prostate cancer. There were no sustained or significant differences between the pamidronate and placebo groups for self-reported pain, analgesic use, or mobility.

**Zoledronic Acid**

The efficacy of i.v. zoledronic acid in metastatic bone pain from breast cancer ($n = 1,130$) and multiple myeloma ($n = 513$) has been assessed in a Phase III randomized trial. Patients received zoledronic acid 4 mg dose infused over 15 minutes or pamidronate 90 mg via two-hour infusion, every 3–4 weeks for 12 months. Pain, analgesic use, and performance status were secondary efficacy parameters. While pain scores fell below baseline, the statistical significance of this change was not reported. Analgesic scores either decreased or remained fairly stable. Performance status was stable in patients with multiple myeloma, but worsened in all breast cancer patients during the study. There were no significant differences between the two treatment groups for any of these parameters. A paper reporting two-year data did not include bone pain results.

In a Phase III, placebo-controlled trial of zoledronic acid 4 mg in patients with advanced prostate cancer, bone pain scores increased in both groups compared to baseline throughout the 15-month trial. The increases in scores were significantly lower with zoledronic acid than placebo at three and nine months, but did not differ significantly from placebo at 12 and 15 months. At the end of the

<table>
<thead>
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<th>No. Patients/Primary Cancer</th>
<th>Scheduling</th>
<th>Study Description</th>
<th>Results</th>
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<tbody>
<tr>
<td>Ibandronate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>466 breast cancer</td>
<td>6 mg i.v. every 3 weeks</td>
<td>Multicenter, double-blind, placebo-controlled trial</td>
<td>Bone pain remained below baseline for 2 years</td>
<td>41,42</td>
</tr>
<tr>
<td>564 breast cancer</td>
<td>50 mg/day oral</td>
<td>Multicenter, double-blind, placebo-controlled trial</td>
<td>Bone pain remained below baseline for 2 years. At endpoint, bone pain scores were reduced significantly from baseline compared to placebo ($P = 0.001$). Analgesic use was significantly reduced ($P = 0.019$)</td>
<td>43,44</td>
</tr>
<tr>
<td>99 multiple myeloma for up to 2 years</td>
<td>2 mg i.v. every month placebo-controlled trial</td>
<td>Double-blind study</td>
<td>Bone pain was significantly reduced compared to baseline ($P &lt; 0.047$). No difference in analgesic use</td>
<td>45</td>
</tr>
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BPI = Brief Pain Inventory, VAS = Visual Analog Scale, FACT-G = Functional Assessment of Cancer Therapy-General scale.
In a 15-month study, patients were given the option to continue treatment in a nine-month extension phase. During months 12 through 24, both zoledronic acid and placebo groups had increases in pain from baseline. However, patients receiving zoledronic acid had smaller increases compared to placebo, which were significantly different at 21 months (P = 0.024) and 24 months (P = 0.034). In a reanalysis of these Phase III data, significantly more patients in the zoledronic acid group experienced clinically meaningful decreases in pain from baseline (defined as a decrease of ≥2 points on a 10-point scale) compared to the placebo group (P = 0.036). In a placebo-controlled study of patients with skeletal metastases from lung and other solid tumors, excluding breast and prostate, bone pain scores and analgesic use increased and performance status worsened throughout the nine-month trial with both placebo and zoledronic acid.

In Japanese patients with breast cancer and bone metastases (n = 227), changes in bone pain were also assessed in a randomized, placebo-controlled study of zoledronic acid 4 mg, infused over 15 minutes every four weeks. Patients treated with zoledronic acid experienced a statistically significant decrease from baseline in their mean composite Brief Pain Inventory (BPI) pain scores at every time-point over the 12-month study, except for Week 2. Analgesic scores were not different between treatment groups.

Unblinded studies of zoledronic acid 4 mg have also investigated its palliative effect on bone pain in patients with metastatic bone disease due to various primary malignancies. Significant bone pain relief was reported for zoledronic acid in a small, uncontrolled study of prostate cancer patients, but only over one and three months of treatment. In a prospective study of patients with bone metastases due to various primary cancers (n = 604), zoledronic acid reduced mean visual analog scale (VAS) pain scores significantly from baseline to treatment end (36 weeks, P < 0.0001). The mean analgesic score also decreased over this period (P < 0.0001). The secondary efficacy variables of BPI composite, European Cooperative Oncology Group score, and Functional Assessment of Cancer Therapy-General (FACT-G) remained stable throughout the study, indicating steady quality of life and bone pain. Another trial of patients with bone metastases due to multiple myeloma, breast cancer, and prostate cancer (n = 613), showed reductions in mean VAS scores from baseline over six study visits (3–4 week interval between visits). However, statistically significant reductions were only seen at Visits 4 (P = 0.05) and 5 (P = 0.03). Total mean FACT-G quality-of-life score remained constant.

In another uncontrolled, unblinded study, patients with breast cancer and bone metastases (n = 101) were randomized to receive three infusions of zoledronic acid 4 mg administered in the community or hospital setting, following a lead-in phase of three infusions in the hospital. Patients then received a further three infusions in the opposite venue; in total, patients received nine infusions. At the end of the study, there were significant reductions in worst pain (P = 0.008) and average pain in the last seven days (P = 0.039) and interference with general activity (P = 0.012), as measured with the BPI.

Also, in an uncontrolled, unblinded, multicenter study of patients with breast cancer metastatic to bone, zoledronic acid 4 mg (infused over 15 minutes every 3–4 weeks) was shown to reduce mean pain and analgesic scores from baseline for up to 12 months.

**Ibandronate**

The single nitrogen bisphosphonate, ibandronate, has both i.v. and oral formulations for the prevention of skeletal events in patients with breast cancer and bone metastases. In a multicenter, randomized trial, patients with advanced breast cancer were given i.v. ibandronate 6 mg (n = 154) or placebo (n = 158) every 3–4 weeks for up to 96 weeks. In the ibandronate group, bone pain scores (measured using a five-point scale where 0 = none and 4 = intolerable) fell within a few weeks and remained below baseline throughout the study (median baseline pain score = 1 in both groups); the mean change in pain score after 96 weeks was significantly different from that of the placebo group (−0.28 vs. +0.21, P < 0.001) (Fig. 1). Patients given i.v. ibandronate needed less additional analgesia than those receiving placebo (mean change in analgesic use +0.51 vs. +0.90), indicating that the
improvement was not due to an increased use of other pain-relieving drugs. However, the difference in analgesic use between groups was not significant. There was significantly less deterioration in quality of life for up to two years with i.v. ibandronate than with placebo (mean overall change in quality of life from baseline $-10.3$ vs. $-45.4$, $P = 0.005$).

Two randomized, placebo-controlled, multicenter Phase III studies involving a total of 564 women with breast cancer and bone metastases examined the efficacy and safety of oral ibandronate 50 mg once daily for up to 96 weeks. Data from the two trials were pooled for analysis, as predefined in the protocols. As seen with i.v. ibandronate, oral ibandronate reduced and maintained bone pain scores (measured using a five-point scale where $0 =$ none and $4 =$ intolerable) below baseline throughout the study (mean baseline pain score $= 1.33$ in the ibandronate group and $1.12$ in the placebo group), and the change in mean bone pain score from baseline to last assessment was significantly different from that of placebo ($-0.1$ vs. $+0.2$, $P = 0.001$) (Fig. 2). Analgesic use increased significantly less in the ibandronate group than in the placebo group (mean change in analgesic use $+0.60$ vs. $+0.85$, $P = 0.019$), while quality of life showed less deterioration in patients treated with ibandronate over 96 weeks (mean overall change in quality of life from baseline $-8.3$ vs. $-26.8$, $P = 0.032$).

In a randomized, placebo-controlled trial of patients with multiple myeloma, there were no significant differences in bone pain, analgesic drug use, or quality of life between patients given a subtherapeutic dose of i.v. ibandronate (2 mg) and those given placebo. Both were given monthly for 12–24 months. However, at the final evaluation, ibandronate patients with confirmed osteolytic lesions had significantly lower bone pain scores than at baseline ($P < 0.047$). It is important to note that the ibandronate dose was lower than standard; the recommended i.v. dose for metastatic bone disease for breast cancer is 6 mg.

**Acute and High-Dose Bisphosphonate Treatment**

Clinical trials have investigated whether higher-than-standard doses of bisphosphonates, or intensive or loading-dose schedules, are useful in severe metastatic bone pain that is not effectively managed by other analgesics. The first of these studies used i.v. clodronate or pamidronate (Table 2) and there was evidence for an analgesic effect with both agents. More recently, intensive ibandronate treatment for metastatic bone pain was investigated in patients with skeletal metastases from various tumors (Table 2). Loading doses of ibandronate are feasible because ibandronate appears to lack dose-limiting and cumulative renal toxicity seen with zoledronic acid, pamidronate, and i.v. clodronate.

**Ibandronate Studies**

An open-label, pilot study assessed the efficacy of i.v. ibandronate 4 mg, infused over two hours on four consecutive days (total 16 mg), in treating moderate-to-severe, opioid-resistant
bone pain in 18 patients with breast cancer or other tumors. High-dose i.v. ibandronate significantly reduced mean pain scores on a VAS within seven days ($P < 0.001$). Pain scores remained below baseline at Day 21 ($P < 0.0001$) and Day 42, the study endpoint ($P < 0.05$). This was achieved without an increase in analgesics. There were also significant improvements in quality of life and performance status ($P < 0.05$ at Day 42 vs. baseline for both parameters).

In an open-label, nonrandomized study of 45 patients with hormone refractory prostate cancer and painful bone metastases, ibandronate 6 mg was infused over one hour each day for three days (loading dose), followed by a single infusion of ibandronate 6 mg every four weeks. Forty-four of 45 patients (83%) had pain relief (defined as a 3-point reduction in VAS and a 50% reduction in analgesic use) from Day 2, and 25% of patients were completely pain free. The mean VAS score on Day 3 was significantly reduced from baseline (2.5 vs. 6.8, $P < 0.001$) and remained below baseline for the rest of the study. Patients had improved functioning on the Karnofsky scale, allowing some who were previously bedridden to

<table>
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<th>Table 2</th>
<th>Summary of Studies Assessing Metastatic Bone Pain with High or Loading Doses of Bisphosphonates</th>
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<tr>
<td>No. Patients/Primary Cancer</td>
<td>Scheduling</td>
</tr>
<tr>
<td>Clodronate 20 breast cancer</td>
<td>450 mg i.v./day for 5 days then 100 mg i.v./day for 10 days</td>
</tr>
<tr>
<td>32 breast cancer</td>
<td>300 mg/day i.v. for 5–7 days or 600 mg/day i.v. for 2 days or 1,500 mg/day i.v. for 1 day</td>
</tr>
<tr>
<td>22 breast cancer</td>
<td>300 mg/day i.v. for 5–15 days or 600 mg/day i.v. for 8–10 days</td>
</tr>
<tr>
<td>60 various neoplasms</td>
<td>600 mg i.v. or 1,500 mg i.v. every 14 days</td>
</tr>
<tr>
<td>85 prostate cancer</td>
<td>300 mg i.v. for 8 days</td>
</tr>
<tr>
<td>Pamidronate 52 various neoplasms</td>
<td>120 mg i.v. on Day 1 then 120 mg i.v. every 4 weeks if symptoms worsened</td>
</tr>
<tr>
<td>34 various neoplasms</td>
<td>120 mg i.v. on Day 1 then 120 mg i.v. every 4 weeks if symptoms worsened</td>
</tr>
<tr>
<td>Ibandronate 18 various neoplasms</td>
<td>4 mg i.v. on Days 1–3</td>
</tr>
<tr>
<td>45 prostate cancer</td>
<td>6 mg i.v. on Days 1–3 then 6 mg every 4 weeks</td>
</tr>
<tr>
<td>53 urological cancer</td>
<td>Open, uncontrolled study</td>
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</table>
become mobile and independent within a few days.\textsuperscript{52}

\textbf{Discussion}

While the primary intent of bisphosphonate use is considered to be the reduction of overall skeletal events, clinical trials have established that these agents have an analgesic effect on patients with metastatic bone pain from a variety of tumors. The results vary considerably, and comparison of bisphosphonates across studies is difficult because of differences in patient populations and the methods for assessing bone pain and analgesic use. Direct comparisons of bisphosphonates in randomized trials are needed to determine their relative effects on bone pain. Furthermore, while pain appears to be relieved both acutely and long-term with bisphosphonates, formal comparisons to other methods of pain relief or cost-effectiveness studies have not been performed. In addition, there are no cost-benefit analyses specifically assessing bone pain control. Bisphosphonates have a major impact on drug budgets;\textsuperscript{53} however, although they have not yet been shown to significantly improve survival, their impact on bone pain is coupled with other benefits such as reducing the incidence of skeletal-related events. Pharmacoeconomic studies coupled to clinical trials are warranted to investigate the comparative cost-benefits of bisphosphonates with respect to each other and alongside other analgesic regimens.

Many advanced cancer patients, particularly those with breast cancer, will live with their disease and bone pain for several years. The data to date indicate that ibandronate (both i.v. 6 mg and oral 50 mg) maintains pain reduction below baseline levels for up to two years of treatment in randomized clinical trials in breast cancer, with less deterioration in quality of life or physical functioning compared to placebo.\textsuperscript{41\textendash}44 Bone pain relief below baseline was shown over one year of treatment with zoledronic acid 4 mg and pamidronate 90 mg in a Phase III study of patients with breast cancer and multiple myeloma. Metastatic bone pain scores increased from baseline over time with zoledronic acid therapy in trials of patients with prostate cancer, although significantly less than with placebo. Pamidronate had no effect in pain in patients with prostate tumors in two randomized studies. It remains unclear if the underlying mechanisms of pain control with bisphosphonates vary between tumor types or with the presence or predominance of osteolytic, osteoblastic, or mixed lesions. A study of intravenous pamidronate found some correlation between metastatic bone pain relief and changes in bone resorption markers,\textsuperscript{54} but further randomized studies are required to investigate the relationship of these and other markers in more detail.

Intravenous clodronate was the first bisphosphonate to be used with an intensive (consecutive) eight-day regimen that alleviated the severe pain with metastatic bone disease. Studies of loading-dose ibandronate have shown greater relative reductions in moderate-to-severe bone pain (including opioid-resistant pain) in patients with breast cancer or other tumor types.\textsuperscript{42,44,49\textendash}52 Across-trial comparisons suggest that intensive dosing should produce faster reductions in pain (i.e., within days) than standard dosing (i.e., within weeks). While the results of pilot studies are promising, large-scale randomized studies are needed to confirm the effects of loading-dose schedules. It will be particularly interesting to assess whether the loading-dose pain relief can be maintained for prolonged periods with i.v. or oral bisphosphonates at standard doses and intervals.

In addition to long-term pain relief caused by effects on skeletal integrity, bisphosphonates may also elicit acute analgesic effects.\textsuperscript{55} The early pain-relieving effects of bisphosphonates may be explained by direct analgesic properties. The exact mechanism of bisphosphate pain relief is unknown; however, these drugs may have multiple effects on bone cancer pain, including reduced acidosis, growth factor release, and peripheral sensitization of neurons.\textsuperscript{56}

Bisphosphonates may have an important role as coanalgesics in patients with metastatic bone pain. Other interventions such as radiotherapy and high-dose opioids can have side effects that need additional management or limit dose increments. In a small pilot study, ibandronate was shown to augment palliative radiotherapy by increasing bone pain relief without adverse drug-related side effects.\textsuperscript{57} Surveys in the United States, Europe, and
Canada recently showed that some clinicians did not recognize the pain-relieving properties of bisphosphonates, suggesting a need for greater awareness of their potential benefits and further research into optimal dosing regimens in combination with other analgesic therapies.

The main adverse events associated with bisphosphonate therapy are acute-phase reactions, gastrointestinal toxicity, renal toxicity, and osteonecrosis of the jaw. Osteonecrosis of the jaw is a rare but serious complication, which appears as painful oral ulcerations that expose underlying bone. The pathophysiology of this disease is not fully understood yet. However, risk factors include treatment with intravenous bisphosphonates, dental extractions, and presence of oral infection. It is recommended that a dental examination should be performed in all patients due to receive bisphosphonates and in patients who have been given bisphosphonates within the last three months.

Both health care professionals and patients recognize that metastatic bone pain management as currently practiced can be suboptimal. A survey by the Radiation Therapy Oncology Group found that 83% of radiologists believed that most patients were undertreated and 40% thought that the pain relief achieved was fair or poor. In a recent survey of 518 patients, a third of those with moderate-to-severe metastatic bone pain were found to have symptoms despite treatment. As inadequate assessment of pain may make it difficult to tailor therapy to patients’ needs, collecting and evaluating metastatic bone pain scores may help to optimize relief. Better symptom monitoring using bone pain diaries or record cards might aid communication during consultations, allowing therapy options (including bisphosphonates) to be better tailored to patient needs.

References


