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Optimizing Clinical Benefits of Bisphosphonates in Cancer Patients with Bone Metastases

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Key Words. Bisphosphonates • Neoplasm metastasis • Skeleton • Therapeutics

Disclosures: Matti Aapro: *Consultant/advisory role:* Novartis (zoledronic acid), Roche (ibandronate), Schering (clodronate), Amgen (denosumab); **Fred Saad:** *Consultant/advisory role:* Novartis (zoledronic acid), Amgen (denosumab); *Honoraria:* Novartis (zoledronic acid); *Research funding/contracted research:* Novartis (zoledronic acid); **Luis Costa:** *Consultant/advisory role:* Novartis (speakers' bureau, zoledronic acid), Amgen (denosumab).

The article discusses the best and safe use of various bisphosphonates used in the treatment of bone metastases from solid tumors.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Bisphosphonates are important treatments for bone metastases. Considerations for optimizing the clinical benefits of bisphosphonates include efficacy, compliance, and safety. Several bisphosphonates are approved for clinical use; however, few have demonstrated broad efficacy in the oncology setting and been compared directly in clinical trials. Among patients with bone metastases from breast cancer, the efficacy of approved bisphosphonates was evaluated in a Cochrane review, showing a reduction in the risk of skeletal-related events (SREs) ranging from 8% to 41% compared with placebo. Between-trial comparisons are confounded by inconsistencies in trial design, SRE definition, and endpoint selection. Zoledronic acid has demonstrated clinical benefits beyond those of pamidronate in a head-to-head trial that included patients with breast cancer or multiple myeloma. Compliance and adherence also have effects on treatment efficacy. In a comparison study, the adherence rates with oral bisphosphonates were found to be significantly lower compared with those of intravenous bisphosphonates. The safety profiles of oral and intravenous bisphosphonates differ. Oral bisphosphonates are associated with gastrointestinal side effects, whereas intravenous bisphosphonates have dose- and infusion rate–dependent effects on renal function. Osteonecrosis of the jaw is an uncommon but serious event in patients receiving monthly intravenous bisphosphonates or denosumab. The incidence of this event can be reduced with careful oral hygiene. A positive benefit-risk ratio for bisphosphonates has been established, and ongoing clinical trials will determine whether individualized therapy is possible. ***The Oncologist*** 2010; 15:1147–1158

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INTRODUCTION

Malignant bone disease is common in patients with advanced solid tumors or multiple myeloma. Among patients with lung cancer, bladder cancer, or melanoma, approximately 40% develop bone metastases during the course of their disease [1]. Breast cancer (BC) and prostate cancer (PC) have an especially high potential for metastasis to bone, which occurs in approximately 75% of patients with stage IV disease [1]. Because these patients may have a median survival of several years after the development of bone metastases, they have a long-term risk of developing skeletal-related events (SREs) including pathologic fractures, spinal cord compression, the requirement for surgery (including vertebroplasty, kyphoplasty, and cementoplasty) or radiotherapy to bone, and hypercalcemia of malignancy. Indeed, in the absence of bone-specific therapies, SREs occur in 46%–68% of patients with bone metastases from solid tumors, and patients may experience multiple SREs [2–4]. Furthermore, the risk of subsequent SREs increases after the first SRE [5, 6]. These SREs can have negative consequences for patients' functional independence. Among men with PC and women with BC, there are consistent decreases in physical and emotional well-being after SREs [7, 8]. Moreover, in patients with PC or BC, pathologic fractures have been associated with reduced survival [9]. Therefore, prevention of SREs is an important therapeutic goal.

In recent years, treatment innovations have significantly extended survival, even for patients with stage III or IV lung cancer and castration-resistant PC [10, 11]. However, prolonging survival may increase the likelihood that cancer and its treatment effects on the skeleton will manifest in skeletal morbidity within patients' lifetimes. Therefore, an important goal of therapy is to preserve patients' bone health, thereby preserving their functional independence to the extent possible throughout the course of the disease. The therapeutic repertoire for managing skeletal morbidity and slowing the erosion in quality of life includes analgesics, radiotherapy, surgery, and bisphosphonates. Bisphosphonates can reduce bone pain, analgesic use, and need for radiation to bone [12]. However, bisphosphonates also treat the underlying cause of SREs—malignant osteolysis—and can therefore delay the onset and reduce the incidence of SREs [13, 14]. Although several bisphosphonates are approved for clinical use, relatively few have demonstrated efficacy for broad application in the oncology setting, and the majority of bisphosphonates are approved only for use in BC metastatic to bone (Figure 1). Moreover, few of these agents have been compared directly in clinical trials, and between-trial comparisons are confounded by inconsistencies in trial design, SRE definition, and endpoint selection. In optimizing the clinical benefits of bisphosphonates, important considerations for bisphosphonate selection include not only efficacy but also safety profiles and compliance.

	Indication				
	HCM	Breast cancer	Multiple myeloma	Prostate cancer	Other solid tumors
Clodronate (oral)	■	■	■		
Pamidronate (IV)	●	●	●		
Zoledronic acid (IV)	●	●	●	●	●
Ibandronate (oral)	■	■			

■ = European registration
● = Global registration

Figure 1. Approved bisphosphonate indications in the oncology setting. Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous. (Note: In the United States, prostate cancer must have progressed despite hormone therapy.)

EFFICACY OF BISPHOSPHONATES

Bisphosphonates have been recommended for the treatment of primary bone lesions from multiple myeloma or bone metastases from solid tumors [15–18]. Although bisphosphonates are administered systemically, they are deposited at sites of active bone remodeling. Bisphosphonates accumulate in the bone and are ingested by osteoclasts during bone resorption, wherein they inhibit osteolysis [19]. There are two classes of bisphosphonates with different mechanisms of action: non–nitrogen-containing and nitrogen-containing [19]. Non–nitrogen-containing bisphosphonates such as clodronate are metabolized by osteoclasts to cytotoxic compounds. Nitrogen-containing bisphosphonates such as zoledronic acid, pamidronate, and ibandronate inhibit a key enzyme in the mevalonate pathway, inducing apoptosis of osteoclasts. Both classes are currently used for the treatment of bone metastases in patients with cancer. Clinical trials providing evidence for the efficacy of these agents have used similar definitions of skeletal morbidity, but not all trials have selected robust clinical endpoints that provide objective and quantitative measurements of patient benefit. For example, pain scores, analgesic use, and quality of life associated with bone metastases are difficult to objectively measure and may be confounded by observer bias [6]. These clinical endpoints are, therefore, not easily comparable in different patient populations. In contrast, SREs can be objectively measured and provide clinically relevant information for the evaluation of bisphosphonates. Indeed, the SRE has been used as an example of a clinically relevant composite endpoint by the U.S. Food and Drug Administration (FDA) [20]. However, the definition for SREs has varied. Skeletal morbidity rate ([SMR] mean SRE rate per person-year) is a less robust endpoint in clinical trials because it assumes a constant event rate for all patients and cannot adjust for inter- and intrapatient variations in SRE

rates over the course of disease progression [6]. Different statistical models, based on various statistical assumptions, have been used in clinical trials, including multiple event analyses such as Andersen-Gill that provide robust methodology for reporting treatment effects by adjusting for variability in event rates over time [6].

Breast Cancer

Guidelines from the American Society of Clinical Oncology (ASCO) recommend intravenous pamidronate or zoledronic acid in patients with bone metastases from BC, the only two agents approved for that indication in the United States [17]. Both have produced significant reductions in the risk of SREs compared with placebo in this setting [2, 21]. In the only head-to-head phase III trial of bisphosphonates in this setting, 4 mg of zoledronic acid demonstrated efficacy at least comparable to and some significant benefits beyond those of 90 mg of pamidronate in patients with bone lesions from multiple myeloma or BC [22, 23]. In the subset of patients with BC, Andersen-Gill multiple event analysis revealed that zoledronic acid reduced the risk of developing SREs by an additional 20% compared with pamidronate ($p = .025$) [3, 4, 23, 24]. The efficacy of bisphosphonates in patients with BC was also evaluated in a Cochrane review, which confirmed the utility of this class of agents to prevent SREs from bone metastases and reported a range of SRE risk reductions for bisphosphonates [25]. Versus placebo, reported risk reductions were 41% for intravenous zoledronic acid, 23% for intravenous pamidronate, and 18% and 14% for intravenous and oral ibandronate, respectively. The risk reduction with oral ibandronate fell short of statistical significance, as did the risk reduction with oral clodronate in most of the cited studies. However, differences in patient populations, trial designs, SRE definitions, and endpoint selection confound any between-trial comparisons. Overall, these data indicate a benefit for all approved agents.

Among the oral bisphosphonates studied in patients with bone metastases from BC, there was a significant reduction in the skeletal morbidity period rate (number of 12-week periods with new SREs) with ibandronate versus placebo; however, this assessment cannot be compared with SMR endpoints [26]. The remaining two clinical endpoints, proportion of patients with an SRE and time to first SRE, were not significantly different between oral ibandronate and placebo (Table 1) [2, 21, 25–28]. Oral clodronate has also demonstrated benefits in patients with metastatic BC. Efficacy results for the prevention of SREs, however, have been inconsistent between studies, especially with regard to bone pain endpoints and incidence of radiotherapy to bone [25, 28–30]. In a comparison study, intravenous pamidronate was found to be more effective than oral clodronate in improving pain scores ($p < .05$) [31].

Prostate Cancer

Among patients with bone metastases from PC, zoledronic acid is the only bisphosphonate to provide statistically significant and durable reductions in the risk of SREs versus placebo in a randomized, controlled trial and to have received widespread regulatory approval. In the phase III trial, patients with bone metastases from PC ($N = 643$) were randomized to receive either zoledronic acid or placebo for up to 2 years [4, 32]. At 24 months compared with placebo, zoledronic acid significantly reduced the proportion of patients with an SRE (49% versus 38%, respectively; $p = .028$) and the SMR (1.47 versus 0.77 SREs per year, respectively; $p = .005$), and increased mean time to first SRE (321 versus 488 days, respectively; $p = .009$) [4]. Zoledronic acid also reduced the risk of SREs by 36% versus placebo (Andersen-Gill multiple event analysis; $p = .002$) [3, 4, 23, 24]. Moreover, zoledronic acid provided long-term reductions in bone pain versus placebo ($p < .05$ at 21 and 24 months [33]. In contrast, in randomized, placebo-controlled trials, pamidronate and clodronate failed to demonstrate significant benefits in these endpoints versus placebo [34]. Similar results have been reported for oral clodronate [35].

Other Solid Tumors

Zoledronic acid has been shown to reduce SREs in patients with bone metastases from lung cancer, kidney cancer, and a broad range of other solid tumors. In the phase III trial, patients with lung cancer or other solid tumors ($N = 773$) were randomized to receive either zoledronic acid or placebo for up to 21 months [3]. At 21 months, 4 mg of zoledronic acid reduced the proportion of patients who developed an on-study SRE including hypercalcemia of malignancy (39% versus 48% with placebo; $p = .039$), significantly delayed the time to first SRE (236 days versus 155 days with placebo; $p = .009$), and reduced the SMR (1.74 versus 2.71 SREs per year with placebo; $p = .012$). In an Andersen-Gill analysis, zoledronic acid significantly reduced the risk of SREs by 31% compared with placebo ($p = .003$) [3, 4, 23, 24]. In a retrospective subset analysis from this trial of patients with renal cell carcinoma ($n = 74$), zoledronic acid significantly reduced the proportion of patients with an SRE at 9 months (37% versus 74% for placebo; $p = .015$) and significantly prolonged the time to first SRE (median not reached versus 72 days for placebo; $p = .006$) [36]. Multiple event analysis also demonstrated that zoledronic acid reduced the risk of SREs by 61% versus placebo ($p = .008$) [36]. Such randomized placebo-controlled data have not been reported for other bisphosphonates.

Table 1. Efficacy of bisphosphonates in placebo-controlled studies of patients with breast cancer

	Agent versus placebo (p)				
	IV zoledronic acid 4 mg [21]	**IV pamidronate 90 mg [2]**	**IV ibandronate 6 mg [27]**	**Oral ibandronate 50 mg [26]**	**Oral clodronate 1,600 mg [25,28][d]**
Randomized patients, n[a]	228	754	312	564	185
Endpoint					
Patients with ≥ 1 SRE, %	30.7 versus 52.2 (.001)	53 versus 68 (<.001)	50.6 versus 62.0 (.052)	45.3 versus 52.2 (.122)	
Time to first SRE	NR versus 360 days (.004)	12.7 versus 7.0 mo (<.001)	50.6 versus 33.1 wk (.018)	90.3 versus 64.9 wk (.089)	9.9 versus 4.9 mo (.022)
Skeletal morbidity rate		2.5 versus 4.0 (<.001)[c]			218.6 versus 304.8/100 patient-years (<.001)
SRE rate ratio[b]	0.57 (.016)[c]				
Skeletal morbidity period rate			1.19 versus 1.48 (.004)[c]	0.95 versus 1.18 (.004)[c]	
Multiple event analysis, RR	0.56; 95% CI: 0.363, 0.867; (.009)				
Poisson regression analysis, HR				0.62; 95% CI: 0.48, 0.79; (<.001)	

IV bisphosphonates were administered every 3–4 weeks, and oral bisphosphonates are administered daily.
[a]The randomized patients are for indicated arm and placebo.
[b]SRE rate in the zoledronic acid group/SRE rate in the placebo group.
[c]Primary endpoint.
[d]Primary endpoint was proportion of patients who experienced one or more of the following: hypercalcemia, vertebral or nonvertebral fracture, and requirement for radiotherapy for bone pain.
Abbreviations: CI, confidence interval; HR, hazard ratio; IV, intravenous; NR, not reached; RR, relative risk; SRE, skeletal-related event (pathologic fractures, spinal cord compression, requirement for surgery or radiotherapy to bone, and hypercalcemia of malignancy).

Importance of Early Treatment with Bisphosphonates

Bone pain is usually the earliest and most common symptom of bone metastases, and bone metastases often are not diagnosed until after the onset of bone pain [37]. However, bone pain can have debilitating effects on a patient's quality of life, and treatment after pain develops may not be the optimal strategy. Therefore, identification of patients at risk for bone metastases, earlier diagnosis, and earlier treatment for bone metastases may be more beneficial.

In the adjuvant BC setting, aromatase inhibitor (AI) use is increasing, and AIs have been associated with accelerated bone loss and increased fracture risk [38]. In fact, bone loss associated with AIs may occur at a twofold higher rate than that observed in healthy postmenopausal women (PMW) [39]. Among the oral bisphosphonates, 3 years of clodronate, 1,600 mg/day, reduced treatment-induced bone loss of the lumbar spine in 73 patients with BC compared with control [40]. Risedronate, 35 mg once weekly for 24 months, stabilized bone mineral density (BMD) at the hip from baseline and curtailed spinal BMD loss versus placebo (2.8% versus 4.8%, respectively, from baseline) in PMW with BC receiving an AI [41]. In another study with cyclic risedronate (30 mg/day for 2 weeks followed by 10 weeks of no drug) for 2 years in patients with BC and treatment-induced menopause, risedronate increased BMD versus placebo ($p \leq .041$ for both) [42]. However, weekly risedronate failed to prevent lumbar spine BMD loss in patients with BC [43]. Ibandronate, 150 mg/day, increased BMD from baseline in osteopenic PMW with BC receiving anastrozole ($n = 50$) during 2 years of treatment [44]. Intravenous pamidronate (60 mg every 3 months) inhibited bone loss versus placebo in 40 premenopausal women for 1 year but did not improve BMD versus baseline [45]. Intravenous zoledronic acid (4 mg every 6 months) for 3 years stabilized BMD in premenopausal women with BC treated with endocrine therapy ($n = 404$) [46]. At the 5-year follow-up, BMD continued to decrease with placebo, whereas it continued to increase versus baseline with zoledronic acid. In another study with immediate or delayed treatment with zoledronic acid, 4 mg biannually, for 5 years in patients with BC receiving letrozole, immediate zoledronic acid increased BMD at 12 months compared with delayed treatment ($p <$ .0001 for both) [47]. Therefore, bisphosphonates can reduce cancer treatment–associated bone loss in BC patients, and

there are similar data for BMD preservation during androgen-deprivation therapy (ADT) for PC, although no treatments are currently approved in the United States or Europe for these specific indications [48–51].

Guidelines have been published regarding the use of bisphosphonates in BC. One expert panel recommends that bisphosphonate therapy should be started in any patient initiating or receiving AI therapy with a T-score less than −2.0 or if other risk factors are present [52]. A British expert panel recommended bisphosphonate therapy in women experiencing premature menopause receiving AIs if the annual rate of bone loss exceeds 4% at lumbar spine or total hip sites, or if there is a history of vertebral fracture or T-score less than −1.0 [53]. The recommendations for PMW were similar, but the T-score threshold was reduced to less than −2.0. An international expert panel made similar recommendations, but also recommended amino-bisphosphonates for patients with bone metastases from BC, and zoledronic acid for patients with bone metastases from other solid tumors [54].

In exploratory analyses of the phase III trials, zoledronic acid produced a more profound reduction versus placebo in patients with PC or versus pamidronate in patients with BC in the proportion of patients with one or more SREs and in patients with no pain at baseline compared with patients with pain at baseline [55, 56]. Moreover, zoledronic acid also reduced the SMR by a greater extent in patients with PC and no pain at baseline (49%) compared with patients who had pain at baseline (39%) [56]. Among patients with BC and no prior fractures at baseline, zoledronic acid reduced the SMR by a greater extent compared with patients who had a prior fracture at baseline (by 0.33 and 0.78, respectively) [21].

Pain levels often increase during disease progression and may indicate advancing bone disease. A greater number of bone metastases results in an increased risk of SREs. Indeed, patients with solid tumors and more than three bone metastases have an approximately 1.5-fold increase in the risk of SREs [57]. Furthermore, after patients experience SREs, they are at a higher risk of subsequent SREs. Among patients with bone metastases from BC, a first SRE increases the risk of a subsequent SRE twofold [58]. Moreover, pathologic fractures increase risk of death by 23%–32% in patients with bone metastases from PC or BC, respectively [9].

Bisphosphonates may have effects beyond bone health. Preclinical results demonstrated that zoledronic acid, pamidronate, clodronate, and ibandronate exhibit antitumor activity in BC cell lines and animal models of early BC disease [59, 60]. However, clinical studies have yielded mixed results. Two studies suggest a survival benefit for patients receiving clodronate as adjuvant therapy for breast cancer [61, 62]. However, a meta analysis of seven clinical studies evaluating oral clodronate (1,600 mg/day for 2–3 years) versus placebo or no additional treatment found no significant difference in overall survival or bone-metastasis–free survival in patients with either early or advanced BC [63]. Pamidronate, 90 mg every 4 weeks, has shown similar results versus placebo in patients with advanced BC [64, 65]. Overall disease benefits have not been reported with ibandronate. Zoledronic acid reduced the risk of disease progression (hazard ratio [HR] = 0.64; 95% confidence interval [CI]: 0.46, 0.91; $p = .01$) and produced a trend toward reduced risk of death (HR = 0.60; 95% CI: 0.32; 1.11; $p = .11$) versus no zoledronic acid in premenopausal patients receiving endocrine therapy for early BC [66]. A recent exploratory analysis of data from three companion studies of zoledronic acid in combination with adjuvant letrozole therapy in postmenopausal women with early BC shows significantly improved disease-free survival in the ZO-FAST study [67], but no clear benefit in the other two studies [68]. This is primarily a result of the low rates of disease recurrence, differences in the length of follow-up, and lack of follow-up after discontinuation in one study, among other confounding factors. Results from these and other clinical trials indicating that the antitumor effects of bisphosphonates may translate into clinical benefits have been recently reviewed [69].

Clinical Benefits of Continuing Bisphosphonate Treatment in Cancer Patients with Bone Metastases

Data from the placebo-controlled arms of bisphosphonate trials have revealed that patients are at risk for SREs throughout the course of their advanced disease and that long-term treatment may therefore be needed [3, 4, 23]. However, results from bisphosphonate studies that focus on clinical benefits that may occur after the first years of treatment are scarce. Intravenous ibandronate (6 mg every 3–4 weeks for up to 2 years) in patients with bone metastases from BC has significantly reduced the mean number of new SREs by 38% ($p = .032$) and significantly increased the time to a first new SRE ($p = .018$) compared with placebo [27]. However, this trial did not assess the possible benefits of ibandronate during the second year of treatment separately and, therefore, presents a limitation on assessing the clinical benefits beyond the first year. Intravenous pamidronate (90 mg every 3–4 weeks for up to 2 years) significantly reduced the incidence and delayed the onset of SREs compared with placebo in patients with bone metastases from BC, but the same assessment limitation as in the ibandronate study is present [2]. Exploratory analyses of the

zoledronic acid database from the phase III efficacy trial of PC demonstrated that the risk of SREs in patients with PC receiving zoledronic acid during months 16 to 24 was significantly reduced by 53% compared with the placebo group (HR = 0.467; $p = .022$) [70]. This risk reduction was greater than that observed during the first 15 months of the study (HR = 0.643; $p = .004$). During months 16 to 24 of treatment, zoledronic acid also continued to provide significant reductions in proportion of patients with an SRE ($p = .017$), time to first SRE ($p = .036$), and SMR ($p = .016$) compared with placebo [70]. Exploratory analyses of the subset of patients with bone metastases from BC who entered the second year of treatment demonstrated that zoledronic acid significantly reduced the risk of developing an SRE by an additional 41% compared with pamidronate ($p = .026$) during the second year of treatment [71]. During the second year of therapy, zoledronic acid also continued to provide reductions in the proportion of patients with an SRE ($p = .072$), time to first SRE ($p = .067$), and SMR ($p = .058$) compared with pamidronate [71].

Bisphosphonate treatment continues to provide clinical benefits after a patient experiences an SRE, as shown by further exploratory analyses. A multiple event analysis of data from patients with PC receiving zoledronic acid showed that when the first SRE is excluded, there is a greater risk reduction of subsequent SREs compared with the placebo group (HR = 0.601; $p = .011$) [70]. Zoledronic acid also significantly reduced the proportion of patients who experienced a second SRE ($p = .017$) and the SMR after excluding the first event ($p = .014$) [70]. Furthermore, the median time to a second SRE was significantly delayed among patients with PC receiving zoledronic acid compared with the placebo group ($p = .006$) [70]. Among patients with PC who had experienced an SRE before study entry, zoledronic acid, 4 mg, reduced the proportion of patients who experienced an on-study SRE (41% versus 51%, respectively; $p = .215$) and provided a significant 65% relative reduction in mean SMR compared with placebo (0.80 versus 2.30, respectively; $p = .036$) [70]. Among patients with bone lesions from multiple myeloma or bone metastases from BC, zoledronic acid produced a trend toward a lower proportion of patients who experienced a second SRE ($p = .170$) and the SMR after excluding the first event ($p = .105$) compared with pamidronate [72]. However, in the patients who had experienced an SRE before study entry, zoledronic acid significantly reduced the proportion of patients who experienced an on-study SRE compared with pamidronate (54% versus 61%, respectively; $p = .039$) and the SMR by 24% relative to pamidronate (1.22 versus 1.61; $p = .038$).

Practical Considerations of Bisphosphonate Treatment

Four parameters should be considered when selecting a bisphosphonate: efficacy, compliance, adherence, and safety. Efficacy results presented in the previous sections show that, among patients with bone metastases from BC, the approved intravenous and oral bisphosphonates all reduce the risk of SRE compared with placebo [25]. However, broad generalizations regarding the relative efficacy of bisphosphonates should be avoided because direct comparative studies between bisphosphonates (other than pamidronate versus zoledronic acid) have not been done. Among patients with PC, lung cancer, or other solid tumors, zoledronic acid is the only approved bisphosphonate for the treatment of bone metastases.

Compliance (administration regimen implemented as indicated on product label, e.g., with regard to dosing frequency), adherence (degree to which patients follow physician's advice, e.g., with regard to the duration of therapy), and convenience of administration are important considerations when selecting a bisphosphonate. For example, oral bisphosphonates may be taken at home, whereas intravenous bisphosphonates require a visit to the doctor's office or hospital. However, the tablets of oral clodronate are large and may be hard for patients to swallow, causing patients to discontinue treatment [73], but oral ibandronate tablets are smaller. Patients must also fast overnight before taking an oral bisphosphonate (because food interferes with absorption), remain upright, and continue to fast after administration from at least 30 minutes for up to 2 hours—depending on the agent—to minimize the risk of gastrointestinal adverse events [73]. The requirements for administration of oral bisphosphonates are associated with reduced compliance and may lead to reduced adherence and, therefore, to suboptimal efficacy [74, 75]. Furthermore, patient adherence with the prescribed treatment regimen cannot be adequately monitored with oral agents. A retrospective analysis of insurance claims in Germany showed that the median duration of therapy was 112 days for oral bisphosphonates [76]. After 3 months of treatment, 44% of patients had stopped therapy, and, after 6 months, 64% of patients had stopped therapy (Figure 2A) [76]. In contrast, adherence with intravenous bisphosphonates is generally high, with approximately 90% of patients remaining on treatment after 6 months (Figure 2B) [4, 23, 77]. A comparison of intravenous versus oral bisphosphonate adherence rates in patients with advanced cancer showed that at 6 months oral bisphosphonates had a significantly lower adherence rate compared with intravenous bisphosphonates (36% versus 92%; $p = .0012$) [77]. An intravenous treatment allows greater contact with healthcare providers and promotes ad-

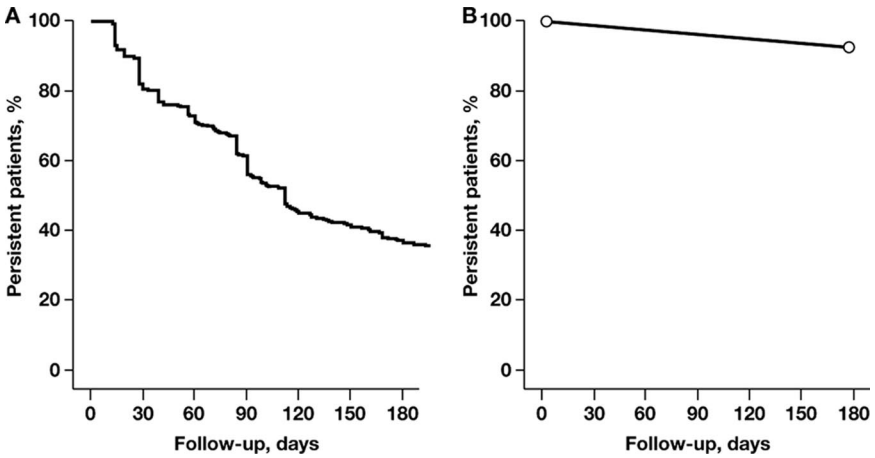

Figure 2. Adherence of approved bisphosphonate treatments by route of administration. **(A):** Oral bisphosphonates except for ibandronate. Adapted from Hoer A, Goethe H, Barghout V et al. Low persistency with oral bisphosphonates in cancer patients [poster]. Presented at: 5th European Oncology Nursing Society Spring Convention; April 20–22, 2006; Innsbruck, Austria; Abstract 2, with permission. **(B):** Intravenous bisphosphonates. Data from Mangiapane S, Hoer A, Gothe H et al. Higher persistency with i.v. bisphosphonates in patients with bone metastasis [abstract]. J Clin Oncol 2006;24(suppl):698s. Abstract 18623.

herence mostly through provider attention and proactive management. Patient adherence with an intravenous regimen is then known to the healthcare providers, and the physicians can be assured that their patients will receive the full efficacy afforded by the treatment.

Safety considerations among patients who receive oral bisphosphonates relate to gastrointestinal side effects. In clinical trials, the incidences of diarrhea, dyspepsia, nausea, and esophagitis have typically been higher in the oral bisphosphonate group compared with the placebo group [26, 73]. In contrast, safety considerations among patients who receive intravenous bisphosphonates relate to renal function, and osteonecrosis of the jaw (ONJ). All intravenous bisphosphonates are associated with dose- and infusion rate–dependent effects on renal function, and monitoring of serum creatinine levels is recommended to ensure renal safety [74]. Therefore, the product labels for zoledronic acid and pamidronate recommend checking serum creatinine levels before each infusion [78–80]. In patients with decreased renal function, the product label for zoledronic acid recommends appropriate dose modifications (Table 2) [78]. These modifications achieve the same exposure to zoledronic acid as that in patients with a creatinine clearance of 75 ml/min. Dose adjustments for patients with reduced renal function are also included in the product label for ibandronate (Table 2) [80]. Additionally, mild to moderate acute-phase reactions (flu-like symptoms) may occur, typically only after first infusion, and patients may stop treatment. However, acute-phase reactions are usually self-limited and manageable with nonsteroidal anti-inflammatory agents or acetaminophen [81].

Table 2. Recommended zoledronic acid and ibandronate dose reductions in patients with decreased renal function

Baseline creatinine clearance, ml/min	ZOL dose,[a] mg/infusion time	IBN dose,[b] mg/infusion time
>60	4.0/15 minutes	6.0/15 minutes
50–60	3.5/15 minutes	6.0/15 minutes
40–49	3.3/15 minutes	6.0/1 hour
30–39	3.0/15 minutes	6.0/1 hour
<30		2.0/1 hour

[a]Doses calculated to achieve an area under the curve of 0.66 mg-h/ml with a creatinine clearance of 75 ml/min (using Cockcroft-Gault formula). Data from zoledronic acid prescribing information [78].
[b]Administration every 3 to 4 weeks. Data from ibandronate summary of product characteristics [80].
Abbreviations: ZOL, zoledronic acid; IBN, ibandronate.

Recently, exposed bone in the jaw—ONJ—has been reported as an uncommon event among patients with cancer whose treatment includes a monthly intravenous bisphosphonate [81–88]. Furthermore, ONJ has been reported in a very small number of patients who were receiving oral bisphosphonates for noncancer indications [82, 86, 87]. In one retrospective study, in 4,835 patients with multiple myeloma, BC, or PC treated with intravenous bisphosphonates, 0.7% developed ONJ [89]. In another retrospective study of 1,338 patients with BC treated with intravenous bisphosphonates, 16 (1.2%) developed ONJ [84]. In two recent prospective studies in patients with solid tumors or

multiple myeloma ($N = 1,776$) and BC ($N = 2,046$), the incidence of ONJ in patients receiving denosumab was similar to that of patients receiving zoledronic acid (1.1% and 1.3%, respectively, in multiple myeloma or other solid tumors; 2.0% and 1.4%, respectively, in BC) [90, 91]. Identified risks for ONJ included dental extractions (HR = 53.19; $p < .0001$), treatment with zoledronic acid (HR = 15.01; $p = .0037$), and treatment with pamidronate followed by zoledronic acid (HR = 4.00; $p = .078$). Other studies have shown that dental extractions or surgery may be an inciting event for ONJ [92, 93]. Moreover, a recent study showed that preventive dental measures (such as those of Weitzman et al [94]) before the initiation of bisphosphonate treatment decrease the occurrence of ONJ (0.7% versus 3.0% for "after" versus "before" the introduction of preventive dental measures, per protocol analysis) [95]. Guidelines from recent multidisciplinary panels recommend that patients with cancer have preventive dental measures before the initiation of bisphosphonate therapy and be encouraged to maintain good oral hygiene [94, 96]. Patients may have routine dental hygiene and restorative procedures during bisphosphonate therapy, but the least invasive procedures should be used. A conservative approach to the management of ONJ is recommended and includes oral rinses, antibiotics, pain control, and limited debridement by dental professionals. Current trials have been designed to monitor oral health, and additional prospective data should be forthcoming.

Discussion

An important goal of therapy for bone metastases is to preserve patients' physical functioning and quality of life by preventing SREs after diagnosis of bone metastases. Intravenous bisphosphonates allow monitoring adherence to therapy. In all solid tumors, the benefits of bisphosphonates are likely to continue throughout an approximately 2-year period. In fact, the risk reductions for SREs were even greater during patients' second year of therapy compared with those for the overall patient population in the first year of treatment in a study of zoledronic acid. Thus, ASCO guidelines for use of bisphosphonates in patients with BC recommend that treatment be continued as long as it is tolerated or until there is a substantial decline in patients' performance status [17].

Other cancer patients with bone metastases who are benefiting from effective anticancer therapies may also benefit from bisphosphonate therapy. Indeed, although the current regulatory approval for zoledronic acid in the United States stipulates that patients with bone metastases from PC must have had disease progression despite ADT, the National Comprehensive Cancer Network guidelines encourage early intervention with intravenous bisphosphonates in men receiving ADT [15]. Moreover, benefits seem to be especially profound before the onset of pain. However, the optimal timing for the initiation of bisphosphonate treatment in this setting has not been established.

The recommended dose and schedule of bisphosphonate therapy have been established in registration trials, although alternate treatment schedules for bisphosphonate therapy are under investigation. Several nonstandard, intensive treatment regimens of intravenous ibandronate have been evaluated in patients with metastatic bone disease for acute bone pain relief, followed by the approved monthly infusions [97–99]. Results from these pilot studies suggest that alternate ibandronate schedule provided acute pain relief, and that more flexible or individualized bisphosphonate treatment may provide clinical benefits. However, the efficacy of this alternate dosing schedule has not been confirmed in a large, randomized clinical trial.

An ongoing study of the cost-effective use of bisphosphonates in metastatic bone disease, a comparison of bone marker–directed zoledronic acid therapy to a standard schedule (BisMARK), will determine whether using bone marker levels to direct zoledronic acid treatment is comparable with the current fixed schedule of every 3–4 weeks in patients with BC [100]. The primary comparison is the frequency and timing of SREs. Secondary comparisons include quality of life and pharmacoeconomics. Final trial results are not expected until 2013; however, interim results are eagerly awaited. Finally, the efficacy of monthly zoledronic acid will be compared with administration every 12 weeks for up to 1 year in patients with bone metastases from BC (OPTIMIZE 2). The primary endpoint is the time to first SRE [101]. These clinical studies are evaluating whether efficacy can be maintained using alternate dosing schedules that may increase the flexibility of treatment for patients without compromising efficacy. The alternate schedules could also reduce the number of infusions, thereby improving benefit-risk ratios. Currently, only the approved doses and schedules of bisphosphonate therapy have established efficacy and safety profiles, and any other regimens are investigational.

In addition to bisphosphonates, several phase III clinical trials have examined the efficacy of denosumab, a recombinant human monoclonal IgG2 antibody against the receptor activator of nuclear factor-κB ligand, for prevention of SREs in patients with bone lesions from cancer (Table 3) [90, 91, 102]. Overall, the results from three trials have shown that monthly denosumab (120 mg subcutaneous) achieved the primary endpoint of statisti-

Table 3. Summary of clinical trials comparing the efficacy of denosumab with zoledronic acid in patients with advanced malignancies involving bone

	BC [91]		PC [102]		MM and ST [90]	
	DEN	ZOL	DEN	ZOL	DEN	ZOL
Patients, *n*	1026	1020	950	951	886	890
First SRE						
Median time, months	NR	26.5	20.7	17.1	20.6	16.3
Difference in median time, mo	NA		3.6		4.3	
Hazard ratio (95% CI)	0.82 (0.71, 0.95)		0.82 (0.71, 0.95)		0.84 (0.71, 0.98)	
Noninferiority *p* value[a]	<.0001		.0002		.0007	
Superiority *p* value[b]	.01		.008		.06	
First and subsequent SREs						
Rate ratio (95% CI)	0.77 (0.66, 0.89)		0.82 (0.71, 0.94)		0.90 (0.77, 1.04)	
Superiority *p* value[b]	.001		.008		.14	

[a]Primary endpoint.
[b]Secondary endpoint.
Abbreviations: BC, breast cancer; CI, confidence interval; DEN, denosumab; MM, multiple myeloma; NA, not applicable; NR, not reached; PC, prostate cancer; SRE, skeletal-related event (pathologic fracture, radiation or surgery to bone, or spinal cord compression); ST, solid tumors (not BC or PC); ZOL, zoledronic acid.

cal noninferiority to monthly zoledronic acid (4 mg intravenous) for time to first SRE in patients with BC [91], PC [102], and multiple myeloma and other solid tumors (not BC or PC) [90], and was statistically superior to zoledronic acid in the secondary endpoints in the first two studies. Nevertheless, there was no statistical difference between denosumab and zoledronic acid for overall survival, disease progression, or bone pain improvement. Currently, in the oncology setting, the European Medicines Agency (EMA) has approved denosumab (60 mg subcutaneous every 6 months) in the treatment of bone loss associated with hormone ablation in men with PC at increased risk of fractures (defined as >70 years or <70 years with a BMD T-score at the lumbar spine, total hip, or femoral neck less than −1.0, or a history of an osteoporotic fracture) [103], based on a significant decrease in vertebral fracture risk in the Hormone Ablation Bone Loss Trial (HALT)-PC trial [104]. Denosumab also has been approved for the treatment of postmenopausal osteoporosis [103] and has shown activity for treatment of bone loss associated with AI therapy in postmenopausal women with breast cancer based on the HALT-BC trial [105]. Other oncology indications for denosumab are under review by the FDA and EMA.

The role of the different antiresorptive agents in oncology is likely to evolve with the emergence of denosumab and the maturation of clinical trials investigating the potential anticancer benefits of bisphosphonates, especially zoledronic acid.

Acknowledgments

Financial support for research and medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

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We thank Tamalette Loh, Ph.D., ProEd Communications, Inc., for her medical editorial assistance, for copyediting (grammatical assistance and stylistic suggestions), and for production assistance (assembling figures and tables).

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