Role of Bisphosphonates for the Management of Skeletal Complications and Bone Pain from Skeletal Metastases

Luis Costa,1 Allan Lipton,2 Robert E. Coleman3

Abstract

Bone metastases are common in patients with advanced-stage cancer; they can lead to skeletal complications (ie, pathologic fractures, spinal cord compression, tumor-induced hypercalcemia, and severe bone pain) that often require orthopedic surgery or palliative radiation therapy and negatively affect quality of life. The primary role of bisphosphonates for the management of bone metastases in patients with advanced-stage cancer is the prevention of these painful skeletal complications. In placebo-controlled trials, a number of bisphosphonates, including oral clodronate, oral and intravenous (I.V.) ibandronate, I.V. pamidronate, and I.V. zoledronic acid, have been shown to significantly reduce skeletal complications in patients with bone metastases from breast cancer. Furthermore, zoledronic acid provided benefit compared with pamidronate in patients with bone metastases from breast cancer in a large, comparative trial. Zoledronic acid also provided long-term benefits in randomized placebo-controlled trials in patients with bone metastases from prostate cancer, lung cancer, and other solid tumors, whereas other bisphosphonates that have been investigated have failed to demonstrate objective long-term benefits in placebo-controlled trials. In addition, although systemic analgesics and radiation therapy are primary treatments for the management of bone pain, bisphosphonates can also play an important secondary role in reducing bone pain associated with skeletal metastases. Notably, several economic analyses of bisphosphonate therapy have demonstrated that these agents are cost-effective by reducing health-care costs associated with skeletal complications and providing clinically significant quality of life benefits to patients with malignant bone disease.

Introduction

In the United States alone, approximately 1.4 million new cancer cases are expected in 2006.1 In patients with advanced malignancies, bone metastases are the most common cause of cancer-associated pain.2 Approximately 65%-75% of patients with advanced-stage breast cancer, 65%-75% of patients with advanced-stage prostate cancer, and 40% of patients with advanced-stage lung cancer develop bone metastases.3,4 These patients are at high risk for clinically significant skeletal complications, including spinal cord compression, pathologic fracture, and severe bone pain requiring palliative radiation therapy (RT).4-9 Skeletal complications can have a debilitat-
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Assessing the Clinical Benefits of Bisphosphonates

Assessment of Skeletal Complications

The clinical benefits of bisphosphonate therapy for the prevention of skeletal complications have been evaluated in many clinical trials. In the recent pamidronate and zoledronic acid trials, clinical benefit was assessed using a skeletal-related event (SRE), a composite endpoint defined as pathologic fracture, spinal cord compression, RT to bone, or surgery to bone.15 Analysis of such a composite endpoint captures objective data on all clinically relevant events when disease morbidity and treatment effects are complex.16 Analysis of the proportion of patients with ≥ 1 SRE and time to the first SRE are conservative endpoints that account for only the first SRE but ignore subsequent events (Figure 1).15 Evaluation of the skeletal morbidity rate (ie, annual incidence of SREs) provides a more comprehensive analysis by taking into account all skeletal events occurring during the follow-up period. Multiple event analyses, such as the Andersen-Gill method used in the zoledronic acid trials, provide a statistically robust and comprehensive assessment of skeletal morbidity during the entire length of follow-up by assessing the total number and timing of all skeletal events in the patient population.17

Assessment of Bone Pain

Various methods have been used to assess the severity of bone pain in patients with bone metastases, including unidimensional and multidimensional scales. The Brief Pain Inventory (BPI) multidimensional pain scale is one such instrument that measures patients’ self-reported severity of pain, the extent to which pain interferes with activities of daily living, pain quality and location, and the perceived cause of pain.18 The BPI scores pain as worst, average, and least pain and expresses the mean of the interference items over the past 24 hours or the past week on a 0- to 10-point scale. Unidimensional scales such as visual analog scales and numeric rating scales that rate pain intensity are also commonly used and can be described using a 0- to 10-point scale, a 100-mm scale, or smaller increments such as a 5-point patient-rated scoring system used in recent ibandronate trials involving patients with breast cancer.19,20 Because these unidimensional scales measure only 1 aspect of pain, many experts recommend the use of multidimensional scales for the assessment of long-term pain.21 Furthermore, assessment of pain alone only measures 1 dimension of the morbidity. Analgesic consumption and mobility or activity levels are important additional components of the pain caused by disease. Some pain assessments have amalgamated pain, performance status, and analgesic consumption into a single score to try to capture these interrelated components more accurately.22

Bisphosphonates for the Prevention of Skeletal Complications

Breast Cancer

Intravenous (I.V.) and oral bisphosphonates have been shown to provide significant clinical benefits in patients with bone metastases from breast cancer in randomized placebo-
controlled trials (Table 1). In these trials, bisphosphonates significantly reduced the incidence or rate of skeletal complications and delayed their onset. Oral bisphosphonates, including clodronate and ibandronate, are currently used only outside the United States, but they are being assessed in clinical trials in the United States. The American Society for Clinical Oncology guidelines for the use of bisphosphonates in patients with breast cancer recommend treatment with I.V. pamidronate (90 mg) or I.V. zoledronic acid (4 mg) for the prevention of skeletal complications. Moreover, the panel recommended that, once initiated, I.V. bisphosphonate therapy should be continued as long as tolerated or until evidence of a substantial decline in a patient’s performance status. Results from several key trials of oral and I.V. bisphosphonates are summarized herein.

**Clodronate.** In patients with bone metastases from breast cancer, oral clodronate (1600 mg per day) demonstrated significant clinical benefits compared with placebo or controls. In a randomized trial involving 173 patients, treatment with oral clodronate significantly reduced the incidence of all skeletal events, as well as the incidence of vertebral fractures and the rate of vertebral deformity, compared with placebo \((P < 0.025)\). Similarly, in a randomized open-label trial involving 100 patients, oral clodronate (1600 mg per day for 24 months) significantly prolonged the time to first skeletal event \((P = 0.015)\) and reduced the incidence of fractures \((P = 0.023)\) compared with patients who did not receive clodronate.

**Ibandronate.** In a pooled analysis of 2 phase III trials in patients with bone metastases from breast cancer, oral ibandronate (50 mg per day for as many as 96 weeks) significantly reduced the mean skeletal morbidity period rate \((P = 0.004)\); however, analysis of this endpoint excluded data collected from the first 12-week period on study and included events after study withdrawal. Ibandronate also significantly reduced the risk of a new bone event by 38% compared with placebo \((P < 0.001)\) by Poisson regression analysis. Nevertheless, ibandronate did not significantly reduce the percentage of patients with a new bone event or time to first bone event and did not reduce the incidence of vertebral and nonvertebral fractures. In a randomized placebo-controlled trial of 2-mg or 6-mg I.V. ibandronate administered every 3-4 weeks for 2 years, 6-mg ibandronate was also shown to significantly reduce the mean skeletal morbidity period rate compared with placebo \((P = 0.004)\) and extend the median time to first new bone event by approximately 5 months \((P = 0.018)\) in patients with bone metastases from breast cancer. Ibandronate (6 mg) also demonstrated a trend toward reducing the percentage of patients with \(\geq 1\) new bone event \((P = 0.052)\); however, the incidence of vertebral fractures was not reduced. In contrast, 2-mg ibandronate demonstrated no significant clinical benefit compared with placebo. More recently, in a randomized placebo-controlled trial in patients with bone metastases from breast or colorectal cancer \((N = 102)\), 6-mg ibandronate significantly reduced the percentage of patients with a skeletal event \((36\% \text{ vs. } 48\%)\).

### Table 1

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Benefit Relative to Placebo for Study Endpoint (<em>P</em> Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with (\geq 1) SRE or New Bone Event, % Reduction</td>
<td>-</td>
</tr>
<tr>
<td>Increased Time to First SRE or New Bone Event, Days</td>
<td>277 vs. 137 (0.022)</td>
</tr>
<tr>
<td>SMR, % Reduction</td>
<td>28 (&lt; 0.001)†</td>
</tr>
<tr>
<td>SMPR, % Reduction</td>
<td>–</td>
</tr>
<tr>
<td>Multiple Event Analysis, % Risk Reduction</td>
<td>–</td>
</tr>
</tbody>
</table>

*Expressed as total events per 100 person-years.
†By Andersen-Gill multiple event analysis.
‡By Poisson regression analysis.

Abbreviations: NR = not reached; SMPR = skeletal morbidity period rate; SMR = skeletal morbidity rate

Adapted with permission from Lipton A. Bisphosphonate therapy for patients with breast cancer. Cur Cancer Ther Rev. In press.
Bisphosphonates and Pain from Bone Metastases

for placebo; $P = 0.027$), significantly delayed the time to first event (median, 457 days vs. 304 days for placebo; $P = 0.007$), and significantly reduced the risk of developing a skeletal event by 32% (hazard ratio, 0.69; $P = 0.003$) based on a multiple event analysis.31

Pamidronate. Pamidronate was the first I.V. bisphosphonate to demonstrate a statistically significant reduction in skeletal complications compared with placebo in patients with breast cancer with bone metastases.32-34 In the mid-1990s, I.V. pamidronate (90 mg via 2-hour infusion every 3-4 weeks) became the standard of care for patients with breast cancer with bone metastases on the basis of evidence from 2 randomized placebo-controlled trials involving 754 patients. These trials demonstrated that pamidronate significantly reduced the incidence and delayed the onset of SREs compared with placebo over 2 years ($P < 0.001$).14 Overall, approximately one third of SREs were prevented.

Zoledronic Acid. In a randomized phase III trial, 4-mg zoledronic acid was shown to be at least as effective as 90-mg pamidronate in patients with bone lesions secondary to multiple myeloma or bone metastases from breast cancer.35,36 In this trial, 1122 patients were randomized to receive zoledronic acid (4 mg) or pamidronate (90 mg) every 3-4 weeks for as many as 24 months. Results showed that the percentage of patients with ≥ 1 SRE was similar between treatment groups (47% vs. 51% for pamidronate) at 25 months.35 However, zoledronic acid reduced the percentage of patients with each type of SRE and significantly reduced the overall risk of experiencing an SRE by an additional 16% compared with pamidronate based on the Andersen-Gill multiple event analysis ($P = 0.03$).35,37 Moreover, in the subset of 766 patients with breast cancer, zoledronic acid was superior to pamidronate and significantly reduced the risk of developing an SRE by an additional 20% compared with pamidronate ($P = 0.025$).35

Zoledronic acid has also demonstrated superiority to pamidronate for the treatment of hypercalcemia of malignancy in patients with multiple myeloma, breast cancer, and a variety of other solid tumors. In a pooled analysis of 2 randomized controlled trials involving 287 patients with hypercalcemia of malignancy, treatment with zoledronic acid (4 mg) resulted in a complete response rate (defined as normalization of corrected serum calcium to ≤ 2.7 mmol/L) of 88.4% compared with 69.7% in patients treated with pamidronate (90 mg) at day 10 ($P = 0.002$).38

Recently, in a placebo-controlled trial involving 228 Japanese women with bone metastases from breast cancer, zoledronic acid (4 mg every 4 weeks) significantly reduced the percentage of patients with ≥ 1 SRE at 1 year by 20% compared with placebo, the largest benefit shown in any bisphosphonate trial in bone metastasis (50% for zoledronic acid vs. 50% for placebo; $P = 0.003$).25,39 In addition, zoledronic acid significantly reduced the SRE rate ratio (defined as the total number of SREs divided by the total years on study) by 39% (adjusted SRE rate ratio, 0.61; $P = 0.027$), delayed the onset of skeletal complications ($P = 0.004$), and significantly reduced the overall risk of developing an SRE by 44% compared with placebo using Andersen-Gill multiple event analysis (hazard ratio, 0.56; $P = 0.009$).

Prostate Cancer

Several bisphosphonates, including etidronate, clodronate, pamidronate, and ibandronate, have been evaluated in patients with bone metastases secondary to prostate cancer.40-50 Although short-term relief of pain has been reported, none of these agents has demonstrated statistically significant, long-term clinical benefits in randomized placebo-controlled trials in this patient population. However, zoledronic acid has demonstrated statistically significant clinical benefit. In a randomized, placebo-controlled trial, patients with bone metastases from advanced-stage prostate cancer progressing after hormone treatment were treated with 4-mg zoledronic acid (via 15-minute infusion every 3 weeks) for as many as 24 months.13,51 Zoledronic acid significantly reduced the percentage of patients with an SRE ($P = 0.028$), delayed the onset of SREs by approximately 6 months ($P = 0.009$), and reduced the risk of SREs compared with placebo by 36% ($P = 0.002$) using the Andersen-Gill analysis.13

Lung Cancer and Other Solid Tumors

In a similar phase III trial, patients ($N = 507$) with bone metastases from lung cancer or other solid tumors (excluding breast or prostate cancers) were randomized to receive 4-mg zoledronic acid (via 15-minute infusion every 3 weeks) or placebo for as many as 21 months. Fewer patients developed ≥ 1 SRE at 21 months in the zoledronic acid group compared with the placebo group (39% for zoledronic acid vs. 46% for placebo). Furthermore, zoledronic acid significantly delayed the median time to first SRE (236 days vs. 155 days for placebo; $P = 0.009$), reduced the annual incidence of SREs ($P = 0.012$), and reduced the risk of developing an SRE by 31% compared with placebo (robust $P = 0.003$).52,53 Thus far, zoledronic acid is the only bisphosphonate that has demonstrated efficacy in this patient population.

Selection of Patients for Bisphosphonate Therapy

In patients with malignant bone disease, it has been reported that those who experience an SRE are more likely to experience subsequent SREs.53 Therefore, delaying or preventing skeletal complications in this patient population provides a clinically significant benefit. Retrospective exploratory analyses based on data from the phase III zoledronic acid
trials demonstrated that patients with bone metastases from breast or prostate cancer who had an SRE before study entry were at higher risk of developing subsequent skeletal complications. Therefore, early intervention with bisphosphonates to prevent skeletal complications before any have occurred is advised. Recent data have also indicated that the rate of bone resorption is a powerful predictor of SREs. Patients with elevation of the N-telopeptide (Ntx) of type 1 collagen \( \geq 100 \) nmol/mmol creatinine are much more likely to develop an SRE. Additionally, increased Ntx predicts a shorter time to first SRE, progression of disease, and worse survival, indicating an urgent need to intervene with bisphosphonates and change the underlying systemic treatment.

**Safety of Bisphosphonates**

Generally, I.V. bisphosphonates are well tolerated with long-term use in patients with bone metastases and require only monthly dosing. The risk of decreased renal function is similar to the risk observed with placebo when I.V. bisphosphonates are administered at the recommended dose and infusion times. Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving a wide variety of treatment regimens including bisphosphonates; however, the true incidence of ONJ is not known. Many of these patients were treated with chemotherapy and corticosteroids and have multiple risk factors for ONJ. Because the majority of reported ONJ cases have been associated with dental procedures and tooth extractions, a dental examination with appropriate preventive dentistry should be considered before treatment with bisphosphonates in patients with concomitant risk factors such as cancer, chemotherapy, corticosteroids, and poor oral hygiene.

**Management of Pain in Patients with Metastatic Cancer**

**Etiology of Pain**

Current estimates suggest that approximately 9 million people worldwide are afflicted with cancer-related pain, including > 75% of patients with advanced metastatic disease and approximately 30%-50% of patients receiving active treatment. Among patients with advanced metastatic disease, pain is moderate to severe in > 50% of patients, and this cancer-associated pain could be intractable despite standard therapy. Patients with advanced-stage cancer can have 2 types or etiologies of pain: neuropathic and nociceptive pain. Neuropathic pain results from lesions that arise in the nervous system or from neurologic deficits. Nociceptive pain is caused by tissue injury that results in a release of a variety of chemical mediators that activate nociceptors. Traditional therapies for the management of cancer-related pain include systemic analgesics and RT. Nociceptive pain responds to chemotherapy, radiation, and surgery, which slow tumor growth and thereby control pain.

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**Figure 2**

**Metaanalysis of Several Trials of Bisphosphonates for the Relief of Pain from Bone Metastases**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with Pain Relief</th>
<th>Odds Ratio, Random (95% CI)</th>
<th>Weight (%)</th>
<th>Odds Ratio, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arican et al (1999)</td>
<td>26/33, 5/17</td>
<td>8.3</td>
<td>8.91 (2.34, 33.91)</td>
<td></td>
</tr>
<tr>
<td>Conte et al (1994)</td>
<td>54/131, 38/134</td>
<td>49.7</td>
<td>1.77 (1.06, 2.96)</td>
<td></td>
</tr>
<tr>
<td>Elomaa et al (1992)</td>
<td>10/36, 6/39</td>
<td>11.4</td>
<td>2.12 (0.68, 6.58)</td>
<td></td>
</tr>
<tr>
<td>Heim et al (1995)</td>
<td>12/77, 4/80</td>
<td>10.6</td>
<td>3.51 (1.08, 11.4)</td>
<td></td>
</tr>
<tr>
<td>Kylmälä et al (1997)</td>
<td>10/28, 6/29</td>
<td>10.5</td>
<td>2.13 (0.65, 6.97)</td>
<td></td>
</tr>
<tr>
<td>Siris et al (1983)</td>
<td>2/5, 0/5</td>
<td>5.3</td>
<td>1.37 (0.25, 7.38)</td>
<td></td>
</tr>
<tr>
<td>Smith (1989)</td>
<td>8/43, 2/14</td>
<td>3</td>
<td>6.5 (0.70, 60.14)</td>
<td></td>
</tr>
<tr>
<td>Vinholes et al (1997)</td>
<td>5/25, 1/27</td>
<td>100</td>
<td>2.37 (1.61, 3.5)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI = confidence interval

growth, whereas neuropathic pain only responds to analgesics and adjuvant compounds.61 Pain from bone metastases, particularly neuropathic pain, is often resistant to conventional analgesic therapy and requires a multidisciplinary approach.65 Radiation to bone or the use of radionuclides is often required for palliation of severe bone pain that is refractory to analgesics; RT generally provides pain relief in approximately 80% of patients, although this is sustained in only approximately half of the responders.66,67

Role of Bisphosphonates in Management of Bone Pain

Current strategies to manage pain associated with bone metastases are often not completely effective, and many patients will experience severe and incapacitating pain at some point during the course of their disease.68 Bisphosphonates are effective in the treatment of bone pain in patients with bone metastases and are an important adjunct to standard therapy. In a review by Wong and Wiffen,69 the authors evaluated data from 30 studies involving 3682 patients with bone metastases from a variety of primary tumors and noted a significant benefit in favor of the use of bisphosphonates for the relief of pain at 4, 8, and 12 weeks compared with control. These results suggest that bisphosphonates have an important role in the management of pain associated with bone metastases. A metaanalysis of randomized controlled studies has provided further evidence that bisphosphonates significantly reduce bone pain compared with controls in this patient population (Figure 2).41,47,69-76 Across a number of studies in different tumor types, treatment with bisphosphonates showed a consistent trend toward pain reduction compared with the control, and in some individual studies, this effect was statistically significant.

The palliative effects of bisphosphonates can result from inhibition of bone resorption and/or antitumor activity. By maintaining skeletal integrity, bisphosphonates can prevent painful microfractures. In patients with breast cancer, bisphosphonates have also been shown to reduce the development of new bone metastases,77,78 and bisphosphonates can inhibit the progression of established bone lesions.14,76 In a rat model of metastatic cancer pain, zoledronic acid demonstrated antinociceptive and bone-preserving therapeutic effects.79 Further studies are under way to understand the mechanisms responsible for the antitumor effects of bisphosphonates in patients with advanced malignancy.

Table 2

Summary of Randomized Placebo-Controlled Trials with Bisphosphonates for Reducing Bone Pain13,14,19,20,23,48,80-82

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Dose and Regimen</th>
<th>Measurement of Pain</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid</td>
<td>Kohno et al23,80</td>
<td>228 4-mg I.V. every 4 weeks for up to 1 year</td>
<td>BPI</td>
<td>Significantly reduced mean composite BPI from baseline in patients with breast cancer (P = 0.0004 at 12 months)</td>
</tr>
<tr>
<td></td>
<td>Saad et al13</td>
<td>422 4-mg I.V. every 3 weeks for up to 2 years</td>
<td>BPI</td>
<td>Significantly reduced mean composite BPI in patients with prostate cancer compared with placebo (P = 0.024 at 24 months)</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Lipton et al14</td>
<td>754 90-mg I.V. every 3-4 weeks</td>
<td>Bone pain severity and frequency scoring*</td>
<td>Significantly reduced mean pain scores from baseline in patients with breast cancer compared with placebo at 24 months (P = 0.015)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Body et al19  (Pooled Analysis of 2 Trials)</td>
<td>564 50 mg per day orally for up to 96 weeks</td>
<td>5-Point pain scale</td>
<td>Significantly reduced pain scores below baseline in patients with breast cancer compared with placebo (P = 0.001)</td>
</tr>
<tr>
<td></td>
<td>Diet al20</td>
<td>466 2-mg or 6-mg I.V. every 3-4 weeks for up to 96 weeks</td>
<td>5-Point pain scale</td>
<td>6-mg dose significantly reduced pain scores below baseline in patients with breast cancer compared with placebo (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>Clodronate</td>
<td>144 1600 mg per day orally for up to 1 year</td>
<td>Visual pain scale</td>
<td>Significantly reduced pain in patients with breast cancer compared with placebo (P &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>Tubiana-Hulin et al81</td>
<td>209 1500-mg I.V. every 3 weeks</td>
<td>6-Point PPI index</td>
<td>No significant improvement in palliative response in patients with prostate cancer compared with placebo</td>
</tr>
</tbody>
</table>

*Bone pain was evaluated using a scoring system that quantified the severity and frequency of bone pain. Abbreviation: PPI = present pain intensity
Adapted with permission from Lipton A. The role of bisphosphonates in malignant bone disease. Oncology Special Edition 2005; 8:99-103.
controlled trial involving patients with breast cancer with bone metastases (N = 144), oral clodronate (1600 mg per day for ≤ 1 year) significantly reduced pain compared with placebo (P = 0.01) based on a 10-point visual analog scale.\(^{81}\) However, in an open-label trial involving patients with breast cancer with bone metastases (N = 100), the need for RT to treat bone pain increased in patients treated with clodronate (1600 mg per day for 2 years) compared with the control group at 15 months.\(^{30}\) In patients with prostate cancer, early placebo-controlled trials of etidronate and oral and I.V. clodronate showed some reductions in bone pain and analgesic use compared with placebo; however, these effects were transient and not statistically significant.\(^{41,46-48,74}\) In a small open-label study, clodronate (1600 mg per day) significantly decreased analgesic use compared with baseline levels, but the mean duration of this clinical benefit was only 9 weeks.\(^{42}\) Furthermore, in patients with hormone-refractory prostate cancer (N = 209) with bone metastases receiving concomitant mitoxantrone/prednisone treatment, I.V. clodronate (1500 mg every 3 weeks) provided no significant reduction in bone pain or analgesic use (palliative response) compared with placebo (Table 2); the median duration of response was 6.2 months in the clodronate group compared with 6.4 months in the placebo group (P = 0.79).\(^{48}\)

**Ibendronate.** In patients with breast cancer with bone metastases, oral and I.V. ibandronate have been shown to significantly reduce bone pain.\(^{19,24}\) Oral ibandronate (50 mg per day) significantly reduced pain scores (assessed on a 5-point scale) below baseline throughout the 96-week study period (P = 0.001).\(^{19}\) Analgesic use increased in both treatment groups, but patients treated with oral ibandronate reported a significantly smaller increase in analgesic use compared with the placebo group (P = 0.019). Similarly, I.V. ibandronate (6 mg every 3–4 weeks) significantly reduced mean pain scores from baseline compared with increased pain scores in the 2-mg ibandronate and placebo groups at 24 months (P < 0.001).\(^{20}\)

**Pamidronate.** In the pooled analysis of 2 pamidronate trials, patients with bone metastases from breast cancer treated with 90-mg pamidronate (every 3–4 weeks for 2 years) had significantly less pain at 24 months compared with the placebo group (P < 0.001), although pain scores increased over time in both treatment groups.\(^{14}\) Among patients with pain at study entry (79% of patients), significantly fewer patients treated with pamidronate experienced an increase from their baseline pain score compared with the placebo group (40% vs. 52% for placebo; P = 0.003). However, in a randomized placebo-controlled trial in patients with advanced-stage prostate cancer (N = 378), 90-mg pamidronate (every 3 weeks for 27 weeks) failed to significantly reduce bone pain compared with placebo at 9 or 27 weeks.\(^{44}\)

**Zoledronic Acid.** Zoledronic acid has demonstrated palliative benefits in patients with breast or prostate cancer. In a comparative phase III trial in patients with bone metastases of breast cancer or osteolytic lesions of multiple myeloma, 4-mg zoledronic acid was at least as effective as 90-mg pamidronate in reducing composite BPI scores at 13 months.\(^{36}\) The composite BPI score was defined as the average of pain right now and worst pain, least pain, and average pain over the past 7 days. Among patients with pain at baseline, 53%–69% of patients in both treatment groups experienced a decrease from baseline in their composite pain scores at 13 months, and analgesic use remained stable. The reductions in pain scores were similar in both treatment groups. Moreover, over 25 months, significantly fewer patients treated with zoledronic acid required RT to bone compared with the pamidronate group (19% vs. 27% for pamidronate; P = 0.011).\(^{37}\) In a placebo-controlled trial of Japanese women with bone metastases from breast cancer, 4-mg zoledronic acid every 4 weeks significantly reduced composite BPI scores throughout the 12-month study (P = 0.0004 at 12 months compared with baseline; Figure 3).\(^{23}\) In contrast, patients in the placebo group had a steady increase from mean baseline pain scores over the entire duration of the study. There was no difference between treatment groups in analgesic use.

Similarly, in patients with metastatic prostate cancer treated with 4-mg zoledronic acid or placebo every 3 weeks for up to 24 months, bone pain was consistently lower in...
the zoledronic acid group compared with placebo at all time points, and this difference reached statistical significance at 3, 9, 21, and 24 months.13,51

Economic Burden of Skeletal Complications

In patients with malignant bone disease, skeletal complications can negatively affect QOL and survival and can result in increased health-care costs. For example, it has been estimated that the cost of treating skeletal complications accounts for 65% of total hospital costs for patients with advanced-stage breast cancer.83 In patients with bone lesions from multiple myeloma, a retrospective observational study involving 835 patients, of whom 352 (42%) had experienced ≥ 1 SRE, demonstrated that the expected lifetime health-care cost associated with SREs was $10,247 per patient over 17.5 months of follow-up.84 Approximately 64% of these costs occurred associated with SREs was $9783 per patient. Furthermore, total medical costs were $20,484 more for patients experiencing SREs compared with the medical costs for patients who did not experience SREs ($59,522 vs. $39,038, respectively). These data are consistent with a retrospective cost analysis conducted in The Netherlands that showed that the medical costs directly attributable to skeletal complications in patients with prostate cancer comprised nearly half of the total cost of care.86

Lastly, in a recent retrospective study involving 534 patients with bone metastases from lung cancer, the estimated lifetime SRE-related cost per patient was $11,979.87 The most common SRE in this population was RT (68%), which accounted for the greatest proportion of health-care costs (61%). In a follow-up to this analysis, patients experiencing SREs were matched with patients without SREs based on baseline disease characteristics.88 This analysis demonstrated that, in the SRE group, the expected health-care cost directly resulting from SREs was $9494 per patient. Furthermore, total expected health-care costs were $28,223 more in patients experiencing SREs compared with the expected costs for patients with no SREs ($59,926 vs. $31,704, respectively).

Thus, therapies that prevent skeletal complications can provide significant savings in terms of direct and indirect health-care costs. Pharmacoeconomic studies have shown that, although bisphosphonates are associated with higher total treatment costs, they provide significant clinical benefit to patients and warrant the additional expenditure by preventing costly SREs and improving overall QOL.27,69 For example, a recent metaanalysis completed by Ross et al concluded that bisphosphonate therapy was cost effective for the treatment of hypercalcemia and the prevention of skeletal morbidity, particularly for the prevention of fractures in patients with breast cancer.90 In addition, in a post hoc cost-effectiveness analysis of 2 pamidronate trials involving patients with bone metastases from breast cancer receiving hormonal therapy or chemotherapy, treatment with pamidronate resulted in a gain of 0.026 quality-adjusted life-years (approximately 9 days) for patients in the hormonal therapy group and 0.037 quality-adjusted life-years (approximately 13 days) for patients in the chemotherapy group compared with placebo.90 In this study, the projected net costs per SRE avoided were $3940 and $9390 in the chemotherapy and hormonal therapy groups, respectively. In a similar post hoc cost-effectiveness analysis of zoledronic acid versus placebo in patients with bone metastases from prostate cancer, the nominal cost per SRE avoided was $12,300.91 Considering that the cost to treat a hip fracture is approximately $33,000 and the average cost for a hospital stay is approximately $17,000, bisphosphonates are an economically sound treatment option.92,93

An even more cost-effective use of bisphosphonates is currently being investigated.94 The usual schedule of treatment in metastatic bone disease is one that is 6-14 times more intense than that required for the treatment of osteoporosis or cancer therapy-induced bone loss. Although this is entirely appropriate when the disease is progressing and not controlled by systemic therapy, it is probably overtreatment for patients in remission during an effective anticancer treatment. For these cases, it might be possible to reduce the frequency of bisphosphonate administration. A large national trial (BISMARK) to address this is under way in the United Kingdom. Patients with breast cancer and bone metastases will be randomized to receive zoledronic acid via the standard I.V. schedule (every 3–4 weeks) or a schedule determined every 4 months based on the rate of bone resorption as determined by the urinary excretion of Ntx.

Conclusion

Bone metastases are common in patients with advanced-stage cancer and lead to painful skeletal complications that negatively affect QOL and increase health-care costs. The primary goal of bisphosphonate therapy in the management of bone metastases is to prevent skeletal complications. Bisphosphonates have been shown to significantly reduce the incidence and delay the onset of painful skeletal complications in patients with bone metastases from breast cancer. Bisphosphonates also provide significant pain relief in patients and play an important secondary role in the management of bone pain. However, zoledronic acid is the only bisphosphonate shown to reduce and delay skeletal complications compared with placebo in patients with advanced-stage prostate cancer. Early and continued use of bisphosphonates could help to maintain skeletal integrity and improve QOL in patients with malignant bone disease.
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