Metastatic Bone Disease in Patients with Solid Tumors—Burden of Bone Disease and the Role of Zoledronic Acid

Vera Hirsh

Departments of Medicine and Oncology, McGill University Health Centre, Royal Victoria Hospital, Montreal, QC, Canada.

Abstract: Bisphosphonates have become an integral component of the therapeutic repertoire for cancer patients at risk for skeletal-related events (SREs) such as pathologic fractures, bone pain requiring palliative radiotherapy, the need for orthopedic surgery, spinal cord compression, and hypercalcemia of malignancy because of bone metastases. Administered via monthly 15-minute infusion of up to 4 mg (depending on creatinine clearance rate), zoledronic acid (ZOL) has been approved for preventing SREs in patients with bone metastases from any solid tumor or bone lesions from multiple myeloma. Although there have been limited head-to-head comparison trials between bisphosphonates, ZOL displayed benefits beyond pamidronate in a large-scale comparative trial in patients with bone metastases from breast cancer. Monitoring of serum creatinine levels and oral health is important to ensure safety and comfort during treatment. In addition to the established benefits of bisphosphonates in the advanced cancer setting, there is a strong preclinical rationale and emerging clinical evidence that ZOL has antitumor activities and can delay metastasis in patients with early breast cancer. Studies are underway in patients with other tumor types, and the role of bisphosphonates is likely to evolve.

Keywords: bisphosphonates, bone metastases, zoledronic acid

Introduction

The current era of targeted therapies and improvements in patient management offers significantly prolonged survival to cancer patients, including many with advanced solid tumors. However, the skeleton is frequently the most common site for distant metastasis, and cancer that has metastasized to bone is generally considered to have reached an incurable—although still treatable—stage. The efficacy of treatments on soft-tissue metastases does not necessarily translate into efficacy in the setting of bone metastases because of the nature of the bone microenvironment.[1] As bone metastases progress, interactions between cancer and bone can result in chronic bone pain and potentially debilitating or life-threatening sequelae such as spinal cord compression and hypercalcemia of malignancy (HCM).[2] For this reason, bone-targeted therapy is emerging as an essential component of care for patients with advanced malignancies involving bone.[3]

Advanced cancer is often symptomatic, and patients' quality of life (QOL) typically decreases during disease progression.[4] In addition to improving survival, an important goal of oncologists should be preserving patients' QOL throughout the continuum of care. Skeletal morbidity from bone metastases can add substantially to the overall burden of disease and loss of functional independence for cancer patients.[5] Zoledronic acid (ZOL) significantly delays the onset and reduces the ongoing risk of skeletal morbidity in patients with bone metastases from breast cancer, prostate cancer, lung cancer, and a broad range of other solid tumors.[6–9] Zoledronic acid is the only bisphosphonate to receive international regulatory approval for treating bone metastases secondary to any solid tumors other than breast cancer.

This review examines the pathophysiology of malignant bone disease and how ZOL and other bisphosphonates act to break the vicious cycle of bone destruction and tumor growth that results in formation

Correspondence: Vera Hirsh, MD, Departments of Medicine and Oncology, McGill University Health Centre, Royal Victoria Hospital, Room E3.53, 687 Pine Avenue West, Montreal, Quebec H3A 1A1, Canada.
Tel: +1 514.934.1934 (Ext: 36952); Fax: +1 514.843.1417; Email: vera.hirsh@muhc.mcgill.ca

of bone lesions. Additionally, the pharmacokinetics and pharmacodynamics of ZOL will be summarized. The clinical efficacy data for ZOL and other bisphosphonates and the burden of skeletal morbidity that affects patients' lives will be discussed. Finally, this review will provide insight into the potential additional benefits of ZOL that are emerging in clinical trials in the early breast cancer setting.

Chemistry and Biologic Activities of Zoledronic Acid

Bisphosphonates are an established component of care in the benign and oncologic settings for patients with bone health issues.[3–10] Understanding their mechanisms of action requires an appreciation of normal bone remodeling and how bone metastases cause dysregulation of this process.

Pathophysiology of bone metastases

Maintenance of the skeleton is orchestrated by the concerted activities of the body's bone remodeling machinery.[10] In response to stress signals from weak or damaged bone, osteoclasts are recruited to the bone surface. Osteoclasts resorb bone tissue, creating a resorption cavity on the bone surface and releasing growth factors that had been embedded within the bone matrix. These growth factors then stimulate osteoblasts to synthesize new bone matrix to fill in the resorption cavity. Excess bone formation triggers further osteolysis by osteoclasts. These tightly regulated processes are thereby spatially coupled and balanced, resulting in no net increase or loss in bone volume in healthy adults.[11]

When cancer cells colonize the bone marrow or attach to bone surfaces, they can interact with the bone remodeling machinery. Many cancer cells secrete factors that act on nearby osteoclasts or osteoblasts, increasing their levels of bone resorption or formation.[12] Bone lesions associated with direct stimulation of osteoclasts appear as areas of increased radiolucency on radiographs and are called osteolytic lesions (Fig. 1A).[13] In contrast, bone lesions associated with stimulation of osteoblasts appear as areas of increased intensity on radiographs and are called osteoblastic lesions (Fig. 1B).[13] Although increases in osteolysis might not be apparent by the appearance of osteoblastic lesions, osteoclasts respond to and are activated by the increased bone formation and other stimuli. Therefore, although bone destruction may be more apparent for osteolytic bone lesions, osteoblastic lesions also contain a strong osteolytic component that can decrease bone integrity.[14,15] Furthermore, aberrant new bone formation in osteoblastic lesions produces

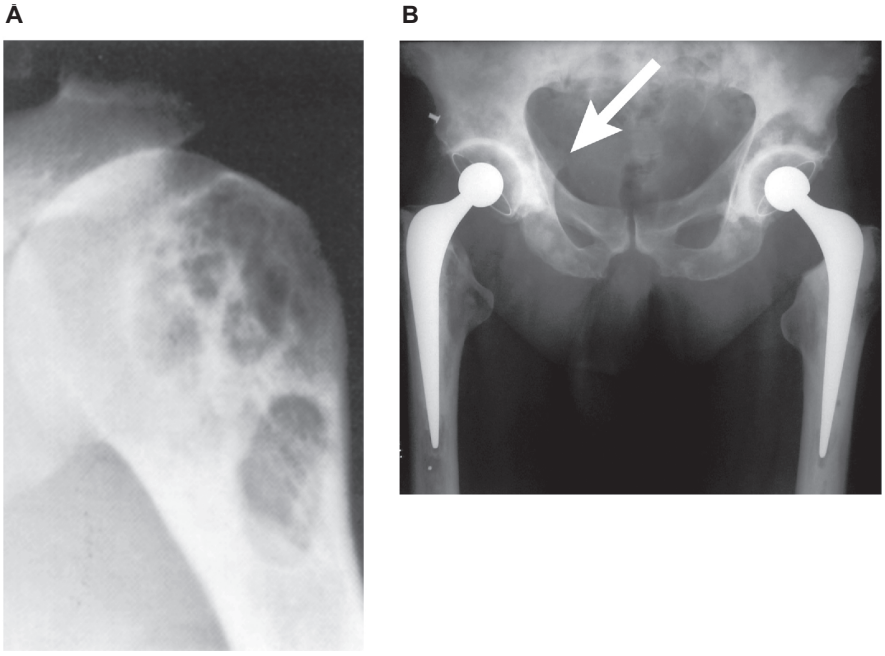

Figure 1. Plain radiographs showing (**A**) a lytic bone lesion, and (**B**) a blastic bone lesion. Reproduced with permission of Informa Clinical Medicine from Lipton A. The role of bisphosphonates to preserve bone health in patients with breast cancer. In: Lyman GH, Burstein HJ, eds. *Breast Cancer: Translational Therapeutic Strategies*. © 2008; permission conveyed through Copyright Clearance Center, Inc.[13]

new bone tissue that is malformed and does not contribute to overall bone strength.[1,15]

In patients with bone metastases, increased osteolysis decreases bone integrity, can cause bone pain, and may overwhelm serum homeostasis by releasing minerals from the bone matrix, resulting in potentially life-threatening HCM.[2] Moreover, the bone matrix-derived growth factors that are released stimulate growth of the metastatic tumors, resulting in a vicious cycle of osteolytic bone destruction and tumor growth.[12,15,16] Regardless of the radiographic appearance of their bone lesions,[14,15,17] most patients with bone metastases experience skeletal-related events (SREs) including pathologic fractures, the requirement for palliative radiotherapy or surgery to bone, spinal cord compression, and HCM.[14,18] This is consistent with increased levels of osteoclast-mediated osteolysis, the underlying cause of each SRE, being associated with both osteolytic and osteoblastic lesions.[17,19,20]

Effects of bisphosphonates on bone metastases

Through the blood stream, bisphosphonates are delivered to sites of active bone remodeling, where they bind to the bone mineral surfaces. During osteolysis, these agents are ingested by osteoclasts, wherein they mediate their biologic effects.[21] Early bisphosphonates (e.g. etidronate, clodronate) contained simple side chains and exerted their effects on osteoclast metabolism mainly by functioning as cellular analogues of inorganic pyrophosphate. These agents were relatively weak, and their utility in the oncology setting was limited.[21] Successive generations of bisphosphonates, each with increasing biologic activity, have since been developed.[10] The introduction of a nitrogen group to the bisphosphonate backbone resulted in a more than 10-fold increase in antiresorptive activity and a different cellular target than the earlier-generation bisphosphonates: farnesyl diphosphonate synthase (FPPS), a key enzyme in the mevalonate pathway.[22] By inhibiting this pathway, nitrogen-containing bisphosphonates inhibit protein prenylation and Ras signaling in osteoclasts, thereby promoting apoptosis.[22] Of the nitrogen-containing bisphosphonates approved for clinical use, ZOL has the greatest antiresorptive efficacy and has demonstrated the broadest clinical utility.

Additionally, in a preclinical model, ZOL produced near-complete inhibition of FPPS activity at a concentration of 0.1 μM, which was 5- to 40-fold lower than the concentrations required for other bisphosphonates (e.g. risedronate, ibandronate, alendronate, pamidronate).[21] Inhibiting this pathway may affect not only osteoclasts that ingest bisphosphonates, but also cancer cells that may be exposed to bisphosphonates in the serum or the bone microenvironment. For example, ZOL has been shown to induce growth arrest and apoptosis in aggressive human osteosarcoma cell lines with mutations in the *p53* or retinoblastoma tumor suppressor genes,[23] and ZOL could therefore be an important alternative to agents that rely on those pathways for their mechanisms of action.

Pharmacokinetics and pharmacodynamics of zoledronic acid

In pharmacokinetic studies in patients with malignant bone disease, ZOL had a multiphasic plasma disposition, with an early, rapid decrease from the end-of-infusion maximum concentration (C_{max}) to $<1\%$ of C_{max} at 24 hours postdose, with very low concentrations between days 2 and 28 postdose.[24] The C_{max} for 4 mg ZOL administered via 15-minute infusion in patients with normal renal function was 264 ± 86 ng/mL.[25] Urinary excretion of ZOL was independent of infusion duration, dose, or number of prior doses, with approximately 40% of the ZOL dose being excreted in urine within 24 hours postinfusion and only trace amounts detected in urine thereafter. Plasma C_{max} was affected by the infusion rate and by baseline creatinine clearance rates.[24–26] Based on the pharmacokinetic model developed from these studies, a modified dosing protocol for patients with impaired creatinine clearance was developed to improve renal tolerability while maintaining ZOL exposure similar to that in patients with normal renal function (Table 1).[25]

One reason for the multiphasic plasma distribution is the dynamics between plasma-bound ZOL and the rapid ZOL uptake at bone surfaces. In biodistribution studies in rats and dogs administered single or multiple intravenous doses of ^{14}C-labeled ZOL, ZOL levels rapidly decreased in plasma and noncalcified tissue, but higher levels persisted in bone and slowly diminished with a half-life of approximately 240 days.[27] In contrast, the *terminal* half-lives (50 to 200 days) were similar in bone and noncalcified tissues, consistent

Table 1. Dosing recommendations for zoledronic acid (15-minute infusion monthly) by baseline creatinine clearance rate.[a]

Baseline CrCl, mL/min	Dose, mg[b]
>60	4.0
50–60	3.5
40–49	3.3
30–39	3.0
<30	NR

[a]If serum creatinine increases during treatment, resume therapy only when creatinine returns to within 10% of baseline.
[b]Should be diluted in saline or 5% dextrose.
Recommendations based on prescribing information.[25]
Abbreviations: CrCl, creatinine clearance; NR, not recommended.

with ZOL rapidly but reversibly binding to bone, being rapidly cleared from the plasma, and then slowly being released from bone surfaces back into circulation over a longer time. Approximately 50% of the total dose administered was deposited in bone, with uptake highest in cancellous bone and the axial skeleton.[27]

The pharmacodynamics of ZOL in terms of effects on bone metabolism was evaluated in patients with bone metastases who received a 4-mg infusion (n = 12) and 3 consecutive (n = 21) ZOL infusions. To this end, breakdown products of bone collagen that are released during osteolysis (e.g. C- and N-terminal telopeptides of type I collagen [CTX and NTX, respectively]) were evaluated over a time course after ZOL was administered. Zoledronic acid produced significant decreases from baseline in creatinine-corrected urinary CTX (by 74%) and NTX (by 69%).[24] The antiresorptive effects were evident within the first 24 hours postinfusion, and marker levels remained below baseline levels for 28 days, after which levels began to increase toward baseline levels, supporting the monthly dosing regimen to maintain suppression of malignant osteolysis.[24] Effects of ZOL on bone marker levels were similar among patients with mild to moderate renal impairment.[26]

Perspectives for Patient Care

Personal implications of bone metastases

Malignant bone disease is the most common source of chronic pain in patients with advanced cancer and has been associated with significant reductions in QOL.[28–30] Skeletal-related events add to the burden of disease and can contribute to the decreases in QOL and autonomy that occur during cancer progression. In addition to being acutely painful and sometimes frightening events for patients, SREs can permanently impair patient mobility and functional independence. Each type of SRE has been associated with decreases in QOL. For example, in a retrospective analysis of a large-scale clinical trial in men with bone metastases from prostate cancer who experienced SREs on study (n = 248), these events were associated with statistically significant decreases in physical, functional, and emotional well being.[31] Therefore, delaying the onset of SREs and reducing the ongoing risk of SREs could provide meaningful benefits to patients with bone metastases.

The placebo-controlled arms of recent trials with bisphosphonates can provide important insight into the burden of SREs in patients with advanced solid tumors. In large-scale clinical trials of approximately 2 years' duration in patients with bone metastases, on-study SREs occurred in the majority of patients, and most patients experienced multiple SREs per year (Fig. 2).[7,8,32–34] Skeletal-related events occurred in patients with cancers that result in primarily osteolytic bone lesions (e.g. multiple myeloma and renal cell carcinoma) or primarily osteoblastic lesions (e.g. prostate cancer). Moreover, in these trials, patients with more aggressive tumors (as indicated by shorter median survival) generally had a shorter median time to first on-study SRE. Therefore, the underlying pathophysiology of bone metastases results in SREs regardless of the primary histology, and SREs from bone metastases have time to develop even in patients with aggressive malignancies and shorter survival.

Pharmacoeconomic implications of bone metastases

Another important consideration for patients and healthcare providers is the cost burden associated with direct treatment of SREs and necessary recuperative care. Although estimates vary greatly depending on tumor type and country, direct SRE-related costs are generally more than $10,000, and overall medical costs for patients with SREs are increased by up to 3 times this amount compared with patients with no SREs, presumably due to indirect costs from recuperative care or long-term disability.[35–39] For example, in a retrospective analysis of a

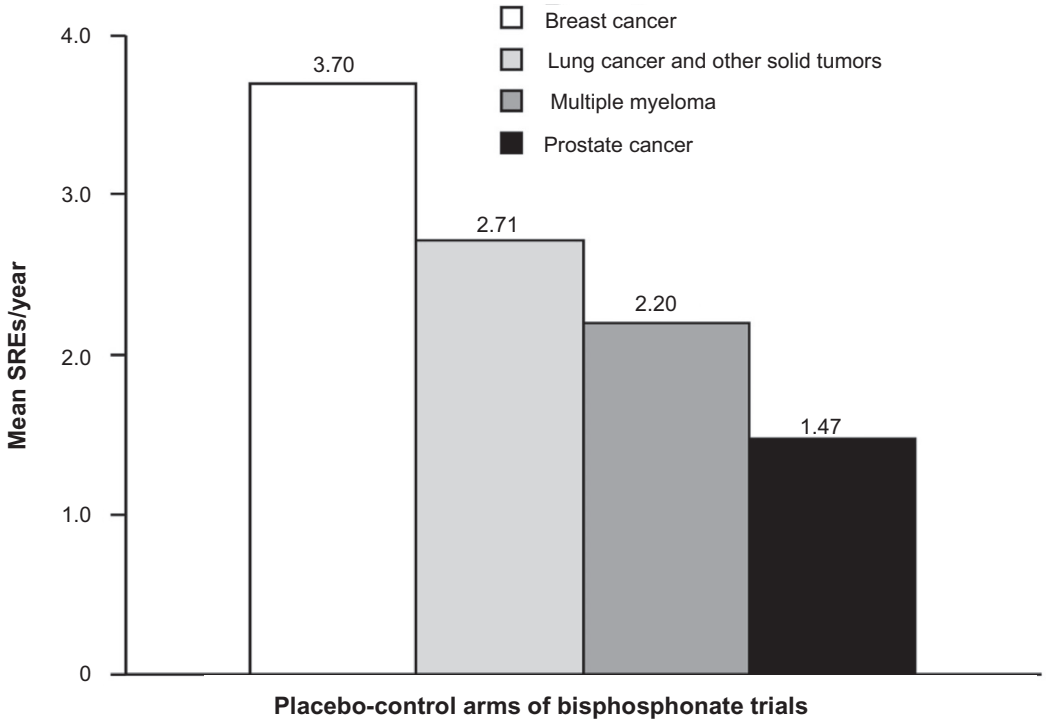

Figure 2. Skeletal morbidity rate among patients with bone lesions from various cancers. Data from the placebo groups of Lipton A, et al[32] (breast cancer); Rosen LS, et al[7] (lung cancer and other solid tumors); Berenson JR, et al[33] (multiple myeloma); and Saad F, et al[8] (prostate cancer). Adapted from Lipton A.[34]

healthcare database containing 534 patients with bone metastases from non-small cell lung cancer (NSCLC), of whom 295 had medical claims associated with SREs,[40] estimated costs directly related to SREs were approximately $12,000 (US dollars, based on 2002 costs) per patient.[40] However, when the analysis was expanded beyond the costs related to the direct management of an SRE (e.g. radiation to bone or surgery to treat a pathologic fracture), medical costs averaged $27,982 per patient higher for the SRE-affected versus SRE-free patients ($P < 0.001$).[35]

Recent pharmacoeconomic analyses of ZOL in various advanced cancer settings in Europe have revealed that much of the cost associated with ZOL treatment is offset by the potential reductions in SRE-related costs. Based on these adjustments, ZOL fell within established cost-effectiveness thresholds per quality-adjusted life-year gained in all populations evaluated, which included patients with hormone-refractory prostate cancer (HRPC, now typically referred to as castration-resistant prostate cancer [CRPC]) in Canada,[41] patients with breast cancer and lung cancer in the United Kingdom,[42–45] and patients with renal cell carcinoma in France.[46]

Clinical implications of bone metastases

In addition to the effects of skeletal morbidity on QOL and healthcare costs, the consequences of SREs (e.g. bone pain, loss of mobility) may result in long-term disability and decreases in performance status. Poor performance status or inability to travel to the hospital for multiple weekly treatments could diminish patients' capacity to receive further chemotherapy regimens for their malignancy. Therefore, SREs could indirectly reduce survival. Indeed, the occurrence of a pathologic fracture was shown to significantly correlate with reduced survival in a retrospective pooled analysis of patients with malignant bone disease in the 3 phase III international ZOL clinical trials in this setting (N = 3,049).[47] Moreover, any SRE was associated with reduced QOL and survival in patients with CRPC (N = 471).[48]

Patient adherence to therapeutic regimens

Although some bisphosphonates can be administered orally, their poor bioavailability, associated gastrointestinal toxicity, and challenges with patient

adherence to rigorous oral treatment regimens may limit the utility of oral bisphosphonate therapy in the oncology setting.[49,50] The orally administered bisphosphonates clodronate and ibandronate have shown some efficacy in preventing SREs in patients with breast cancer.[51] For these agents, the apparent convenience of oral administration is undermined by the need to follow a strict dosing regimen that requires fasting before ingesting the drug and remaining upright for a specified duration afterward. Compliance with dosing regimens for oral bisphosphonates is poor overall,[52] and these regimens may be especially challenging for patients with thoracic tumors that may constrict the esophagus. Insight into adherence to oral bisphosphonate therapy and its impact on treatment efficacy can be obtained from the osteoporosis setting. In a retrospective analysis of health insurance claims in Germany, persistence with oral bisphosphonate therapy was only 35% at the end of 6 months for 497 patients with metastatic cancer.[53] Moreover, persistence with bisphosphonate therapy was significantly lower among patients with bone metastases (n = 109) versus the overall population ($P = 0.005$), despite the high risk of SREs in that setting.

Intravenous bisphosphonates such as ZOL can be administered at substantially lower doses and at a lower frequency than oral agents. Moreover, the monthly dosing regimen of ZOL allows it to be administered during the same infusion center visit as standard chemotherapy regimens, which are typically administered every 3 to 4 weeks. Compared with other intravenous bisphosphonates, ZOL offers the added convenience of a short 15-minute infusion and a well-established safety profile.[54] In addition to ensuring compliance with the dosing regimen, the monthly infusion schedule allows periodic follow-up by clinical staff. This facilitates earlier identification and timely management of adverse events and identification of the need for additional supportive therapy such as radiation or physical therapy to maintain mobility. In this context, the infusion center staff and nurses play an important role in ensuring that treatment is proceeding on schedule.[55]

The importance of ongoing treatment with ZOL was recently underscored by a retrospective claims analysis in patients who experienced at least 1 SRE from bone metastases.[56] Consistent with the phase III trial results, SRE rates were higher among patients who did not receive bone-targeted therapy compared with ZOL-treated patients (0.43 ± 0.4 versus 0.29 ± 0.4 SREs per month; $P < 0.001$). Greater persistency with ZOL was associated with lower SRE rates (Fig. 3; $P < 0.05$).[56] These real-world data support the clinical benefits of ZOL and the importance of persistence with the monthly regimen to ensure ongoing protection against SREs, consistent with the pharmacodynamic studies that demonstrated that monthly

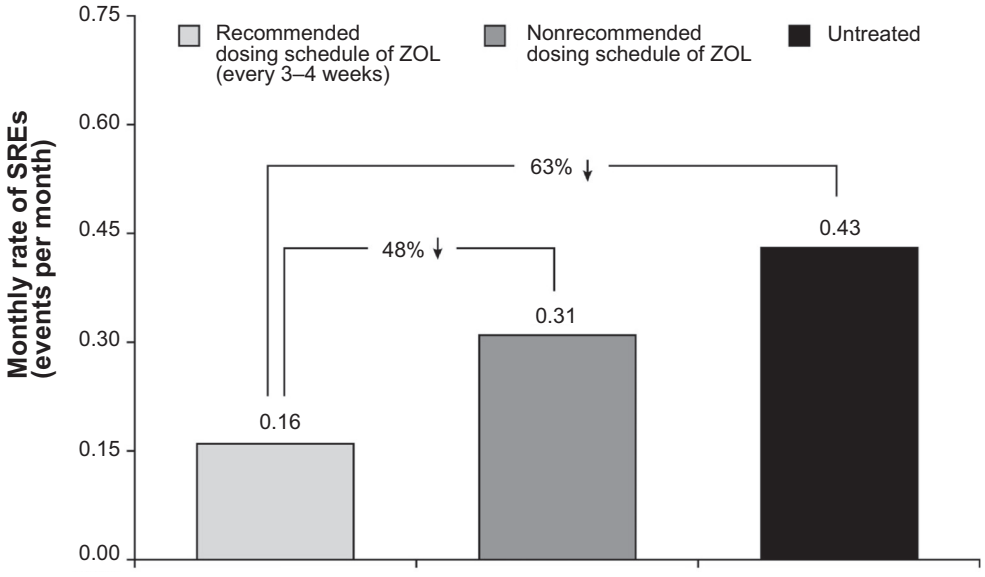

Figure 3. Correlation between skeletal morbidity rate and adherence/persistence with the monthly dosing regimen of zoledronic acid. Adapted with permission from Hatoum HT, et al. *Cancer*. 2008;113(6):1438–45. Copyright 2008, © American Cancer Society. Reproduced with permission of John Wiley and Sons, Inc.[56]
Abbreviations: SRE, skeletal-related event; ZOL, zoledronic acid.

dosing is necessary to maintain suppression of malignant osteolysis.[26]

Zoledronic Acid can Reduce Skeletal Morbidity in Patients with Malignant Bone Disease

Although successive generations of bisphosphonates have been used for treating HCM and preventing SREs in patients with bone lesions from multiple myeloma or breast cancer, it was not until the introduction of ZOL in 2002 that the benefits of bisphosphonate therapy could be extended to patients with other solid tumors, including CRPC and NSCLC.[34]

Breast cancer and multiple myeloma

Zoledronic acid (4 mg via 15-minute infusion every 3 to 4 weeks) was approved for preventing SREs in patients with bone metastases from breast cancer or bone lesions from multiple myeloma. Efficacy and safety results demonstrated that ZOL was at least comparable with pamidronate (90 mg via 2-hour infusion every 3 to 4 weeks) in a 2-year, randomized, controlled, double-blind, double-dummy trial in this patient population (N = 1,648).[6,57] In addition to the shorter infusion time, ZOL demonstrated some significant benefits beyond those of pamidronate in both the overall trial population,[6] in which 4 mg ZOL significantly reduced the overall risk of SREs (including HCM) by 16% compared with pamidronate in a multiple event analysis ($P = 0.030$). In the subset of patients with breast cancer, 4 mg ZOL significantly reduced the overall risk of SREs by 20% compared with pamidronate in a multiple event analysis ($P = 0.037$).[58] Moreover, ZOL benefits were especially profound among patients with breast cancer who were receiving hormonal therapy or who had at least 1 primarily osteolytic bone lesion.[6,58]

Although pamidronate, ibandronate, clodronate, and ZOL have not yet been compared head-to-head in controlled clinical trials, a recent evaluation of biphosphonate benefits was performed by the Cochrane Database in patients with bone metastases from breast cancer (Fig. 4).[59–67] This evaluation revealed that ZOL produced the largest reduction in SRE risk versus placebo of all the bisphosphonates approved in the United States or Europe in this population.

In a placebo-controlled 1-year trial in Japanese women with bone metastases from breast cancer (N = 228), ZOL produced significant early and

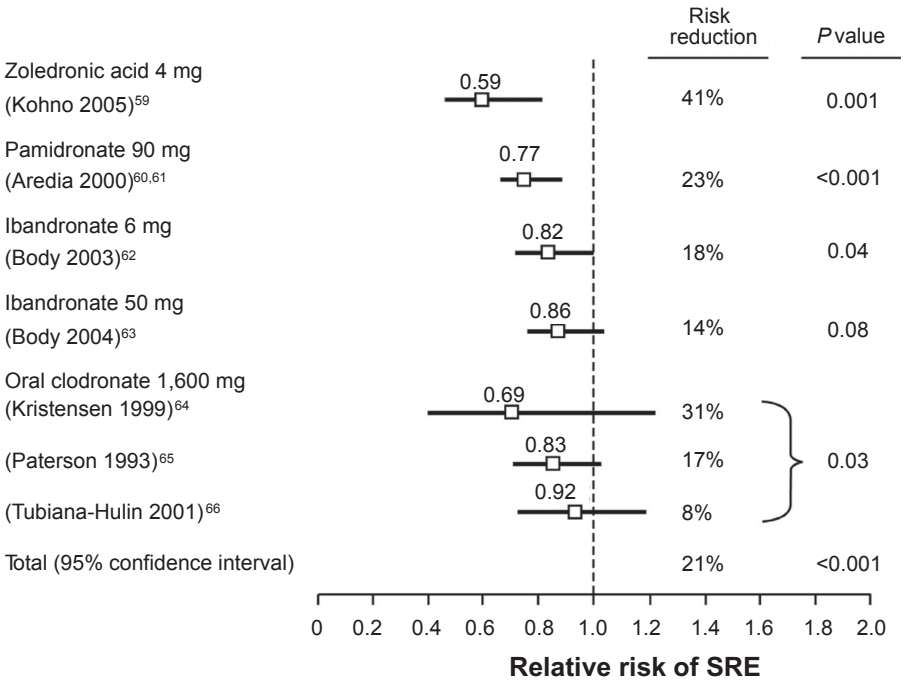

Figure 4. Overall risk of skeletal-related events in patients with bone metastases from breast cancer treated with bisphosphonates.[59–66] Hypercalcemia was not included as a skeletal-related event (SRE) in this analysis. Length of the horizontal line represents the 95% confidence interval. Reproduced with permission from Pavlakis N, Schmidt RL, Stockler M. Bisphosphonates for breast cancer (review). *Cochrane Database Syst Rev*. 2005, Issue 3. Copyright Cochrane Collaboration, reproduced with permission.[67]

sustained decrease in pain scores compared with placebo ($P < 0.05$ at each timepoint).[59] In a later observational study in patients with bone metastases from breast cancer (N = 101), ZOL significantly improved QOL scores versus baseline ($P = 0.013$),[68] supporting a role for ZOL in symptom palliation in this setting.

Prostate cancer

Etidronate, clodronate, pamidronate, and ZOL have been investigated for preventing SREs in patients with bone metastases from CRPC, and most have shown some palliative benefits. Of these agents, however, only ZOL has demonstrated statistically significant, long-term, objective benefits in a large-scale, randomized, placebo-controlled trial (N = 643; Table 2).[7,8,69–77] At the 24-month timepoint, ZOL (4 mg via 15-minute infusion every 3 weeks for up to 24 months) significantly reduced the proportion of patients who experienced an on-study SRE (the primary endpoint) to 38% versus 49% for placebo ($P = 0.028$).[8] Moreover, ZOL 4 mg significantly delayed the median time to first on-study SRE by more than 5 months ($P = 0.009$) and reduced the ongoing risk of SREs by 36% relative to placebo in a multiple event analysis ($P = 0.002$).[8] Although bone pain levels increased during the course of the trial, consistent with the heavy burden of skeletal disease in patients with CRPC, ZOL provided significant palliative benefits.[8] Furthermore, more patients treated with ZOL experienced clinically meaningful reductions in bone pain levels compared with placebo.[78]

Other solid tumors

Studies of earlier-generation bisphosphonates in patients with bone metastases from solid tumors other than breast or prostate cancers have

Table 2. Efficacy of bisphosphonates in randomized, placebo-controlled trials in patients with bone metastases secondary to hormone-refractory prostate cancer.

Drug	Study	Dose	Efficacy results
Etidronate	Smith[69] (N = 57)	7.5 mg/kg (IV, days 1–3), then 400 mg/day (oral)	No significant benefits
Clodronate	Strang et al[70] (N = 55)	300 mg/day (IV, days 1–3), then 3,200 mg/day (oral)	No significant benefits
	Kylmala et al[71] (N = 57)	300 mg/day (IV, days 1–5), then 1,600 mg/day (oral)	↓ Pain by 10% (NS)
	Elomaa et al[72] (N = 75)	3,200 mg/day (first month), then 1,600 mg/day (oral)	↓ Pain and analgesic use (first month only) ↓ Serum calcium levels
	Ernst et al[73] (N = 209)	1,500 mg (IV every 3 weeks)	↓ Pain (NS)
	Dearnaley et al[74] (N = 311)	2,080 mg/day (oral)	↑ Bone progression-free (NS) and overall survival (NS) ↓ Deterioration of WHO PS ($P = 0.008$)
Pamidronate	Small et al[75] (N = 378)	90 mg (IV every 3 weeks)	No significant benefits in pain or proportion of patients with SREs
Zoledronic acid	Saad et al[8,76] (N = 643)	4 mg (IV every 3 weeks)	↓ Proportion of patients with ≥1 SRE ($P = 0.028$) ↓ Rate of skeletal morbidity ($P = 0.005$) ↑ Time to first SRE ($P = 0.009$)

Adapted with permission. This article was published in *Semin Oncol*, Vol 29; Saad F, et al. Treatment of bone complications in advanced prostate cancer: rationale for bisphosphonate use and results of a phase III trial with zoledronic acid; pages 19–27; Copyright Elsevier (2002).[77]
Abbreviations: IV, intravenous; NS, not significant ($P \geq 0.05$); WHO PS, World Health Organization performance status; SRE, skeletal-related event.

been limited. In this setting, ZOL was the first agent to achieve any statistically significant objective benefits in a placebo-controlled trial. In this study, patients with bone metastases from solid tumors other than breast or prostate cancers (N = 773) were randomized to ZOL or placebo every 3 weeks for up to 21 months.[7] In the overall trial population, ZOL significantly reduced the proportion of patients who experienced at least 1 SRE (including HCM; 39% versus 48% for placebo; $P = 0.039$) and reduced the proportion of patients who experienced each type of SRE (Fig. 5).[7] Moreover, ZOL significantly decreased the mean annual incidence of SREs (1.74 versus 2.71 per year for placebo; $P = 0.012$) and significantly delayed the median time to first SRE versus placebo (236 versus 155 days, respectively; $P = 0.009$).[7] Zoledronic acid reduced the risk of SREs by 31% versus placebo in a multiple event analysis of the overall trial population ($P = 0.003$).

In addition to benefits in the overall population, ZOL produced significant benefits within the disease subsets. For example, in the stratum of patients with NSCLC (n = 382), ZOL significantly prolonged median time to first on-study SRE ($P = 0.028$) and reduced ongoing risk of SREs in a multiple event analysis by 38% compared with placebo ($P < 0.001$).[79] In the subset of patients with renal cell carcinoma (n = 46 treated with placebo or ZOL 4 mg), a disease characterized by highly vascularized and especially osteolytic bone lesions, ZOL 4 mg produced especially profound benefits including a 58% reduction in ongoing risk of SREs ($P = 0.010$) and significant delay in median time to bone disease progression compared with placebo ($P = 0.014$).[80] Based on these data and results from the other phase III clinical trials, ZOL is the only bisphosphonate with established efficacy for preventing SREs regardless of the osteolytic or osteoblastic nature of the malignant bone lesions.[81]

Efficacy based on skeletal disease history

It may not be possible to delay the onset of the first SRE in many patients with advanced cancer because their bone metastases might not be diagnosed until after they become symptomatic, thereby denying the opportunity for early intervention. However, initiating treatment is especially important for these patients because they are likely

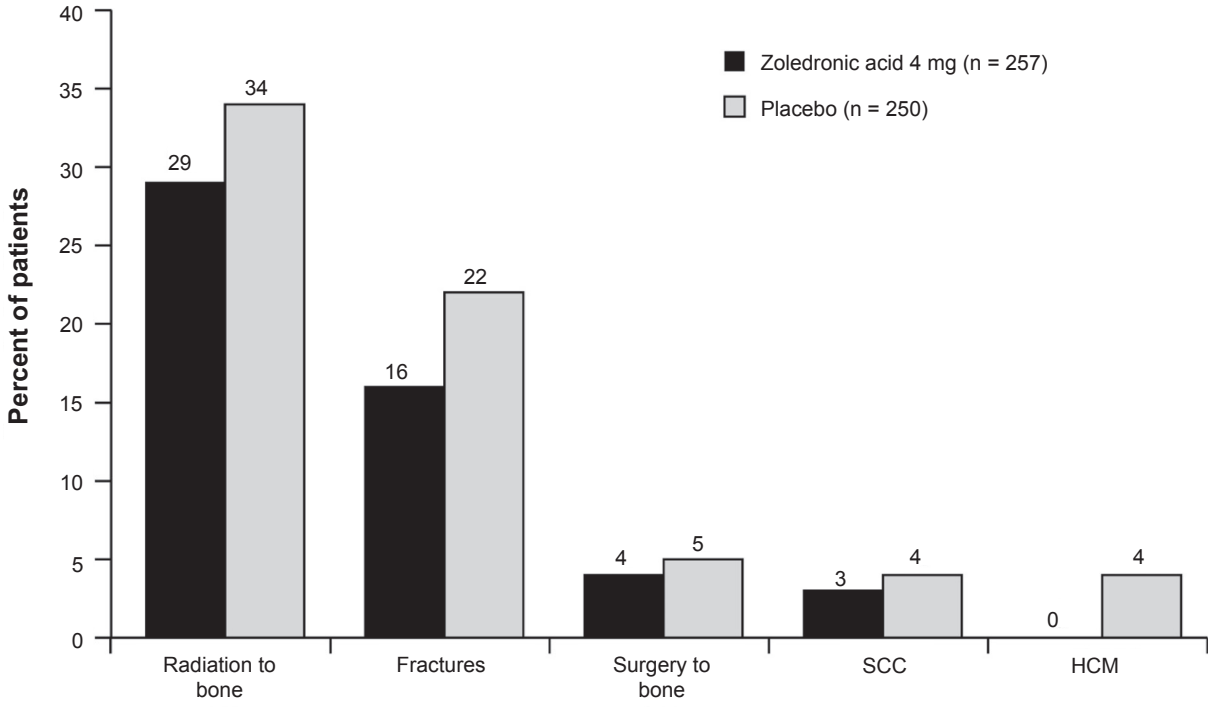

Figure 5. Proportion of patients with each type of SRE for zoledronic acid 4 mg and placebo-treated patients with bone metastases from non-small cell lung cancer or other solid tumors.
Abbreviations: SCC, spinal cord compression; HCM, hypercalcemia of malignancy.
Data from Rosen LS, et al.[7]

to be at especially high risk for SREs. Indeed, in an exploratory analysis of the ZOL phase III trial in patients with NSCLC or other solid tumors, patients with a history of SREs before study entry had a 41% increased risk of experiencing an on-study SRE compared with patients with no history of prior SREs ($P = 0.036$).[9] However, despite their history of SREs, ZOL produced a significant 31% reduction in the risk of developing an on-study SRE compared with placebo in a multiple event analysis ($P = 0.009$), and significantly reduced the skeletal morbidity rate (1.96 versus 2.81 events per year for placebo; $P = 0.030$).[9] Furthermore, ZOL significantly prolonged the median time to first on-study SRE by approximately 4 months compared with placebo in this prior-SRE cohort (215 versus 106 days, respectively; $P = 0.011$).[9] Therefore, ZOL appears to be effective in patients at high risk for SREs and to provide benefits after the onset of SREs.

Analysis of biochemical markers of bone metabolism

Additional insight into the contribution of bone metastases to the overall burden of malignant bone disease can be obtained through the use of biochemical markers of bone metabolism, such as peptides that are released from the bone matrix during osteolysis. For example, in a subset of patients with NSCLC or other solid tumors in the placebo group (n = 238), urinary NTX levels were assessed approximately every 3 months.[82] High NTX levels (≥100 nmol/mmol creatinine) at baseline were associated with shorter time to first SRE (relative risk [RR] = 1.85; $P = 0.026$) and bone disease progression (RR = 1.76; $P = 0.029$) compared with patients with low NTX levels (<100 nmol/mmol creatinine).[82] Moreover, compared with patients with low NTX levels, patients with high NTX levels had a more than 3-fold increased risk of death (RR = 3.03; $P < .001$) and a 5-month reduction in median survival (3.2 versus 8.2 months for patients with low baseline NTX levels).[82]

As illustrated in early pharmacodynamics studies, ZOL is highly effective at lowering NTX levels in patients with bone metastases.[26] In a recent exploratory analysis of the subset of patients who had NTX assessments in the ZOL phase III clinical trials (n = 1,824),[83] ZOL was found to effectively reduce urinary NTX levels. Moreover, ZOL normalized NTX levels within 3 months in the majority of patients with bone metastases from breast cancer, prostate cancer, or NSCLC or other solid tumors.[84] Patients with high baseline NTX levels that normalized within 3 months of ZOL treatment had significantly improved survival versus patients with persistently elevated NTX ($P \leq 0.0116$). In a separate retrospective subset analysis in patients with NSCLC and baseline NTX levels ≥ 64 nmol/mmol creatinine (n = 144), ZOL significantly reduced the risk of death by 35% versus placebo ($P = 0.024$), and benefits remained significant after adjustment for other significant covariates in a multivariate model.[79] Differences in survival between the ZOL and placebo groups did not reach statistical significance in the normal baseline NTX subset, consistent with the lower risks of SREs and death that have been reported for that subset.[79,82] In a separate analysis that pooled data from all of the phase III placebo-controlled ZOL trials, ZOL was also found to significantly reduce the risk of death by 26% versus placebo among patients with baseline NTX ≥100 nmol/mmol creatinine.[83] These benefits could result from reductions in osteolysis causing lower levels of growth factor release from the bone matrix, reduced incidence of potentially life-limiting SREs, or direct antitumor effects.

Safety and tolerability of zoledronic acid

Zoledronic acid was generally well tolerated in clinical trials,[6,7,57,59,76,85,86] and its safety profile has since been well established in clinical practice. The overall pattern of adverse events reported with ZOL is similar to that of the earlier-generation bisphosphonate pamidronate (Table 3).[6,7,59,76,86] The most common adverse events reported during clinical trials of ZOL (i.e. nausea, fatigue, arthralgia, and pyrexia) were related to the flu-like acute-phase reaction that is most prevalent after the first infusion but then becomes less frequent after subsequent doses.[6,7,57,59,76,85,86] Patient management guidelines have been published to ensure patient safety and comfort.[87]

All intravenous bisphosphonates are associated with dose- and infusion rate-dependent effects on renal function. Therefore, the clinical trials of ZOL included routine monitoring of serum creatinine levels. Early in the clinical trials, a shorter (5-minute) infusion time and a higher (8-mg) ZOL

Table 3. Adverse events ≥15% reported in patients with bone metastases from breast cancer, multiple myeloma, prostate cancer, or other solid tumors in phase III clinical trials of zoledronic acid.

Adverse event[a]	Patients, %		
	Zoledronic acid (n = 1,031)[6,7,59,76]	Pamidronate (n = 556)[7]	Placebo (n = 568)[7,59,76]
Bone pain	32–58	57	45–61
Nausea	36–50	48	36–53
Fatigue	32–45	43	26–32
Pyrexia	20–55	31	13–33
Emesis	22–38	33	21–39
Anemia	27–38	32	18–35
Myalgia	12–27	26	13–18
Diarrhea	17–29	29	15–26
Dyspnea	18–35	28	13–30
Cough	21–27	23	17
Constipation	27–36	29	33–38
Arthralgia	15–26	24	16–17
Weakness	21–29	19	19–28
Headache	17–30	27	11–28
Anorexia	20–24	15	17–27
Edema, lower limb	19–24	23	13–21

[a]Regardless of study drug relationship.
Adapted from Lipton A.[86]

dose were investigated, but these were discontinued in favor of the now-standard 4 mg via 15-minute infusion protocol to ensure renal safety in all patients. Nonetheless, differences were reported in rates of notable serum creatinine increases between the ZOL 4 mg and control groups in the phase III clinical trials (Table 4).[6,7,57,59,76,85,86] Therefore, routine monitoring of serum creatinine levels before each ZOL dose and strict adherence to the dosing and infusion-rate guidelines are important to ensure patient safety and comfort.[87] Notably, the introduction of the reduced dosing regimen for patients with impaired renal function (Table 1)[25] was not introduced until after the completion of these clinical trials.

In recent years, there have been reports of osteonecrosis of the jaw (ONJ) as an uncommon event among cancer patients receiving complex treatment regimens including bisphosphonates.[88] This condition, characterized by exposed bone in the oral cavity that does not heal after 6 weeks of appropriate dental care and in the absence of osteoradionecrosis or malignant disease in the jaw, is often associated with dental trauma. In a large retrospective analysis of cancer patients receiving bisphosphonate therapy at the MD Anderson Cancer Center (N = 3,994), the overall frequency of confirmed or suspected ONJ cases was 0.7%.[89] The majority of cases were associated with dental trauma. Osteonecrosis of the jaw occurred in the subsets of patients with metastatic breast cancer (n = 1,338; 1.2%) and multiple myeloma (n = 548; 2.4%) more frequently than in patients with any other cancer type, including CRPC, lung cancer, and renal cancer (n = 2,108; 0%).[89]

Other reports, however, suggest that ONJ may occur at frequencies of up to 6% to 10% in patients with multiple myeloma.[90,91] More recently, an analysis of ONJ among cancer patients treated with intravenous bisphosphonates and/or the angiogenesis inhibitor bevacizumab at the Memorial Sloan-Kettering Cancer Center (N = 8,681) was reported.[92] The frequency of ONJ was 1.1% (72 of 6,561) among patients treated with intravenous bisphosphonates only and 2.0% (8 of 409) among patients treated with both bevacizumab

Table 4. Proportion of patients with elevated serum creatinine levels who received zoledronic acid 4 mg via 15-minute infusion.

	Patients, %	
	Zoledronic acid	**Pamidronate or placebo**
Breast cancer[59]	0.9	6.2
Prostate cancer[76,a]	15.2	11.5
Lung cancer and other solid tumors[7]	10.9	6.7
Breast cancer and multiple myeloma[6,b]	10.7	9.3

[a]Results reported are from the 15-month analysis; however, 24-month results were stated to be similar.
[b]This is the only study with pamidronate as the comparator.
Adapted from Lipton A.[86]

and intravenous bisphosphonates. No ONJ was reported among patients receiving bevacizumab alone.[92] The authors concluded that the concomitant use of intravenous bisphosphonates with angiogenesis inhibitors could increase the risk of ONJ. Similar concerns have been raised recently in patients with CRPC receiving ZOL in addition to antiangiogenic agents.[93] In a retrospective analysis of a study in which bisphosphonates were allowed at study entry, 11 of 60 (18.3%) chemotherapy-naive men receiving bevacizumab, thalidomide, docetaxel, prednisone (ATTP), and enoxaparin experienced ONJ. Further investigations are needed to clarify this potential connection with ONJ. Furthermore, data from prospective studies are needed to determine the frequency of ONJ in patients receiving bisphosphonates for malignant bone disease.

Subsequent studies have shown that implementing preventive measures such as dental hygiene screenings before initiating bisphosphonate therapy and avoiding invasive dental procedures during treatment can significantly reduce the incidence and severity of ONJ.[94,95] For example, Ripamonti et al[95] implemented a proactive dental monitoring and treatment protocol before initiating intravenous bisphosphonate therapy in oncology patients. A per-protocol assessment among patients who received ZOL treatment (only ZOL or ZOL and pamidronate during the course of their treatment) revealed an 86% decrease in the ONJ incidence rate for patients who followed the new protocol versus the prior standard of care ($P = 0.003$ for the difference in incidence proportion between groups).[95]

Investigational Activities with Bisphosphonate Therapy

In addition to reducing the risk of SREs, bisphosphonate therapy may have additional benefits including bone metastasis prevention and antitumor effects, especially in combination with chemotherapy agents. Emerging clinical evidence, especially in the breast cancer setting, suggests that ZOL may be able to slow the disease course in patients with early disease.

Preclinical evidence of potential antitumor activity for zoledronic acid

There is a strong preclinical rationale that bisphosphonates can inhibit proliferation and induce apoptosis in a broad range of human cancers.[21,96] In vitro studies show that ZOL inhibits growth of cell lines derived from a broad range of human primary tumors.[97–103] Moreover, ZOL has also been shown to block motility, adhesion, and invasion by cancer cell lines, all of which are important activities for the establishment of metastatic tumors.[104] Zoledronic acid also exerts antitumor synergy with chemotherapy agents including cisplatin and paclitaxel.[105,106] Zoledronic acid (1 μg/kg/week) inhibited cancer growth and significantly improved survival in mouse models of lung cancer and multiple myeloma ($P < 0.05$ compared with untreated mice).[107,108] Furthermore, ZOL (0.1 mg/kg either 2 or 5 times weekly) prevented development of lung metastases and improved survival ($P = 0.036$ versus untreated mice) in a mouse model of metastatic osteosarcoma.[109] Similar results were observed in a mouse model of breast cancer, wherein high apoptosis rates were detected in bone lesion-associated breast cancer cells after ZOL treatment.[110] The antitumor activities of ZOL may be attributable to multiple mechanisms in addition to direct effects on the tumor cells and the bone microenvironment.[111] These potential mechanisms include inhibition of tumor angiogenesis and immunomodulatory properties (activation of gamma-delta T cells, a subset of T cells that plays a role in immunosurveillance for malignancies).[111–114]

Emerging clinical evidence of zoledronic acid's antitumor activity

Zoledronic acid has demonstrated promising antitumor activity in pilot trials in a variety of

tumor types. In patients with bone metastases from bladder cancer (N = 40), ZOL (4 mg/month) for 6 months not only significantly reduced the incidence of SREs and bone pain ($P \leq 0.015$ for both), but also significantly improved the 1-year survival rate compared with placebo ($P = 0.02$).[115] In patients with previously untreated multiple myeloma (N = 94), adding ZOL (4 mg every 4 weeks) to chemotherapy reduced the incidence of SREs at a median follow-up of 49.6 months and improved 5-year actuarial overall survival (OS) from 46% in the chemotherapy-alone arm to 80% in the chemotherapy-plus-ZOL arm ($P < 0.01$).[116] In a separate study in patients with metastatic solid tumors and no evidence of bone metastases (N = 40), bone-metastasis–free survival (BMFS) was 20% among patients treated with ZOL 4 mg/month versus only 5% in the control arm at 18 months' follow-up ($P = 0.0002$).[117] These data suggest that ZOL can affect the disease course in patients with advanced cancers in the presence or absence of detectible bone metastases.

Recently, ZOL has also demonstrated benefits in patients with early disease. Although ongoing clinical trials of adjuvant therapy with ZOL are accruing more than 20,000 patients with a broad range of malignancies, data from large, randomized, phase III trials are most predominant and mature in the breast cancer setting. In premenopausal women with endocrine-responsive breast cancer, the ABCSG-12 trial (N = 1,803) demonstrated that adding ZOL (4 mg every 6 months) to adjuvant endocrine therapy (ovarian suppression plus tamoxifen or anastrozole) significantly improved disease-free survival (DFS) by 36% (log-rank $P = 0.01$) and recurrence-free survival (RFS) by 35% (log-rank $P = 0.01$), and produced a trend toward improved OS ($P = 0.11$).[118] Interestingly, reduced cancer recurrence with the addition of twice-yearly ZOL was not limited to bone metastasis; reduced contralateral and visceral metastases were also noted.[118]

In the postmenopausal breast cancer setting, 3 parallel trials (Z-FAST, ZO-FAST, and E-ZO-FAST) are evaluating the efficacy of ZOL (4 mg every 6 months) for preventing disease progression and aromatase inhibitor-associated bone loss.[119] In these studies, benefits beyond bone health were apparent after only 1 year of treatment. At 12 months' median follow-up, integrated analyses of the Z-FAST and ZO-FAST trials (total N = 1,667) demonstrated a significant decrease in disease recurrence in patients receiving upfront ZOL (0.84% versus 1.9% in patients for whom ZOL treatment was delayed until only after they developed clinically meaningful bone loss; $P = 0.0401$).[119] The difference in disease recurrence rates was even larger in the 24-month integrated analysis: 3.6% in the upfront-ZOL arm versus 5.5% in the delayed-ZOL arm (DFS hazard ratio = 0.573; $P = 0.0183$).[120] Reductions in disease recurrence rates and increases in DFS were also significant ($P = 0.042$ and $P = 0.034$, respectively) for upfront versus delayed ZOL at the 36-month assessment of the ZO-FAST trial (N = 1,064; Z-FAST 36-month results have yet to mature).[121]

A large, ongoing clinical trial (AZURE; N = 3,360) is evaluating the efficacy of ZOL for preserving skeletal integrity and preventing disease progression in patients with stage II/III breast cancer. Exploratory analysis of the cohort of patients who received neoadjuvant chemotherapy (n = 205) showed that adding ZOL (4 mg/month) to chemotherapy reduced residual invasive tumor size ($P = 0.002$) and improved pathologic complete response rate ($P = 0.03$) compared with chemotherapy alone.[122] Adding ZOL to standard therapies was generally well tolerated in these trials, with no reports of high-grade renal adverse events and a low incidence of ONJ, ranging from no cases for ABCSG-12, to 0.1% for Z-/ZO-FAST, and to 0.4% for AZURE.[118,121,123]

The effects of ZOL versus no ZOL on event-free survival, OS, and BMFS are also being prospectively investigated in the German NATAN trial (targeted accrual, N = 654), which is nearing completion of accrual. Other ongoing studies of potential antitumor effects of bisphosphonates in early breast cancer settings are being conducted by the Southwest Oncology Group (SWOG 0307; targeted accrual, N = 4,500),[124] the National Surgical Adjuvant Breast and Bowel Project (NSABP B-34; targeted accrual, N = 3,323),[125] and the German SUCCESS trial (N = 3,754, enrollment complete).

Phase III studies are ongoing in the adjuvant setting for prostate cancer and in patients with advanced lung cancer to evaluate the activity of ZOL for preventing bone metastases and in other exploratory studies for antitumor activity (Table 5). The STAMPEDE trial is currently accruing patients initiating androgen-deprivation therapy (ADT) for prostate cancer (targeted accrual, N = 3,300), and will compare failure-free survival in patients receiving ADT with or without ZOL, docetaxel, or celecoxib.[126] The ZEUS

Table 5. Ongoing phase III clinical trials of zoledronic acid in the adjuvant setting in patients with solid tumors other than breast cancer.

Study	Patients	Treatments	Primary endpoint	Status
Prostate cancer				
STAMPEDE	521/3,300 (initiating ADT)	6-arm trial with ADT ± DOC, ZOL, CEL	Failure-free survival	Active
ZEUS	1,433 (no distant mets)	ZOL vs. no ZOL	Bone mets rate at 4 yr	Accrual complete
RADAR	1,071 (stage T2b-4)	ADT ± ZOL	PSA-RFS at 5 yr	Accrual complete
Lung cancer				
Trial 2419	385/446 (stage III)	ZOL vs. no ZOL	Progression-free survival	Active

Abbreviations: ADT, androgen-deprivation therapy; DOC, docetaxel; ZOL, zoledronic acid; CEL, celecoxib; mets, metastases; PSA, prostate-specific antigen; RFS, recurrence-free survival.

trial (N = 1,433 patients with prostate cancer and no evidence of bone metastases) has completed accrual and will compare the rate of bone metastases at 48 months in patients receiving standard therapy alone versus standard therapy with ZOL (4 mg every 3 months).[127] The RADAR trial (N = 1,071 patients with stage T2b-4 prostate cancer) is comparing the efficacy of short-term (6 months) versus long-term (18 months) ADT with or without ZOL (4 mg every 3 months for 18 months) to prevent biochemical relapses at 5 years.[128] An ongoing study in NSCLC (study 2419) has nearly completed enrollment of patients with stage IIIA/B lung cancer and no evidence of disease progression after primary therapy (targeted accrual, N = 446).[129] This trial will evaluate the efficacy of ZOL (4 mg/month) for preventing disease relapse (e.g. in bone). Results from all of these studies are eagerly awaited, and the role of bisphosphonate therapy is likely to evolve in the adjuvant setting to prevent both skeletal and visceral metastases.

Conclusions

Although the skeleton is one of the most common sites of distant metastasis from solid tumors, the burden of skeletal disease is often overlooked in the oncology setting. Bone metastases can contribute profoundly to the attrition of QOL and independence experienced by cancer patients during the course of their disease. Preserving skeletal health through the use of bone-targeted therapies such as ZOL is an essential component of care,[3] especially in the context of noncurative but life-prolonging therapies that may leave patients with advanced disease at long-term risk for SREs. As such, early identification of bone metastases and management of SREs may allow better preservation of QOL, thereby containing healthcare costs throughout the continuum of care. Early treatment to maintain bone health may also help maintain patients' performance status and eligibility for subsequent lines of anti-cancer therapy.[9]

Zoledronic acid is the only bisphosphonate that has been shown to significantly reduce the risk of skeletal morbidity in patients with bone metastases from a broad range of solid tumors.[3] In addition, exploratory analyses suggest that ZOL may improve survival in patients with high levels of biochemical markers of bone resorption,[79] possibly by preventing life-limiting SREs or by blocking release of growth factors from the bone matrix. However, other antitumor mechanisms are possible, and emerging evidence suggests that further clinical benefits are possible. In the early breast cancer setting, ZOL has already demonstrated significant benefits in prolonging DFS.[118] Clinical trials of ZOL for preventing bone metastases in patients with other solid tumors including prostate cancer and lung cancer are ongoing, and the role of bisphosphonate therapy will continue to evolve.

Acknowledgments

Funding for medical editorial assistance was provided by Novartis Pharmaceuticals. I thank

Catherine Browning, PhD, for her medical editorial assistance with this manuscript.

References

1. Lipton A. Pathophysiology of bone metastases: how this knowledge may lead to therapeutic intervention. *J Support Oncol.* 2004;2:205–13; discussion follows.
2. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev.* 2001;27:165–76.
3. Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol.* 2008;19:420–32.
4. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (the IDEAL 1 trial) [corrected]. *J Clin Oncol.* 2003;21:2237–46.
5. Berenson JR, Rajdev L, Broder M. Managing bone complications of solid tumors. *Cancer Biol Ther.* 2006;5:1086–9.
6. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer.* 2003;98:1735–44.
7. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer*. 2004;100:2613–21.
8. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96:879–82.
9. Hirsh V, Tchekmedyian NS, Rosen LS, Zheng M, Hei YJ. Clinical benefit of zoledronic acid in patients with lung cancer and other solid tumors: analysis based on history of skeletal complications. *Clin Lung Cancer*. 2004;6:170–4.
10. Fleisch H. Development of bisphosphonates. *Breast Cancer Res*. 2002;4:30–4.
11. Lipton A. Future treatment of bone metastases. *Clin Cancer Res*. 2006;12:6305s–8s.
12. Mundy GR. Mechanisms of bone metastasis. *Cancer*. 1997;80(suppl): 1546–56.
13. Lipton A. The role of bisphosphonates to preserve bone health in patients with breast cancer. In: Lyman GH, Burstein HJ, eds. *Breast Cancer: Translational Therapeutic Strategies*. New York: Informa Healthcare U.S.A. Inc.; 2008:241–56.
14. Coleman RE. Bisphosphonates: clinical experience. *Oncologist.* 2004;9(suppl 4):14–27.
15. Kakonen SM, Mundy GR. Mechanisms of osteolytic bone metastases in breast carcinoma. *Cancer*. 2003;97(suppl):834–9.
16. Saad F, Schulman CC. Role of bisphosphonates in prostate cancer. *Eur Urol*. 2004;45:26–34.
17. Guise TA, Mohammad KS, Clines G, et al. Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. *Clin Cancer Res*. 2006;12(suppl):6213s–6s.
18. Coleman RE. Management of bone metastases. *Oncologist.* 2000; 5:463–70.
19. Goltzman D, Karaplis AC, Kremer R, Rabbani SA. Molecular basis of the spectrum of skeletal complications of neoplasia. *Cancer*. 2000; 88(suppl):2903–8.
20. Koizumi M, Yamada Y, Takiguchi T, et al. Bone metabolic markers in bone metastases. *J Cancer Res Clin Oncol*. 1995;121:542–8.
21. Green JR. Preclinical profile and anticancer potential of zoledronic acid. In: Birch EV, ed. *Trends in Bone Cancer Research*. Vol 24. New York: Nova Science Publishers, Inc.; 2006:217–45.
22. Green JR. Bisphosphonates: preclinical review. *Oncologist*. 2004; 9(suppl 4):3–13.
23. Ory B, Blanchard F, Battaglia S, Gouin F, Redini F, Heymann D. Zoledronic acid activates the DNA S-phase checkpoint and induces osteosarcoma cell death characterized by apoptosis-inducing factor and endonuclease-G translocation independently of p53 and retinoblastoma status. *Mol Pharmacol*. 2007;71:333–43.
24. Chen T, Berenson J, Vescio R, et al. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol*. 2002;42:1228–36.
25. ZOMETA® (zoledronic acid) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2008.
26. Skerjanec A, Berenson J, Hsu C, et al. The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol*. 2003;43:154–62.
27. Weiss HM, Pfaar U, Schweitzer A, Wiegand H, Skerjanec A, Schran H. Biodistribution and plasma protein binding of zoledronic acid. *Drug Metab Dispos*. 2008;36:2043–9.
28. Saba N, Khuri F. The role of bisphosphonates in the management of advanced cancer with a focus on non-small-cell lung cancer. Part 2: clinical studies and economic analyses. *Oncology*. 2005;68:18–22.
29. Ripamonti C, Fulfaro F. Malignant bone pain: pathophysiology and treatments. *Curr Rev Pain*. 2000;4:187–96.
30. Sabino MA, Mantyh PW. Pathophysiology of bone cancer pain. *J Support Oncol*. 2005;3:15–24.
31. Weinfurt KP, Li Y, Castel LD, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol*. 2005;16:579–84.
32. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer*. 2000;88:1082–90.
33. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol*. 1998;16:593–602.
34. Lipton A. Bisphosphonate therapy in the oncology setting. *Expert Opin Emerg Drugs*. 2003;8:469–88.
35. Delea TE, McKiernan J, Brandman J, et al. Impact of skeletal complications on total medical care costs among patients with bone metastases of lung cancer. *J Thorac Oncol*. 2006;1:571–6.
36. Delea TE, McKiernan JM, Brandman J, Sung J, Raut M, Oster G. Effects of skeletal complications on total medical care costs in patients with bone metastases of solid tumors [abstract]. *J Clin Oncol*. 2005; 23(suppl):752s. Abstract 8094.
37. Lage MJ, Barber BL, Harrison DJ, Jun S. The cost of treating skeletal-related events in patients with prostate cancer. *Am J Manag Care*. 2008;14:317–22.
38. McKiernan JM, Delea TE, Liss M, et al. Impact of skeletal complications on total medical care costs in prostate cancer patients with bone metastases [abstract]. *Proc Am Soc Clin Oncol*. 2004;22(suppl):531. Abstract 6057.
39. Felix J, Andreozzi V, Soares M, et al. Direct hospital costs of skeletal-related events (SRE) in Portuguese patients (pts) with breast cancer (BC) and bone metastases [abstract]. *J Clin Oncol*. 2007;25(suppl): 679s. Abstract 17084.
40. Delea T, Langer C, McKiernan J, et al. The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer. *Oncology*. 2004;67:390–6.
41. Botteman M, Barghout V, El Ouagari K. Cost-effectiveness of zoledronic acid vs. pamidronate in the management of hormone refractory prostate cancer (HRPC) patients with bone metastases [abstract]. *J Clin Oncol*. 2006;24(suppl):649s. Abstract 14660.
42. Stephens JM, Aapro MS, Botteman MF, Hay JW, Brandman J. A Markov model to evaluate the cost effectiveness of intravenous (IV) zoledronic acid vs IV generic pamidronate or oral ibandronate in the prevention of bone complications in breast cancer patients with bone metastases [abstract]. *J Clin Oncol*. 2005;23(suppl):44s. Abstract 664.

43. Botteman MF, Aapro MS, Hay JW, Stephens JM, Brandman J. Cost effectiveness of intravenous (IV) zoledronic acid vs other IV bisphosphonates for the prevention of bone complications in breast cancer patients with bone metastases: a Markov model from the UK perspective [abstract]. *J Clin Oncol*. 2005;23(suppl):58s. Abstract 721.
44. Botteman MF, Foley I, Marfatia AA, Brandman J, Langer CJ. Economic value of zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer: the case of the United Kingdom (UK) [abstract]. *J Clin Oncol*. 2007;25(suppl):351s. Abstract 6617.
45. Botteman M, Barghout V, Stephens J, Hay J, Brandman J, Aapro M. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. *Ann Oncol*. 2006;17: 1072–82.
46. Botteman M, Kaura S, Stephens J, Foley I, Chen Y. Cost effectiveness of zoledronic acid in the prevention of skeletal related events in renal cell carcinoma patients with bone metastases: an exploratory analysis for France [abstract]. *J Clin Oncol*. 2008;26(suppl):677s. Abstract 16085.
47. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer*. 2007;110:1860–7.
48. DePuy V, Anstrom KJ, Castel LD, Schulman KA, Weinfurt KP, Saad F. Effects of skeletal morbidities on longitudinal patient-reported outcomes and survival in patients with metastatic prostate cancer. *Support Care Cancer*. 2007;15:869–76.
49. Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. *Oncologist*. 2004;9(suppl 4): 28–37.
50. Major PP, Lipton A, Berenson J, Hortobagyi G. Oral bisphosphonates: a review of clinical use in patients with bone metastases. *Cancer*. 2000; 88:6–14.
51. Petrut B, Trinkaus M, Simmons C, Clemons M. A primer of bone metastases management in breast cancer patients. *Curr Oncol*. 2008;15(suppl 1):S50–S57.
52. Adachi J, Lynch N, Middelhoven H, Hunjan M, Cowell W. The association between compliance and persistence with bisphosphonate therapy and fracture risk: a review. *BMC Musculoskelet Disord*. 2007;8:97.
53. Hoer A, Gol D, Schiffhorst G, Brandman J, Haussler B. Rates and determinants of patient persistency with oral bisphosphonates in cancer patients [abstract]. *Support Care Cancer*. 2005;13:428. Abstract 407–057.
54. Berenson J, Hirschberg R. Safety and convenience of a 15-minute infusion of zoledronic acid. *Oncologist*. 2004;9:319–29.
55. Maxwell C, Swift R, Goode M, Doane L, Rogers M. Advances in supportive care of patients with cancer and bone metastases: nursing implications of zoledronic acid. *Clin J Oncol Nurs*. 2003;7:403–8.
56. Hatoum HT, Lin SJ, Smith MR, Barghout V, Lipton A. Zoledronic acid and skeletal complications in patients with solid tumors and bone metastases: analysis of a national medical claims database. *Cancer*. 2008;113:1438–45.
57. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J*. 2001;7:377–87.
58. Rosen LS, Gordon DH, Dugan W Jr, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer*. 2004;100:36–43.
59. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol*. 2005;23:3314–21.
60. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med*. 1996;335:1785–91.
61. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol*. 1998; 16:2038–44.
62. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol*. 2003;14:1399–405.
63. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain*. 2004;111:306–12.
64. Kristensen B, Ejlertsen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med*. 1999;246:67–74.
65. Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol*. 1993;11:59–65.
66. Tubiana-Hulin M, Beuzeboc P, Mauriac L, et al. [Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases]. *Bull Cancer*. 2001;88:701–7.
67. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev*. 2005:CD003474.
68. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs. hospital bisphosphonate administration. *Br J Cancer*. 2005;92:1869–76.
69. Smith JA Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol*. 1989;141:85–7.
70. Strang P, Nilsson S, Brandstedt S, et al. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Res*. 1997;17:4717–21.
71. Kylmala T, Taube T, Tammela TL, Risteli L, Risteli J, Elomaa I. Concomitant i.v. and oral clodronate in the relief of bone pain—a double-blind placebo-controlled study in patients with prostate cancer. *Br J Cancer*. 1997;76:939–42.
72. Elomaa I, Kylmala T, Tammela T, et al. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostatic cancer. *Int Urol Nephrol*. 1992;24:159–66.
73. Ernst DS, Tannock IF, Winquist EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol*. 2003;21:3335–42.
74. Dearnaley DP, Sydes MR, Mason MD, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst*. 2003;95:1300–11.
75. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol*. 2003;21:4277–84.
76. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94:1458–68.
77. Saad F. Treatment of bone complications in advanced prostate cancer: rationale for bisphosphonate use and results of a phase III trial with zoledronic acid. *Semin Oncol*. 2002;29(suppl 21):19–27.
78. Weinfurt KP, Anstrom KJ, Castel LD, Schulman KA, Saad F. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. *Ann Oncol*. 2006;17:986–9.
79. Hirsh V, Major PP, Lipton A, et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. *J Thorac Oncol*. 2008;3:228–36.
80. Saad F, Lipton A. Zoledronic acid is effective in preventing and delaying skeletal events in patients with bone metastases secondary to genito-urinary cancers. *BJU Int*. 2005;96:964–9.
81. Rosen L, Harland SJ, Oosterlinck W. Broad clinical activity of zoledronic acid in osteolytic to osteoblastic bone lesions in patients with a broad range of solid tumors. *Am J Clin Oncol*. 2002;25(suppl 1):S19–S24.

82. Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst*. 2005;97:59–69.
83. Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol*. 2005; 23:4925–35.
84. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer*. 2008;113:193–201.
85. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol*. 2003;21:3150–57.
86. Lipton A. The safety of zoledronic acid. *Expert Opin Drug Saf*. 2007;6:305–13.
87. Berenson JR. Recommendations for zoledronic acid treatment of patients with bone metastases. *Oncologist*. 2005;10:52–62.
88. Weitzman R, Sauter N, Eriksen EF, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients—May 2006. *Crit Rev Oncol Hematol*. 2007;62:148–52.
89. Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*. 2008;23:826–36.
90. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol*. 2005;23:8580–7.
91. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006;144:753–61.
92. McArthur HL, Estilo C, Huryn J, et al. Osteonecrosis of the jaw (ONJ) among intravenous (IV) bisphosphonate- and/or bevacizumab-treated patients (pts) at Memorial Sloan-Kettering Cancer Center (MSKCC). *J Clin Oncol*. 2008;26(suppl):523s. Abstract 9588.
93. Aragon-Ching JB, Ning YM, Chen CC, et al. Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. *Cancer Invest*. 2009;27:221–6.
94. Dimopoulos MA, Kastritis E, Bamia C, et al. Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Ann Oncol*. 2009;20:117–20.
95. Ripamonti CI, Maniezzo M, Campa T, et al. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. *Ann Oncol*. 2009;20:137–45.
96. Green JR. Antitumor effects of bisphosphonates. *Cancer*. 2003; 97(suppl):840–7.
97. Matsumoto S, Kimura S, Segawa H, et al. Efficacy of combining the third generation bisphosphonate, zoledronate with imatinib mesylate in suppressing small cell lung cancer cell line proliferation [abstract]. *Proc Am Soc Clin Oncol*. 2003;22(suppl):684. Abstract 2750.
98. Berger W, Kubista B, Elbling L, Sutterluty H, Micksche M. The N-containing bisphosphonate zoledronic acid exerts potent anticancer activity against non-small cell lung cancer cells by inhibition of protein geranylgeranylation [abstract]. *Proc Am Assoc Cancer Res*. 2005; 46:1176c. Abstract 4981.
99. Winter MC, Holen I, Coleman RE. Exploring the anti-tumour activity of bisphosphonates in early breast cancer. *Cancer Treat Rev*. 2008; 34:453–75.
100. Soltau J, Zirrgiebel U, Esser N, et al. Antitumoral and antiangiogenic efficacy of bisphosphonates in vitro and in a murine RENCA model. *Anticancer Res*. 2008;28:933–41.
101. Koizumi M, Nakaseko C, Ohwada C, et al. Zoledronate has an antitumor effect and induces actin rearrangement in dexamethasone-resistant myeloma cells. *Eur J Haematol*. 2007;79:382–91.
102. Pandha H, Birchall L, Meyer B, et al. Antitumor effects of aminobisphosphonates on renal cell carcinoma cell lines. *J Urol*. 2006;176: 2255–61.
103. Santini D, Caraglia M, Vincenzi B, et al. Mechanisms of disease: preclinical reports of antineoplastic synergistic action of bisphosphonates. *Nat Clin Pract Oncol*. 2006;3:325–38.
104. Lipton A. Emerging role of bisphosphonates in the clinic—antitumor activity and prevention of metastasis to bone. *Cancer Treat Rev*. 2008;34(suppl 1):S25–S30.
105. Gjyrezi A, O'Brate A, Chanel-Vos C, Giannakakou P. Zoledronic acid synergizes with Taxol in an HDAC6-dependent manner: novel mechanistic implications for combination anticancer therapy with taxanes [abstract]. *Proc Am Assoc Cancer Res*. 2007. Abstract 1425.
106. Ozturk OH, Bozcuk H, Burgucu D, et al. Cisplatin cytotoxicity is enhanced with zoledronic acid in A549 lung cancer cell line: preliminary results of an in vitro study. *Cell Biol Int*. 2007;31:1069–71.
107. Croucher PI, De Hendrik R, Perry MJ, et al. Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma bone disease: evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival. *J Bone Miner Res*. 2003;18: 482–92.
108. Li YY, Chang JW, Chou WC, et al. Zoledronic acid is unable to induce apoptosis, but slows tumor growth and prolongs survival for non-small-cell lung cancers. *Lung Cancer*. 2008;59:180–91.
109. Ory B, Heymann MF, Kamijo A, Gouin F, Heymann D, Redini F. Zoledronic acid suppresses lung metastases and prolongs overall survival of osteosarcoma-bearing mice. *Cancer*. 2005;104: 2522–9.
110. Hiraga T, Williams PJ, Ueda A, Tamura D, Yoneda T. Zoledronic acid inhibits visceral metastases in the 4T1/luc mouse breast cancer model. *Clin Cancer Res*. 2004;10:4559–67.
111. Matsumoto S, Kimura S, Segawa H, et al. Efficacy of the third-generation bisphosphonate, zoledronic acid alone and combined with anti-cancer agents against small cell lung cancer cell lines. *Lung Cancer*. 2005;47:31–9.
112. Landmeier S, Altvater B, Pscherer S, et al. Presentation of Epstein Barr virus (EBV) epitopes by activated human γδ T cells induces peptide-specific cytolytic CD8+ T cell expansion [abstract]. *Blood*. 2006;108. Abstract 1738.
113. Fournier PG, Chirgwin JM, Guise TA. New insights into the role of T cells in the vicious cycle of bone metastases. *Curr Opin Rheumatol*. 2006;18:396–404.
114. Sato K, Kimura S, Segawa H, et al. Cytotoxic effects of gammadelta T cells expanded ex vivo by a third generation bisphosphonate for cancer immunotherapy. *Int J Cancer*. 2005;116:94–9.
115. Zaghloul MS, Boutrus R, El-Hosieny H, A-Kader Y, El-Attar I, Nazmy M. A controlled prospective randomized placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer patients. *J Clin Oncol*. 2008;26(suppl):257s. Abstract 5033.
116. Aviles A, Nambo MJ, Neri N, Castaneda C, Cleto S, Huerta-Guzman J. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Med Oncol*. 2007;24:227–30.
117. Mystakidou K, Katsouda E, Parpa E, Kelekis A, Galanos A, Vlahos L. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. *Med Oncol*. 2005;22:195–201.
118. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009;360:679–91.
119. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist*. 2008;13:503–14.

120. Frassoldati A, Brufsky A, Bundred N, et al. The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 24-month integrated follow-up of the Z-FAST and ZO-FAST trials [poster]. Presented at: 33rd Congress of the European Society for Medical Oncology; September 12–16, 2008; Stockholm, Sweden. Abstract 185PD.
121. Eidtmann H, Bundred NJ, De Boer R, et al. The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving letrozole: 36 months follow-up of ZO-FAST [abstract]. Presented at: 31st Annual San Antonio Breast Cancer Symposium; December 10–14, 2008; San Antonio, TX. Abstract 44.
122. Winter MC, Thorpe HC, Burkinshaw R, Beevers SJ, Coleman RE. The addition of zoledronic acid to neoadjuvant chemotherapy may influence pathological response—exploratory evidence for direct anti-tumor activity in breast cancer [poster]. Presented at: 31st Annual San Antonio Breast Cancer Symposium; December 10–14, 2008; San Antonio, TX. Abstract 5101.
123. Burkinshaw R, Winter M, Thorpe H, Pedlar J, Coleman R. Osteonecrosis of the jaw and dental related adverse events during adjuvant therapy for early breast cancer: initial dental safety findings from the AZURE study [abstract]. *Cancer Treat Rev*. 2008;34(suppl): S75–S76. Abstract P53.
124. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–17.
125. U.S. National Institutes of Health. Clodronate with or without chemotherapy and/or hormonal therapy in treating women with stage I or stage II breast cancer [trial registry]. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00009945?term=nsabp+34&rank=1. Accessed February 23, 2009.
126. James ND, Sydes MR, Clarke NW, et al. Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multi-stage randomized controlled trial. *BJU Int*. 2009;103:464–9.
127. International Standard Randomised Controlled Trial Number Register. Effectiveness of Zometa® treatment for the prevention of bone metastases in high risk prostate cancer patients: a randomised, open-label, multicentre study of the European Association of Urology (EAU) in Cooperation with the Scandinavian Prostate Cancer Group (SPCG) and the Arbeitsgemeinschaft Urologische Onkologie (AUO) [trial registry]. Available at: http://www.controlled-trials.com/ISRCTN66626762/zeus. Accessed February 23, 2009.
128. U.S. National Institutes of Health. RADAR trial—randomized androgen deprivation and radiotherapy [trial registry]. Available at: http://clinicaltrials.gov/ct2/show/NCT00193856. Accessed February 23, 2009.
129. U.S. National Institutes of Health. A study to evaluate the safety and efficacy of zoledronic acid in the prevention or delaying of bone metastasis in patients with stage IIIA and IIIB non-small cell lung cancer [trial registry]. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00172042. Accessed February 23, 2009.