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

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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.

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In addition to osteoporosis, bisphosphonates have been used to prevent and/or treat cancer-related bone complications.[3,13] 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).[14] SREs are a consequence of excessive bone metabolism, primarily bone resorption, which characterizes malignant bone lesions.[3] Local bone pain requiring radiation therapy and pathologic fractures are the most commonly reported SREs.[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.[14–16] Bone metastases are particularly prevalent in patients with advanced metastatic breast or prostate cancers, affecting approximately 70% of patients.[3] Although observed less frequently, bone metastases also occur in patients with lung, kidney, and thyroid tumors.[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.[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.[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.[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.[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.[17] 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.[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.[3,21] Variable side chains determine the potency and side effect profile of each agent.[21] These compounds can be grouped into two classes according to their chemical structure and molecular mechanism of action (Figure 1).[22] The newer nitrogen (N)-containing, second- or third-generation compounds, including alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid, inhibit the enzyme farnesyl diphosphate 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.[21,23,24] The N-containing agents are more potent than the non – N-containing bisphosphonates, inhibiting bone resorption at micromolar concentrations.[3] Only IV zoledronic acid and IV pamidronate are approved by the FDA for cancer-related indications.[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.[3,27] Only zoledronic acid has received US and European approval for the treatment of bone metastases independent of the primary tumor type.[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.[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

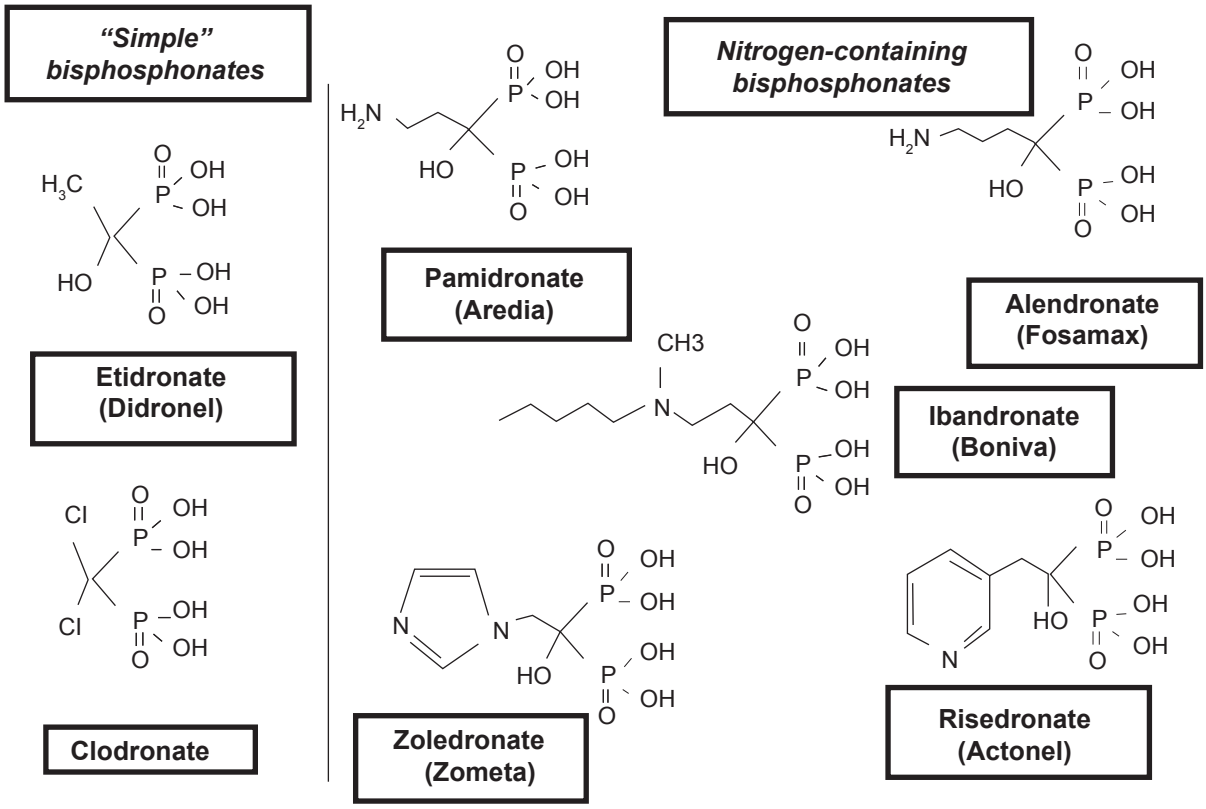

Figure 1 The structure of simple and nitrogen-containing bisphosphonates. Reprinted with permission from Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics*. 2007;119:S150–S162.[22] Copyright © by the AAP.

referred to as skeletal complications or bone events.[30–55] 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.[31,56]

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).[30–42] 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.[35,37] 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).[35–38] 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, $p = 0.007$).[33] Only one study has directly compared zoledronic acid with pamidronate (see Table 1).[30,31] 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.[31] 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

Table 1 Efficacy of bisphosphonates in patients with bone metastases secondary to breast cancer

Study	Study design	Drug	Primary endpoint	Efficacy results	Comments
Rosen et al 2001[30] (N = 1643) Rosen et al 2003[31] (N = 1648)	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[a] 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 $MBC_{hormonal}$ (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 (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_{chemo} (RR, 0.955; p = 0.749)	• 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 2004[32] (N = 1130)	MC, R, DB	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[a] at 13 mo	• 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 2001[30], Rosen et al 2003[31]) • Patients stratified based on ≥1 osteolytic lesion versus nonosteolytic lesion at study entry • ~60% experienced an SRE before study entry
Kohno et al 2005[33] (N = 228)	MC, R, DB, PC	ZOL 4 mg IV every 4 wk × 1 yr versus placebo	SRE rate ratio[a,b]	• 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)	• 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
Carteni et al 2006[34] (N = 312)	MC, OL	ZOL 4 mg IV every 3–4 wk × 12 infusions	Proportion with ≥1 SRE[c]; time to first SRE; SMR[d]	• 30% experienced ≥1 SRE (22% only experienced 1 SRE) • Median time to first SRE was not reached • Mean SMR (up to wk 52), 0.9 ± 3.8	• Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy • Included patients with osteolytic and/or osteoblastic bone lesions

Hortobagyi et al 1996[35] Hortobagyi et al 1998[36] (N = 382)	MC, R, DB, PC	PAM 90 mg IV q 4 wk × 12 cycles versus placebo	Proportion with any skeletal complication[c] at 12 mo and 24 mo	12-mo analysis: • Proportion with any skeletal complication significantly less with PAM ($p = 0.005$) • PAM did not reduce incidence of pathologic vertebral fractures ($p = 0.49$) 24-mo analysis: • Only 82/382 patients (21%) had data available at 24 mo • Proportion with any skeletal complication significantly less with PAM at 24 mo ($p < 0.001$)	• Patients receiving concurrent cytotoxic chemotherapy • Effects of PAM on skeletal complications more apparent with each successive treatment • Primarily osteolytic lesions • Time from diagnosis of bone metastases to study entry ~2 yr • Treatment effect did not diminish with extended duration of therapy
Theriault et al 1999[37] (N = 372)	MC, R, DB, PC	PAM 90 mg IV every 4 wk × 24 cycles versus placebo	SMR[d] (end of phase I); OS rate (end of phase II)	• PAM significantly decreased overall SMR at 12,18, and 24 mo ($p = 0.028$, $p = 0.023$, $p = 0.008$) • Proportion with any SRE[c] significantly lower in PAM at 24 mo (72 vs 83, $p = 0.049$) • OS rate did not significantly vary ($p = 0.685$)	• Patients receiving concurrent hormonal therapy • Primarily osteolytic lesions
Lipton et al 2000[38] (N = 751)	MC, R, DB, PC	PAM 90 mg IV every 3–4 wk × 24 cycles versus placebo	SMR[e]	• Proportion with any skeletal complication[c] was significantly lower in PAM arm (53% vs 68%, $p < 0.001$) • Time to first skeletal complication[c] significantly prolonged by PAM (12.7 vs 7 mo, $p < 0.001$)	• Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998[35]; Theriault et al 1999[36]) • Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)
Body et al 2003[39] (N = 466)	MC, R, DB, PC	IBA 2 mg or 6 mg IV every 3–4 wk × 60–96 wk versus placebo	SMPR[f]	• IBA 6 mg significantly reduced SMPR for all new bone events[g] compared with placebo ($p = 0.004$) • IBA 6 mg significantly reduced new bone events/patient ($p = 0.032$) and increased time to first bone event ($p = 0.018$)	• 58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study • IBA 6 mg maintained bone pain below baseline throughout the study • No evidence of renal toxicity in IBA-treated patients
Body et al 2004[40] (N = 564)	MC, R, DB, PC	IBA 20 mg or 50 mg PO daily up to 96 wk versus placebo	SMPR[f]	• IBA 50 mg significantly reduced mean SMPR for all new bone events[g] ($p = 0.004$), primarily a result of a significant reduction in radiation therapy and surgery to bone	• Pooled results of 2 phase 3 clinical trials • Only results of IBA 50 mg arm reported because this is the dose used in clinical practice • 42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study
Paterson et al 1993[41] (N = 173)	MC, R, DB, PC	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; $p < 0.01$)) • 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, $p < 0.001$) • Trends favoring CLO for nonvertebral fractures and radiation therapy requirements observed	• 26% were not compliant with oral therapy • Toxicities similar between CLO and placebo arms; withdrawal due to difficulty swallowing capsules did occur

(*Continued*)

Table 1 (*Continued*)

Study	Study design	Drug	Primary endpoint	Efficacy results	Comments
Kristensen et al 1999[42] (N = 100)	SC, R, OL	CLO 1600 mg PO daily × maximum of 2 yr versus placebo	Skeletal events[h]	• 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

[a]Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.
[b]Defined as total number of SREs[a] divided by total number of years on study.
[c]Defined as pathologic fracture, radiation therapy to bone, surgery to bone, spinal cord compression, and HCM.
[d]Number of SREs per patient per year.
[e]Defined as the ratio of the number of skeletal complications experienced by patient divided by the time on trial; skeletal complication defined as pathologic fractures, irradiation of or surgery on bone, spinal cord compression, or HCM.
[f]Defined as number of 12-wk periods with new skeletal complications divided by total observation time; skeletal complications included vertebral or pathologic nonvertebral fractures, radiation therapy to bone, or surgery to bone.
[g]Defined as hypercalcemia, courses of radiotherapy for bone pain, and vertebral and nonvertebral fracture.
[h]Defined as hypercalcemia with serum ionized calcium level >1.40 mmol L^{-1}, a new fracture, or radiotherapy to a bone metastasis.
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; PC, placebo-controlled; 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.

proportion of patients with an on-study SRE and delayed the time to first SRE (see Table 1).[39,40] Oral clodronate also appears to reduce the rate and delay onset of SREs, and may reduce bone pain (see Table 1).[41,42] Neither of these drugs, however, has been directly compared with zoledronic acid or pamidronate in this setting.

IV bisphosphonates are recommended for the prevention of skeletal complications in breast cancer patients with bone metastases. Treatment guidelines from the American Society of Clinical Oncology (ASCO) recommend either IV pamidronate (90 mg) or IV zoledronic acid (4 mg) every 3 to 4 weeks for patients with radiographic evidence of bone destruction; the panel concluded that there is insufficient evidence to recommend one bisphosphonate over the other.[57] The National Comprehensive Cancer Network (NCCN) recommends either IV zoledronic acid or IV pamidronate for patients with bone metastases secondary to breast cancer as well.[58] However, the NCCN guidelines suggest that zoledronic acid may be superior to pamidronate therapy for treating osteolytic metastases from breast cancer. Neither clodronate nor ibandronate were recommended; clodronate is not commercially available in the US, and ibandronate does not have a cancer-related FDA indication. Moreover, the Cochrane Breast Cancer Review Group has reported the results of their meta-analysis of 21 randomized trials evaluating bisphosphonates; in 9 studies, bisphosphonates reduced the risk of skeletal complications by 17% compared with placebo or no bisphosphonate (relative risk [RR] 0.83; 95% confidence interval [CI], 0.78–0.89; p = 0.00001).[59] Like the ASCO panel, the authors concluded that zoledronic acid appears to have equivalent efficacy when compared with pamidronate.

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.[60] Thus, inhibition of bone resorption by bisphosphonates may be beneficial for osteoblastic metastases. Several bisphosphonates have been evaluated in patients with prostate cancer and metastatic bone disease, but only zoledronic acid has been shown to decrease SREs (Table 2).[43–46] In a randomized study, patients with hormone-refractory prostate cancer (HRPC) were treated for up to 2 years with zoledronic acid or placebo; zoledronic acid significantly reduced the proportion of patients experiencing at least one SRE (38% vs 49%, 95% CI, –20.2% to –1.3%, p = 0.028) and prolonged the time to the first SRE

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[43] Saad et al 2004[44] (N = 643)	MC, R, DB, PC	ZOL 4 mg or 8 mg IV every 3 wk × 24 mo	Proportion with ≥1 SRE[a]	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[b] (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
Small et al 2003[45] (N = 378)	MC, R, DB, PC	PAM 90 mg IV every 3 wk × 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
Dearnaley et al 2003[46] (N = 311)	MC, R, DB, PC	CLO 2080 mg PO daily × maximum 3 yr	Symptomatic BPFS[c]	• 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)

[a]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.
[b]Number of SREs[a] divided by the time at risk in years.
[c]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.

Table 3 Efficacy of bisphosphonates in randomized, placebo-controlled trials of patients with bone metastases secondary to lung cancer or other solid tumors

Study	Study design	Drug	Primary endpoint	Efficacy results	Comments
Rosen et al 2003[47] Rosen et al 2004[48] (N = 773)	MC, R, DB, PC	ZOL 4 mg or 8 mg IV every 3 wk × 21 mo	Proportion with ≥1 SRE[a]	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 (230 vs 163 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%	• 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
Heras et al 2007[49] (N = 73)	R, PC	IBA 6 mg IV every 4 wk × 9 mo	Proportion with SRE[b]	• 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
Piga et al 1998[50] (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

[a]Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.
[b]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.

(488 vs 321 days, p = 0.009) compared with placebo.[43,44] In this setting, pamidronate did not significantly reduce the SRE rate or reduce bone pain compared with placebo (see Table 2).[45] Compared with placebo, oral clodronate (2080 mg daily) improved bone progression-free survival (defined as the time from randomization to the development of symptomatic bone metastases or death from prostate cancer) and the overall survival time; however, differences in these end points were not statistically significant.[46] Bone progression-free survival is similar to SRE except that it includes only symptomatic events rather than also including asymptomatic events (eg, metastasis identified on bone scan, asymptomatic vertebral fractures). The Cochrane Prostatic Diseases and Urologic Cancers Group has corroborated these findings in its meta-analysis of 10 studies evaluating bisphosphonates in metastatic prostate cancer; compared with controls, bisphosphonates reduced the risk of skeletal events by 21% (odds ratio 0.79; 95% CI, 0.62–1.00; p = 0.05).[61] Currently, risedronate and zoledronic acid are also being evaluated in patients with bone metastases from androgen-sensitive prostate cancer.[62,63] According to consensus guidelines from the NCCN, bisphosphonate therapy should be considered for all patients with HRPC; however, the panel does not recommend a specific bisphosphonate.[60]

Lung cancer and other solid tumors

Only zoledronic acid 4 mg has demonstrated significant long-term clinical benefits in patients with bone metastases from a broad range of solid tumors (Table 3).[47–50] In a randomized, placebo-controlled, phase 3 study assessing patients with lung cancer or other solid tumors (excluding breast or prostate cancer), zoledronic acid 4 mg significantly reduced the proportion of patients developing at least one SRE, including HCM at 21 months (39% vs 48%, p = 0.039) and delayed the onset of skeletal complications (236 vs 155 d, p = 0.009).[47,48] Moreover, when HCM was included, zoledronic acid 4 mg reduced the risk of developing a SRE, including HCM, by 31% (hazard ratio, 0.693; p = 0.003) compared with placebo.[48] Non – small cell lung cancer, renal cell carcinoma, and small cell lung cancer were the most common diagnoses of enrolled patients. Oral clodronate (1600 mg/day for 1 year) was also evaluated in patients with bone metastases from solid tumors poorly responsive to chemotherapy; clodronate did not significantly reduce mean pain scores compared with placebo but significantly reduced use of analgesics (p = 0.042).[50] Ibandronate 6 mg IV, administered every 4 weeks for 9 months to patients with metastatic bone disease from colorectal cancer, significantly 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.[49] 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.[25] Consensus guidelines for the use of bisphosphonates for patients with lung cancer or other solid tumors (except breast and prostate cancer) are not available.[64]

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).[30,31,51–55] 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.[51,52] 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).[30,31] Because of renal safety concerns, the protocol was amended to reduce zoledronic acid from 8 mg to 4 mg.[30] 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.[31] 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.[65] 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.[54] Long-term follow-up indicates that clodronate treatment may also prolong survival time in patients without overt vertebral fractures at diagnosis.[55] Ibandronate has not been shown to reduce skeletal complications in this patient population.[53]

ASCO recently released an update to their clinical practice guidelines for the role of bisphosphonates in MM.[66] 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

Table 4 Efficacy of bisphosphonates in reducing skeletal events in patients with advanced MM

Study	Study design	Drug	Primary endpoint	Efficacy results	Comments
Rosen et al 2001[30] Rosen et al 2003[31] (N = 1643)	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 x 24 mo	Proportion with ≥1 SRE[a] at 13 mo and 25 mo	13-mo analysis (includes all patients except where noted): • Similar proportion of patients with ≥1 SRE[a] 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[a] 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
Berenson et al 1996[51] Berenson et al 1998[52] (N = 377)	MC, R, DB, PC	PAM 90 mg IV every 4 wk × 21 cycles versus placebo	Time to first SRE[a]	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
Menssen et al 2002[53] (N = 214)	MC, R, DB, PC	IBA 2 mg IV monthly × 12–24 mo versus placebo	Number of 3-mo periods with new bone complication[b]	• 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

McCloskey et al 1998[54] (N = 536) McCloskey et al 2001[55] (N = 535)	MC, R, DB, PC	CLO 1600 mg PO daily until disease progression or toxicities versus placebo	Incidence of pathologic fracture, hypercalcemia, performance status, pain, OS time	Minimum follow-up of 2 yr • 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 >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

[a]Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.
[b]Defined as peripheral pathologic fracture, significant vertebral reduction (≥25%), hypercalcemic event (albumin-corrected serum calcium level of >2.8 mmol/L), severe bone pain (requiring opiate treatment), radiation therapy to bone, or surgery to bone.
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 bisphosphonates 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 discontinuing 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 physicians 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. Biochemical 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 bisphosphonate 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 guidelines 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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