Bisphosphonates in oncology: evidence for the prevention of skeletal events in patients with bone metastases

Thomas J Polascik
Division of Urology, Department of Surgery, Duke University Medical Center, Durham, NC, USA

Abstract: Bone metastases frequently occur in patients with advanced solid tumors, particularly breast and prostate cancers, and nearly all patients with multiple myeloma have some degree of skeletal involvement. The strides made in treating these primary tumors have extended median survival times and thereby increased patient risk for skeletal-related events (SREs), including pathologic fractures, spinal cord compression, need for palliative radiation therapy or surgery to bone, and hypercalcemia. Bisphosphonates, inhibitors of osteoclastic bone resorption that were first established as treatment of osteoporosis, have been shown to prevent and/or delay SREs related to malignancy. The results of a large, randomized phase 3 study comparing zoledronic acid and pamidronate in breast cancer or multiple myeloma patients with osteolytic lesions showed that the incidence of SREs, time to first SRE, and risk of developing a SRE were similar between treatment groups. However, in patients with solid tumors (excluding breast or prostate cancer) metastatic to the bone, only zoledronic acid has demonstrated clinical efficacy. Although bone turnover marker levels, such as N-telopeptide of type I collagen, have been shown to correlate with clinical response, additional studies are needed to validate their ability to predict response to bisphosphonate therapy.

Keywords: bisphosphonates, prevention, skeletal-related events, bone metastases, cancer

Introduction

Osteoporosis, a skeletal condition common in postmenopausal women and aging men, is characterized by low bone mass, destruction of bone microarchitecture, and increased bone turnover resulting in decreased bone strength and consequent susceptibility to fractures.1,2 Osteoporotic fractures, such as fractures of the hip, vertebral body, and distal forearm, may lead to decreased quality of life (QOL), disability, and possibly death. In the last decade, bisphosphonates, compounds that inhibit osteoclastic bone resorption, have been the most significant contribution to the advancement in osteoporosis treatment; clinical trials have demonstrated a reduction in vertebral fractures of 40% to 50% and nonvertebral fractures (including hip fractures) of 20% to 40%.1,3 Bisphosphonates approved by the United States Food and Drug Administration (FDA) for the prevention and/or treatment of osteoporosis include alendronate, alendronate plus vitamin D, ibandronate, risedronate, risedronate with calcium, and zoledronic acid.4–10 Because their bioavailability is quite low, oral agents usually require daily or weekly administration (with the exception of ibandronate, which may be administered monthly) that can contribute to low patient compliance rates.6–9 Intravenous (IV) bisphosphonates may be administered less frequently (eg, on a monthly, quarterly, or yearly basis).6,10–12 In general, patient compliance rates with prescribed IV bisphosphonate regimens are higher than with oral bisphosphonates.
In addition to osteoporosis, bisphosphonates have been used to prevent and/or treat cancer-related bone complications.\textsuperscript{3,11} Patients who develop bone metastases are at increased risk for developing skeletal-related events (SREs), such as intractable bone pain requiring opioid analgesics or palliative radiation therapy, pathologic fractures, spinal cord compression, a need for surgery, and hypercalcemia of malignancy (HCM).\textsuperscript{14} SREs are a consequence of excessive bone metabolism, primarily bone resorption, which characterizes malignant bone lesions.\textsuperscript{3} Local bone pain requiring radiation therapy and pathologic fractures are the most commonly reported SREs.\textsuperscript{3}

As a result of advancements in the primary treatment of several solid tumors and hematologic malignancies, patients are surviving longer, placing them at an increased risk for developing bone metastasis and SREs that may complicate their clinical course, adversely affect QOL, and increase medical costs.\textsuperscript{14–16} Bone metastases are particularly prevalent in patients with advanced metastatic breast or prostate cancers, affecting approximately 70% of patients.\textsuperscript{3} Although observed less frequently, bone metastases also occur in patients with lung, kidney, and thyroid tumors.\textsuperscript{17} Nearly all patients with advanced multiple myeloma (MM) develop bone involvement during the course of their disease since this malignancy colonizes in the bone marrow.\textsuperscript{14,18}

**Metastatic bone disease**

Under normal circumstances, bone homeostasis is achieved through balanced resorption of old bone by osteoclasts and formation of new bone by osteoblasts.\textsuperscript{19} Metastatic bone disease alters the normal bone remodeling process by causing osteolytic bone destruction and abnormal osteoblastic bone formation, often with one process more dominant than the other, resulting in an imbalance in normal bone homeostasis.\textsuperscript{18–20} Although historically bone metastases from breast cancer or MM have been characterized as osteolytic lesions and prostate cancer bone metastases have been primarily osteoblastic in nature, recent evidence suggest that both bone processes are present in many patients.\textsuperscript{18,20} Without bisphosphonate treatment, it is estimated that patients with bone metastases from advanced cancer will experience, on average, 2 to 4 SREs per year.\textsuperscript{15} Thus, bone complications of cancer are a considerable clinical concern, and preventing or delaying the occurrence of such events is an important treatment objective. Although palliation has traditionally been the primary goal of therapy, the introduction of bisphosphonates has afforded oncologists with an effective therapeutic option for preventing and/or treating SREs associated with bone metastases.

**Mechanism of action of bisphosphonates**

Because of their ability to diminish bone resorption and subsequently normalize calcium levels, prevent development of new osteolytic lesions, and reduce the risk of fractures, bisphosphonates are the treatment of choice for skeletal complications of malignancy.\textsuperscript{21} Bisphosphonates are pyrophosphate analogs that preferentially bind to bone at sites of active metabolism, are released from the bone matrix during bone resorption, and inhibit osteoclast activity and survival.\textsuperscript{3,21} Variable side chains determine the potency and side effect profile of each agent.\textsuperscript{21} These compounds can be grouped into two classes according to their chemical structure and molecular mechanism of action (Figure 1).\textsuperscript{22} The newer nitrogen (N)-containing, second- or third-generation compounds, including alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid, inhibit the enzyme farnesyl dipiphosphate synthase in the cholesterol mevalonate pathway and thereby suppress osteoclast-mediated bone resorption, whereas the non–N-containing, first-generation bisphosphonates, such as clodronate, etidronate, and tiludronate, induce osteoclast apoptosis via metabolism into cytotoxic analogues of adenosine 5’-triphosphate.\textsuperscript{21,23,24} The N-containing agents are more potent than the non–N-containing bisphosphonates, inhibiting bone resorption at micromolar concentrations.\textsuperscript{3} Only IV zoledronic acid and IV pamidronate are approved by the FDA for cancer-related indications.\textsuperscript{25,26} In Europe, oral clodronate, IV pamidronate, and oral and IV ibandronate have received regulatory approval for patients with bone metastases secondary to breast cancer.\textsuperscript{3,27} Only zoledronic acid has received US and European approval for the treatment of bone metastases independent of the primary tumor type.\textsuperscript{25,28}

**Evaluating efficacy of bisphosphonates**

Developing composite end points of similar clinical significance may be appropriate when the clinical benefit of a drug is multifaceted as is the case with bisphosphonates.\textsuperscript{29} Using a SRE as a quantifiable clinical end point was first applied to studies assessing pamidronate for prevention of SREs. This end point included one or more of the following: pathologic fracture, radiation therapy for local pain, surgery to stabilize near-fractures, or spinal cord compression. Subsequently, SREs were used as the primary end points for most of the trials assessing a bisphosphonate for this indication. However, the definition or names for SREs have differed slightly between studies (see Tables 1–4), sometimes being
referred to as skeletal complications or bone events. Furthermore, HCM has been excluded from the definition of a SRE in some trials because bisphosphonates have been shown to be effective for the treatment of HCM before studies investigating bisphosphonates as preventive therapy for SREs were developed.

Several clinical studies designed to evaluate bisphosphonates to prevent skeletal complications have demonstrated clinical benefit. This article reviews the results of clinical studies assessing bisphosphonates as prevention and/or treatment for cancer-related bone complications in a variety of tumor types.

**Clinical studies**

**Breast cancer**

Clinical trial results show that bisphosphonates reduce the occurrence of skeletal complications in patients with breast cancer and bone metastases (Table 1). Based on the results of two randomized, placebo-controlled clinical studies in patients with osteolytic bone metastases from breast cancer being treated with either chemotherapy or hormonal therapy, IV pamidronate was approved by the FDA for preventing SREs. Pamidronate (90 mg administered IV over 2–4 hours q 3–4 weeks) significantly prolonged the time to the first SRE and reduced the overall incidence of SREs for up to 2 years (see Table 1). In another placebo-controlled trial of breast cancer patients with at least one osteolytic lesion, zoledronic acid significantly lowered the risk of SREs by 39% (p = 0.027), reduced the proportion of patients experiencing a SRE at 1 year by 20% (29.8% vs 49.6%, p = 0.003), and significantly prolonged the time to first SRE excluding HCM (median not reached vs 364 days, p = 0.007). Only one study has directly compared zoledronic acid with pamidronate (see Table 1). This large, randomized phase 3 study was designed to demonstrate the equivalence of zoledronic acid and pamidronate in reducing the incidence of SREs in patients with breast cancer or MM. Among the breast carcinoma stratum, the overall incidence of SREs other than HCM was comparable between the two study groups. The median time to first SRE was also similar; however, in patients receiving hormonal therapy for breast cancer, zoledronic acid 4 mg IV significantly delayed the time to first SRE (415 vs 370 days; p = 0.047). Oral and IV ibandronate have also been evaluated in breast cancer patients with metastatic bone disease; compared with placebo, both formulations of ibandronate (6 mg IV and 50 mg oral) have significantly reduced the
| Study                | Study design | Drug                        | Primary endpoint | Efficacy results                                                                                                                                  | Comments                                                                                     |
|---------------------|--------------|-----------------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Rosen et al 2001³⁰  | MC, R, DB    | ZOL 4 mg or 8 mg IV every 3–4 wk × 24 mo versus PAM 90 mg IV every 3–4 wk × 24 mo | Proportion with ≥1 SRE at 13 mo and 25 mo | 13-mo analysis (includes all patients except where noted):  
• Proportion of patients with a SRE was similar between treatment groups  
• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM overall (15% vs 20%, p = 0.031) and in MBC_{overall} (16% vs 25%, p = 0.022)  
25-mo analysis (includes all patients except where noted):  
• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM overall (19% vs 24%, p = 0.037)  
• ZOL 4 mg reduced risk of skeletal complications by 16% compared to PAM (RR = 0.841 (95% CI, 0.719–0.983, p = 0.030)  
• Risk of developing SRE comparable between ZOL 4 mg and PAM in MBC_{event} (RR, 0.955; p = 0.749)  
• Among all patients with MBC, proportion with ≥1 SRE was comparable (43% ZOL 4 mg vs 45% PAM)  
• In patients with only osteolytic lesions, ZOL 4 mg reduced proportion with ≥1 SRE (48% vs 58%, p = 0.058) and significantly prolonged time to first SRE (p = 0.013)  
| Stage IV breast carcinoma and multiple myeloma patients  
Noninferiority trial  
Patients stratified prospectively by tumor type  
Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity  
Included patients with osteolytic and/or osteoblastic bone lesions |
| Rosen et al 2003³¹  | (N = 1648)   | ZOL 4 mg or 8 mg IV every 3–4 wk × 24 mo versus PAM 90 mg IV every 3–4 wk × 24 mo | Proportion with ≥1 SRE at 25 mo | 25-mo analysis (includes all patients except where noted):  
• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM overall (19% vs 24%, p = 0.037)  
• ZOL 4 mg reduced risk of skeletal complications by 16% compared to PAM (RR = 0.841 (95% CI, 0.719–0.983, p = 0.030)  
• Risk of developing SRE comparable between ZOL 4 mg and PAM in MBC_{event} (RR, 0.955; p = 0.749)  
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• In patients with only osteolytic lesions, ZOL 4 mg reduced proportion with ≥1 SRE (48% vs 58%, p = 0.058) and significantly prolonged time to first SRE (p = 0.013)  
| Analysis of MBC stratum of phase 3 trial (Rosen et al 2001³⁰, Rosen et al 2003³¹)  
Patients stratified based on ≥1 osteolytic lesion versus nonosteolytic lesion at study entry  
∼60% experienced an SRE before study entry  
Japanese patients with MBC  
Median time from diagnosis of bone metastases to study treatment was short (3.9 mo)  
Patients with ≥1 osteolytic lesion  
Pathologic fracture and bone irradiation were the most common SREs  
Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy  
Included patients with osteolytic and/or osteoblastic bone lesions |
| Rosen et al 2004³²  | (N = 1130)   | ZOL 4 mg or 8 mg IV every 3–4 wk × 12 mo versus PAM 90 mg IV every 3–4 wk × 12 mo | Proportion with ≥1 SRE at 25 mo | 25-mo analysis (includes all patients except where noted):  
• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM overall (19% vs 24%, p = 0.037)  
• ZOL 4 mg reduced risk of skeletal complications by 16% compared to PAM (RR = 0.841 (95% CI, 0.719–0.983, p = 0.030)  
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Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy  
Included patients with osteolytic and/or osteoblastic bone lesions |
| Kohno et al 2005³³   | (N = 228)    | ZOL 4 mg IV every 4 wk × 1 yr versus placebo | SRE rate ratio |
|                     |              | Proportion with ≥1 SRE at 25 mo | 0.63 ZOL versus 1.10 placebo (SRE rate ratio 0.57, p = 0.016) when not adjusted for prior fracture  
• ZOL reduced proportion with ≥ SRE by 20% (p = 0.003) and prolonged time to first SRE (p = 0.007)  
| SRE rate (events/yr) 0.63 ZOL versus 1.10 placebo (SRE rate ratio 0.57, p = 0.016) when not adjusted for prior fracture  
• ZOL reduced proportion with ≥ SRE by 20% (p = 0.003) and prolonged time to first SRE (p = 0.007)  
| Median time from diagnosis of bone metastases to study treatment was short (3.9 mo)  
Patients with ≥1 osteolytic lesion  
Pathologic fracture and bone irradiation were the most common SREs  
Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy  
Included patients with osteolytic and/or osteoblastic bone lesions |
| Cartenì et al 2006³⁴ | (N = 312)    | ZOL 4 mg IV every 3–4 wk × 12 infusions | Proportion with ≥1 SRE at 25 mo | 25-mo analysis (includes all patients except where noted):  
• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM overall (19% vs 24%, p = 0.037)  
• ZOL 4 mg reduced risk of skeletal complications by 16% compared to PAM (RR = 0.841 (95% CI, 0.719–0.983, p = 0.030)  
• Risk of developing SRE comparable between ZOL 4 mg and PAM in MBC_{event} (RR, 0.955; p = 0.749)  
• Among all patients with MBC, proportion with ≥1 SRE was comparable (43% ZOL 4 mg vs 45% PAM)  
• In patients with only osteolytic lesions, ZOL 4 mg reduced proportion with ≥1 SRE (48% vs 58%, p = 0.058) and significantly prolonged time to first SRE (p = 0.013)  
| Analysis of MBC stratum of phase 3 trial (Rosen et al 2001³⁰, Rosen et al 2003³¹)  
Patients stratified based on ≥1 osteolytic lesion versus nonosteolytic lesion at study entry  
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Median time from diagnosis of bone metastases to study treatment was short (3.9 mo)  
Patients with ≥1 osteolytic lesion  
Pathologic fracture and bone irradiation were the most common SREs  
Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy  
Included patients with osteolytic and/or osteoblastic bone lesions |
| Study                        | Treatment Details | Outcome Measures                                                                 | Results                                                                                                                                                                                                 | Notes                                                                                                                                                                                                                           |
|------------------------------|-------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------                                 |
| Hortobagyi et al 1996<sup>35</sup> | PAM 90 mg IV q 4 wk × 12 cycles versus placebo | Proportion with any skeletal complication<sup>1</sup> at 12 mo and 24 mo            | 12-mo analysis:<br>• Proportion with any skeletal complication significantly less with PAM (p = 0.005)<br>• PAM did not reduce incidence of pathologic vertebral fractures (p = 0.49)  | Patients receiving concurrent cytotoxic chemotherapy<br>Effects of PAM on skeletal complications more apparent with each successive treatment<br>Primarily osteolytic lesions<br>Time from diagnosis of bone metastases to study entry <2 yr<br>Treatment effect did not diminish with extended duration of therapy                                                                                                                                                        |
| Hortobagyi et al 1998<sup>36</sup> | (N = 382) | | 24-mo analysis:<br>• Only 82/382 patients (21%) had data available at 24 mo<br>• Proportion with any skeletal complication significantly less with PAM (p = 0.001)  |                                                                                                                                                                                                                                                                          |
| Theriault et al 1999<sup>37</sup> | PAM 90 mg IV every 4 wk × 24 cycles versus placebo | SMR<sup>4</sup> (end of phase I); OS rate (end of phase II) | Proportion with any skeletal complication significantly lower in PAM (72 vs 83, p = 0.049) | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>36</sup>; Theriault et al 1999<sup>37</sup>)<br>Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)<br>58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study<br>IBA 6 mg maintained bone pain below baseline throughout the study<br>No evidence of renal toxicity in IBA-treated patients<br>Pooled results of 2 phase 3 clinical trials<br>Only results of IBA 50 mg arm reported because this is the dose used in clinical practice<br>42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study<br>26% were not compliant with oral therapy<br>Toxicities similar between IBA and placebo arms; withdrawal due to difficulty swallowing capsules did occur                                                                                                                                 |
| Lipton et al 2000<sup>38</sup> | PAM 90 mg IV every 3–4 wk × 24 cycles versus placebo | SMR<sup>4</sup> | Proportion with any skeletal complication significantly lower in PAM arm (53% vs 68%, p < 0.001) | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>36</sup>; Theriault et al 1999<sup>37</sup>)<br>Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)<br>58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study<br>IBA 6 mg maintained bone pain below baseline throughout the study<br>No evidence of renal toxicity in IBA-treated patients<br>Pooled results of 2 phase 3 clinical trials<br>Only results of IBA 50 mg arm reported because this is the dose used in clinical practice<br>42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study<br>26% were not compliant with oral therapy<br>Toxicities similar between IBA and placebo arms; withdrawal due to difficulty swallowing capsules did occur                                                                                                                                 |
| Body et al 2003<sup>39</sup> | IBA 2 mg or 6 mg IV every 3–4 wk × 60–96 wk versus placebo | SMPR<sup>i</sup> | IBA 6 mg significantly reduced SMPR for all new bone event<sup>i</sup> compared with placebo (p = 0.004)<br>IBA 6 mg significantly reduced new bone event<sup>i</sup>/patient (p = 0.032) and increased time to first bone event (p = 0.018) | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>36</sup>; Theriault et al 1999<sup>37</sup>)<br>Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)<br>58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study<br>IBA 6 mg maintained bone pain below baseline throughout the study<br>No evidence of renal toxicity in IBA-treated patients<br>Pooled results of 2 phase 3 clinical trials<br>Only results of IBA 50 mg arm reported because this is the dose used in clinical practice<br>42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study<br>26% were not compliant with oral therapy<br>Toxicities similar between IBA and placebo arms; withdrawal due to difficulty swallowing capsules did occur                                                                                                                                 |
| Body et al 2004<sup>40</sup> | IBA 20 mg or 50 mg PO daily up to 96 wk versus placebo | SMPR<sup>i</sup> | IBA 50 mg significantly reduced mean SMPR for all new bone event<sup>i</sup> (p = 0.004), primarily a result of a significant reduction in radiation therapy and surgery to bone | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>36</sup>; Theriault et al 1999<sup>37</sup>)<br>Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)<br>58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study<br>IBA 6 mg maintained bone pain below baseline throughout the study<br>No evidence of renal toxicity in IBA-treated patients<br>Pooled results of 2 phase 3 clinical trials<br>Only results of IBA 50 mg arm reported because this is the dose used in clinical practice<br>42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study<br>26% were not compliant with oral therapy<br>Toxicities similar between IBA and placebo arms; withdrawal due to difficulty swallowing capsules did occur                                                                                                                                 |
| Paterson et al 1993<sup>41</sup> | CLO 1,600 mg PO daily × 3 yr versus placebo | Number of hypercalcemic episodes, vertebral and nonvertebral fractures, patients requiring radiation therapy to bone | Significantly fewer hypercalcemic events occurred with CLO (52 vs 28; p < 0.011)<br>CLO significantly reduced cumulative incidence of vertebral fractures (p = 0.025) and overall incidence of morbid skeletal events per 100 patient-yr (218.6 vs 304.8, p < 0.001)<br>Trends favoring CLO for nonvertebral fractures and radiation therapy requirements observed | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>36</sup>; Theriault et al 1999<sup>37</sup>)<br>Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)<br>58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study<br>IBA 6 mg maintained bone pain below baseline throughout the study<br>No evidence of renal toxicity in IBA-treated patients<br>Pooled results of 2 phase 3 clinical trials<br>Only results of IBA 50 mg arm reported because this is the dose used in clinical practice<br>42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study<br>26% were not compliant with oral therapy<br>Toxicities similar between IBA and placebo arms; withdrawal due to difficulty swallowing capsules did occur                                                                                                                                 |

(Continued)
Prostate cancer

Although prostate cancer is most commonly associated with osteoblastic lesions, increased osteoclastic activity also disrupts normal bone metabolism when prostate cancer invades the skeleton. Thus, inhibition of bone resorption by bisphosphonates may be beneficial for osteoblastic metastases. Several bisphosphonates have been evaluated in patients with hormone-refractory prostate cancer (HRPC) who were treated for up to 2 years with zoledronic acid or placebo. Zoledronic acid significantly reduced the proportion of patients with SREs (Table 2). In a randomized study, patients with HRPC were randomized to treatment with placebo or zoledronic acid for 2 years. Zoledronic acid significantly reduced the risk of SREs by 38% compared with placebo (RR = 0.62; 95% CI, 0.49–0.78; p = 0.00001). The authors concluded that zoledronic acid is effective in reducing SREs in patients with HRPC. However, the National Comprehensive Cancer Network (NCCN) guidelines recommend either IV zoledronic acid or IV pamidronate for patients with bone metastases secondary to breast cancer.

The Cochrane Breast Cancer Review Group has reported the results of a meta-analysis of 21 randomized trials evaluating bisphosphonates in 9 studies. Zoledronic acid was superior to placebo in reducing the risk of SREs by 34% (RR = 0.66; 95% CI, 0.53–0.83; p = 0.0004). Pamidronate was also effective in reducing the risk of SREs by 38% (RR = 0.62; 95% CI, 0.50–0.78; p = 0.00001). The panel concluded that there is sufficient evidence to recommend both zoledronic acid and pamidronate for patients with hormone-refractory prostate cancer who have bone metastases.

| Study                | Study design | Drug            | Primary endpoint | Efficacy results                                      | Comments                                                                 |
|----------------------|--------------|-----------------|------------------|-------------------------------------------------------|---------------------------------------------------------------------------|
| Kristensen et al 1999 | SC, R, OL    | CLO 1600 mg PO daily x maximum of 2 yr versus placebo | Skeletal events | • All skeletal events occurred less frequently in CLO arm (14 vs 21)  
  • CLO significantly increased the time to first skeletal event (p = 0.015)  
  • CLO significantly decreased incidence of fractures (p = 0.023) | Most skeletal events in control arm occurred within 3–5 mo of randomization, whereas events in CLO arm occurred within 15–20 mo |

Table 1 (Continued)

| Study                | Study design | Drug            | Primary endpoint | Efficacy results                                      | Comments                                                                 |
|----------------------|--------------|-----------------|------------------|-------------------------------------------------------|---------------------------------------------------------------------------|
| Kristensen et al 1999 | SC, R, OL    | CLO 1600 mg PO daily x maximum of 2 yr versus placebo | Skeletal events | • All skeletal events occurred less frequently in CLO arm (14 vs 21)  
  • CLO significantly increased the time to first skeletal event (p = 0.015)  
  • CLO significantly decreased incidence of fractures (p = 0.023) | Most skeletal events in control arm occurred within 3–5 mo of randomization, whereas events in CLO arm occurred within 15–20 mo |

**Table 1**

| Study | Study design | Drug            | Primary endpoint | Efficacy results                                      | Comments                                                                 |
|-------|--------------|-----------------|------------------|-------------------------------------------------------|---------------------------------------------------------------------------|
| Kristensen et al 1999 | SC, R, OL    | CLO 1600 mg PO daily x maximum of 2 yr versus placebo | Skeletal events | • All skeletal events occurred less frequently in CLO arm (14 vs 21)  
  • CLO significantly increased the time to first skeletal event (p = 0.015)  
  • CLO significantly decreased incidence of fractures (p = 0.023) | Most skeletal events in control arm occurred within 3–5 mo of randomization, whereas events in CLO arm occurred within 15–20 mo |

**Abbreviations:** Chemo, chemotherapy; CI, confidence interval; CLO, clodronate; DB, double blind; HCM, hypercalcemia of malignancy; IBA, ibandronate; IV, intravenous; MC, multicenter; MBC, metastatic breast cancer; OL, open-label; OS, overall survival; PAM, pamidronate; PO, oral; R, randomized; RR, risk ratio; SC, single center; SRE, skeletal-related event; SMR, skeletal morbidity rate; SMPR, skeletal morbidity period rate; ZOL, zoledronic acid.
# Table 2: Efficacy of bisphosphonates in randomized, placebo-controlled trials of prostate cancer patients with bone metastases

| Study                  | Study design | Drug       | Primary endpoint | Efficacy results                                                                 | Comments                                             |
|------------------------|--------------|------------|------------------|---------------------------------------------------------------------------------|------------------------------------------------------|
| Saad et al 2002<sup>43</sup> | MC, R, DB, PC | ZOL 4 mg or 8 mg IV every 3 wk x 24 mo | Proportion with ≥ 1 SRE<sup>a</sup> | 15-mo analysis:  
  - Urinary markers of bone resorption significantly decreased in patients receiving ZOL (p = 0.001)  
  - ZOL significantly reduced SRE (44.2% vs 33.2%, p = 0.021) and SMR<sup>b</sup> (p = 0.006), and increased median time to first SRE (p = 0.011)  
  24-mo analysis:  
  - ZOL significantly reduced SREs (38% vs 49%, p = 0.028) and increased median time to first SRE (p = 0.009)  
  - ZOL 4 mg produced 36% reduction in ongoing risk of SREs (p = 0.002) | Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity  
  - Only 122 patients completed total 24 mo of study |
| Saad et al 2004<sup>44</sup> | (N = 643)    |            |                  |                                                                                 |                                                      |
| Small et al 2003<sup>45</sup> | MC, R, DB, PC | PAM 90 mg IV every 3 wk x 27 wk | Reduction in bone pain or analgesic use | • No significant change from baseline pain scores  
  • 36% patients able to decrease or stabilize analgesic use | Pooled results of 2 double-blind randomized trials |
| (N = 378)              |              |            |                  |                                                                                 |                                                      |
| Dearnaley et al 2003<sup>46</sup> | MC, R, DB, PC | CLO 2080 mg PO daily x maximum 3 yr | Symptomatic BPFS<sup>c</sup> | Patients receiving CLO had longer symptomatic BPFS times (HR 0.79, 95% CI, 0.61–1.02, p = 0.066) | Patients were starting or responding to hormonal therapy  
  - PSA levels were lower among patients receiving CLO (p = 0.053) |
| (N = 311)              |              |            |                  |                                                                                 |                                                      |

<sup>a</sup>Defined as pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes), or a change of antineoplastic therapy to treat bone pain.

<sup>b</sup>Number of SREs<sup>a</sup> divided by the time at risk in years.

<sup>c</sup>Defined as the time from randomization to the development of symptomatic bone metastases (ie, the need to initiate further treatment) or to death from prostate cancer.

**Abbreviations:** BPFS, bone progression-free survival; CI, confidence interval; CLO, clodronate; DB, double blind; HR, hazard ratio; IV, intravenous; MC, multicenter; PAM, pamidronate; PC, placebo-controlled; PO, oral; PSA, prostate specific antigen; R, randomized; SMR, skeletal morbidity rate; SRE, skeletal-related event; ZOL, zoledronic acid.
| Study            | Study design | Drug | Primary endpoint                                                                 | Efficacy results                                                                                                                                                                                                 | Comments                                                                                           |
|------------------|--------------|------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Rosen et al 2003 | MC, R, DB, PC| ZOL 4 mg or 8 mg IV every 3 wk × 21 mo | Proportion with ≥ 1 SRE<sup>a</sup> | 9-mo analysis:  
• ZOL 8/4 mg (p = 0.023), but not ZOL 4 mg (p = 0.127), reduced proportion with ≥ 1 SRE  
• When HCM was included, both ZOL groups significantly reduced SRE  
• ZOL 4 mg significantly extended time to first SRE (2.30 vs 1.63 d, p = 0.023)  
21-mo analysis:  
• ZOL 4 mg did not significantly reduce SRE when HCM was excluded  
• When HCM was included, ZOL 4 mg significantly reduced SREs (39% vs 48%, p = 0.039) and increased median time to first SRE (236 vs 155 d, p = 0.009)  
• ZOL 4 mg reduced risk of developing an SRE (including HCM) by 31%  
| (N = 773)        |              |      |                                                                                  |                                                                 ($_)$ Various solid tumors (approximately 50% NSCLC, 10% RCC, 10% SCLC)  
• Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity  
• Long-term (21 mo) follow-up confirms results demonstrated at 9 mo                                                                                       |
| Rosen et al 2004 |              |      |                                                                                  |                                                                 ($_)$ Various solid tumors (approximately 50% NSCLC, 10% RCC, 10% SCLC)  
• Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity  
• Long-term (21 mo) follow-up confirms results demonstrated at 9 mo                                                                                       |
| (N = 73)         | R, PC        | IBA 6 mg IV every 4 wk × 9 mo | Proportion with SRE<sup>b</sup> | IBA significantly reduced proportion with SREs (39% vs 78%, p = 0.019)  
• Delayed time to first SRE by 6 mo (p = 0.009)                                                                                                         | Patients with metastatic bone disease from CRC                                                                                                        |
| Heras et al 2007 |              |      |                                                                                  |                                                                 ($_)$ Various poorly responsive solid tumors  
• Short survival of most patients did not allow for adequate follow-up of bone lesions                                                                    |                                                                 ($_)$ Various poorly responsive solid tumors  
• Short survival of most patients did not allow for adequate follow-up of bone lesions                                                                    |
| (N = 50)         | R, DB, PC    | CLO 1600 mg PO daily × 1 yr | Symptom control, prevention of skeletal complications, and evolution of bone metastases | CLO did not significantly lower mean pain scores  
• Patients receiving CLO had significantly lower analgesic requirement (p = 0.042)                                                                 |                                                                 ($_)$ Various poorly responsive solid tumors  
• Short survival of most patients did not allow for adequate follow-up of bone lesions                                                                    |

<sup>a</sup>Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.

<sup>b</sup>Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in antineoplastic therapy, or surgery to bone.

**Abbreviations:** CLO, clodronate; CRC, colorectal cancer; DB, double-blind; HCM, hypercalcemia of malignancy; IBA, ibandronate; IV, intravenous; MC, multicenter; NSCLC, non–small cell lung cancer; PC, placebo-controlled; PO, oral; R, randomized; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SRE, skeletal-related event; ZOL, zoledronic acid.
reduced the proportion of patients who experienced SREs (39% vs 78%, p = 0.019) and delayed time to the first SRE by at least 6 months (>279 vs 93 days, p = 0.009) compared with placebo. Ibandronate has not been evaluated in other solid tumors. For bone metastases related to solid tumors other than breast or prostate cancer, zoledronic acid is the only bisphosphonate that has received worldwide regulatory approval. Consensus guidelines for the use of bisphosphonates for patients with lung cancer or other solid tumors (except breast and prostate cancer) are not available.

Multiple myeloma
The long-term efficacy and safety of bisphosphonate therapy for prevention of SREs in patients with advanced MM and osteolytic lesions is well established (Table 4). In a randomized, placebo-controlled trial, pamidronate (90 mg IV administered over 4 hours q 4 weeks) significantly delayed the onset (p = 0.016) and reduced the incidence of skeletal complications (p = 0.016) for up to 21 months. Consequently, a large, international, randomized, phase 3 trial was designed to demonstrate equivalence (defined as difference in SRE rate of less than 8%) between either 4 or 8 mg zoledronic acid and standard-dose pamidronate (90 mg). Because of renal safety concerns, the protocol was amended to reduce zoledronic acid from 8 mg to 4 mg. After 25 months of follow-up, the percentage of MM patients who developed a SRE excluding HCM (47%, 4 mg zoledronic acid vs 51%, pamidronate), the median time to first SRE including HCM (380 vs 286 days, p = 0.538), and the risk of developing a skeletal complication (RR, 0.932; p = 0.593) were similar between the treatment groups. Most of these studies assessed zoledronic acid administered every 3 to 4 weeks; however, because of its long half-life and evidence supporting the use of longer dosing intervals for other indications, less frequent dosing (every 12 wk) is being evaluated. Furthermore, oral clodronate (1600 mg daily) has established its ability to significantly reduce the incidence of nonvertebral and vertebral fractures compared with placebo in MM patients. Long-term follow-up indicates that clodronate treatment may also prolong survival time in patients without overt vertebral fractures at diagnosis. Ibandronate has not been shown to reduce skeletal complications in this patient population.

ASCO recently released an update to their clinical practice guidelines for the role of bisphosphonates in MM. For MM patients who have radiographic evidence of osteolytic bone destruction or spinal compression, ASCO recommends treatment with either pamidronate 90 mg IV delivered over...
| Study                          | Study design | Drug                          | Primary endpoint | Efficacy results | Comments                                    |
|-------------------------------|--------------|-------------------------------|------------------|------------------|---------------------------------------------|
| Rosen et al 2001<sup>30</sup> | MC, R, DB    | ZOL 4 mg or 8 mg IV every 3–4 wk × 24 mo versus PAM 90 mg IV every 3–4 wk × 24 mo | Proportion with ≥ 1 SRE<sup>a</sup> at 13 mo and 25 mo | 13-mo analysis (includes all patients except where noted):  
• Similar proportion of patients with ≥ 1 SRE<sup>a</sup> among treatment groups (ZOL 4 mg, 47%; ZOL 8/4 mg, 49%; PAM, 49%)  
• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg overall (15% vs 20%, p = 0.031)  
25-mo analysis (includes all patients except where noted):  
• Similar proportion of patients with ≥ 1 SRE<sup>a</sup> among treatment groups (ZOL 4 mg, 47%; PAM, 51%)  
• ZOL 4 mg reduced risk of skeletal complications by 16% in overall population (RR = 0.841, 95% CI: 0.719–0.983, p = 0.030)  
• RR of developing skeletal complication comparable in myeloma patients (RR, 0.932; p = 0.593)  
• Time to first SRE comparable for myeloma patients (p = 0.538) | • Durie-Salmon Stage III MM and stage IV breast cancer  
• Noninferiority trial  
• Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity |
| Rosen et al 2003<sup>31</sup>  |              |                               |                  |                  |                                             |
| (N = 1643)                    |              |                               |                  |                  |                                             |
| Berenson et al 1996<sup>51</sup> | MC, R, DB, PC | PAM 90 mg IV every 4 wk × 21 cycles versus placebo | Time to first SRE<sup>a</sup> | 9-mo analysis:  
• PAM significantly increased time to first SRE (p = 0.001)  
• Time to first pathologic fracture (p = 0.006) and first radiation treatment to bone (p = 0.05) were significantly longer with PAM  
• OS time did not differ significantly between the 2 groups  
21-mo analysis:  
• Time to first SRE significantly longer with PAM (p = 0.016)  
• Proportion of patients with SREs remained lower with PAM at each time point up to 21 mo (p = 0.016) | • Durie-Salmon Stage III MM  
• Patients stratified into 2 stratum based on line of chemotherapy |
| Berenson et al 1998<sup>52</sup> |              |                               |                  |                  |                                             |
| (N = 377)                     |              |                               |                  |                  |                                             |
| Menssen et al 2002<sup>53</sup> | MC, R, DB, PC | IBA 2 mg IV monthly × 12–24 mo versus placebo | Number of 3-mo periods with new bone complication<sup>b</sup> | Number of 3-mo periods with new bone complications, time to first SRE, and SRE/patient-yr were similar between the 2 groups  
• OS time was not statistically different between the 2 groups | • Durie-Salmon Stage II or III MM |
| (N = 214)                     |              |                               |                  |                  |                                             |
Bisphosphonates for skeletal events in patients with bone metastases

McCloskey et al. 1998\textsuperscript{54} (N = 536)  
McCloskey et al. 2001\textsuperscript{55} (N = 535)

| Study | Treatment | Incidence of pathologic fracture, hypercalcemia, performance status, pain, OS time | Minimum follow-up of 2 yr |
|-------|-----------|---------------------------------------------------------------------------------|-------------------------|
| MC, R, DB, PC | CLO 1600 mg PO daily until disease progression or toxicities versus placebo | - CLO significantly reduced pathologic vertebral (p = 0.01) and nonvertebral fractures (p = 0.04)  
- Lower incidence of hypercalcemia with CLO (39% vs 48%)  
- Significantly lower incidence of back pain (p = 0.05) and poor performance status with CLO (p = 0.03)  
- No difference in OS time (p = 0.74)  
Minimum follow-up of 5 yr |

- No significant difference in OS time between 2 groups (p = 0.38)  
- Patients receiving CLO with no skeletal fracture at study entry had significant survival advantage (p = 0.006)

- Bone marrow plasma cells &gt; 20% or if less, evidence of monoclonal bone marrow plasmacytosis; paraprotein detectable in blood or urine; and skeletal radiographs showing osteolytic lesions  
- Long-term follow-up study only evaluated survival

\textsuperscript{1}Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.  
\textsuperscript{2}Defined as peripheral pathologic fracture, significant vertebral reduction (≥ 25%), hypercalcemic event (albumin-corrected serum calcium level of &gt; 2.8 mmol/L), severe bone pain (requiring opiate treatment), radiation therapy to bone, or surgery to bone.

\textbf{Abbreviations:} CI, confidence interval; CLO, clodronate; DB, double-blind; HCM, hypercalcemia of malignancy; IBA, ibandronate; IV, intravenous; MC, multicenter; MM, multiple myeloma; OS, overall survival; PAM, pamidronate; PC, placebo-controlled; PO, oral; R, randomized; RR, risk ratio; SRE, skeletal-related event; ZOL, zoledronic acid.
at least 2 hours or zoledronic acid 4 mg IV delivered over
15 minutes every 3 to 4 weeks for a period of 2 years. IV or
oral clodronate is an alternative in other countries, but it is
not commercially available in the United States.

Duration of therapy
A consensus has not been reached regarding the appropriate
duration of bisphosphonate therapy. Most studies of bisphos-
phonates in cancer patients with bone metastases did not
treat patients beyond 2 years. However, ASCO has tried to
place some clarity on the issue in both their clinical practice
guidelines for patients with breast cancer and MM.57,66 In
patients with breast cancer metastatic to bone, ASCO advises
to continue bisphosphonates until evidence of a progressive
decline in performance status develops, even in the presence
of SREs.57 No evidence addressing the consequences of dis-
continuing bisphosphonate therapy after developing a SRE in
breast cancer patients exists. Among patients with osteolytic
metastases secondary to MM, 2 years of bisphosphonate
therapy is recommended.66 After 2 years, treating physi-
cians should consider treatment discontinuation if the MM
is responding to therapy or is stable. Guidelines addressing
duration of therapy in other solid tumors are not available.

Bone turnover markers
Investigators frequently assess markers of bone turnover
as secondary end points in bisphosphonate studies. Bio-
chemical markers of bone metabolism are indicative of either
bone formation or bone resorption and may help identify
patients likely to respond to and benefit from bisphos-
phonate therapy.67 N-telopeptide of type I collagen (NTX) is
of particular interest; patients with bone metastases and
elevated NTX levels in urine have a significantly increased
risk of SREs, disease progression, and death compared with
patients with low NTX levels.68 In addition, urinary NTX
normalization with pamidronate treatment has been linked
with delays in bone lesion progression and a trend toward
fewer fractures.69 Thus, NTX may be useful for monitoring
therapeutic response to bisphosphonate therapy. However,
because of the lack of sufficient, rigorous, prospective trials
validating this approach, ASCO’s clinical practice guide-
lines recommend that the use of these markers be confined
to research protocols; currently, they should not be used in
routine clinical practice.57,66

Conclusion
Skeletal complications are a major source of cancer-related
morbidity. In patients with bone metastases, bisphosphonates
have become the standard of care for preventing or delaying
SREs. In patients with breast cancer or MM involving bone,
zoledronic acid and pamidronate were comparable in their
ability to decrease the incidence of SREs and delay the onset
of skeletal events. In patients with solid tumors (except
breast cancer) that metastasize to the bone, only zoledronic
acid has been proven effective; ibandronate is effective
in colorectal cancer. Despite their impressive efficacy in
the prevention of skeletal complications associated with
malignancy, several questions related to bisphosphonate
use remain. Studies are ongoing to evaluate the appropriate
duration of therapy, validate the usefulness of bone markers
in predicting response to therapy, understand management
of toxicities such as osteonecrosis of the jaw, and determine
the most appropriate and cost-effective time to initiate
bisphosphonate therapy.70

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