Treatment of Bone Metastases and Bone Pain with Bisphosphonates

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Abstract

Many solid tumors metastasize to bone, leading to debilitating skeletal complications such as intractable bone pain and pathologic fractures. Patients who experience a skeletal-related event (SRE) are at higher risk for subsequent events. After an SRE such as a pathologic fracture, spinal cord compression, or the requirement for orthopedic surgery or palliative radiation therapy, a patient’s quality of life and functional independence could decline substantially. Prevention or delay of skeletal complications provides clinical benefit to patients with bone metastases secondary to solid tumors. Treatment for the prevention of the first SRE might substantially improve patients’ quality of life, functional independence, and pain throughout the course of their disease. Bisphosphonates have shown a palliative benefit in this setting. In particular, zoledronic acid is the only bisphosphonate that has provided benefits for patients with bone metastases secondary to a broad range of solid tumors. Among patients with metastatic breast or prostate cancer, zoledronic acid has demonstrated significant reductions in pain and skeletal morbidity compared with placebo. Zoledronic acid has also shown significant reductions in skeletal morbidity in patients with lung cancer or other solid tumors compared with placebo. Pamidronate, oral clodronate, and ibandronate compared with placebo have each shown significant benefits in reductions of pain and skeletal complications for patients with metastatic breast cancer. Further improvements in the management of skeletal health in patients with malignant bone disease could be achieved through ongoing bisphosphonate investigations to optimize dose, timing, and duration of treatment.

Introduction

The skeleton is the most common organ for distant metastasis in patients with cancer. For example, bone metastases form in the vast majority of patients with breast or prostate cancer, in > 50% of patients with advanced thyroid cancer, in 30%-40% of patients with advanced lung cancer, and in 20%-25% of patients with advanced renal cancer.1 Primary bone lesions also develop in > 70% of patients with advanced multiple myeloma (MM) because this malignancy colonizes the bone marrow. Because of the advances in primary tumor treatment, patients with cancer are surviving longer, and the skeletal effects of their cancer are being manifested to a greater extent.
Bone metastases are associated with clinically meaningful skeletal morbidity. Typically, the first symptom is bone pain that could be intermittent with increased pain at night and alleviated by activity. Pain could increase gradually and become more constant until opioid analgesia or palliative radiation therapy (RT) becomes necessary. However, analgesics are frequently underused, are often only partially effective, and are limited by intolerable side effects such as constipation, sedation, and patient fear of addiction. Moreover, acute pain episodes despite analgesia (“breakthrough pain”) can develop in patients with advanced bone disease, and this requires palliative RT.

Malignant bone disease is associated with other potentially debilitating skeletal-related events (SREs), including pathologic fractures, spinal cord compression or vertebral collapse, the need for surgery, and hypercalcemia of malignancy, each of which could decrease patients’ quality of life (QOL) and reduce their functional independence. Indeed, pathologic fractures are associated with shorter survival in patients with bone metastases from breast or prostate cancer. Bone pain and SREs share the same underlying pathophysiology: increases in osteoclast-mediated osteolysis caused by malignant bone disease. Therefore, in addition to palliating bone pain, it is important to consider the preservation of bone health.

The introduction of bisphosphonates has provided oncologists with an important tool for the prevention of skeletal morbidity from bone metastases. Zoledronic acid has been shown to reduce the incidence and delay the onset of SREs, including pathologic fractures and the need for palliative RT to bone compared with placebo in patients with bone metastases from a broad range of solid tumors. Bisphosphonates also provide significant palliative benefits in patients with bone metastases and are recommended supportive care for patients with malignant bone disease. Internationally, intravenous (I.V.) pamidronate is approved for the treatment of primary bone lesions from MM or bone metastases secondary to breast cancer. In Europe, oral clodronate is also approved for these indications. Oral and I.V. ibandronate are approved in Europe for the treatment of bone metastases secondary to breast cancer. Only zoledronic acid has received worldwide approval for the treatment of bone metastases independent of the primary tumor type.

**Prevention of Skeletal Complications**

Skeletal complications that arise from bone metastases in patients with advanced cancer result in significant morbidity and mortality. Therefore, an important goal of therapy is to maintain patients’ functional independence and QOL through preventing and delaying SREs. In placebo-controlled trials in patients with breast cancer and bone metastases, bisphosphonates have been shown to reduce the occurrence of skeletal complications. Zoledronic acid significantly reduced the proportion of patients with any skeletal complication compared with placebo (30% vs. 50%, respectively; \( P = 0.003 \)) and increased the median time to first SRE (median, not reached vs. 364 days, respectively; \( P = 0.007 \)) in this patient population. In fact, among the bisphosphonates investigated in this setting, zoledronic acid produced the largest reduction in skeletal morbidity (Figure 1). Only zoledronic acid and pamidronate have been compared head-to-head in a double-blind randomized phase III trial, and zoledronic acid produced significant benefits beyond those of pamidronate. Zoledronic acid reduced the risk of SREs by an additional 20% (\( P = 0.025 \)) compared with pamidronate. Pamidronate has shown similar results in SRE delay and reduction compared with...
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Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose</th>
<th>Efficacy Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saad et al.26</td>
<td>Zoledronic</td>
<td>4 mg (I.V. every 3 weeks)</td>
<td>↓ Proportion of patients with ≥ 1 SRE (P = 0.028)</td>
</tr>
<tr>
<td></td>
<td>Acid</td>
<td></td>
<td>↑ Time to first SRE (P = 0.009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Rate of skeletal morbidity (P = 0.005)</td>
</tr>
<tr>
<td>Dearnaley et al27</td>
<td>Clodronate</td>
<td>2080 mg per day (orally)</td>
<td>↑ Bone progression-free (NS) and overall survival (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Worsening of WHO PS (P = 0.008)</td>
</tr>
<tr>
<td>Small et al28</td>
<td>Pamidronate</td>
<td>90 mg (I.V. every 3 weeks)</td>
<td>No significant benefits in proportion of patients with SREs</td>
</tr>
</tbody>
</table>

Abbreviations: NS = not significant, P ≥ 0.05; PS = performance status; WHO = World Health Organization

placebo (P < 0.001 for both).24 Compared with placebo, ibandronate has also significantly reduced the proportion of patients with an on-study SRE (36% vs. 48%, respectively; P = 0.027) and increased the mean time to a first SRE (457 days vs. 304 days, respectively; P = 0.007).25 Several bisphosphonates have been investigated in patients with prostate cancer; however, only zoledronic acid has demonstrated significant objective long-term benefits (Table 1).7,26-28 A randomized study in patients with hormone-refractory prostate cancer (N = 643) who were treated for up to 2 years with zoledronic acid 4 mg or placebo showed that zoledronic acid significantly decreased the proportion of patients with ≥ 1 SRE compared with placebo (38% vs. 49%, respectively; P = 0.028), and zoledronic acid also reduced the skeletal morbidity rate (0.77 vs. 1.47; P = 0.005).7,26 Moreover, zoledronic acid significantly increased the time to first SRE (488 days vs. 321 days; P = 0.009) compared with placebo. In this setting, oral clodronate (2080 mg per day) produced a 29% reduction in the risk of worsening World Health Organization performance status (during 3 years of treatment and a median follow-up of 59 months) compared with placebo (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.56-0.92; P = 0.008).27 Furthermore, overall survival and bone lesion progression-free survival were improved with clodronate compared with placebo, but the benefit was not statistically significant (HR, 0.8; 95% CI, 0.62-1.03; P = 0.082 and HR, 0.79; 95% CI, 0.61-1.02; P = 0.066, respectively). However, patients treated with clodronate reported more gastrointestinal adverse events, increased lactate dehydrogenase levels, and a higher rate of dose adjustments compared with placebo (HR for any adverse event, 1.71; 95% CI, 1.21-2.41; P = 0.002). Pamidronate 90 mg did not significantly reduce the rate of SREs or palliate bone pain compared with placebo in patients with bone metastases secondary to prostate cancer.28

In the treatment of patients with a broad range of other solid tumors, only zoledronic acid 4 mg has demonstrated significant benefits and received widespread regulatory approval (Table 2).29-31 Among patients with lung cancer or other solid tumors such as renal cell carcinoma, zoledronic acid 4 mg significantly delayed the median time to first SRE compared with placebo (236 days vs. 155 days, respectively; P = 0.009) and reduced the skeletal morbidity rate (1.74 vs. 2.71, respectively; P = 0.012).31 Furthermore, zoledronic acid reduced the risk of developing an SRE by 31% compared with placebo (HR = 0.693; P = 0.003). In patients with bone metastases from solid tumors who responded poorly to chemotherapy, oral clodronate 1600 mg per day for 1 year did not significantly reduce mean pain scores compared with placebo.30 However, compared with placebo, clodronate significantly reduced the requirement for analgesics (P = 0.042). Ibandronate 6 mg administered every...
4 weeks for 9 months in patients with bone metastases from solid tumors reduced skeletal morbidity compared with placebo.29 However, no significant difference was reported. At this time, zoledronic acid is the only approved agent for the treatment of patients with bone metastases from lung cancer or other solid tumors.

**Bone Pain**

Bone pain is a significant clinical problem in patients with advanced cancer. In fact, bone metastases are the most common source of pain in this patient population.32 Pain associated with malignant bone disease occurs in 2 different varieties.2 The first type of pain is ongoing, characterized as dull, aching, or throbbing, and the severity of which increases with disease progression. The second type of pain is incident pain (also called “breakthrough” pain), which occurs intermittently and is acute in nature. Patients experience this type of pain spontaneously or when they move or place weight on the affected bone. Typically, bone pain is not adequately managed, and 75%-95% of patients with advanced cancer experience severe pain. Suboptimal pain management is associated with decreased functional independence and QOL for affected patients.33

A broad range of pain management strategies are available. Pharmacologic management targeted at nerve injury or at inflammation-associated pain, such as nonsteroidal antiinflammatory drugs and opioids, are clinically valuable, but patients experience many adverse events.2 In fact, the high doses of opioids necessary to manage bone pain in patients with advanced metastatic cancer often result in con-
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Table 3B

Summary of Trials with Bisphosphonates for Reducing Bone Pain5,7,19,22,28,36-46

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Pain Measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate, placebo</td>
<td>BPI</td>
<td>Reduced pain score (not significant)</td>
</tr>
<tr>
<td>Clodronate, placebo</td>
<td>PPI (0-5 scale)</td>
<td>Reduced pain scores (not significant)</td>
</tr>
<tr>
<td>Clodronate, placebo</td>
<td>Visual pain scale</td>
<td>Significantly reduced pain intensity ($P &lt; 0.01$)</td>
</tr>
<tr>
<td>Clodronate, placebo</td>
<td>10-Point pain scale</td>
<td>Decreased average pain intensity from baseline at 2 months (no $P$ given)</td>
</tr>
</tbody>
</table>

Abbreviation: PPI = present pain intensity scale of the McGill-Melzack Pain Questionnaire

Radiation to bone is standard therapy for palliation of severe bone pain refractory to pharmacologic management but is associated with acute skin, gastrointestinal, and hematologic toxicity, resulting in exposure limits.34,35 In contrast to these purely palliative interventions, bisphosphonates normalize bone metabolism. Bisphosphonates therefore reduce bone resorption and the risk of SREs, thereby preempting acute painful events. An additional class effect is clinically meaningful palliative effects for patients with refractory bone pain. Recent studies have provided further evidence that, in general, bisphosphonates significantly reduce bone pain secondary to the treatment of bone metastases. In a separate, smaller study, patients’ QOL was improved after zoledronic acid treatment, and pain (measured with a visual analog scale) was reduced from a median pain score of 5.1 at baseline to 1.8 at 6 months.40 Zoledronic acid has also been shown to reduce the requirement for palliative RT to bone. In the zoledronic acid arm of placebo-controlled trials, there was a 50% relative reduction in the proportion of
patients needing palliative RT for breast cancer (9% vs. 18% for placebo), a 21% relative reduction for prostate cancer (26% vs. 33% for placebo), and a 15% relative reduction for lung cancer and other solid tumors (29% vs. 34% for placebo).5,31,37 In patients with breast or prostate cancer, zoledronic acid reduced pain at rest and incident pain.50,51 Moreover, zoledronic acid significantly reduced pain scores after treatment with other bisphosphonates (P < 0.05) in patients with breast cancer, prostate cancer, or MM.38 Taken together, these recently completed studies provide further evidence that, in addition to the established efficacy for preventing SREs, zoledronic acid provides clinically meaningful palliation of pain in patients with malignant bone disease from MM or solid tumors.

The pain palliation effects of I.V. pamidronate and clodronate have each been assessed in patients with advanced breast or prostate cancer. In patients with bone metastases from breast cancer, pamidronate 90 mg (via 2-hour infusion) every 3-4 weeks has been shown to significantly reduce mean pain scores (P = 0.015) and the requirement for palliative RT to bone (P < 0.001) at 24 months.24 Among pamidronate-treated patients, 25% required palliative RT, which was a significant reduction compared with 37% of patients in the placebo arm (P < 0.001). However, in a 27-week placebo-controlled trial in patients with bone metastases from prostate cancer, pamidronate 90 mg (via 2-hour infusion) every 3 weeks did not provide a significant decrease in mean BPI scores compared with placebo.28 In both treatment groups, the mean average baseline BPI score was approximately 4 on a 10-point scale, and the mean average BPI score decreased < 1 point throughout the study. Oral clodronate has shown palliative benefits that are similar to those of pamidronate in patients with breast or prostate cancer. For example, clodronate (1600 mg per day orally for up to 1 year) was shown to significantly reduce visual analog scale pain in patients with bone metastases from breast cancer (P = 0.01).22 However, at 44 months in patients with bone metastases from prostate cancer, clodronate 1500 mg (via 3-hour infusion) every 3 weeks did not provide a significant decrease in the present pain intensity scale compared with placebo (P = 0.34).41 In a small study of patients with prostate cancer (N = 78), low-dose clodronate (2 × 400 mg/day, orally) reduced the average pain intensity from 8 at baseline to 4 at 2 months.42

Intravenous and oral ibandronate have recently demonstrated palliation of bone pain in patients with breast cancer.19,43 Intravenous ibandronate 6 mg (via 1- to 2-hour infusions) every 3-4 weeks significantly reduced the mean baseline bone pain scores compared with placebo at 96 weeks (P < 0.001).43 Similar reductions from baseline bone pain were observed with oral ibandronate 50 mg at 96 weeks (P = 0.001), although analgesic use increased and bone pain was not significantly decreased at every time point throughout the study.19 Patients with a broad range of

### Table 3C

Summary of Trials with Bisphosphonates for Reducing Bone Pain

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Dose and Regimen</th>
<th>Pain Measurement</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Ibandronate</td>
<td>Ibandronate, placebo</td>
<td>2 or 6 mg I.V. every 3-4 weeks for up to 96 weeks</td>
<td>5-Point pain scale</td>
<td>6 mg significantly reduced pain scores below baseline compared with placebo (P &lt; 0.001)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Ibandronate</td>
<td>4 mg I.V. for 4 consecutive days</td>
<td>Mean VAS (0-10 points)</td>
<td>Significantly reduced VAS score from baseline within 7 days (P &lt; 0.001) and was sustained throughout study (6 weeks)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Ibandronate, placebo</td>
<td>50 mg per day orally for up to 96 weeks</td>
<td>5-Point pain scale</td>
<td>Significantly reduced pain scores below baseline compared with placebo (P = 0.001)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Ibandronate</td>
<td>6 mg I.V. for 3 consecutive days</td>
<td>Numeric rating scale (0-10 points)</td>
<td>Reduced pain from baseline within 7 days (no P given)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Ibandronate</td>
<td>6 mg I.V. for 3 consecutive days</td>
<td>Pain scale not given</td>
<td>Reduced pain from baseline within 7 days (no P given)</td>
</tr>
</tbody>
</table>

Abbreviation: VAS = visual analog scale
Among patients with breast cancer who had no pain at study with 18% decrease relative to placebo in the proportion of patients relative differences compared with placebo were lower among placebo.54 Although zoledronic acid still provided benefits, decreased the proportion of patients with breast cancer; however, patients without pain at baseline after the development of pain in patients with prostate or zoledronic acid.6,7,31 

**Practical Considerations in the Use of Bisphosphonates**

Currently, there are no prospective data on the optimal initiation and duration of bisphosphonate treatment in patients with advanced cancer, especially after the onset of SREs. However, recent retrospective analyses of data from zoledronic acid randomized studies have addressed these questions. Specifically, benefits before and after the development of pain and SREs and during the second year of treatment have been evaluated using the phase III registration trial database for bisphosphonates.52 Investigations of other alternate administration schedules for more rapid pain palliation, such as loading-dose ibandronate, are under way. Recently, 2 pilot studies found that loading-dose ibandronate 6 mg for 3 consecutive days can reduce bone pain within approximately 2-7 days of infusion, regardless of tumor type.45,46,53 However, because pain is a symptom of the underlying pathophysiology, pain outcomes and bone health are important to consider, and these studies have not assessed whether this dosing schedule reduced SREs.

Zoledronic acid was found to provide benefits before and after the development of pain in patients with prostate or breast cancer; however, patients without pain at baseline might have better outcomes. Among patients with prostate cancer who had no pain at study entry, zoledronic acid decreased the proportion of patients with ≥ 1 SRE by 39% and reduced the skeletal morbidity rate by 49% compared with placebo.54 Although zoledronic acid still provided benefits, relative differences compared with placebo were lower among patients with prostate cancer who had pain at study entry: 18% decrease relative to placebo in the proportion of patients with ≥ 1 SRE and 39% decrease in the skeletal morbidity rate. Among patients with breast cancer who had no pain at study entry, zoledronic acid decreased the proportion of patients with ≥ 1 SRE by 40% relative to pamidronate and reduced the skeletal morbidity rate by an additional 35% compared with pamidronate.55 Among patients with breast cancer who had pain at baseline, similar proportions of both treatment groups experienced an SRE, but zoledronic acid reduced the skeletal morbidity rate by 40% compared with pamidronate. These exploratory analyses suggest that early diagnosis and treatment of bone metastases before the onset of pain might provide clinical benefits.

The occurrence of an SRE during bisphosphonate therapy does not appear to reduce the efficacy of ongoing therapy. Among patients with prostate cancer, zoledronic acid significantly decreased the proportion of patients with a second SRE by 32% relative to placebo (P = 0.017) and reduced the risk of subsequent SREs by 40% compared with placebo (P = 0.011).56 Among patients with breast cancer who received hormonal therapy, zoledronic acid decreased the proportion of patients with a second SRE by 22% relative to pamidronate (P = 0.059) and reduced the risk of subsequent SREs by 31% compared with pamidronate (P = 0.045).57 Similarly, patients who have received ≥ 1 year of therapy appear to benefit from ongoing treatment. In patients with prostate cancer, zoledronic acid significantly reduced the risk of developing SREs by 53% compared with placebo during months 16-24 of therapy (P = 0.022), which was greater than the reduction obtained in the first 15 months (core study, 36%).56 Among patients with breast cancer, zoledronic acid significantly reduced the risk of developing SREs by 41% compared with pamidronate during the second year of therapy (P = 0.026).57 The results of these analyses support continuing long-term treatment with zoledronic acid, at least through year 2, in patients with prostate or breast cancer.

Ongoing studies are also examining alternate administration schedules for zoledronic acid. Bone metastases are associated with increases in bone metabolism, and biochemical markers of bone metabolism might be effective indicators of the ongoing bone pathophysiology.1,58 Therefore, one study is evaluating the efficacy of a variable treatment interval for zoledronic acid based on levels of biochemical markers of bone metabolism compared with the standard every 3-4-week schedule (BiSMAK).59 The frequency and timing of SREs is the primary endpoint. Results are eagerly awaited for this study.

**Conclusion**

Bone metastases are common in patients with advanced malignancies, especially in patients with breast or prostate cancer, and are associated with bone pain and skeletal-related
events. Moreover, patients who experience ≥ 1 SRE, such as a pathologic fracture, are at higher risk for subsequent events. For example, patients with bone metastases secondary to breast cancer who have had a first fracture are at a 2-fold increased risk for a second fracture.60 Similarly, among patients with bone lesions from MM or bone metastases from prostate cancer, those who had an SRE before study entry had a higher SRE rate on study than those without a previous SRE.60,61 Therefore, treatment for the prevention of the first SRE might substantially improve patients’ QOL, functional independence, and pain throughout the course of their disease.

The introduction of bisphosphonates has provided an important tool for the prevention of skeletal morbidity. In patients with bone metastases from various solid tumors, zoledronic acid has significantly reduced skeletal morbidity compared with placebo. Ibandronate has not yet demonstrated significant reductions in skeletal morbidity in patient populations other than breast cancer. By reducing and preventing SREs and improving skeletal health, zoledronic acid has the additional palliative benefit of pain reduction. Of the available agents, all have produced reductions in bone pain, but zoledronic acid has demonstrated the broadest range of clinical benefits in all solid tumors.

Further research in this setting might allow for improvements in skeletal health management for patients with malignant bone disease. Ongoing trials are investigating the optimal timing and duration of treatment with bisphosphonates.

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References

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Supportive Cancer Therapy